UNIVERSITY OF SOUTHAMPTON

SULFUR CHEMISTRY ON THE SOLID PHASE

BY

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A Thesis submitted for the degree of Doctor of Philosophy

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ABSTRACT

FACULTY OF SCIENCE

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Sulfur Chemistry on the Solid Phase

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This thesis is concerned with the chemistry of thioesters immobilised on solid supports, and radical cyclisations of solid-supported 1,6-dienes using sulfur-centred radicals.

A new method for linking substrates to a solid support using a thioester linkage is described, in which a thioamide is reacted with either Merrifield resin or a brominated Wang linker on a polystyrene bead, in the presence of aqueous DMF and sodium iodide. New methods for cleaving substrates linked to a solid support through a thioester linker are discussed, leading to tertiary alcohols, ketones and lactones, all in good yield.

The cyclisation of a range of 1,6-dienes using phenylthiyl radicals is described, both for resin-bound substrates and those in solution. The 1,6-dienes are immobilised on solid-support using a malonate linker. The diastereoselectivity of the cyclisation reaction is also reported.

Radical cyclisations of the aforementioned 1,6-dienes using *p*-tolyl benzeneselenosulfonate are also described, for both resin-bound substrates and those in solution. The diastereoselectivity of the cyclisation reaction is also reported.

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Preface

The research described in this thesis was carried out under the supervision of Dr. D. C. Harrowven and Prof. M. Bradley at the University of Southampton between October 1998 and June 2002. No part of this thesis has previously been submitted for a degree.

Acknowledgements

Firstly and foremostly, many thanks to David Harrowven for his very large helpings of advice, support and encouragement, not to mention his Christmas parties... Thanks also to Mark Bradley and Richard Brown for their input and ideas, and to Rhone-Poulenc-Rorer for the CASE award.

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I would also like to thank Graham "Sibs" Sibley and Stifun Mittoo, for their help and support in my first year, Jon Wilden for his help and support in my first two years, and Nikki Newman for help, support and softly spoken words of guidance for the same time period. Also, thanks to Mell Tyte for ensuring there was never a dull moment, Heather Bourne for participating in general silliness to keep me bouyant, Matthieu "Teu! Teu! Teu!" Carpentier for teaching me some French and introducing me to some "different" music, Ben Sutton for extremely thorough proof-reading, "Young" Stuart Flanagan for introducing us all to the delights of his "suicide tape", and Nigel Blumire for keeping my expectations in check. I would also like to thank all of the above for putting up with the terrible smells my research generated. Many members of the Bradley group, too numerous to list here individually, also deserve thanks for the help, support and materials they have given me over the last three and a half years.

Of course, the help of all of the above would have been in vain without the sterling efforts of the analytical staff. To that end, I would like to thank John Langley and Julie Herniman keeping the mass spectrometry machines working in the face of a relentless barrage of contamination (but not by me I hasten to add!), and Joan Street and Neil Wells keeping the NMR machines working through thick and thin.

Finally, I would like to thank Karen for her kindness, support and sticking with me through this struggle, but most of all for agreeing to marry me. Without her I would never have finished this.

Abbreviations

AIBN	2,2'-azobisisobutyronitrile
amu	atomic mass units
APCI	atmospheric pressure chemical ionisation
approx.	approximately
aq.	aqueous
Ar	aryl
Bn	benzyl
BOP	Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
cat.	catalytic
*c*Hex	cyclohexyl
CHN	combustion analysis
CI	chemical ionisation
conc.	concentrated
COSY	correlated spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIC	1,3-Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

EI	electron ionisation
eq.	equivalents
Et	ethyl
FT	Fourier Transform
GC	gas chromatography
h	hours
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infra red
LDA	lithium diisopropylamine
lit.	literature
LRMS	low resolution mass spectroscopy
M	molar
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minutes
Mol. Wt.	molecular weight
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
Py	pyridine
RP-HPLC	reverse phase high performance liquid chromatography

r.t.	room temperature
TBAF	*tert*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	Tri-*n*-butylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
Tol	toluene
Ts	*p*-toluenesulfonyl
UV	ultra violet

Chapter 1

Previously Reported Radical Chemistry on the Solid Phase

1.1 Introduction

Solid phase synthesis began nearly 40 years ago, with the pioneering work of Merrifield[1] which allowed the rapid and facile production of peptides built up one amino acid at a time. Solid phase organic chemistry remained little more than an academic curiosity until the advent of high-throughput screening in the pharmaceutical industry. This stimulated demand for large numbers of molecules to be rapidly produced on a regular basis. Combinatorial chemistry met this demand and, as one of the primary techniques of split and mix synthesis is best carried out on the solid phase, the impetus was present for the advancement of solid phase organic chemistry. Consequently, a vast array of reactions have been adapted to the solid phase[2].

To date few examples of radical chemistry on solid-supported substrates have been reported[3-11, 13-26, 28]. Radical chemistry offers significant advantages over two-electron processes. Despite their high reactivity, radical reactions often proceed under mild, neutral conditions, and the absence of bulky counterions or solvation spheres permits the generation of bonds between sterically crowded centres. Furthermore, carbon-centred radicals are inert to hydroxyl, amino and related functional groups so protection chemistry is often avoidable, and reactions do not demand dry conditions. For these reasons, radical chemistry has become an important tool for the construction of carbon skeletons of complex molecules, including many natural products.

One significant disadvantage of radical chemistry is that much of it utilises organotin reagents, which are toxic and produce toxic residues. Removal of these residues from product mixtures can be difficult, and here conducting radical chemistry on the solid phase offers a further advantage. Either the tin reagent or the substrate may be immobilised on a solid support[98], and thus the other can be washed away allowing for simple and effective

purification, reducing the likelihood of tin contamination of the products. This is especially significant when the high toxicity of tin is considered, as this can adversely affect the results of biological activity screening trials.

Thus it is desirable to develop radical reactions that will work with solid-supported substrates.

This review summarises radical reactions conducted on the solid phase published before May 2002.

1.2 Solid phase radical chemistry involving tin

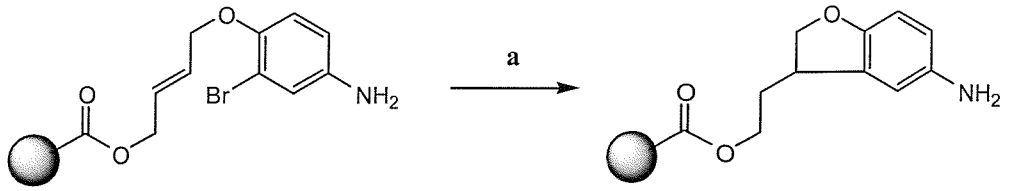
A good proportion of radical chemistry carried out on polymer-supported substrates has utilised tin reagents. As well as investigations into radical chemistry on solid-supported substrates, interest is growing in solid-supported tin reagents. Although outside the scope of this review, such reagents offer many of the advantages of solid phase chemistry (e.g. easy removal of the tin residues after the reaction), whilst allowing the substrate to be handled in solution phase.

1.2.1 Radical cyclisations and other intramolecular radical reactions

The first reported example of radical chemistry on substrates immobilised on the solid phase was published in 1997 by Balasubramanian[3] *et al.*, and involved the reaction of an aryl radical with a double bond to form a dihydrobenzofuran (Scheme 1).

The radical was generated from the corresponding aryl halide **1** by tributyltin hydride and AIBN. The reaction worked well, with greater than 90 % conversion to the expected 5-*exo*-trig cyclised product **2**, and no uncyclised product was detected. This latter point is of

interest, since uncyclised material can be a significant side product in analogous solution phase reactions when high concentrations of tributyltin hydride are employed.



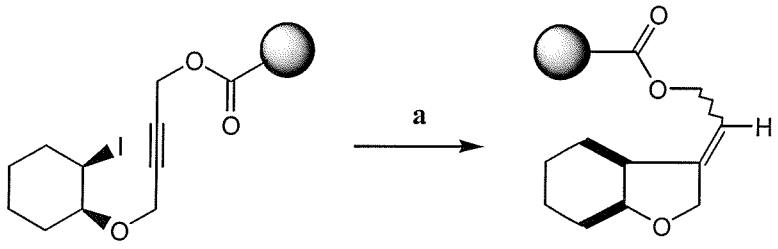
1 **2**

> 90%

a. Bu_3SnH, *t*-BuOH, AIBN, Toluene, Δ.

Scheme 1

Encouraged by this result, radical cyclisation to a carbon-carbon triple bond was attempted. Such cyclisations are known to be about four orders of magnitude slower than the corresponding cyclisation of an aryl radical to a double bond[4], and should have a greater tendency to form byproducts in the presence of high concentrations of tributyltin hydride[5]. In fact the cyclisations were fast and clean, going to completion in less than two hours and giving only the *E* and *Z* isomers of **4** with no reduced or other byproducts detected (Scheme 2).



3 **4**

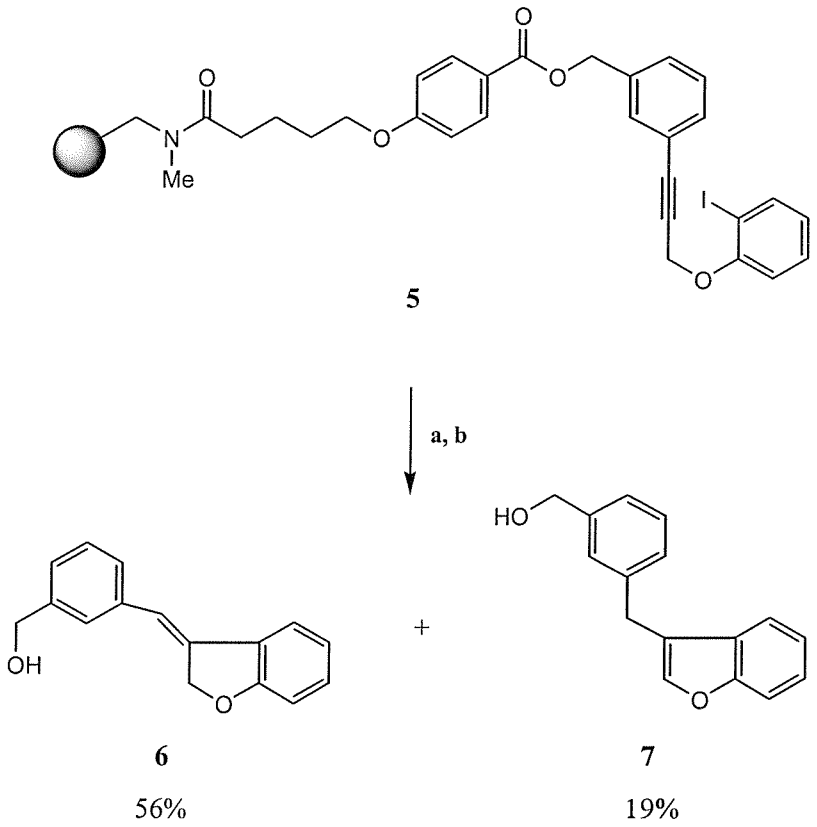
69%
E:*Z* 1.2:1

a. Bu_3SnH (20-25 eq.), AIBN (5 mol %), toluene, 70-80 °C, 2 h

Scheme 2

Several examples of the reaction were reported. Notably, the analogous solution phase reaction did not proceed as cleanly, giving several additional products which could not be identified.

A similar cyclisation of an aryl radical to an alkyne has been described by Mesmaeker[6] *et al.* Thus, treatment of aryl iodide **5** with tributyltin hydride led to a 3:1 mixture of dihydrobenzofuran **6** and benzofuran **7** (Scheme 3).

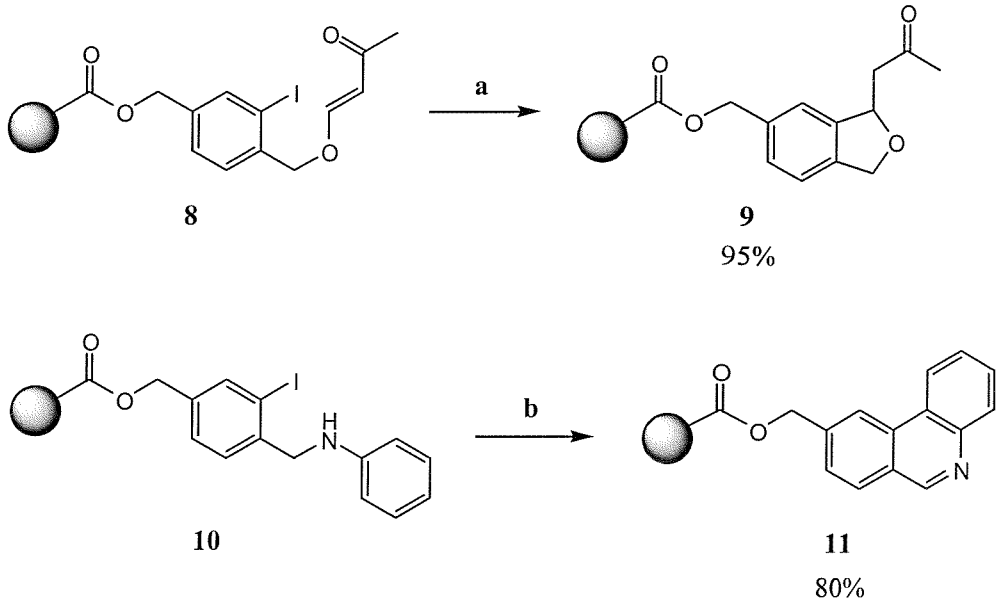


a. 3 eq. Bu_3SnH, 0.6 eq. AIBN, benzene, Δ, 46 h; **b.** 6 eq. MeONa, MeOH / dioxane (1/4), RT, 24 h.

Scheme 3

Mesmaeker[7] *et al.* also reported a similar cyclisation to produce a dihydrobenzo[b]furan in very high yield, and then extended their methodology to produce a phenanthridine (Scheme 4). However, a large excess of AIBN was required in the latter case, suggesting that isobutyronitrile radicals were required for the rearomatisation of the cyclised radical

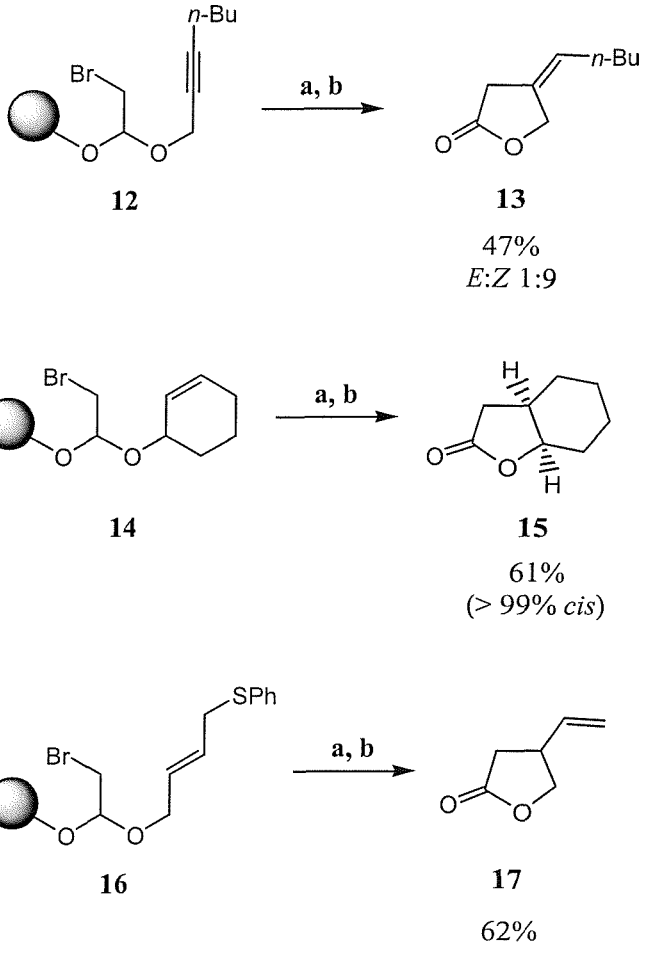
intermediate by abstraction of the *ipso*-hydrogen atom. The authors claim that by "using this methodology, highly diverse bicyclic and tricyclic structures could be produced on solid support".



a. 3 eq. Bu_3SnH, 0.6 eq. AIBN, benzene, reflux, 48 h. **b.** 16 eq. Bu_3SnH, 13.5 eq. AIBN, benzene, reflux.

Scheme 4

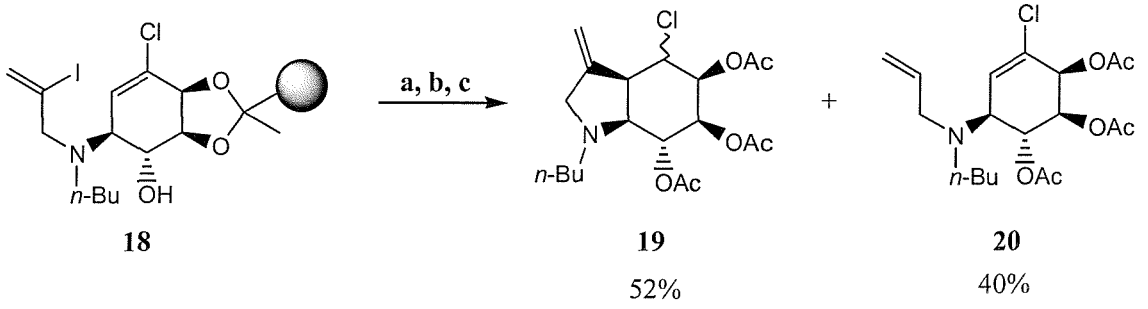
More recently, Toru[8] and co-workers have reported a radical cyclisation in which a primary alkyl radical is the agent of cyclisation (Scheme 5). Five equivalents of tributyltin hydride and half an equivalent of AIBN were required, and these were all added in a single portion. Cyclisation was effected in good to excellent yields with a range of substrates. Three observations were particularly notable. Firstly, cyclisation onto an alkyne showed good stereoselectivity, giving an *E*:*Z* ratio of 1:9 for the resultant alkene **13**. Secondly, cyclisation onto the C-C double bond of a cyclohexene ring gave a 5,6-ring system, with a *cis*-ring fusion, **15**. Finally, cyclisation onto an allyl thiophenyl ether led to β-elimination of the phenylthiyl radical, leading to a terminal alkene product (**17**) in 62 % yield.



a. Bu_3SnH (5 eq.), AIBN (0.5 eq.), benzene, Δ. **b.** Jones reagent (2 eq.), r.t., 3 h.

Scheme 5

Wendeborn[9] *et al.* have reported a tin-mediated radical cyclisation involving a vinylic radical, which was used to produce what the authors described as "relatively complex bicyclic systems with the potential for diversity" (Scheme 6).

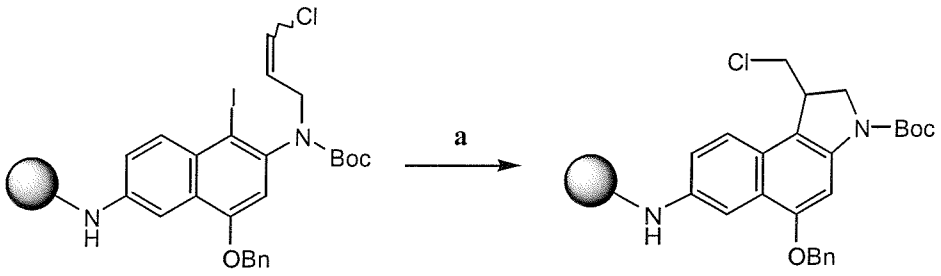


a. 3 eq. *n*-Bu_3SnH, 0.6 eq. AIBN, benzene, Δ, 48 h. **b.** TFA, H_2O, DCM, r.t., 1 h. **c.** 20 eq. Ac_2O, 10 eq. Et_3N, pyridine, r.t., 16 h.

Scheme 6

The radical cyclisation proceeded in fair yield, producing the cyclised product as a mixture of epimers. However, a substantial amount of the reduced, non-cyclised product was also isolated. Impressively, no products arising from reduction of the chloride were isolated.

Lown[10] and co-workers have also synthesised several complex molecules on solid phase, utilising a tin-mediated intramolecular aryl radical cyclisation (Scheme 7). Interestingly, the vinylic chlorine present in the substrate is left intact by this reaction, which used only 1.3 equivalents of tributyltin hydride.

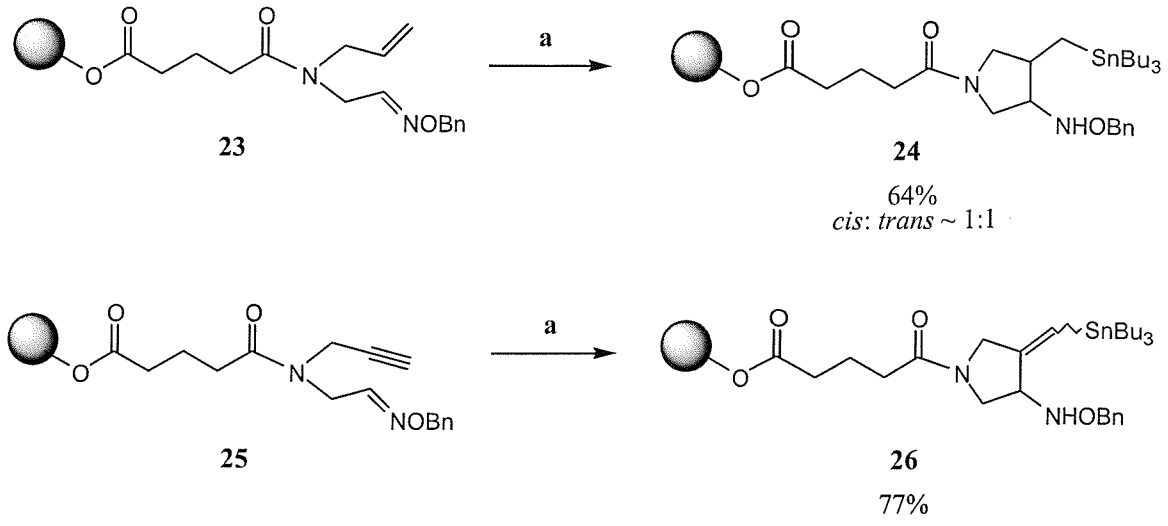


21 **22**

a. Bu_3SnH (1.3 eq.), AIBN, benzene, Δ, 8 h.

Scheme 7

The examples so far have looked at the use of tin radicals as mediators in solid phase radical chemistry. Naito[23] *et al.* have developed a solid phase radical cyclisation in which the tributyltin radical itself adds to a carbon-carbon double or triple bond, promoting a radical cyclisation onto an oxime ether. An excess of triethylborane acted as the radical initiator (Scheme 8). Yields were good for the addition-cyclisation reactions with both the alkene and the alkyne, although diastereoselectivity was very poor, as is typical for radical cyclisations of this type[12]. Interestingly, the use of AIBN as a radical initiator for the reaction led to lower yields. 9-BBN was also investigated as a possible radical initiator but found to be ineffective.



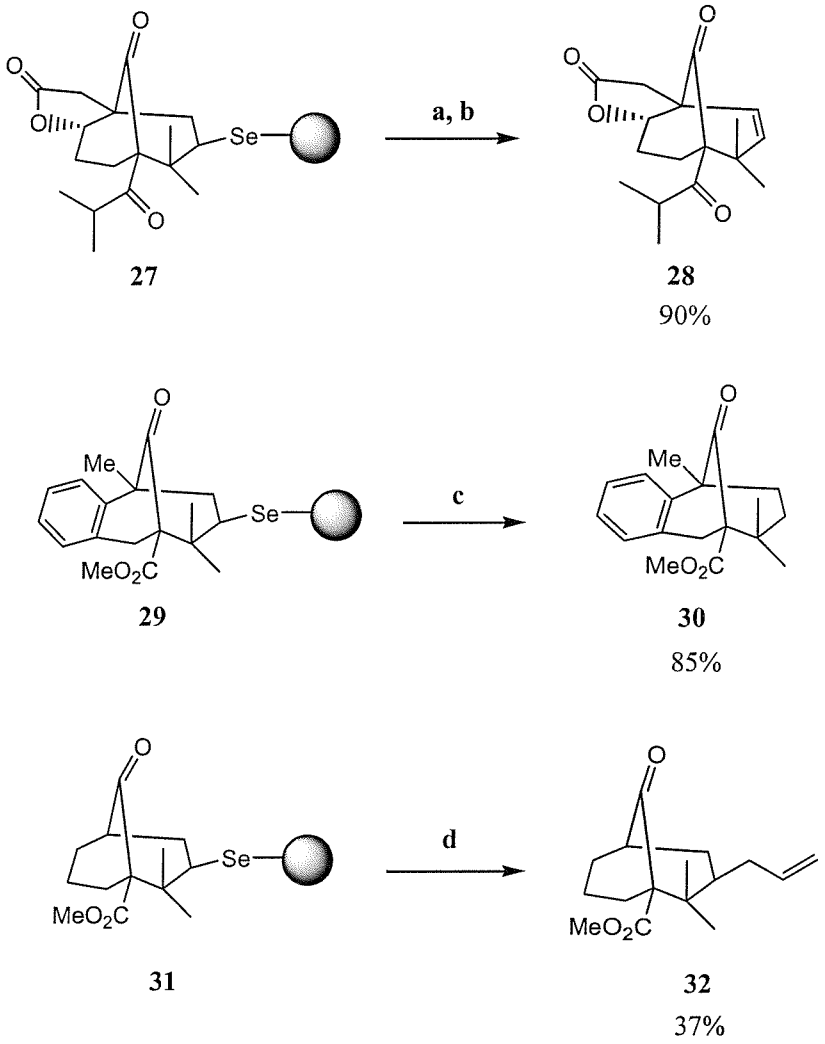
23 **24** 64% *cis*: *trans* ~ 1:1

25 **26** 77%

a. Bu_3SnH, Et_3B, toluene, Δ, 8 h.

Scheme 8

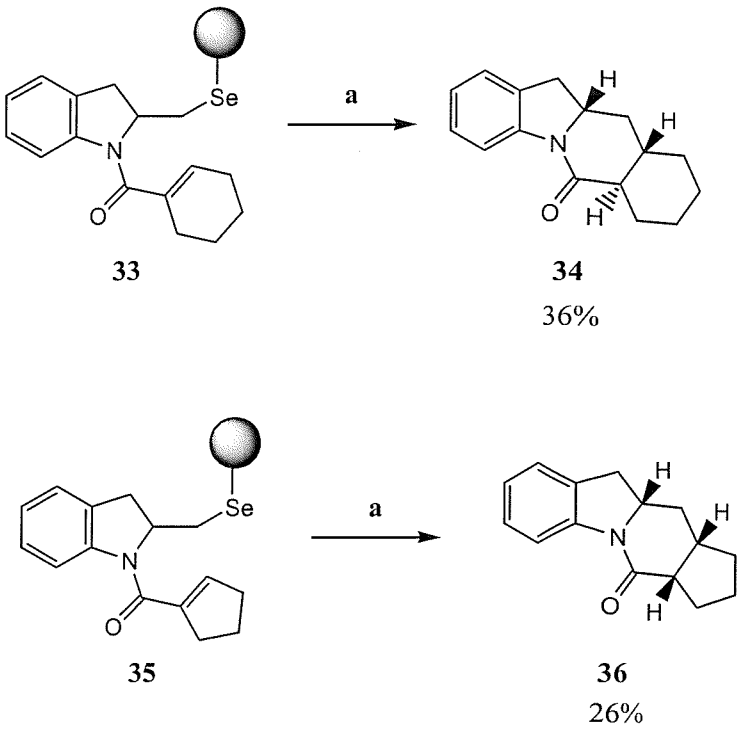
Substrates attached to a solid support with a selenium linker have been cleaved using tributyltin radicals. The tin radical attacks the selenium, releasing the substrate as a primary alkyl radical. Nicolaou[13] *et al.* have taken advantage of this in their construction of substituted [3.3.1]-bicycles on solid phase. Three possible methods for cleaving the resin-bound substrate from its selenium linker were demonstrated (Scheme 9). The first (non-radical) method uses hydrogen peroxide to effect an oxidation-elimination liberating the substrate as an alkene, **28**. The second method uses five equivalents of tributyltin hydride and AIBN as the initiator to cleave the substrate from the selenium in a "traceless" fashion. The third method uses allyltributyltin which replaces the selenium with an allyl group.



a. 30 % H_2O_2 (10.0 eq.), THF, 0 °C, 2 h; **b.** CCl_4, 80 °C, 10 min; **c.** Bu_3SnH (5.0 eq.), AIBN (0.1 eq.), benzene, 80 °C, 2 h; **d.** $Bu_3SnCH_2CH{=}CH_2$ (5.0 eq.), AIBN (0.1 eq.), benzene, 80 °C, 2 h.

Scheme 9

If a carbon-carbon double bond is in close proximity to the radical generated on the cleaved substrate, a cyclisation can take place immediately after the molecule is released from the resin[14] (Scheme 10):



33 **34** 36%

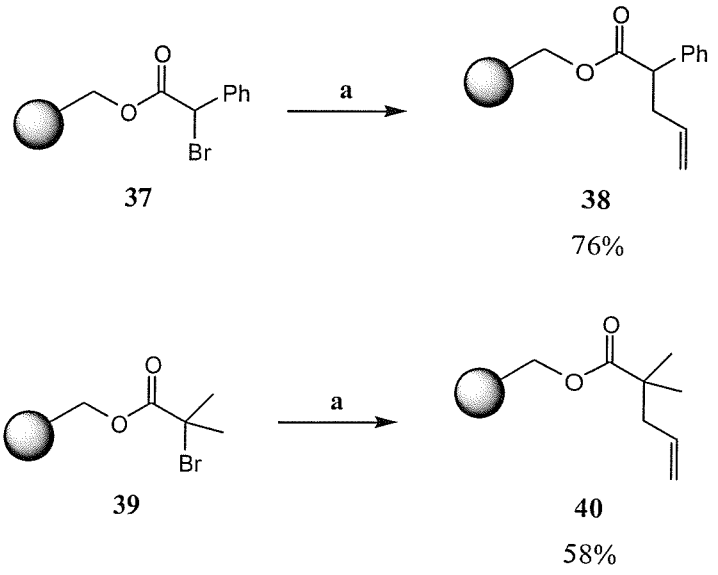
35 **36** 26%

a. Bu_3SnH (4.0 eq.), AIBN (1.3 eq.), toluene, 90 °C, 4 h.

Scheme 10

1.2.2 Intermolecular radical reactions

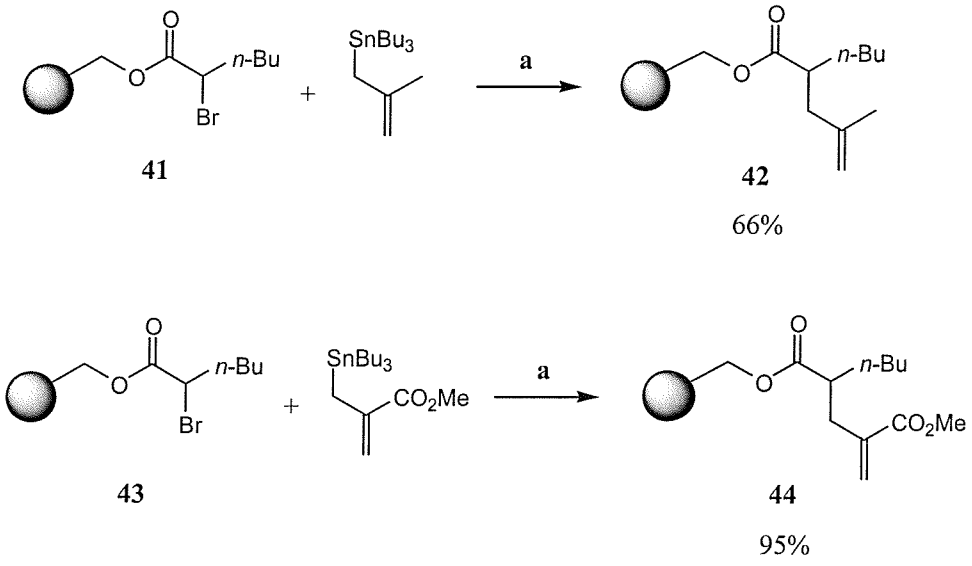
Intermolecular radical reactions are second order, and hence there is much more potential for quenching or other competing reactions to occur. Despite this, several examples of successful intermolecular radical reactions on the solid phase using tin radicals have been reported. In 1997, Sibi[15] and co-workers carried out one of the first investigations into radical chemistry on the solid phase, examining the free radical allylation of resin-bound α-bromoesters with allyltributyltin (Scheme 11). The methodology required 3-4 equivalents of AIBN and 10 equivalents of allyltributyltin to drive reactions to completion. This suggested that radical chain processes were not being propagated. Nonetheless, yields were generally good; albeit lower for sterically hindered α-bromoesters.



a. Allyltributyltin (10 eq.), AIBN (3-4 eq.), benzene, 80 °C.

Scheme 11

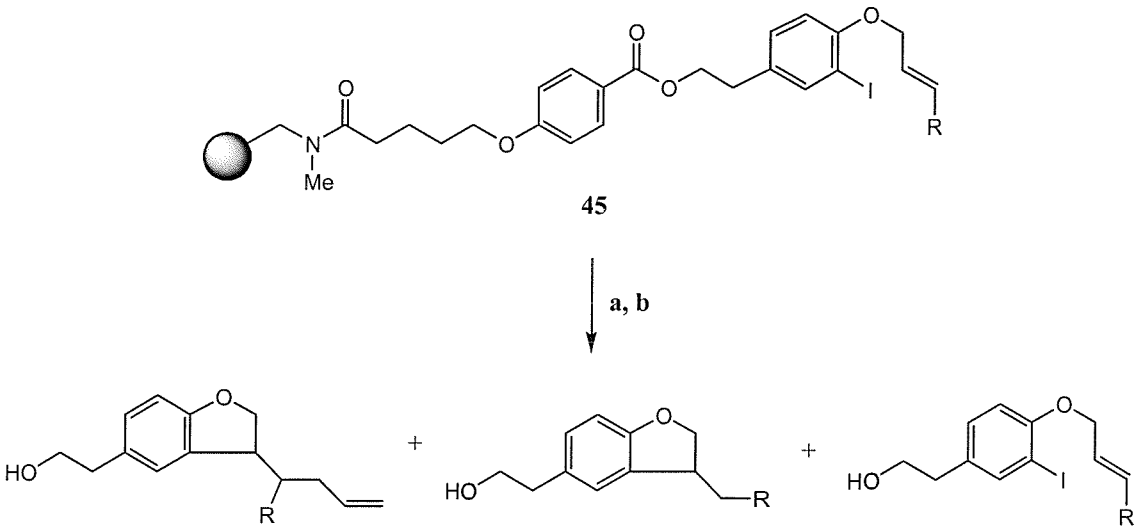
The reaction was also successful with substituents at the 2-position of the allyl stannane. An electron withdrawing substituent in the 2-position provided higher chemical yields in the allylation (Scheme 12).



a. AIBN (3 eq.), benzene, 80 °C.

Scheme 12

Mesmaeker[6] *et al.* have reported a tandem radical reaction, which relies on exploiting the difference in rate between intramolecular and intermolecular radical reactions for its success. In the work, a radical cyclisation is followed by an intermolecular radical reaction trapping the resulting radical with allyltributyltin (Scheme 13).



46, R = H: 78 % **47**, R = H: 22 % **48**, R = H: 0 %

49, R = Me: 49 % **50**, R = Me: 22 % **51**, R = Me: 29 %

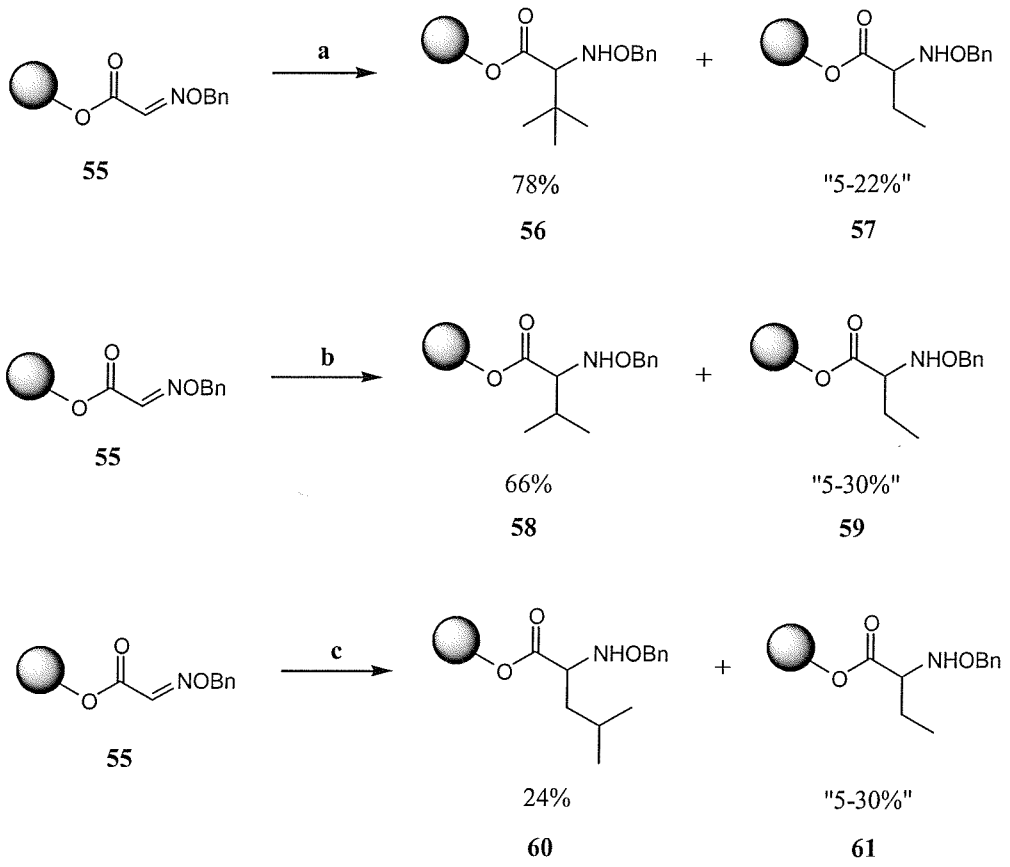
52, R = Ph: 10 % **53**, R = Ph: 10 % **54**, R = Ph: 80 %

a. Allyltributyltin (15 eq.), AIBN (1.5 eq.), benzene, Δ, 46 h. **b.** 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24 h.

Scheme 13

When R = H (i.e. the radical-acceptor is a terminal alkene), the yield of allylated product is good, with 22 % of reduced product **47** being given, and no reduced product. When R = Me, the yield of the allylated product **49** is fair, but the product of hydrogen atom abstraction is once again significant and the uncyclised product **51** accounts for almost a third of the mass balance. Disappointingly, with R = Ph the results are poor; four fifths of the mass balance is uncyclised product **54**.

Meanwhile, Naito[11] *et al.* have reported a method for alkyl radical addition to the carbon-nitrogen double bond of resin-bound glyoxylic oxime ethers. Tributyltin hydride was used to propagate the reaction, which proceeded in yields ranging from good to poor depending on the alkyl radical precursor; more stabilised radicals give higher yields (Scheme 14).



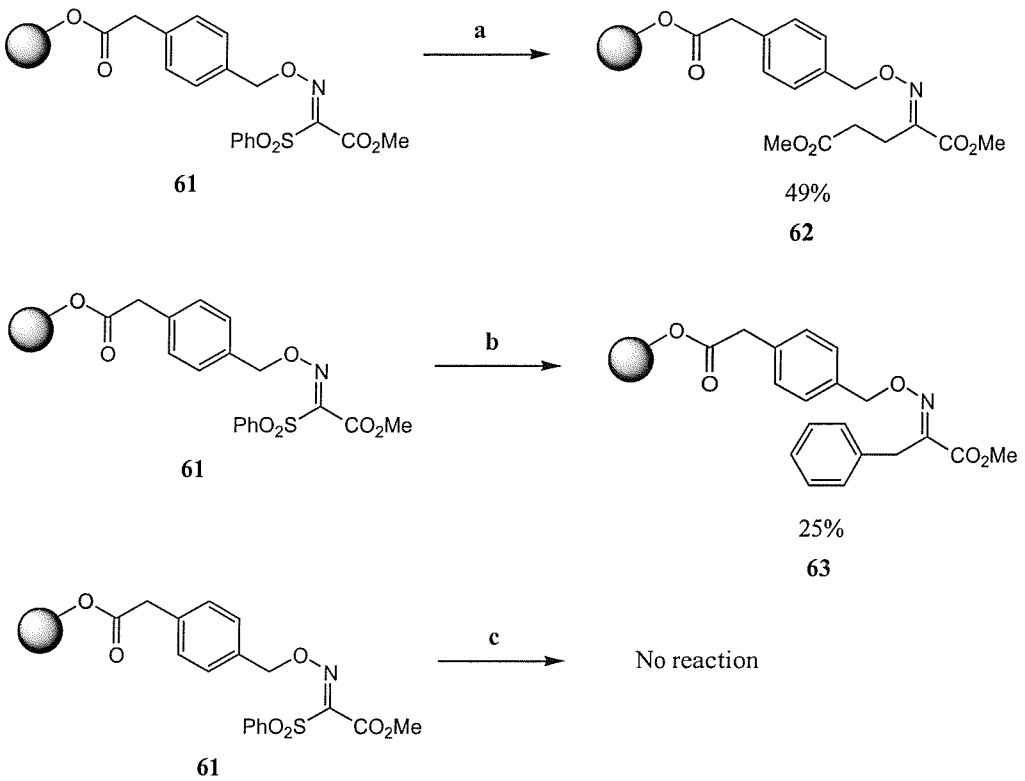
a. *t*-BuI (7.1 eq.), Bu_3SnH (2.1 eq.), Et_3B (1.1 eq.), r.t., 1 h. **b.** *i*-PrI (7.1 eq.), Bu_3SnH (2.1 eq.), Et_3B (1.1 eq.), r.t., 1 h. **c.** *i*-BuI (7.1 eq.), Bu_3SnH (2.1 eq.), Et_3B (1.1 eq.), r.t., 1 h.

Scheme 14

Interestingly, triethylborane was used as the radical initiator in stoichiometric amount. It offers a significant advantage over AIBN for the initiation of radical reactions at lower temperature (even at -78 °C). AIBN by contrast requires elevated temperatures or irradiation with ultraviolet light in order to be effective. The authors claim that "the reaction will be particularly useful because there currently exists no general synthetic method for the construction of a wide range of aliphatic α-amino acids using glyoxylic imines as the starting

material". One significant problem derived from the use of triethylborane is that ethyl radicals, generated directly from the initiator through its reaction with oxygen, compete with other alkyl radicals in reaction with the oxime. Yields of ethyl adducts ranged "from 5 – 30 %", although no specific details were given.

More recently, solid phase radical chemistry has been extended to include radical substitution reactions. Resin-bound phenyl sulfonyl oxime ethers have been subjected to radical substitution reactions by Kim[16] *et al.*, with a range of carbon-centred radicals displacing the phenyl sulfonyl group. Oxime ethers result from this reaction in which a new carbon-carbon bond is formed (Scheme 15).

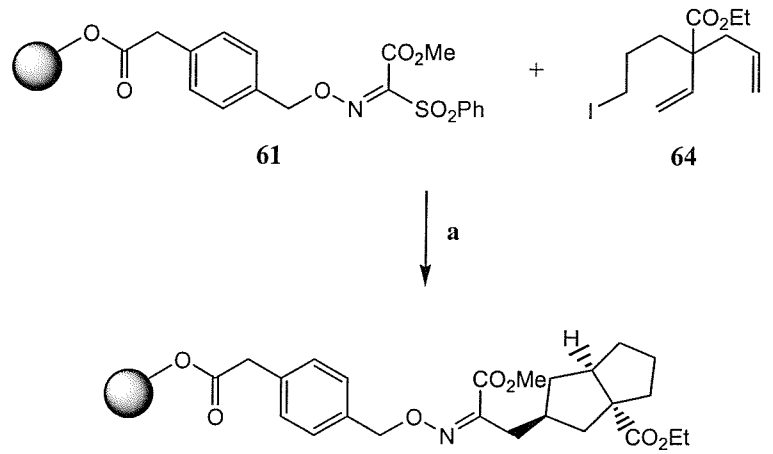


a. I-$CH_2CH_2CO_2Me$ (3 eq.), $(Me_3Sn)_2$ (3 eq.), benzene, *hυ*. **b.** Benzyl bromide (3 eq.), $(Me_3Sn)_2$ (3 eq.), benzene, *hυ*. **c.** I-CH_2CO_2Me (3 eq.), $(Me_3Sn)_2$ (3 eq.), benzene, *hυ*.

Scheme 15

The radicals are generated from their corresponding halides, with an excess of hexamethylditin using ultraviolet irradiation to initiate homolysis of the weak tin-tin bond.

According to the authors, the stereochemistry of the oxime ether is retained in the reaction. Yields, where quoted, varied from good to fair, depending on the nature of the radical intermediate. More stabilised radicals tend to give lower yields, and when the reaction was attempted using an iodoacetate, there was no reaction at all. However, the scope of the reaction appears broad, its versatility being extended to a tandem radical cyclisation-trapping sequence, which proceeded in 24 % yield (Scheme 16).



a. $(Me_3Sn)_2$, benzene, hυ, 24 h.

Scheme 16

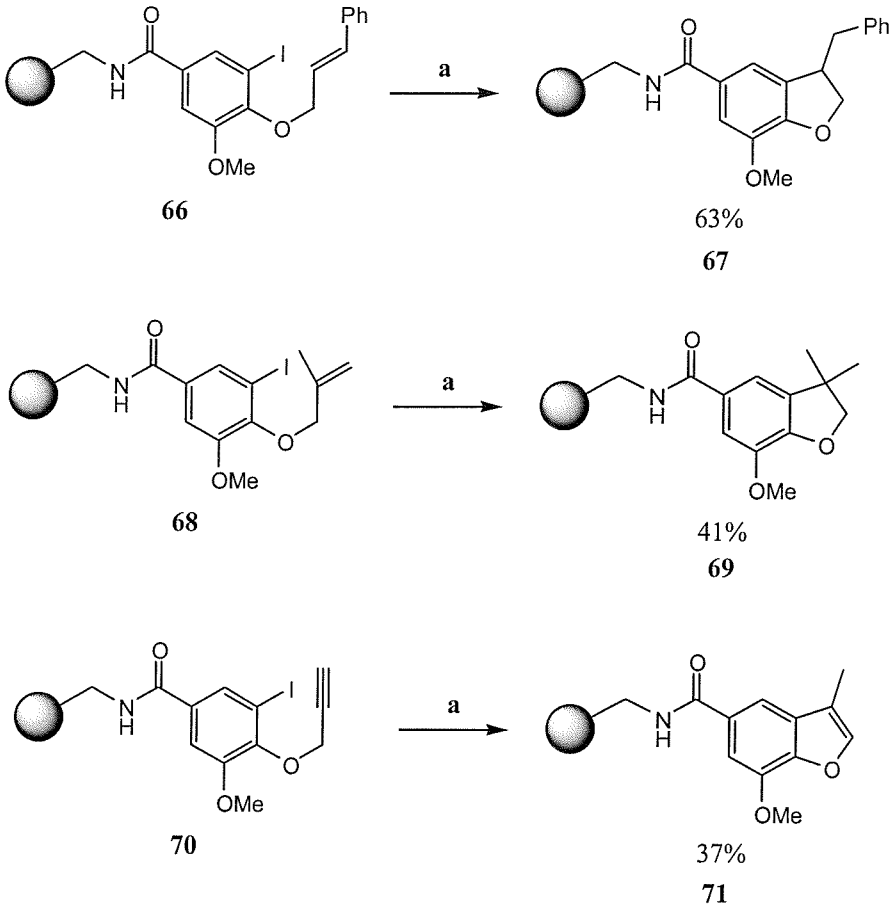
1.3 Solid phase radical chemistry without tin

1.3.1 Samarium diiodide initiated radical chemistry

Samarium diiodide provides an alternative method of generating carbon centred radical intermediates. It offers several advantages over tin, including reduced toxicity. Additionally, reactions can often be carried out at room temperature or below.

Armstrong[17] *et al.* were the first to investigate samarium diiodide reactions on the solid phase. The cyclisation of an aryl radical to produce a dihydrobenzofuran was used for their study; essentially the same reaction studied by Balasubramian[3] *et al.*, only with SmI_2 in place

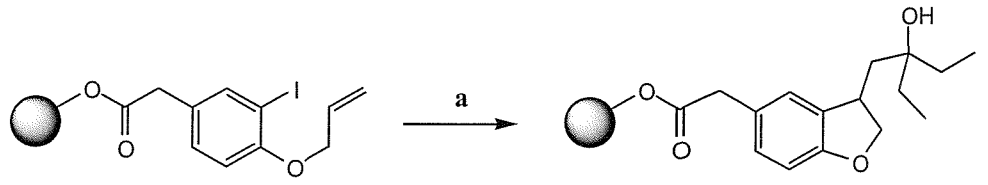
of tributyltin hydride. A range of substrates were studied, and yields were generally good (Scheme 17). The cyclisations proceeded quickly and cleanly, with only a small amount of direct reduction occurring. Significantly, it was observed that cyclisations with a substituent group at the terminal alkene carbon are higher yielding than those with a substituent at the internal carbon of the alkene. When CO_2Et was substituted at the terminal carbon of the alkene however, no reaction took place.



a. SmI_2, HMPA, THF, 1 h.

Scheme 17

The authors extended this methodology to carry out reactions in which the radical on the cyclised product is converted to an anion by a further molecule of SmI_2 (such reactions are known as "polar crossover reactions")[18]. Consequently the resin-bound organosamarium intermediate was trapped with an electrophile, either an aldehyde or a ketone (Scheme 18).



72

33%

73

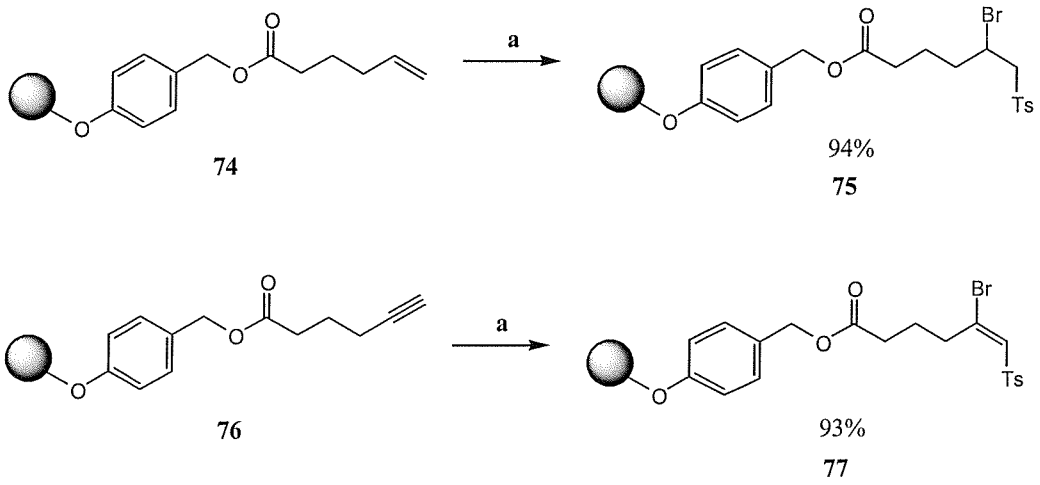
a. SmI_2, HMPA, THF, 3-pentanone.

Scheme 18

The methodology allows two significant steps to be performed rapidly (under 10 minutes) in one pot. A range of electrophiles are compatible, with yields ranging from fair to poor. The methodology is highly substrate dependent, both in solution and on the solid phase, and the authors noted that this "may limit its general utility in combinatorial construction".

1.3.2 Sulfur radicals

Sulfur radical chemistry on the solid phase is not an area that has been widely explored. To date, only two examples of sulfur radical chemistry on resin-bound substrates have been reported. The first, published by Caddick[19] *et al.*, demonstrated the addition of tosyl bromide across unactivated double and triple carbon-carbon bonds *via* a tosyl radical pathway (Scheme 19). Evidence that the reaction proceeds *via* a radical pathway is provided by the fact that AIBN is necessary for the reaction to occur.

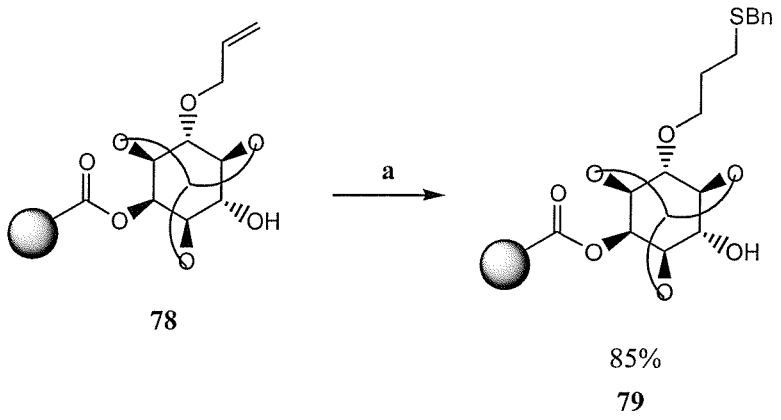


a. TsBr, AIBN, toluene, 65-70 °C.

Scheme 19

Addition to alkynes produced *trans* alkenes. Optimised yields for addition to both alkenes and alkynes are excellent, this being the first example of a radical addition to an *unactivated* resin-bound radical acceptor.

The second example concerns thiyl radical addition to a resin-bound allyl ether, as reported by Plourde[20] and co-workers. A range of alkyl and benzyl thiols were added to resin-bound allyl ethers giving the corresponding thioethers in good to excellent yields. In all cases addition was exclusively to the unsubstituted terminus of the alkene (Scheme 20). However, the reaction did not proceed "to any significant degree" with aryl or hetereoaryl thiols.

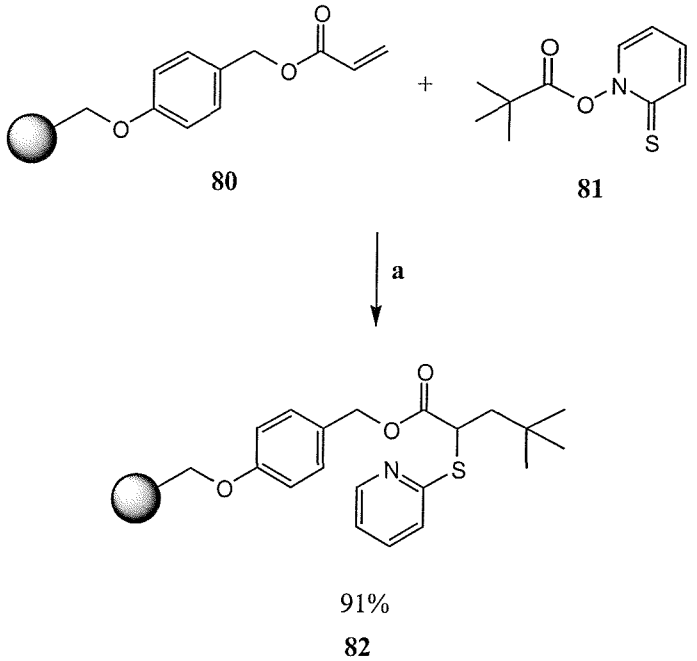


a. Benzylthiol, AIBN, benzene, 80 °C, 24 h.

Scheme 20

1.3.3 Radicals from Barton esters

Ganesan and Zhu[21] have conducted an extensive investigation into the usefulness of radicals generated from Barton esters for solid phase organic chemistry. In their study, acrylic acid was immobilised on a solid support, then radicals generated by irradiation of a range of Barton esters underwent conjugate addition to the acrylate (Scheme 21). Yields were generally very good, and comparable to analogous solution phase reactions. Exceptions to this rule were the adamantyl radical which gave only a reasonable yield (63 %), and the benzyl radical which gave a poor yield (32 %).



a. hυ, DCM, 0 °C, 4 h.

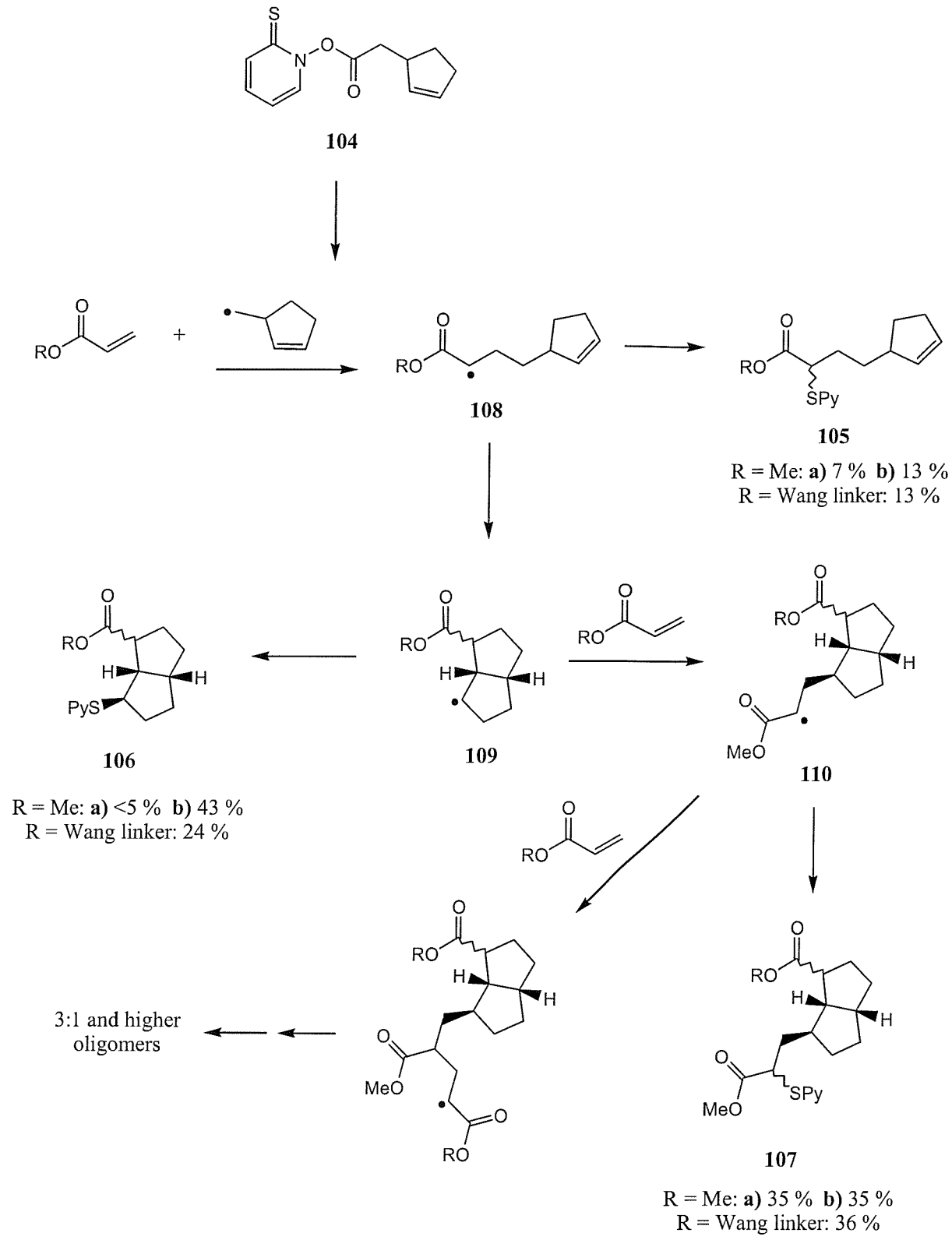
Scheme 21

The authors then extended their study to produce bicyclic systems both on solid phase and in solution, using a Barton ester derived from cyclopent-2-enylacetic acid. The methodology is shown in scheme 61. On solid phase, three products were isolated from the reaction: the 2:1 adduct **107** (36 %, *cis* : *trans* 1:4), the non-cyclised product **105** (13 %), and the cyclised product **106** (24 %). Two analogous solution phase reactions were carried out; one using a

low concentration of Barton ester, and the other using the same number of equivalents of Barton ester as were used in the solid phase reaction. When a low concentration of Barton ester was used, **105** was isolated in 7 % yield, a trace amount of **106** (< 5 %) was isolated, and **107** was the major product, with an isolated yield of 35 %. In addition, two more products were isolated: 1-(2-thiopyridyl)-methyl-2-cyclopentene (8 %, the result of direct chain transfer with the cyclopentenylmethyl radical), and 18 % of a 3:1 adduct of methyl acrylate and cyclopentenylmethyl radical.

When a high concentration of Barton ester was used, **105** was isolated in 13 % yield, **106** (now the major product) was isolated in 43 % yield, and **107** again was isolated in 35 % yield, as a 1:1 mixture of diastereomers. No other products were reported.

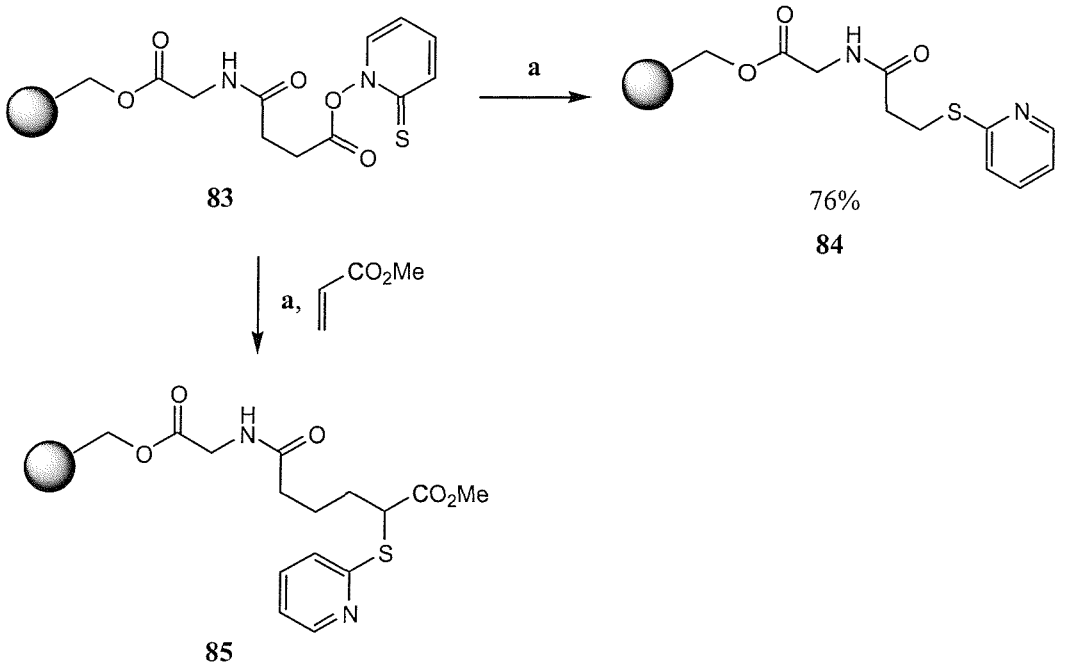
Interestingly, these results suggest that site isolation of the intermediate **109** on solid phase is not significant, as the radical is clearly able to access a second acrylate, leading to **107**. The results also show that the fate of intermediate radical **109** is determined largely by the concentration of Barton ester. Where this is high, pyridinethiyl radical quench is the dominant reaction pathway, however where the concentration of Barton ester is low, further conjugate additions can occur. Ganesan considers that the "slower kinetics on solid phase relative to homogeneous conditions are probably responsible for the lower accumulation of **106** (24 versus 43 %)".



Scheme 61

a. Methyl acrylate, Barton ester (2 eq), hυ, CH_2Cl_2, 4h. **b.** Methyl acrylate / resin-bound acrylate, Barton ester (10 eq), hυ, CH_2Cl_2, 4h.

A related study by Taddei[22] *et al.*, investigated the chemistry of immobilised Barton esters when irradiated with ultraviolet light. The Barton ester was successfully fragmented, as shown in Scheme 22.



a. DMF, hυ, 20 min.

Scheme 22

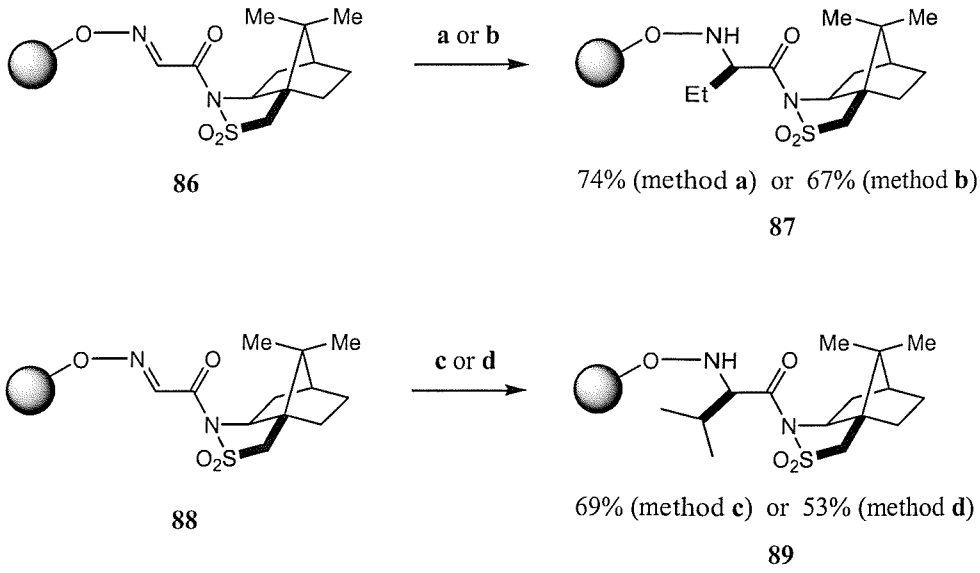
It was postulated that the R· and ArS· generated on irradiation of the resin-bound Barton ester might add across an electron-poor alkene in the solution phase, such as methyl acrylate or 1-nitro-1-pentene. However the expected trapped products could only be obtained when 100 equivalents or more of the alkenes were employed. Yields were not reported.

1.3.4 Triethylborane and diethylzinc as radical chain carriers

Work in this area has been carried out primarily by Naito[11, 23-25] *et al.* Early studies used triethylborane as a radical initiator for tin-mediated radical reactions[11, 23]. However, in later work it was observed that the radical addition reaction could proceed even in the absence of tributyltin hydride. Consequently, the team have so far reported two studies in which

triethylborane acts as a Lewis acid, a radical initiator, and a radical chain carrier, all within the same reaction[24, 25].

In the first of two studies[24], a comparison was made between the effectiveness of triethylborane and diethylzinc as initiators and chain carriers for the stereoselective addition of alkyl radicals to a resin-bound oxime ether derived from Oppolzer's camphorsultam chiral auxiliary (Scheme 23). Yields were generally good when triethylborane was used as the radical mediator, but lower when diethylzinc was used. Diastereoselectivity was very good (all cases >90 % d.e.) and reactions could be effected at 0 °C in most cases.



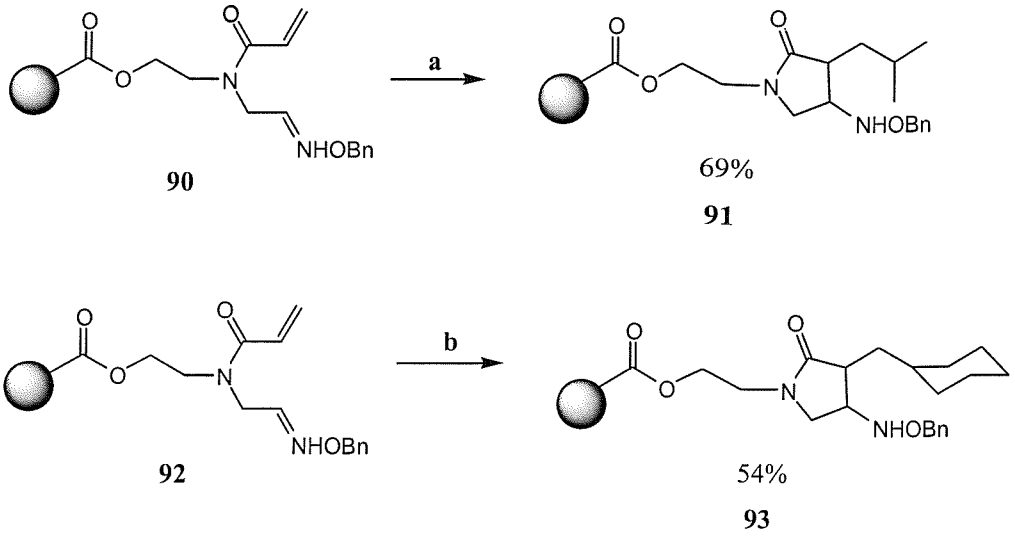
86 74% (method **a**) or 67% (method **b**) **87**

88 69% (method **c**) or 53% (method **d**) **89**

a. Et_3B (5 eq.), -78 °C, DCM, 30 min; **b.** Et_2Zn (5 eq.), -78 °C, DCM, 30 min; **c.** Et_3B (10 eq.), 0 °C, *i*-PrI / toluene (4:1, v/v); **d.** Et_2Zn (10 eq.), 0 °C, *i*-PrI / toluene (4:1, v/v).

Scheme 23

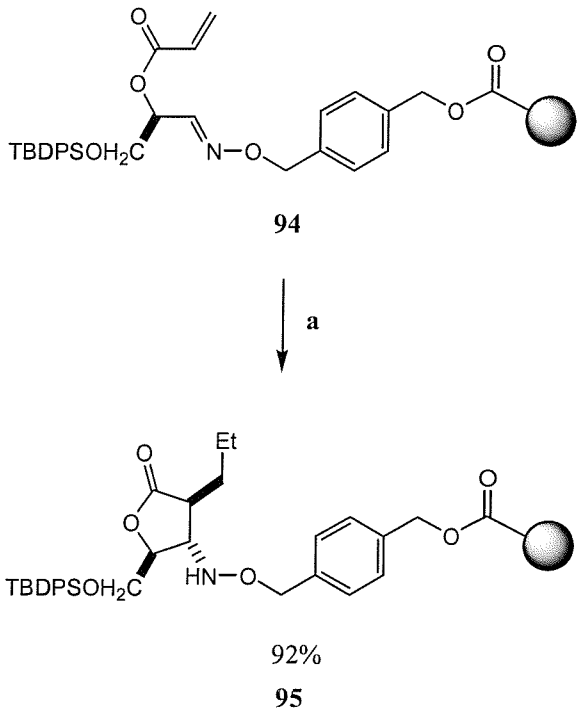
Triethylborane has also been used as a mediator for radical addition-cyclisation reactions[25]. Thus, addition of an alkyl radical to the terminus of an α,β-unsaturated carbonyl was followed by a radical cyclisation to an oxime ether. In this way a range of γ-lactams were produced in good yield (scheme 24). The stereochemical course of the reaction was not reported. In contrast to the previous reaction, elevated temperatures (100 °C) were needed to bring about reaction.



a. *i*-PrI, Et_3B in hexane, toluene, 100 °C **b.** *c*-hexylI, Et_3B in hexane, toluene, 100 °C

Scheme 24

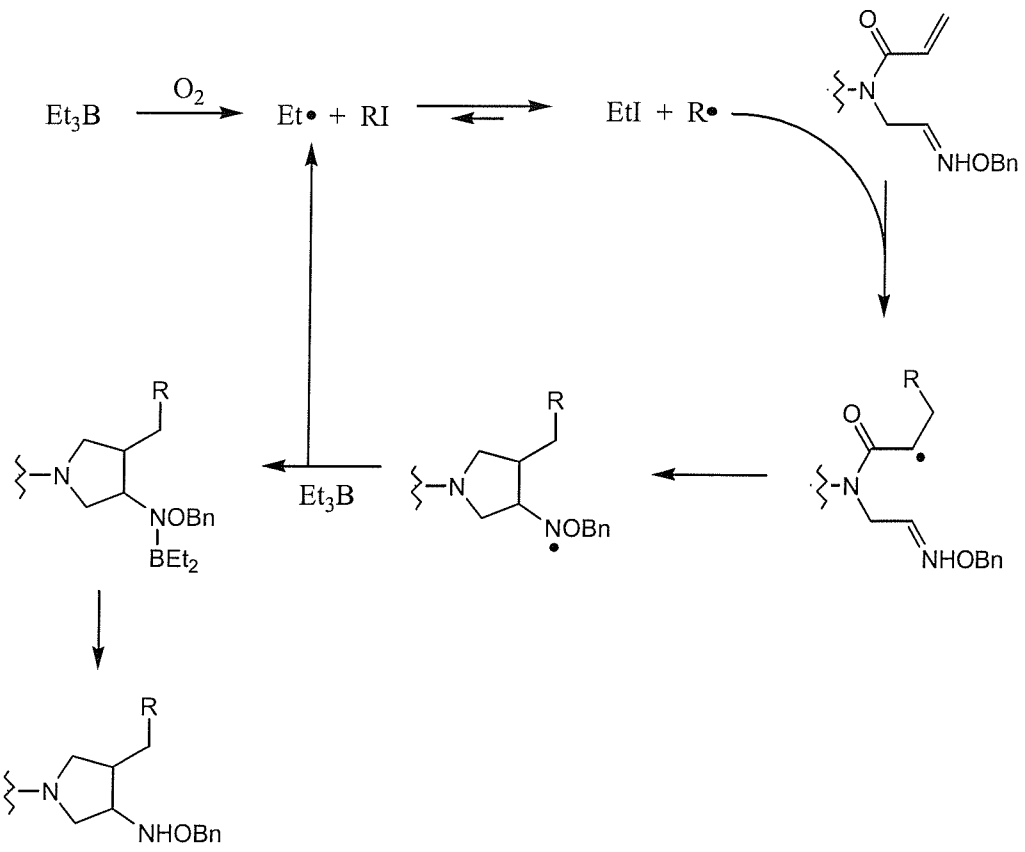
With chiral substrates, diastereoselectivities were generally good, with an 8:1 ratio being typical (scheme 25). The yield for the radical addition of an ethyl group was excellent, however when other alkyl radicals were used yields were substantially lower.



a. Et_3B in hexane, 100 °C.

Scheme 25

The mode of action of triethylborane is illustrated in scheme 26 and requires molecular oxygen. In the first step, molecular oxygen attacks the triethylborane, releasing an ethyl radical. This can then abstract an iodine atom from an alkyl or aryl iodide: provided such species are present in vast excess, the equilibrium shown above will favour R· over Et·. The R· species is then free to attack a radical acceptor, in this case the alkene bond of an α,β-unsaturated amide. Cyclisation then swiftly follows, generating a radical on the nitrogen of the oxime. This can be quenched with further triethylborane, in the process liberating another ethyl radical which propagates the chain. The mode of action of diethyl zinc is assumed to be similar.

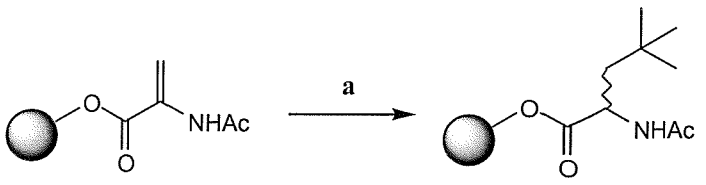


Scheme 26

1.3.5 Other radical sources

To date, only one example of the use of organomercury compounds for the generation of radicals on the solid phase has been described[26]. The radicals were generated by treatment of

organomercury chlorides with sodium borohydride at room temperature. These were then trapped by a resin bound α,β-unsaturated ester (scheme 27).



96 49% **97**

a. *t*-BuHgCl, $NaBH_4$, DCM / H_2O, RT, 90 min.

Scheme 27

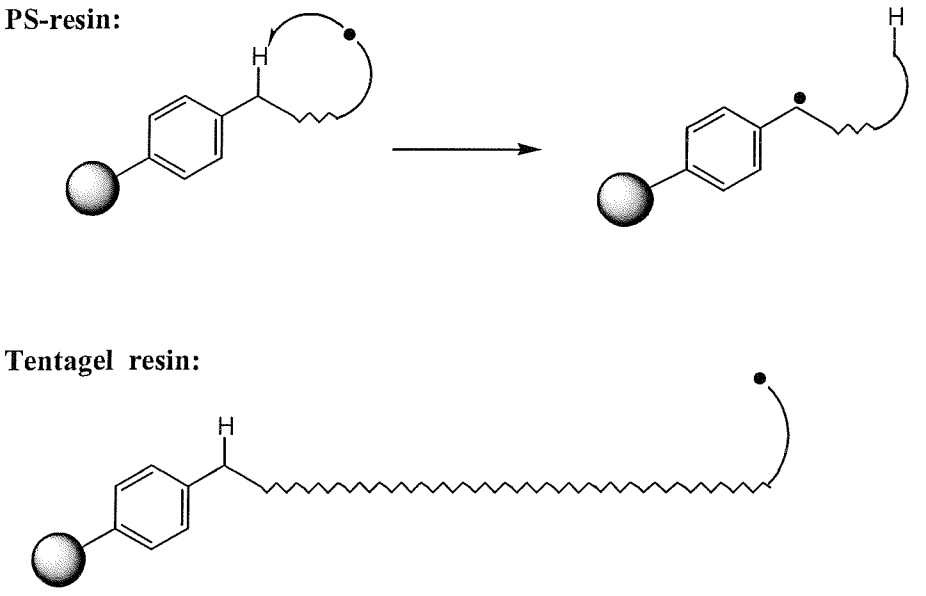
The reaction required only 90 minutes, and yields ranging from 49 % to 60 % for the 3 steps were recorded. Interestingly, when the same reaction was tried using AIBN, tributylstannane and the corresponding alkyl iodide, only a very small amount of the desired product was obtained, with much starting material recovered. The authors claim that the removal of mercuric residues from the resin prior to cleavage was "easily accomplished" by washing the resin. None-the-less, the high toxicity associated with organomercury compounds, coupled with the difficulty of disposing of mercury-containing wastes, severely limits the usefulness of this method.

1.4 Choice of resin for solid phase radical chemistry

1.4.1 PS vs. Tentagel resin

In the early stages of investigation into solid phase radical chemistry, researchers were very concerned at the possibility that radicals in solution might abstract hydrogen atoms from the solid support, rather than react with the substrate tethered to the support[3]. Balasubramanian[3] *et al.* believed they had found early evidence of this when they compared the efficiency of cyclisation of an aryl radical onto an alkene with the substrate supported on carboxylated polystyrene, and on Tentagel resins. The researchers found that the radical cyclisation on

carboxylated polystyrene required over 1 equivalent of AIBN, compared to 0.06 equivalents of AIBN for the substrate tethered to Tentagel resin. They postulated this was due to radicals abstracting hydrogen atoms from the benzylic positions of the polystyrene backbone in preference to propagating the chain reaction. They reasoned such a situation was less likely to occur with Tentagel resin since the substrate was kept at some distance from the polystyrene of the resin, by the PEG chains of the Tentagel. (See Scheme 28.)



Scheme 28

The next piece of work relevant to this discussion was published shortly afterwards by Armstrong[17] and co-workers. They carried out their early studies of samarium diiodide mediated radical cyclisations on both PS-Rink and Tentagel-Rink resins, and found the resins to be *equally effective* at supporting their radical cyclisation reactions. Interestingly, their later work in this area[18] proved to be more effective on Tentagel than PS-Rink resin. The authors suggested this was probably due to "the relatively poor swelling properties of polystyrene beads, or the free amide proton on the Rink linker quenching the reductive anionic species". They did not consider hydrogen atom abstraction from benzylic carbon of the polystyrene resin backbone to be an important factor. The authors also noted another

significant advantage of Tentagel resin for their work: it swells well in aqueous solvents, allowing the Sm^{3+} impurities in the beads to be washed away by saturated sodium hydrogen carbonate solution. This process proved to be much more difficult for the polystyrene supported substrates.

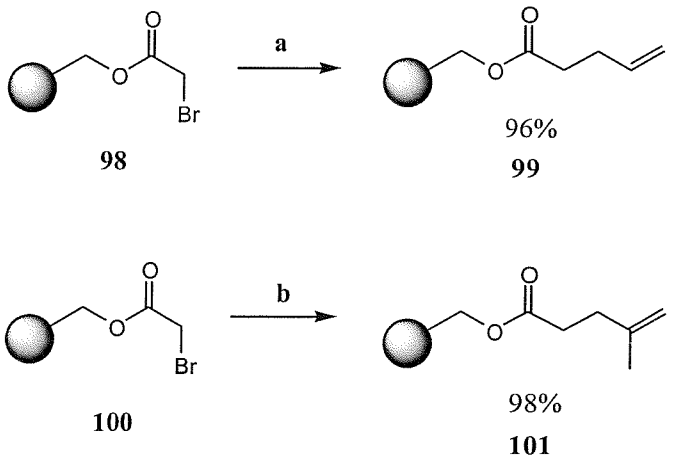
Contemporaneous studies by Sibi[15] *et al.* on the reduction of resin-bound halide with tributyltin deuteride (Bu_3SnD) found that the reduction gave 93 % deuterium incorporation in the reduced product. This suggests that hydrogen atom transfer from the polymer backbone could only account for ca. 7 % of quenching events. Coupled with the observations of Armstrong, these results suggest that radical abstraction of benzylic hydrogens from the resin backbone is insignificant in most cases. Further evidence was provided by Ganesan[21] and Naito[11], who each report studies into solid phase radical chemistry with substrates bound to polystyrene-Wang and Tentagel-Wang resin. In both cases the reactions on PS-Wang resin gave significantly higher yields than those on Tentagel-Wang.

In conclusion, many solid-phase radical reactions have been successfully carried out on polystyrene resins, without significant interference from the polystyrene backbone of the resin. Despite keeping the substrates tethered to it at some distance from its polystyrene backbone, Tentagel resin has seldom demonstrated significant benefit over polystyrene resin as a solid support for radical reactions. In fact in many cases researchers have reported lower yields for solid phase radical reactions supported on Tentagel than for the same reactions supported on polystyrene resin. Polystyrene resin is now coming to the fore as the resin of choice for solid phase radical chemistry, with substrates attached *via* a range of linkers, of which Wang is the most popular.

1.4.2 Soluble polymer radical chemistry

The bulk of solid phase organic chemistry developed so far has used insoluble resins to anchor the substrates which undergo transformations. A new branch of solid phase chemistry emerged several years ago in which the substrate is bound to a polymer that is soluble in some, but not all, solvents (non-cross-linked polystyrene is often used for this purpose). Reactions can be carried out in a solvent in which the polymer is soluble, allowing the advantages of solution phase chemistry. At the end of the reaction, a solvent in which the polymer is insoluble is added, precipitating the polymer, which can then be trapped by filtration in the same way that conventional resin beads are. Soluble polymer solid phase chemistry has not been widely utilised, probably due to practical problems with recovering the polymer at the end of reactions[27]. To date, only two examples of radical chemistry on a substrate bound to a soluble polymer have been reported[28, 99]. The first, by Janda *et al.*, used tributyltin hydride initiated by AIBN to cleave a thioether from the soluble polymer, generating a thiol in solution. However, the authors noted that "homolysis of the C-S bond proceeded at a slow rate", and further investigations centred on cleaving the substrate using Raney Nickel.

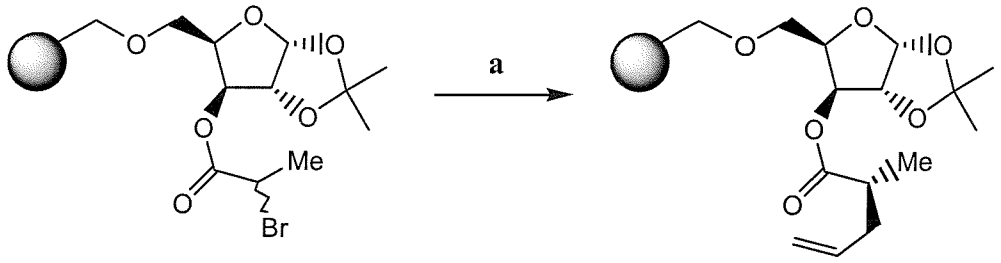
The second reaction is an allylation of an α-bromoester, which proceeds in very high yield with both allyltributyltin and methallyltributytin (scheme 29).



a. Allyltributyltin, AIBN, benzene, 80 °C **b.** Methallyltributyltin, AIBN, benzene, 80 °C

Scheme 29

The authors claim the products were free of tin when cleaved from their polymer supports. They also extended it to substrates containing a chiral auxiliary placed between the polymer chain and the substrate (Scheme 30). With D-xylose pentose used as the auxiliary, high stereoselectivity was observed, and the authors claim this was the first time that a carbohydrate had been used as a removable chiral auxiliary for a radical reaction. The best diastereoselectivity was observed when the reaction was run at -78 °C with added diethylzinc. Under these conditions the desired product was obtained in 80 % yield, in 97 % ee.



102

93%

103

a. Allyltributyltin, AIBN, benzene, 80 °C

Scheme 30

1.5 Conclusion

Despite early concerns about its plausibility[3], radical chemistry on resin-bound substrates has proven to be a versatile new tool for the creation and manipulation of organic molecules tethered to resin beads. Both intramolecular and intermolecular radical reactions have been demonstrated on a variety of substrates tethered to both polystyrene and Tentagel resins. The often mild and neutral conditions of radical reactions have made them compatible with a wide range of linkers on these resins. The yield and stereoselecitivity of radical reactions carried out on resin-bound substrates generally reflect their solution phase analogues, though a considerable excess of reagent and initiator is often required for the solid phase reactions.

Although tin reagents remain the most popular method of propagating radical chain reactions, a range of other mediators have been shown to be effective. In all cases, separation of the spent reagents from the resin-bound product was achieved by simply washing the resin beads. This is particularly advantageous for tin reagents, which can be difficult to remove after solution phase radical reactions.

In summary, radical chemistry on the solid phase is a rapidly expanding area of interest, due to the range of substrates, resins and radical sources which have been shown to be compatible with the conditions of solid phase chemistry.

Chapter 2: Results and Discussion 1

Thioester Chemistry on the Solid Phase

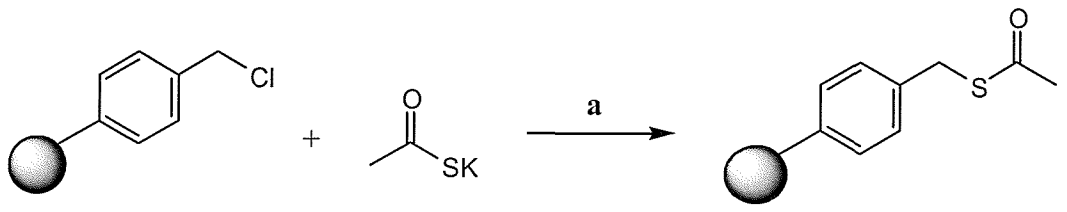
2.1 Introduction

This work will report new solid phase chemistry involving *S*-alkyl thioesters. Such thioesters are activated carboxylic acid derivatives which exhibit acylating properties similar to those of acid anhydrides[29]. Thioesters have been used in organic synthesis as precursors to aldehydes, ketones, acids, esters, lactones, amides, lactams and heterocycles[30], however to date thioester chemistry on the solid phase has not been widely investigated, as will be discussed below.

2.2 Previously reported work on *S*-alkyl thioesters on the solid phase

2.2.1 Resin-bound thioester synthesis

A variety of methods for producing resin-bound thioesters have been described in the literature. Kobayashi[31] *et al.* have pioneered two methods of generating such thioesters. Their first method employs the reaction of the salt of a thioacid with Merrifield resin, generating the thioester through S_N2 attack by the sulfur on the benzylic chloride of the resin (scheme 31).

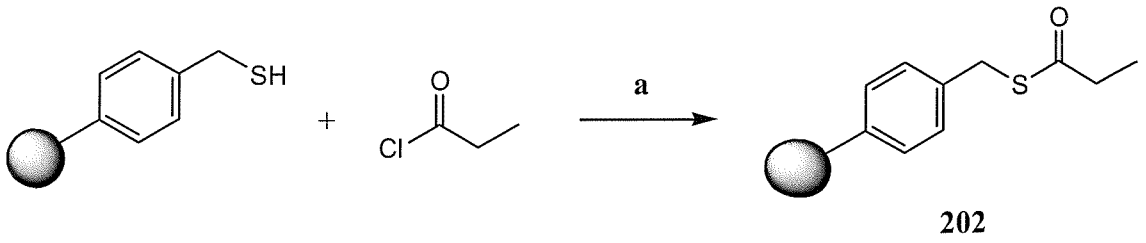


201

a. DMF

Scheme 31

The second method relies on the facile reaction between a resin-bound thiol and an acid chloride (scheme 32).

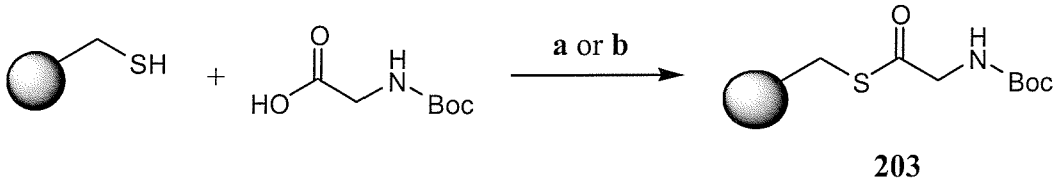


202

a. Et_3N, CH_2Cl_2

Scheme 32

An alternative preparation involves coupling a carboxylic acid to a thiol. Two examples of this have been reported[32, 33], and are illustrated in scheme 33. In each case the resin-bound moiety has been the thiol, though the method of coupling differs (DCC / DMAP or HOBt / BOP).



203

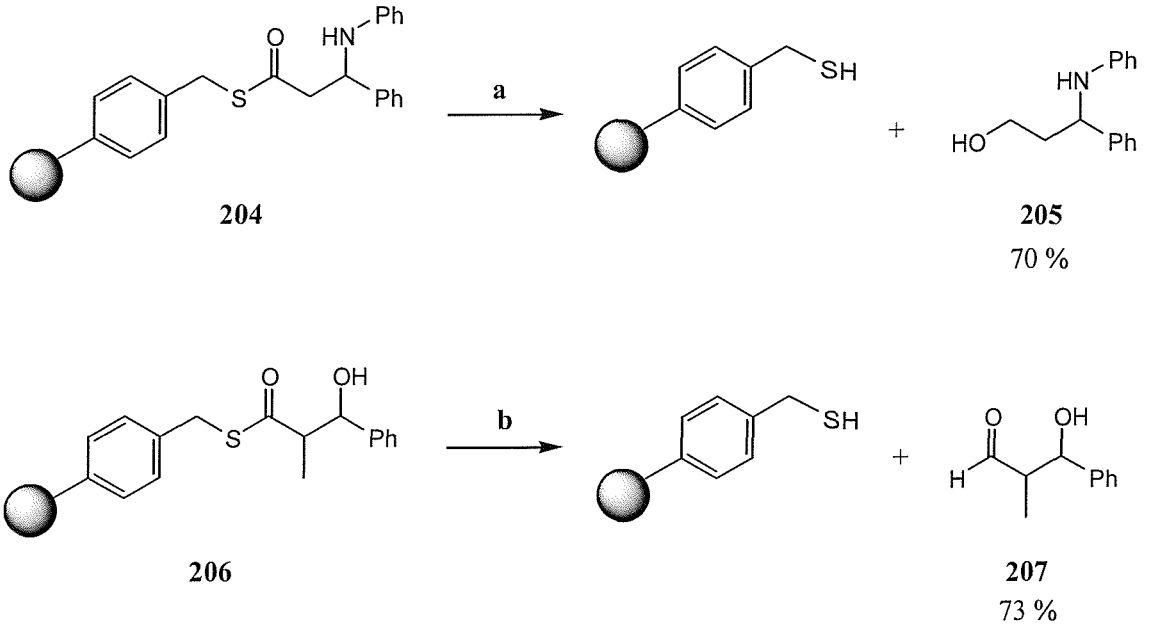
a. DCC (4 eq.), DMAP (4 eq.), DCM, 24h **b.** BOP, HOBt, DIEA, 1h

Scheme 33

2.2.2 Methods of cleaving thioesters from the solid phase

Several methodologies for cleaving thioesters from the solid phase have been reported, each resulting in the production of a different functionality in the cleaved product.

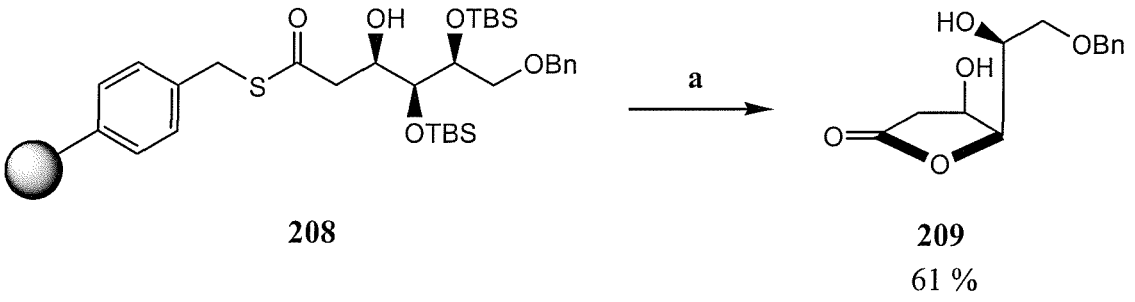
The first reported method for cleaving thioesters from the solid phase utilises HF, and generates the corresponding thioacid[34]. Significant efforts were then undertaken by Kobayashi *et al.*, who cleaved resin-bound thioesters with lithium borohydride and diisobutylaluminium hydride (DIBAL-H) to generate the corresponding alcohols[31] and aldehydes[35] respectively (scheme 34).



a. $LiBH_4$ (5 eq.), Et_2O, r.t., 12h **b.** DIBALH, DCM, -78°C, 19h

Scheme 34

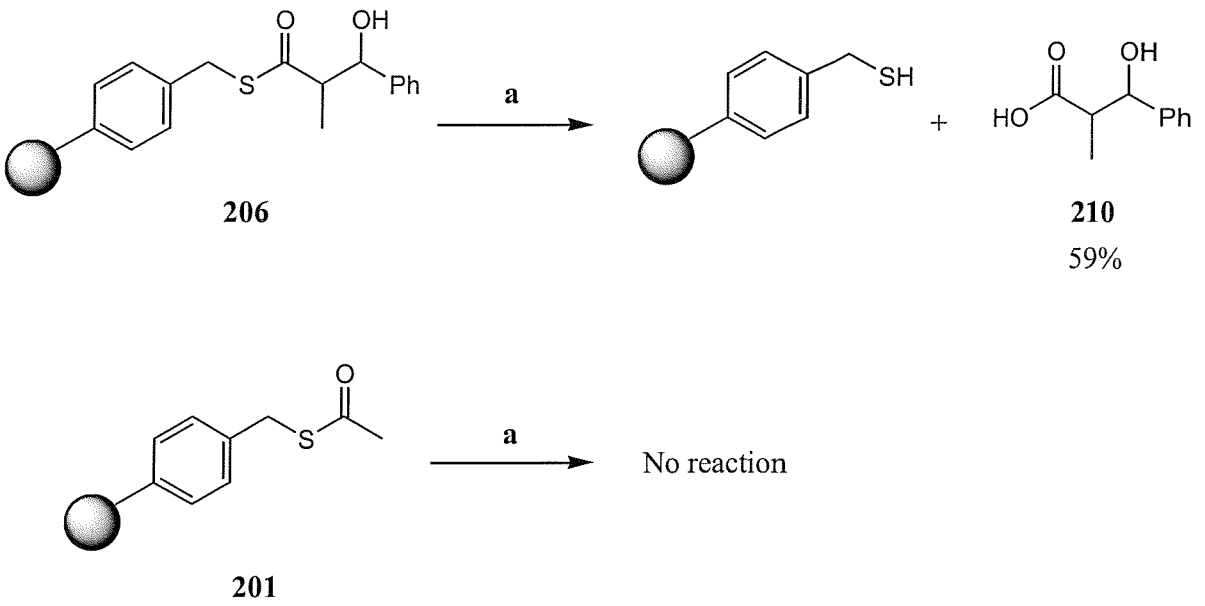
Kobayashi and coworkers also employed thioester chemistry in a solid phase synthesis of mono-saccharide derivatives. A key feature was the deprotection of an alcohol group within the resin-bound substrate, which then added to the thioester linkage, simultaneously forming a lactone and liberating the monosaccharide from the resin[36] (scheme 35).



a. TBAF, AcOH, THF, 40°C, 6h.

Scheme 35

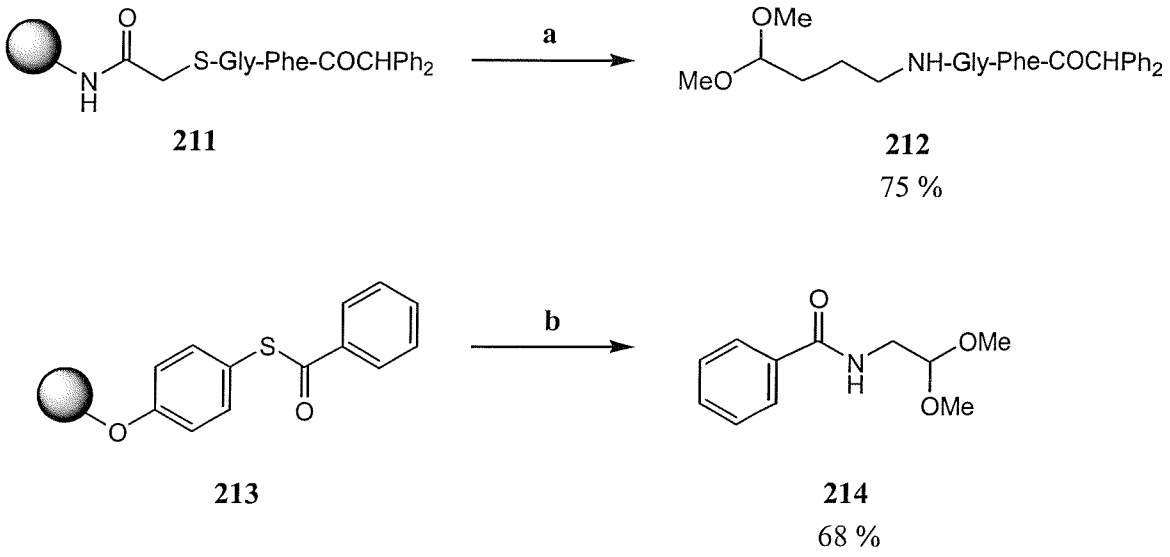
One area in which Kobayashi and coworkers have had only limited success, is in the cleavage of resin-bound thioesters by saponification. In the case of **206**, treatment with IM NaOH led to **210** in 59 % yield whereas with **201** no cleavage was observed when it was treated similarly (scheme 36).



a. 1M NaOH (aq), Dioxane (1:4), 100°C, 6h

Scheme 36

The final reported method of cleavage uses amines and gives rise to amides. The method was first carried out by Vlattas[33] *et al.*, who found that thioesters can be readily cleaved with primary amines, generating the corresponding amides in solution. However, cleavage with more sterically hindered amines required a special linker to activate the thioesters. Both methods of cleavage are illustrated in Scheme 37.



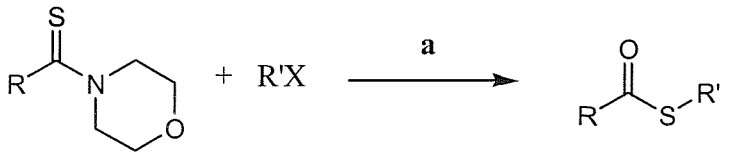
a. $(MeO)_2CH(CH_2)_3NH_2$ (3 eq.), *i*-propanol, 75 °C, 24 h. **b.** $H_2NCH_2CH(OCH_3)_2$, dioxane, 75 °C, 24 h.

Scheme 37

2.3 A new method for making thioesters on solid phase

As discussed above, previous resin-bound thioester syntheses have relied upon either the reaction of a thioacid salt with Merrifield resin, or the reaction of a resin-bound thiol with an acylating agent. Thioacid salts are prepared from their corresponding thioacids, and thioacids are not without their difficulties. The main problem is that they are rapidly hydrolysed in the presence of moisture[37], and they also readily acylate alcohols and amines, so will not be tolerant of these functional groups in any coupling reaction. Coupling a resin-bound thiol with an acylating agent avoids many of these difficulties, however the acylating agent will also be subject to the handling difficulties outlined above.

Recently, a new way of making thioesters was described by Harrowven[38] *et al.* In this method, thioesters are generated from their corresponding thioamides, by refluxing in aqueous THF in the presence of an activated bromide or an alkyl iodide (scheme 38).



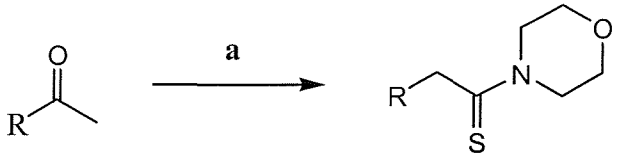
a. THF (aq), Δ, 24 h. (R'X = activated bromide or alkyl iodide.)

Scheme 38

It was postulated that this method could be adapted to produce thioesters on the solid phase, which could be used as a new type of linker, capable of generating a variety of new functional groups in the substrate when cleaved. In order to test this hypothesis, a number of thioamides had to be prepared, and their synthesis is described below.

2.3.1 Preparation of the substrates

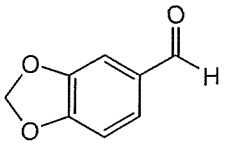
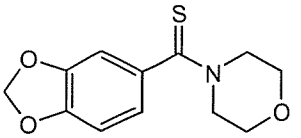
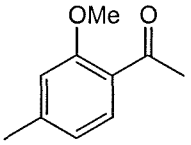
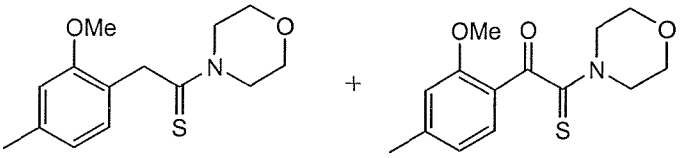
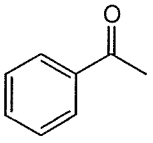
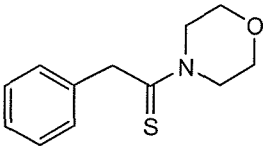
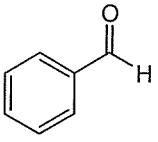
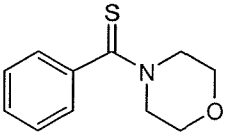
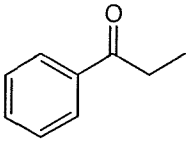
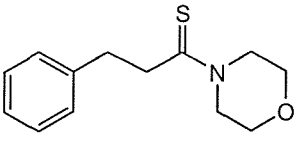
Thioamides can be prepared from aldehydes and ketones by means of the Willgerodt-Kindler reaction[39] (scheme 39).



a. Sulfur, morpholine, Δ, 24 – 72 h.

Scheme 39

The reaction is most effective when the amine used in the reaction is morpholine. Consequently all the thioamides prepared for this work were thiomorpholides (table 1).

Starting Carbonyl	Product Thioamide
 **215**	 **216** (83 %) Sulfur, Morpholine, DMF, 55°C, 6 h
 **217**	 **218** (40%) + **219** (7%) Sulfur, Morpholine, 110°C, 24 h
 **220**	 **221** (90%) Sulfur, Morpholine, 100°C, 24 h
 **222**	 **223** (91%) Sulfur, Morpholine, 100°C, 15 h
 **224**	 **225** (64%) Sulfur, Morpholine, 100°C, 15 h

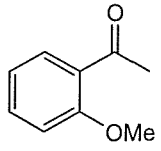
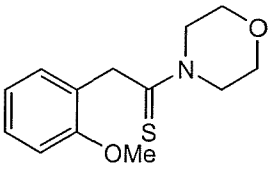
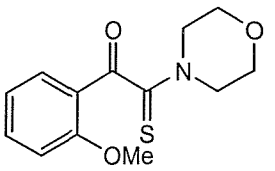
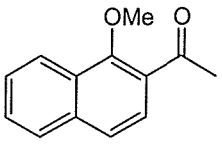
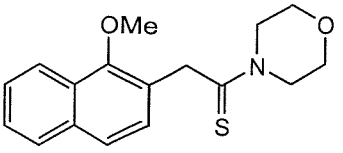
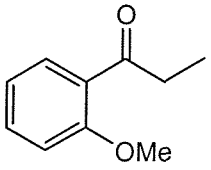
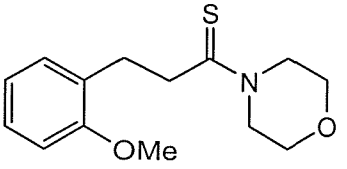
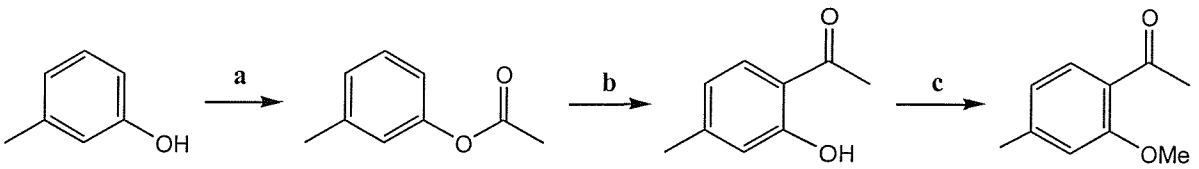
 **226**	 **227** (41%) +  **228** (21%) Sulfur, Morpholine, 90°C, 18 h
 **229**	 **230** (45%) Sulfur, Morpholine, 100°C, 72 h
 **231**	 **232** (38%) Sulfur, Morpholine, 90°C, 72 h

Table 1

Most of the thiomorpholides used in this work were prepared in one step from commercially available aldehydes and ketones. However, ketones **217** and **229** required multi-step syntheses (schemes 40 and 41).

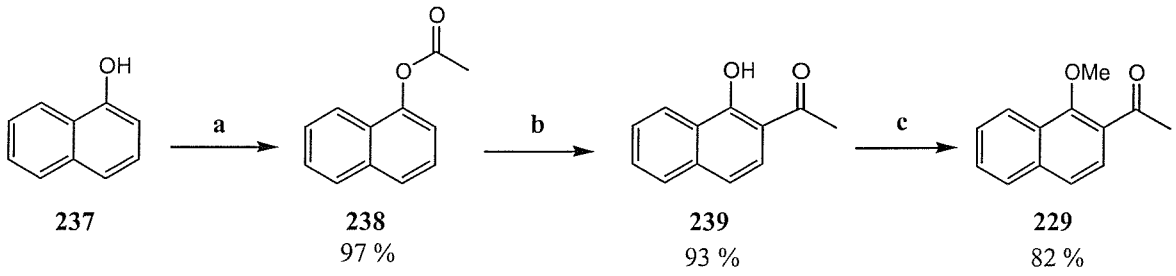


233 → **234** 99 % → **235** 70 % → **217** 100 %

a. Ac_2O, DMAP, py, CH_2Cl_2, r.t., 15h. **b.** $ZrCl_4$,))))), CH_2Cl_2, 24h. **c.** Me_2SO_4, KOH, acetone, r.t., 15h.

Scheme 40

Acylation of **233** furnished **234** in quantitative yield, which then underwent a Fries rearrangement to give **235** (70 %). Finally, protection of **235** yielded the desired ketone **217** in 98 % yield. **229** was prepared in an analogous fashion (scheme 41).



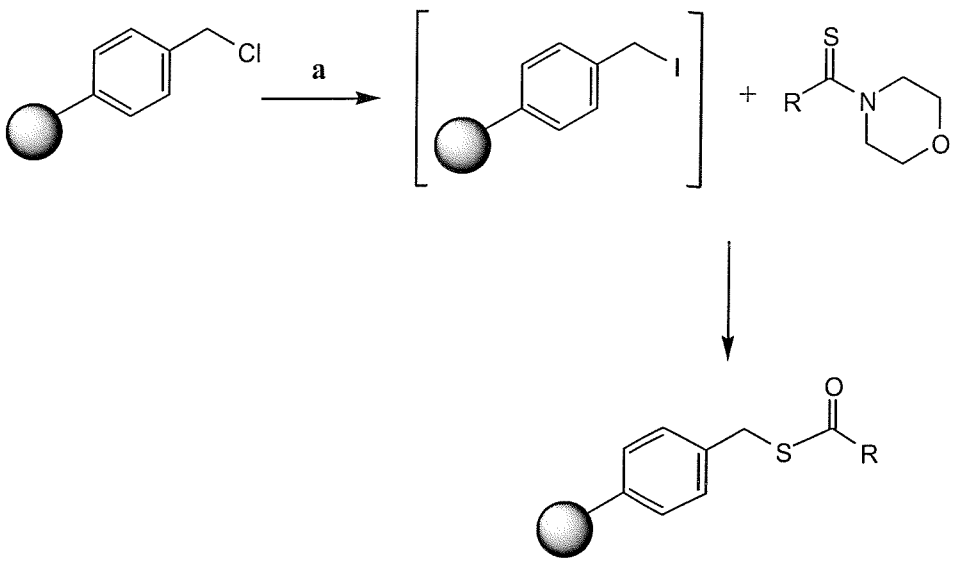
237 **238** 97 % **239** 93 % **229** 82 %

a. Ac_2O, DMAP, py, CH_2Cl_2, r.t., 15h. **b.** $ZrCl_4$,))))), CH_2Cl_2, 24h. **c.** Me_2SO_4, KOH, acetone, r.t., 15h.

Scheme 41

2.3.2 Synthesis of Resin-Bound Thioesters

With the thioamides in hand, attempts were made to attach them to solid supports by adapting the thioester synthesis of Harrowven[38] *et al.* Merrifield resin was the first resin to be tested, since it is a commonly-used resin in solid phase organic chemistry, and it contains an activated halide – in this case a benzylic chloride. However, the solution phase studies of the thioester formation reaction showed it to be very slow with activated chlorides. It was therefore decided that the reaction would be modified by the addition of a large excess of sodium iodide. It was hoped that the sodium iodide would perform a Finkelstein reaction, replacing the benzylic chloride with the more reactive iodide which could then react rapidly with the thioamide (scheme 42).



a. NaI, DMF (aq.), Δ, 18 – 72 h.

Scheme 42

Success of the loading reaction was determined by the appearance of a peak corresponding to the C=O stretch of the thioester in subsequent IR spectroscopic analysis of the beads. Initially, two thioamides and a ketothioamide were loaded onto the resin. The resultant resin-bound thioesters are shown in table 2, overleaf.

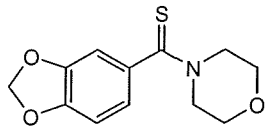
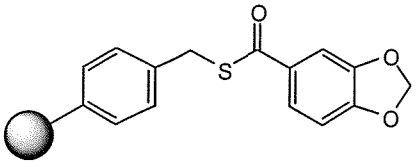
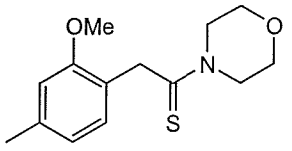
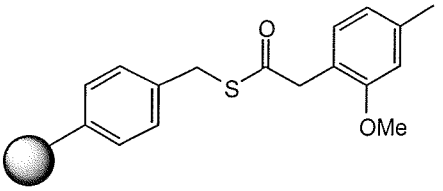
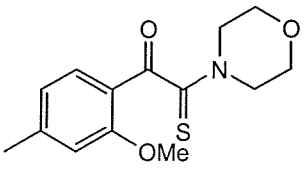
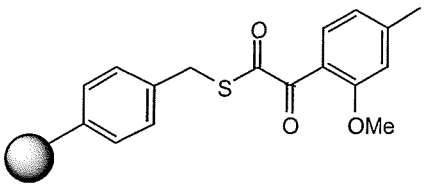
Thioamide	Corresponding Thioester
 **216**	 **240** NaI, aq. DMF, 100°C, 48h
 **218**	 **241** NaI, aq. DMF, 100°C, 72h
 **219**	 **242** NaI, aq. DMF, 100 °C, 60h

Table 2

In order to determine yields, it was decided to cleave the thioesters from the resin using the method of Kobayashi[31] *et al.*, in which lithium borohydride is employed to reductively cleave the thioesters to their corresponding primary alcohols. This method is believed to be near-quantitative, and thus determination of the yield of primary alcohol allows a very good approximation to loading efficiency. Disappointingly, yields for the cleaved alcohols (based on the specified concentration of active sites on the resin) were fairly low, at 30-40 %, implying that at best, the resin-loading reaction was achieving 40 % efficiency. Interestingly, the resin-bound ketothioester **242** was cleaved to give alcohol **244**, indicating complete reduction of the ketone function. Full results are shown in table 3.

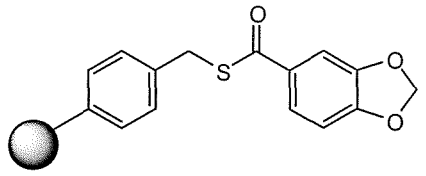
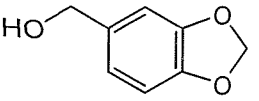
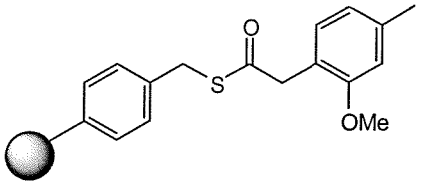
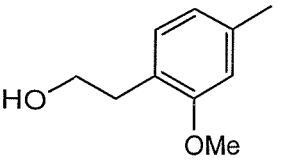
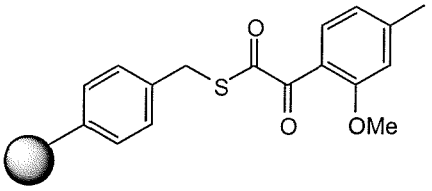
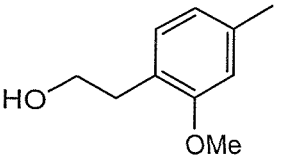
Resin-Bound Thioester	Cleaved Alcohol
 **240**	 **243** (33%) $LiBH_4$, THF, 6 h
 **241**	 **244** (23%) $LiBH_4$, THF, 6 h
 **242**	 **244** (20%) $LiBH_4$, THF, 6 h

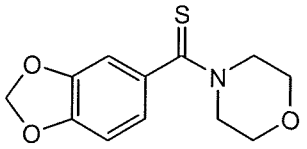
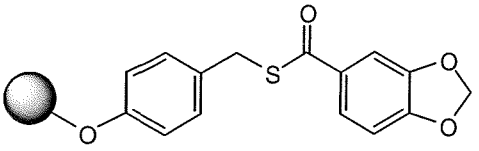
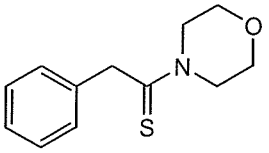
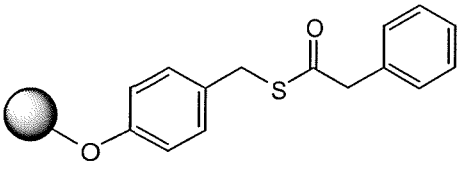
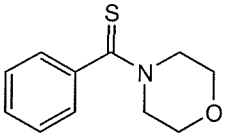
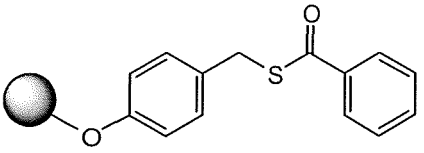
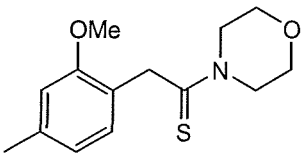
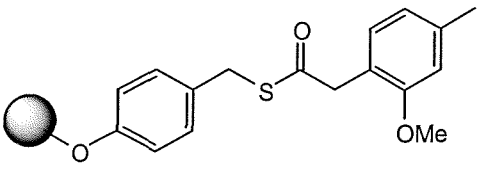
Table 3

It was hypothesised that the iodide ions added to accelerate the reaction were surrounded by a solvent cage of water molecules and thus unable to enter the hydrophobic resin. Thus the activated chlorides are not converted to activated iodides, and the reaction proceeds far more slowly as a consequence. In order to test this hypothesis, two phase transfer catalysts were employed: Adogen® 464 and tetrabutylammonium iodide. Unfortunately, the loading of the thioester (as determined by the strength of the thioester peak) was *lower* when phase transfer catalysts were employed. The failure to improve the loading level of resin-bound thioesters through this investigation prompted an evaluation of alternative solid supports.

One alternative which theoretically had good potential was commercially available Bromo-Wang resin. This solid support offers two advantages over Merrifield resin: firstly, the active site is a benzylic bromide, which is much more reactive than the benzylic chloride

active sites of Merrifield resin. Secondly, the reactivity of the active site of the Wang linker is further aided by the spacer effect; the Wang linker keeps the active site separated from the polystyrene backbone of the resin.

Consequently, a range of thioamide substrates were loaded onto Bromo-Wang resin generating the corresponding thioesters (table 4).

Thioamide	Corresponding Thioester
 **216**	 **245** NaI, aq. DMF, 100 °C, 72 h
 **221**	 **246** NaI, aq. DMF, 100 °C, 24 h
 **223**	 **247** NaI, aq. DMF, 100 °C, 24 h
 **218**	 **248** NaI, aq. DMF, 100 °C, 24 h

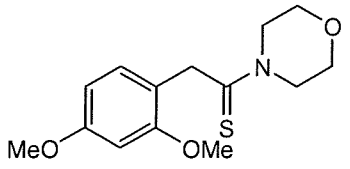
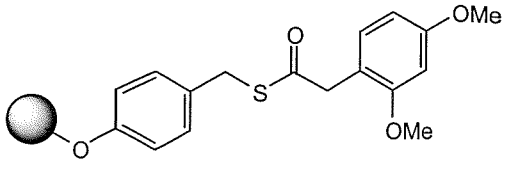
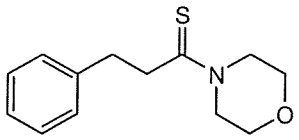
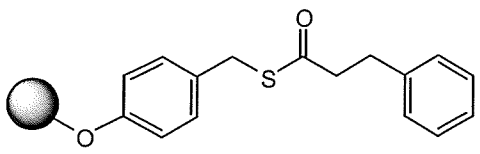
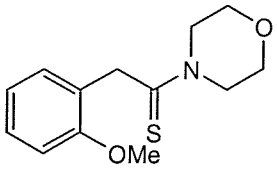
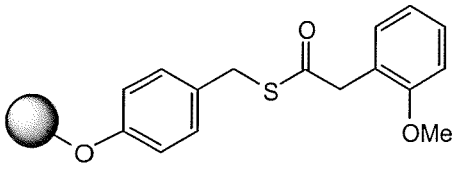
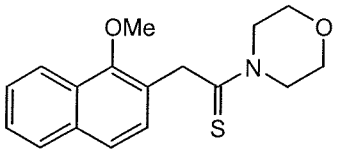
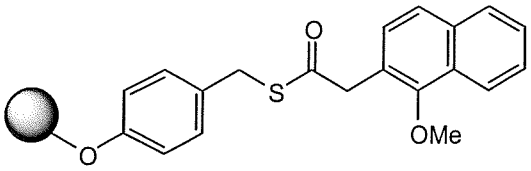
 **249**	 **250** NaI, aq. DMF, 100 °C, 30 h
 **214**	 **251** NaI, aq. DMF, 100 °C, 30 h
 **227**	 **252** NaI, aq. DMF, 100°C, 48 h
 **230**	 **253** NaI, aq. DMF, 100°C, 48 h

Table 4

Cleavage with lithium borohydride was then effected for several of the resin-bound thioesters. Pleasingly, the yields of the corresponding primary alcohols were much higher than was the case with Merrifield resin, showing that the thioester loading reaction was now reasonably efficient (table 5).

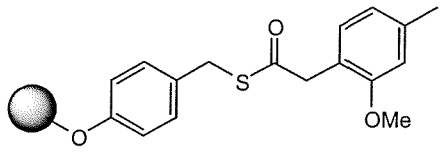
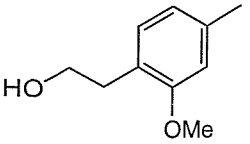
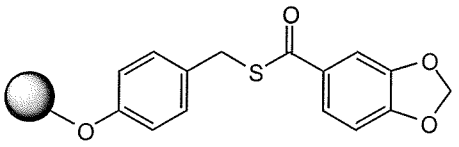
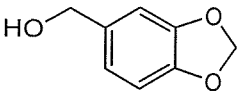
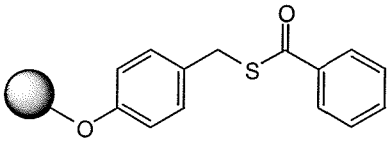
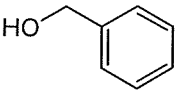
Resin-Bound Thioester	Cleaved Product Alcohol
 **248**	 **244** (70%) $LiBH_4$, THF, 5 h
 **245**	 **243** (88%) $LiBH_4$, THF, 5 h
 **247**	 **254** (81%) $LiBH_4$, THF, 5 h

Table 5

Thus it was concluded that Bromo-Wang resin was the solid support of choice for the thioamide loading reaction, and this was used in all subsequent studies.

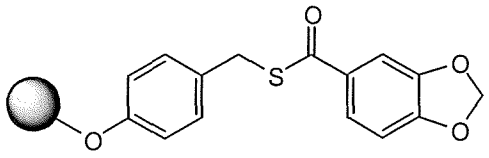
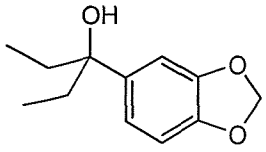
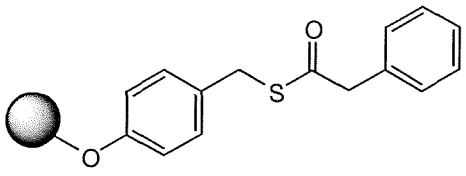
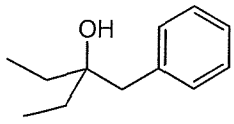
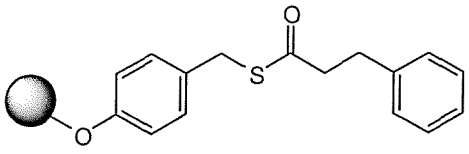
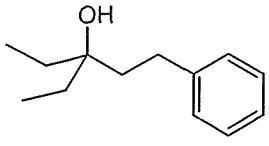
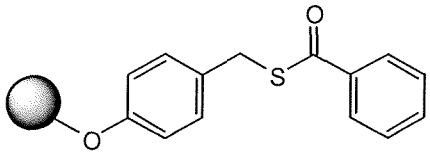
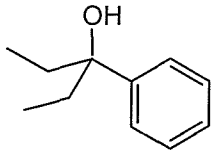
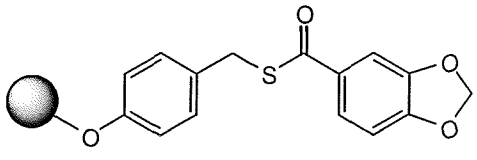
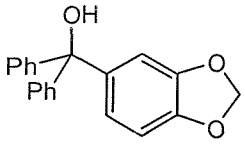
2.4 New methods of cleavage

Having developed a new method for the formation of a thioester linker, the next step was to develop novel cleavage methods which would provide a range of functionalities on cleavage. These methods are described below.

2.4.1 Cleavage to form tertiary alcohols

It is well known that in solution phase, reaction of a thioester with a Grignard reagent will normally produce a tertiary alcohol. Only one previous example of a reaction between a

resin-bound thioester and a Grignard reagent has been reported, and interestingly, this gave a ketone[33]. In this study, all the resin-bound thioesters attacked with Grignard reagents gave tertiary alcohols as cleavage products (table 6).

Resin-Bound Thioester	Grignard	Cleaved Product	Yield
 **245**	EtMgBr	 **255** THF, r.t., 16 h	60% (71%)
 **246**	EtMgBr	 **256** THF, r.t., 16 h	55% (71%)
 **251**	EtMgBr	 **257** THF, r.t., 16 h	58% (73%)
 **247**	EtMgBr	 **258** THF, r.t., 16 h	53% (73%)
 **245**	PhMgBr	 **259** THF, r.t., 36 h	21% (74%)

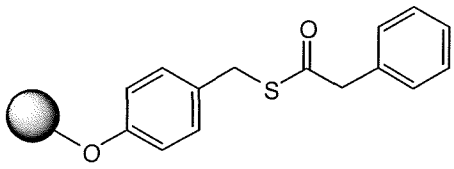
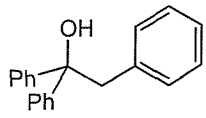
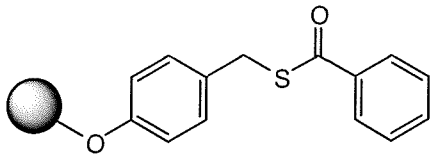
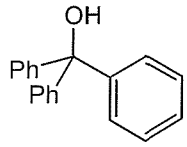
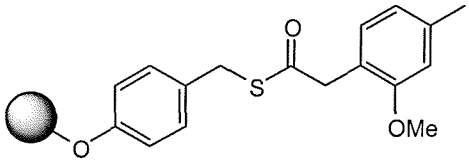
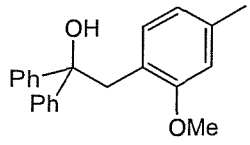
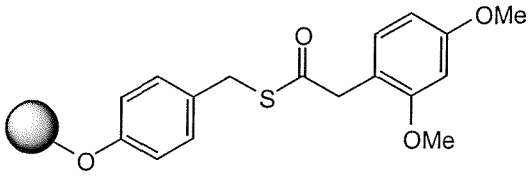
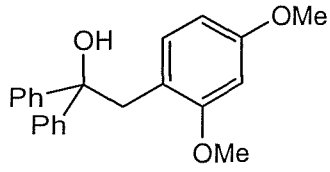
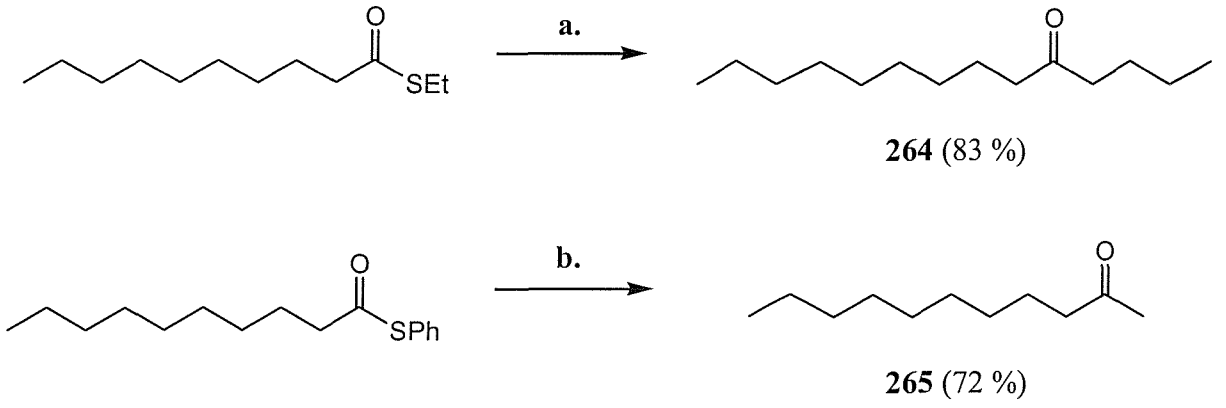
 **246**	PhMgBr	 **260** THF, r.t., 16 h	28% (51%)
 **247**	PhMgBr	 **261** THF, r.t., 16 h	30% (74%)
 **248**	PhMgBr	 **262** THF, r.t., 16 h	32% (71%)
 **250**	PhMgBr	 **263** THF, r.t., 16 h	28% (60%)

Table 6
(Figures in brackets refer to crude yields.)

Crude yields for this reaction were quite good, however yields for the triarylmethanols dropped significantly when purification by chromatography was undertaken. It is presumed this is due to the acid-sensitive nature of the products.

2.4.2 Cleavage to form ketones

Achieving a new ketone functionality in a substrate through its cleavage from a solid support is a feat that has reported on only a very few occasions[41]. A solution phase method for the production of ketones from thioesters has been reported by Anderson[42] *et al.*, utilising organocuprates to effect the transformation (scheme 43).



a. (n-Bu)$_2$CuLi (1.1 eq.), THF, - 40 °C, 1.5 h. **b.** Me_2CuLi (1.1 eq.), Et_2O, -78 °C, 1 h.

Scheme 43: Anderson *et al.*'s work on the reaction of thioesters with organocuprates

The reaction is clean, quick and high yielding, and thus it was decided to attempt the reaction on resin-bound thioesters. The reaction was successful, cleaving a range of solid-supported thioesters to give the corresponding ketones in solution (table 7). Yields (for the two step process of loading and cleavage) were good.

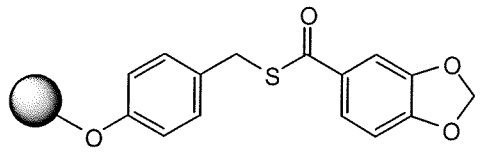
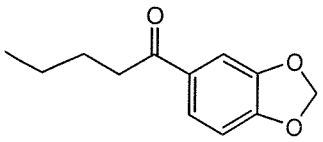
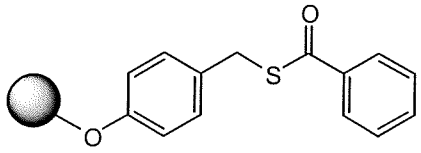
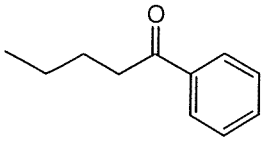
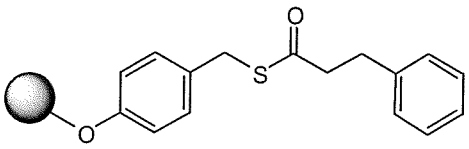
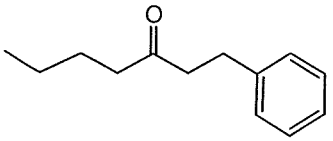
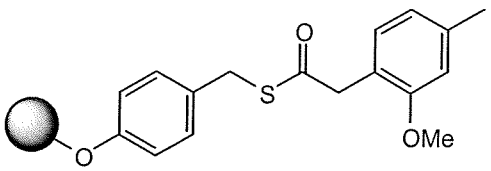
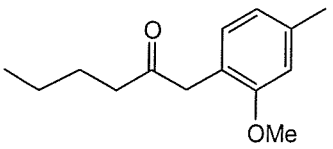
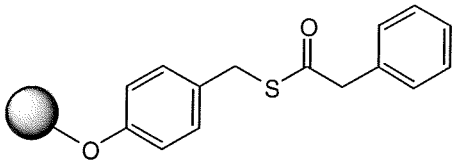
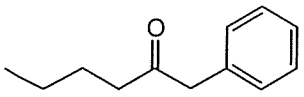
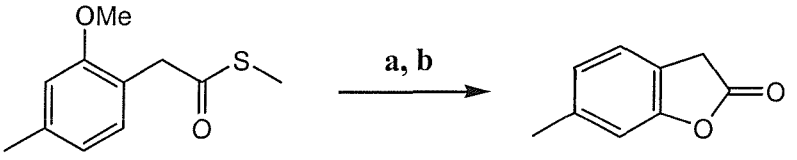
Resin-Bound Thioester	Cleaved Product Ketone
 **245**	 **266** (61%) $(n\text{-}Bu)_2CuLi$, THF, -40°C, 14h
 **247**	 **267** (62%) $(n\text{-}Bu)_2CuLi$, THF, -40°C, 15h
 **251**	 **268** (58%) $(n\text{-}Bu)_2CuLi$, THF, -40°C, 15h
 **248**	 **269** (59%) $(n\text{-}Bu)_2CuLi$, THF, -40°C, 15h
 **246**	 **270** (53%) $(n\text{-}Bu)_2CuLi$, THF, -40°C, 15h

Table 7

2.4.3 Cleavage to form lactones

Very few methods for generating lactones upon cleavage of a substrate from its solid support have been reported[36, 43]. Harrowven *et al.* have reported a method for lactonising thioesters with an *o*-methoxy group on the benzene ring[44], which relies upon deprotection of the methoxy group followed by attack by the phenolic anion on the thioester (scheme 44).



271 **272**

72 %

a. BCl_3, CH_2Cl_2, 0 °C, 1 h. **b.** H_3O^+ then NaOH (aq), 2 min.

Scheme 44

A slightly modified methodology was thus used on suitable substrates tethered to resin beads. The reaction was high yielding, though somewhat slower than its solution phase counterpart. Examples are shown in table 8. Interestingly, in all cases some of the lactone had cleaved before the resin-bound substrate was treated with base. For resin-bound thioester **253**, all of the lactone **274** had cleaved before the resin was treated with base.

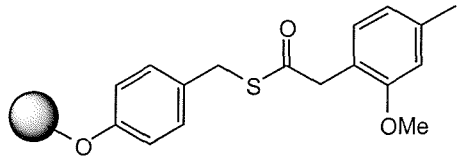
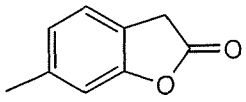
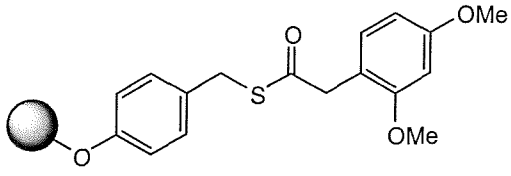
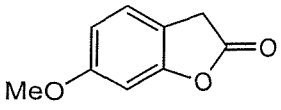
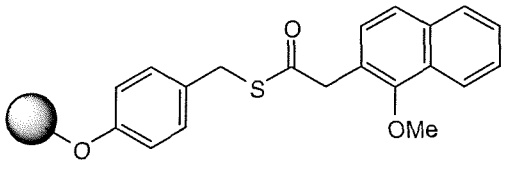
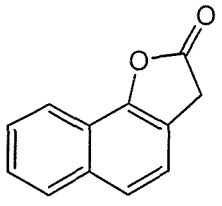
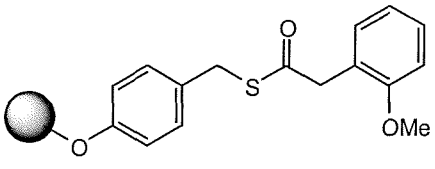
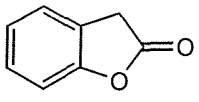
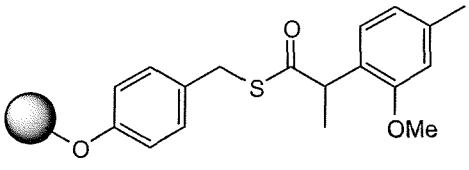
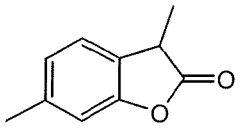
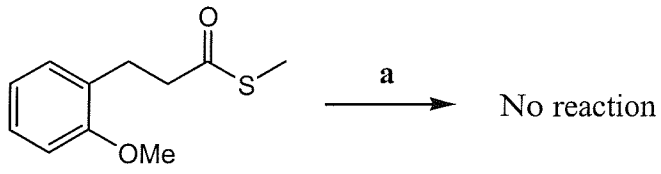
Resin-Bound Thioester	Cleaved Product Lactone
 **248**	 **272** (69%) **a.** BCl_3, CH_2Cl_2, r.t., 15 h. **b.** HCl, THF (aq), 1 h. **c.** CH_2Cl_2, Et_3N, 15 h.
 **250**	 **273** (56%) **a.** BCl_3, CH_2Cl_2, r.t., 15 h. **b.** HCl, THF (aq), 1 h. **c.** CH_2Cl_2, Et_3N, 15 h.
 **253**	 **274** (68%) **a.** BCl_3, CH_2Cl_2, r.t., 15 h. **b.** HCl, THF (aq), 1 h.
 **252**	 **275** (59%) **a.** BCl_3, CH_2Cl_2, r.t., 15 h. **b.** HCl, THF (aq), 1 h. **c.** CH_2Cl_2, Et_3N, 20 h.
 **276**	 **277** (56%) **a.** BCl_3, CH_2Cl_2, r.t., 15 h. **b.** HCl, THF (aq), 1 h. **c.** CH_2Cl_2, Et_3N, 6 h.

Table 8

(Substrate **276** was synthesised from resin-bound thioester **248** using *tert*-butyllithium with methyl iodide.)

Impressively, when more than one methoxy group is present on the benzene ring, the boron trichloride deprotection is selective for the *ortho* methoxy group, as demonstrated by substrate **250**. An attempt was made to extend the methodology to produce six-membered lactone rings, however when this was attempted in solution phase using thioester **278**, the aryl methoxy group could not be deprotected (scheme 45). Thus the reaction was not attempted on the analogous resin-bound thioester.



278

a. BCl_3, CH_2Cl_2, 0 °C 15 h.

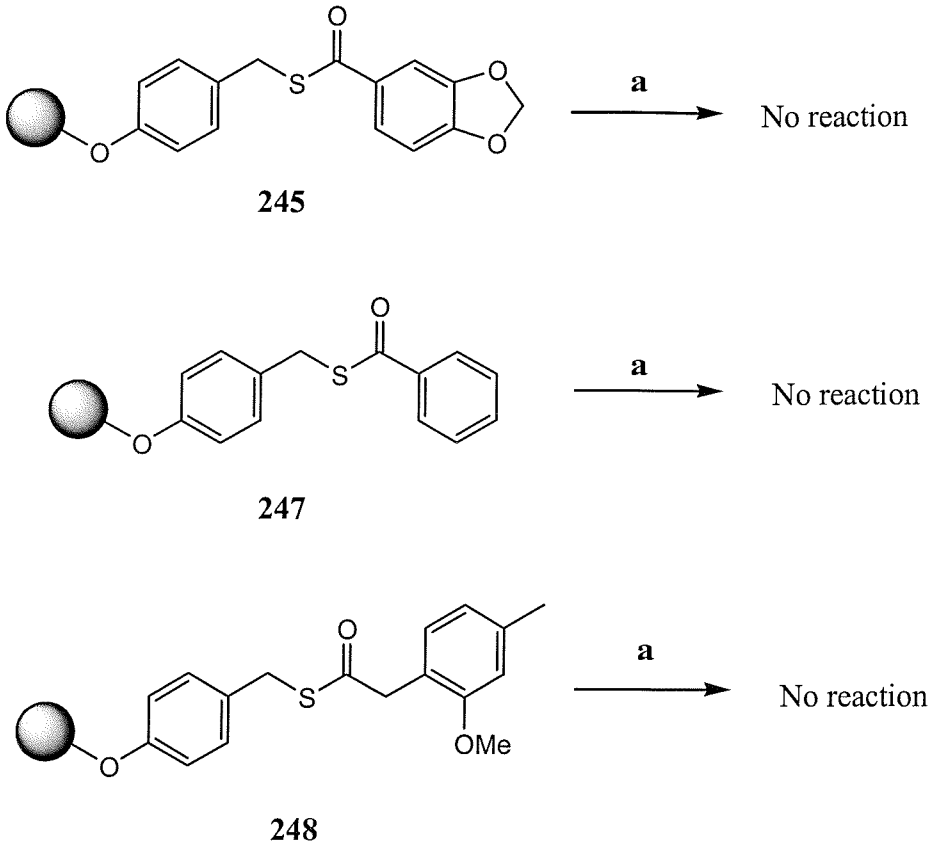
Scheme 45

These observations suggest that in order to deliver the chloride to deprotect the methyl group, the boron trichloride needs to co-ordinate to the oxygen atom of the thioester. Once the boron trichloride has co-ordinated to this oxygen atom, it will only be able to deliver the chloride to a proximal methoxy group. The results above show that only an *ortho* methoxy group will be close enough, and the thioester group should not be separated from the aryl ring by more than one carbon atom.

2.4.4 Attempted cleavage to form carboxylic acids

Three methods of cleaving thioesters to produce carboxylic acids were attempted. The first was cleavage using TFA. Wang resin was originally developed to allow for the

straightforward cleavage of esters to produce carboxylic acids in solution, using TFA[45]. Thus it seemed logical to attempt to extend the methodology to thioesters, which it was hoped would cleave to form thioacids, which hydrolyse rapidly in the presence of moisture to carboxylic acids[37]. Intriguingly, repeated attempts to cleave a range of thioesters with 95% TFA all failed (scheme 46).

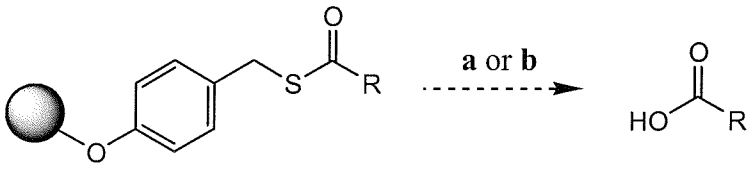


a. TFA (95%), DCM (2.5%), H_2O (2.5%), r.t., 15 h.

Scheme 46

Nucleophilic cleavage using sodium hydroxide was attempted next, on resin-bound thioesters **246** and **247** (scheme 47). However, both resin-bound thioesters tested proved totally resilient, and no cleaved product was isolated. As discussed previously, this method of cleavage has proven to be very capricious[35]. Testing further resin-bound thioesters was deemed unnecessary since all are similar to **246** and **247**.

Finally, acid hydrolysis was tried on **246** and **247**, but again this failed to cleave the substrates (scheme 47). It would appear that resin-bound thioesters are generally stable to basic and acidic conditions, even when strong acids are present.



R = Bz (**246**), Ph (**247**)

a. NaOH (aq) / Dioxane (1:4), Δ, 36h. **b.** H_3O^+, THF, Δ, 36h.

Scheme 47

2.5 Conclusion

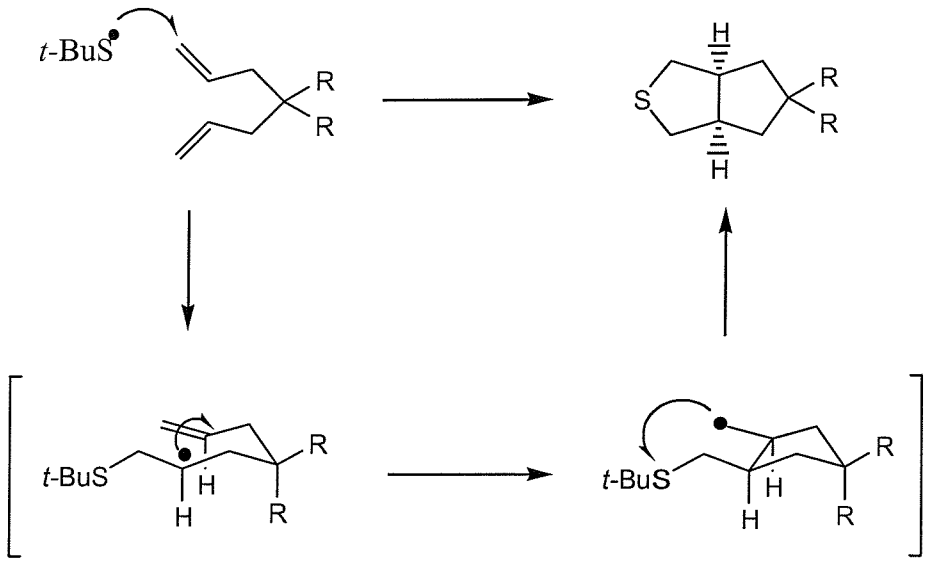
A new, efficient method for the formation of thioesters on solid phase has been developed. The loading reaction is successful with both Merrifield resin and polystyrene resin with a bromo-Wang linker, however the latter gives a much higher loading of thioester. Thioesters have been shown to be versatile linkers for solid phase chemistry, due to the variety of functional groups that can be achieved on cleavage. Primary alcohols, tertiary alcohols, ketones and lactones have all been achieved. Thioester linkers are stable to both acids and bases, yet are readily cleaved under suitable conditions.

Chapter 3: Results and Discussion 2

Thiyl Radical Chemistry on the Solid Phase

3.1 Thiyl Radical Initiated Cyclisations of 1,6-Dienes

Tin reagents have traditionally been used to mediate radical reactions; however the high toxicity of tin[46] coupled with the difficulty of removing tin residues from reaction products[47] has led chemists to search for alternative radical sources. Sulfur (thiyl) radicals are one such source. The addition of thiyl radicals to alkenes is fast and reversible. The usual fate of the intermediate carbon-centred radical is to revert back to starting materials, or to undergo a fast hydrogen atom quench[48]. For 1,6-dienes however, a third possibility exists: cyclisation[49] (scheme 48).



Scheme 48

Thiyl radical induced cyclisations of 1,6-dienes represent an important class of reactions for sulfur radicals. Solution phase thiyl radical cyclisations employing the *t*-butylthiyl radical have been carried out on a range of 1,6-dienes by Harrowven[49] *et al.* The radical can be generated from *t*-butyl disulfide either thermally in the presence of AIBN, or by irradiation with UV light, although the latter technique was found to be superior. The *t*-butylthiyl radical adds to one terminus of the 1,6-diene, inducing a 5-*exo*-trig radical cyclisation. Provided that

the intermediate carbon-centred radical thus formed is proximal (i.e. *cis*) to the sulfide group, the carbon-centred radical can attack the sulfur, forming a second 5-membered ring and ejecting a *t*-butyl radical.

The ejection of the *t*-butyl radical is only possible due to its high stability. Arylthiyl radicals are unable to undergo this second cyclisation, and the carbon-centred radical is quenched by abstracting a hydrogen atom.

An alternative means of generating thiyl radicals is by hydrogen atom abstraction from a thiol. One such thiol that can be used for this purpose is benzenethiol (thiophenol), and it has been previously used in thiyl radical cyclisations[23, 50]. However, there are no published examples of benzenethiyl radical cyclisations of 1,6-dienes, in which the thiyl radical is generated by hydrogen atom abstraction from thiophenol following thermal initiation employing AIBN. Thus it has been the aim of this piece of work to investigate such chemistry, both in solution and on solid phase.

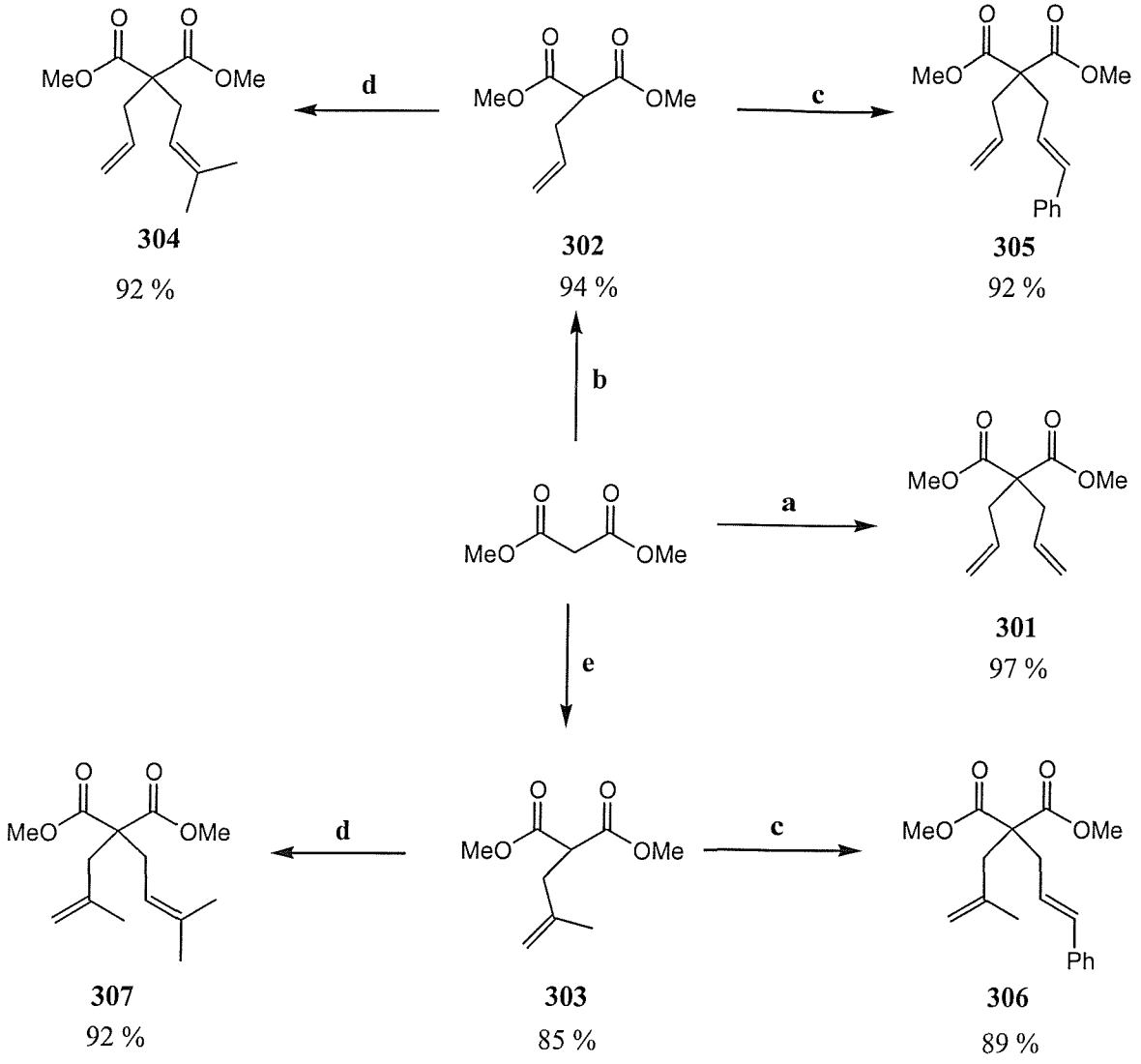
3.2 Benzenethiyl Radical Cyclisations onto 1,6-Dienes

In order to carry out the investigation it was necessary to devise a number of suitable substrates. The work of Harrowven[49] *et al.* had shown that 1,6-dienes with two esters at the C4 carbon gave the best yields and stereoselectivities for cyclisations involving the *t*-butylthiyl radical, and thus it seemed logical to use these for benzenethiyl radical reactions. Thus it was decided to construct such 1,6-dienes by attachment of suitable alkenes to dimethyl malonate.

3.2.1 Preparation of the Substrates

Five substrates were prepared, using the method of Semmelhack[91] *et al.*, as illustrated in scheme 49. Substrate **301** was prepared by the direct bis-allylation of dimethyl malonate. For substrates **304** and **305**, mono-allylation of the diethyl malonate was followed by reaction

with the corresponding allyl halide. Substrates **306** and **307** were prepared by the methallylation of dimethyl malonate, followed by cinnamylation and prenylation respectively.

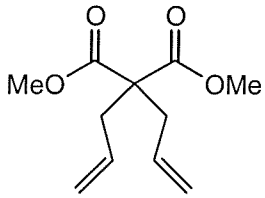
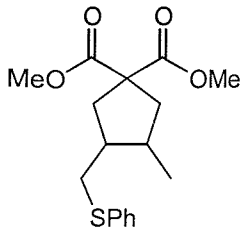
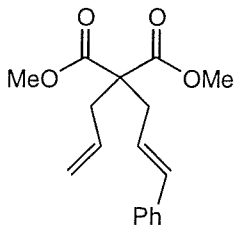
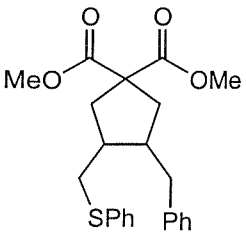
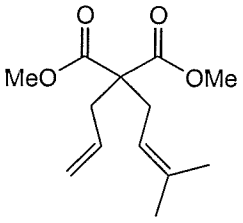
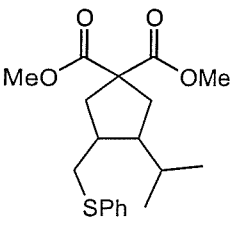


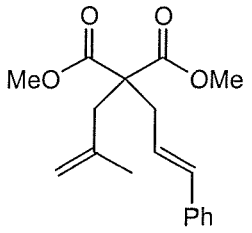
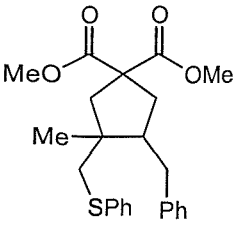
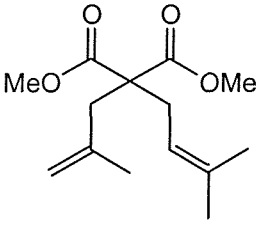
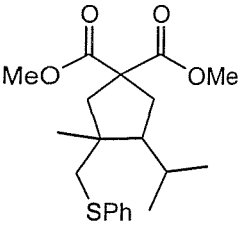
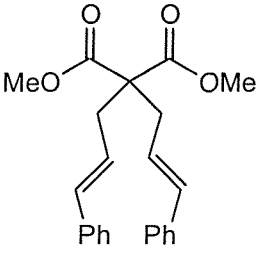
a. Allyl bromide (2.1 eq.), NaH (2.1 eq.), THF, Δ, 15 h. **b.** Allyl bromide (1.0 eq.), NaH (1.0 eq.), THF, Δ, 15 h. **c.** Cinnamyl bromide (1.1 eq.), NaH (1.1 eq.), THF, Δ, 15 h. **d.** Prenyl bromide (1.1 eq.), NaH (1.1 eq.), THF, Δ, 15 h. **e.** Methallyl chloride (1.0 eq.), NaH (1.0 eq.), THF, Δ, 15 h.

Scheme 49

3.2.2 Solution Phase Thiyl Radical Cyclisations

The 1,6-dienes were then subjected to cyclisation conditions by heating them in the presence of thiophenol and AIBN. The results are shown in table 9.

1,6-Diene	Cyclised Product
 **301**	 **308** Overall yield: 87 % *cis* : *trans* 5 : 1[a] PhSH (4.0 eq.), AIBN (1.2 eq.), Tol, 90 °C, 23 h
 **305**	 **309** Overall yield: 86 % *cis* : *trans* 3.5 : 1[a] PhSH (4.7 eq.), AIBN (1.2 eq.), Tol, 90 °C, 23 h
 **304**	 **310** Overall yield: 87 % *cis* : *trans* 3 : 1[a] PhSH (4.5 eq.), AIBN (1.2 eq.), Tol, 90 °C, 23 h

 **306**	 **311** Overall yield: 84 % *cis* : *trans* ~ 1 : 1[a] PhSH (4.6 eq.), AIBN (1.5 eq.), Tol, 90 °C, 25 h
 **307**	 **312** Overall yield: 85 % *cis* : *trans* ~ 1 : 1[a] PhSH (4.0 eq.), AIBN (1.5 eq.), Tol, 90 °C, 25 h
 **313**	No reaction.

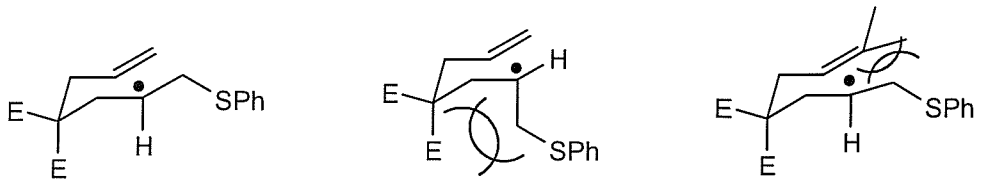
[a]cis : trans ratios determined by n.m.r.

Table 9

Over an equivalent of AIBN was required to drive the reactions to completion, and yields were also found to be very dependent on how the AIBN was added. Addition of AIBN portionwise over a number of hours gave complete reaction. However, if it was all added at the start of the reaction yields were poor and much starting material was recovered. Clearly, nascent radical chain reactions are rapidly quenched in this reaction. Diastereoselectivity was

found to be substrate-dependent, with increased steric bulk on either of the alkenes leading to a drop in stereoselectivity. Where substrates substituted at the internal carbon of the thiyl radical acceptor alkene were employed (as exemplified by **306** and **307**) no significant diastereoselectivity was observed, and reactions required a larger amount of AIBN to drive them to completion.

Regioselectivity and diastereoselectivity in 5-*exo*-trig radical cyclisations can be explained by Beckwith's stereoelectronic model of a chair-like transition state[51], as shown in figure 1.



A **B** **C**

(E = CO_2Me)

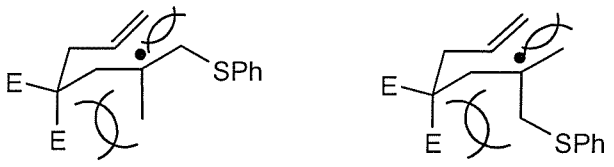
Figure 1

The radical adduct **A** can either add to the internal or terminal carbon of the alkene present. Addition to the internal carbon of the alkene is the dominant process in most cases, since the orbital overlap between the radical and the p-orbital of the internal carbon is vastly superior to the radical's orbital overlap with the terminal carbon, which is much further away.

Beckwith's model also explains the stereoselectivity observed. When the attacking radical attaches to the terminus of one of the alkene double bonds, the bulky substituent introduced α to the radical centre can adopt either an axial or equatorial position in the pseudo-chair transition state. Bulky axial substituents are always disfavoured in the chair conformation, and especially so when bulky substituents are present β to the radical centre, due to 1,3-diaxial steric interactions. This can be seen by comparison of the conformations **A** and **B** in figure 1. Thus the preferred conformation for the transition state is that in which the second alkene and the newly-added group are *cis* to each other. This explains why the *cis* isomer is so predominant in the cyclisation reaction leading to **308**.

That diastereoselectivity drops significantly when groups are introduced at the terminal carbon of the second alkene (**304** and **305**), can be seen from the results presented in table 9. This can also be explained in terms of the model outlined above. In such instances steric interactions between the bulky benzenethiyl group and the substituents at the terminus of the second alkene become more significant, as illustrated by compound **C** in figure 1. Although this interaction will not be as strong as the 1,3-diaxial interaction between the newly-added group and the malonate, it none-the-less reduces the energy difference between the axial and equatorial conformations of the pseudo-chair transition state, allowing a greater proportion of the *trans* product to be formed. Cyclisation through other conformers (e.g. boat) may likewise become more competitive.

Finally, the model can also account for the loss in diastereoselectivity when a methyl group is attached to the internal carbon of the alkene to which the attacking radical adds. In this instance, the difference in energy between the transition state where the newly-added group is axial, and that where it is equatorial is minimal, since 1,3-diaxial interactions and steric interactions with the substituents on the terminus of the second alkene will occur in both cases, as illustrated by **A** and **B** in figure 2.



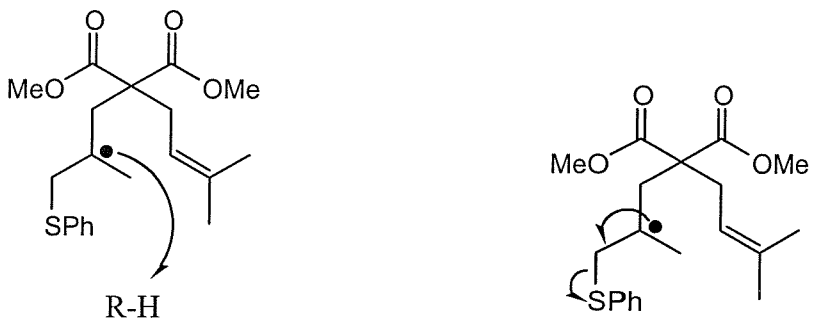
A **B**

(E = CO_2Me)

Figure 2

There is a slight preference for the *cis* product over the *trans*, as might be expected since a methyl group is less bulky than a methylene-*S*-phenyl moiety, however the diastereoselectivity is very small.

It is also noteworthy that these radical cyclisations require high amounts of AIBN to drive them to completion. It is believed this is in part due to the propensity of thiyl radicals to dimerise, i.e. 2 PhS· → PhSSPh. This termination of the nascent radical chains thus requires that an excess of both initiator and thiyl radical source are used in the reaction. The thiyl radical cyclisations of dienes **306** and **307** required a still greater amount of AIBN to drive them to completion than the thiyl radical cyclisations of **301**, **304** and **305**. It is postulated that this is due to the extra steric repulsion between the methyl group attached to the internal carbon of the radical-accepting alkene and the other alkene, which pushes the two branches of the diene further apart than would otherwise be the case. Thus there is a greater energy barrier to be overcome before cyclisation can occur, once the attacking thiyl radical has added to the terminus of the alkene. This slows the cyclisation step and increases the probability of either a hydrogen atom abstraction or β-elimination (figure 3), regenerating the alkene and the thiyl radical.



H-atom Quenching β-Elimination

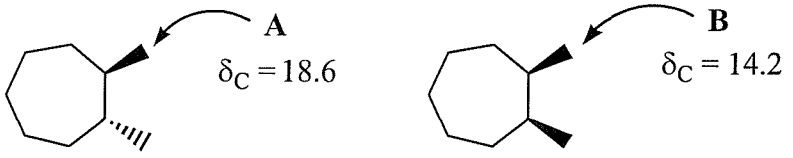
Figure 3

The former possibility can be discounted for this reaction, since no trace of the quenched product was isolated from the product mixture. The reversible nature of thiyl radical additions to alkenes is well established, as is their dimerisation. It therefore seems likely that a greater amount of AIBN is required because termination of the chain reaction becomes more significant when cyclisation proceeds more slowly.

Finally, it was also noted that the benzenethiyl radical *only* adds to terminal alkenes, as evidenced by the results above and also the failed attempt to cyclise dicinnamyl dimethyl malonate.

3.2.3 Determination of the Stereochemistry

The stereochemistry of the products was determined by ^{13}C n.m.r., using the "γ-gauche effect"[52]. This is the nuclear shielding of a carbon atom if it is in a sterically crowded environment, typically due to substituents in the γ-position. The shielding comes about due to Van der Waals interactions, which lead to a sterically induced polarisation of C-H bonds. An example is shown in figure 4. The methyl group labelled **A** in **314** has a significantly higher chemical shift than that labelled **B** in **315**, since the methyl groups in **315** are in a *cis* configuration, and hence **B** experiences shielding as described above.



314 **315**

Figure 4

The same effect is observed in the cyclised products from the thiyl radical cyclisations reported above. **308** provides an example. N.m.r. analysis of the two diastereomers shows significant shielding of the carbon labelled **C** in one diastereomer, relative to the other (figure 5). On the basis of the γ-gauche effect, the diastereomer with the greater shielding of **C** was determined to be the *cis* isomer.

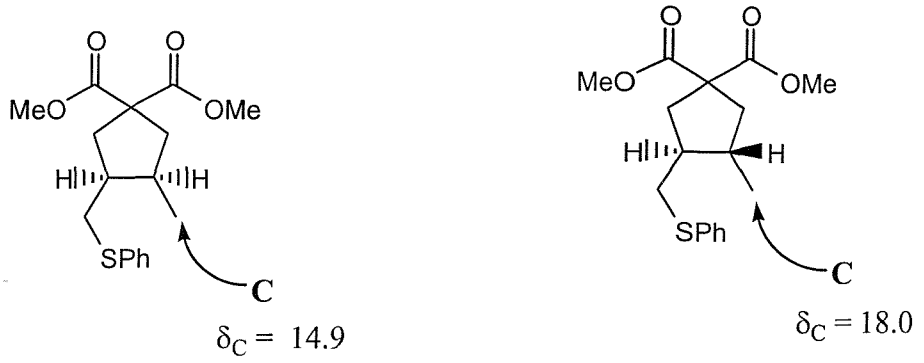


Figure 5

For products **311** and **312**, the situation was a little different. The benzylic carbon in **311**, and the isopropylic carbon in **312** exhibited little difference in chemical shift when *cis* and *trans* isomers were compared. This is due to the presence of the extra methyl group in the molecule, which means that these carbons will experience steric compression in both *cis* and *trans* configurations. This is demonstrated for **312** in figure 6, below:

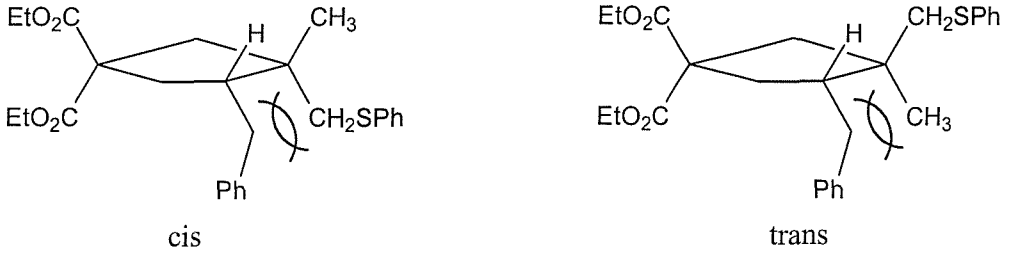


Figure 6

In these two cases, relative stereochemistry was assigned by comparison of the ^{13}C chemical shifts of the methyl group in the two isomers. As can be seen from figure 6, when the two bulky groups are *cis* to each other, the methyl group does not experience any steric compression. Hence its chemical shift will be at lower field than when the two bulky groups are *trans*, as this does lead to steric compression.

Considering **309**, unequivocal identification of the carbon atom adjacent to the sulfur was not possible. It has a chemical shift in the region of 35 ppm; similar to the chemical shifts of the

CH_2 carbon atoms in the ring, and the benzylic CH_2, and unfortunately these four carbons could not be individually identified with absolute certainty.

310 presented a challenge in that, although the isopropyl carbon could be readily identified, the *cis* isomer exhibited only a small (1 ppm) γ-gauche shielding when compared to the *trans* isomer. It was felt this was an insufficient difference to allow the definite determination of relative stereochemistry, and it was therefore necessary to measure the γ-gauche interaction for the carbon atom next to the sulfur.

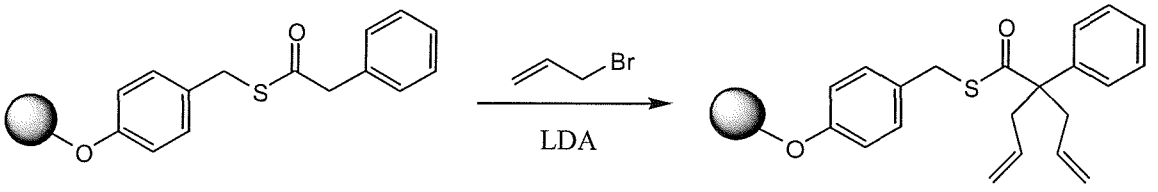
Thus, in order to unambiguously determine the relative stereochemistry of **309** and **310,** in each case the sulfide was oxidised to the sulfone. This shifted the ^{13}C n.m.r. peak for the carbon next to the sulfur up from approximately 35 ppm to between 55 or 60 ppm (according to whether it was *cis* or *trans* respectively to the other bulky group), allowing its identification with full confidence as no other CH_2 carbons were present in this region of the spectrum.

An alternative method often used for determining the relative stereochemistry of organic compounds is the nuclear Overhauser effect; the change in intensity of an NMR resonance when the transitions of another are perturbed (i.e. when it is irradiated). This is a *through space* effect - a dipolar coupling between nuclei. If two groups are close in space, irradiating the proton n.m.r. signal of one of these groups will lead to an observable enhancement in the strength of the other signal. Thus relative stereochemistry can be determined by determination of which groups are close in space.

However, it was decided not to use this method for the determination of the stereochemistry of products **308** - **312**, since n.O.e. experiments require the proton n.m.r. signal being irradiated to be isolated (i.e. with no other signals at similar chemical shift). Unfortunately, since many of the products **308** to **312** could not be separated by HPLC, unambiguous n.O.e. experiments were not always possible, and thus this technique was not used.

3.3 Thiyl Radical Chemistry on Solid-Supported Substrates: The Search for a Suitable Linker

The first task was to identify a suitable linker which would allow a 1,6-diene to be immobilised on the solid phase whilst the radical cyclisation was carried out and then let it be easily cleaved from the resin afterwards. A resin-bound thioester was the first option considered, due to the variety of compounds that can be generated on cleavage, as reported previously. It was hoped that two allyl groups could be installed α to the carbonyl carbon, as shown in scheme 50.

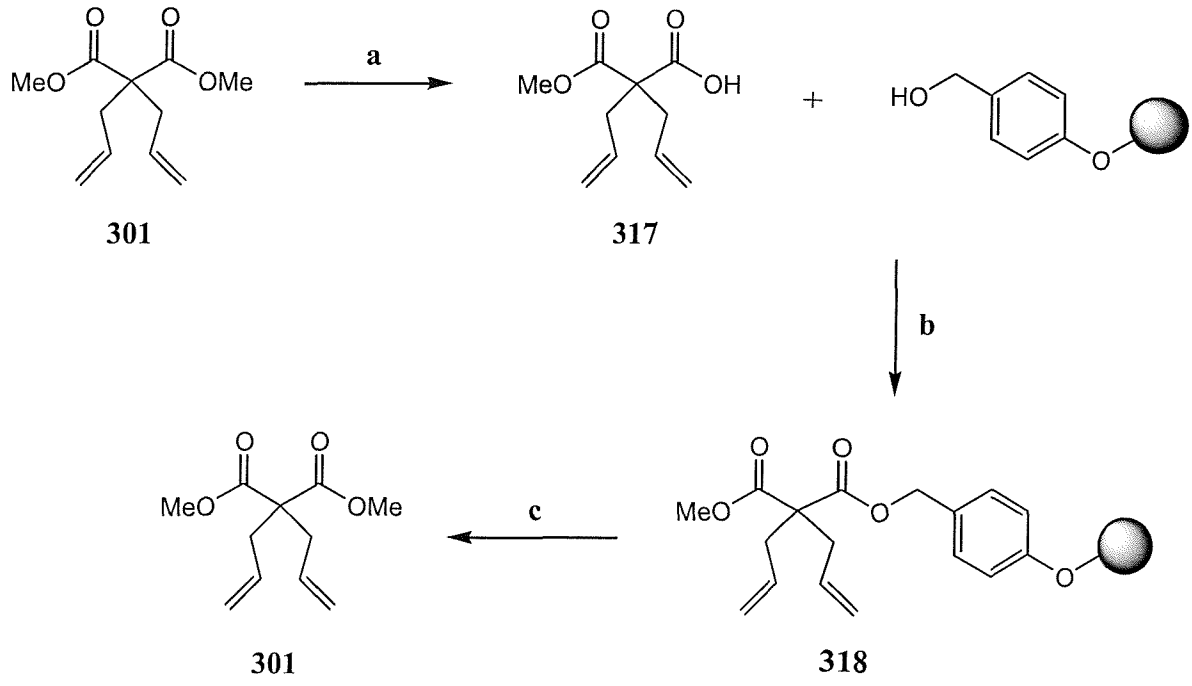


246 **316**

Scheme 50

Unfortunately, studies on an analogous solution-phase thioester showed that whilst one allyl group could be added with relative ease, it was not possible to install a second allyl group on the same carbon. Several attempts were made to diallylate a solution phase thioester using LDA as the base with allyl bromide as the allyl source, however on each attempt a mixture of unidentifiable products was produced, with no trace of starting material or product. Thus an alternative linker had to be found.

Malonates have been used before as a support for 1,6-dienes in solution phase radical reactions[49, 53] due in part to the ease with which two allyl groups can be added to the malonate. It was postulated that partial saponification of a diallyl malonate would yield the half acid, which could then be coupled to a resin containing a hydroxy moiety by means of a suitable coupling reagent (scheme 51).

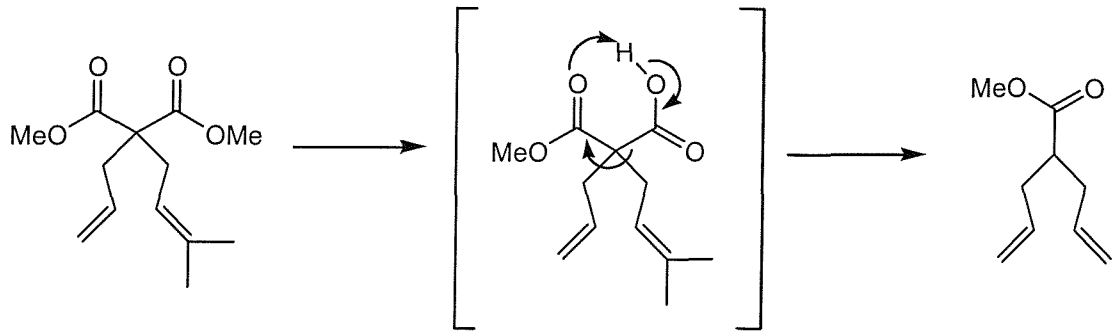


a. Dimethyl allylmalonate, KOH (1.0 eq.), MeOH, Δ, 6 h. **b.** Wang resin, **317** (2.0 eq.), DIC (2.0 eq.), HOBt (2.0 eq.), DMAP (0.2 eq.), DCM, DMF, 15 h. **c.** **318**, MeONa (3 eq.), MeOH, THF, Δ, 18 h, 83 %.

Scheme 51

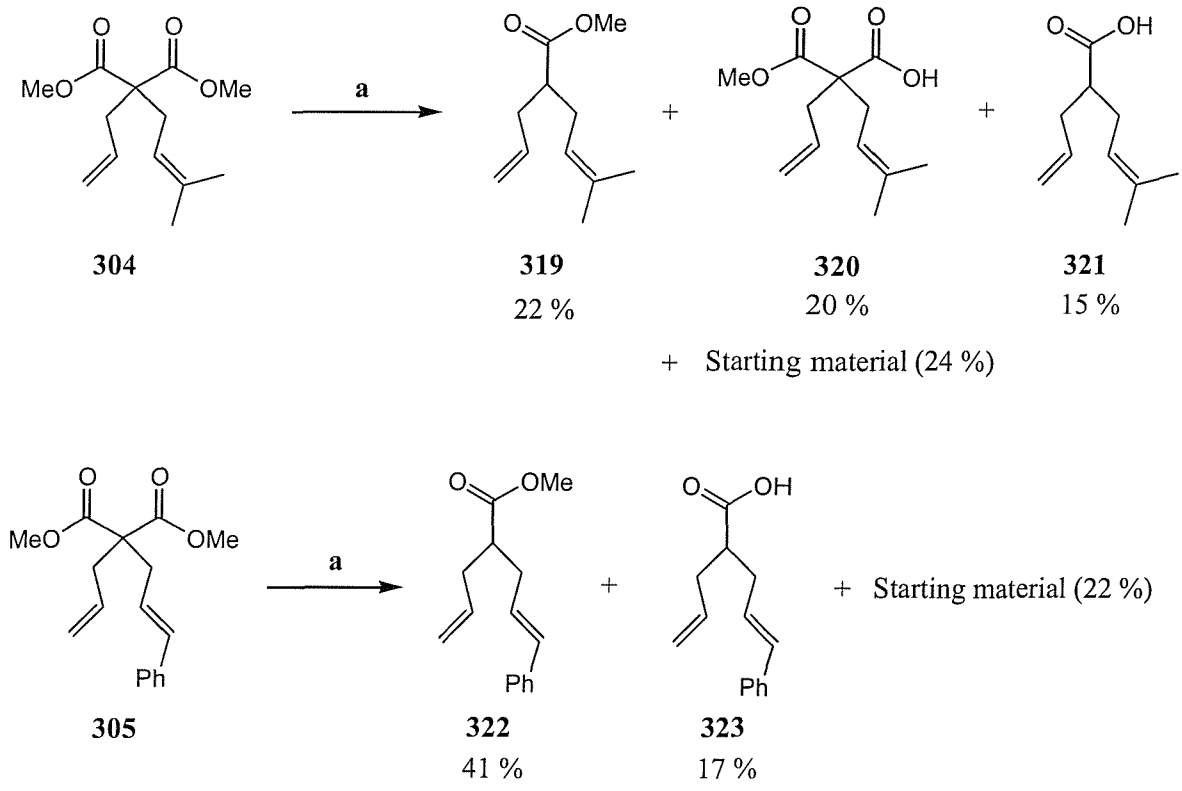
After the radical chemistry has been carried out on the 1,6-diene, it could then be cleaved from the resin by a variety of methods, depending on the functionality desired upon cleavage. This concept worked well for dimethyl diallylmalonate, which gave 50 % of the mono-acid when saponified with one equivalent of hydroxide, as would be expected statistically. The acid coupled readily to Wang linker, and cleavage with sodium methoxide in methanol yielded dimethyl diallylmalonate once again. The overall yield for the two-step process of coupling and cleaving was 83 %.

Unfortunately, this method did not prove suitable for all substrates. When dimethyl allyl-prenylmalonate was partially saponified, only a very small amount of the half acid was isolated; due to decarboxylation *in situ* of the substrate as illustrated in scheme 52.



Scheme 52

For dimethyl allyl-cinnamylmalonate the situation was even worse: all of the half acid was decarboxylated *in situ* and none could be isolated (scheme 53).

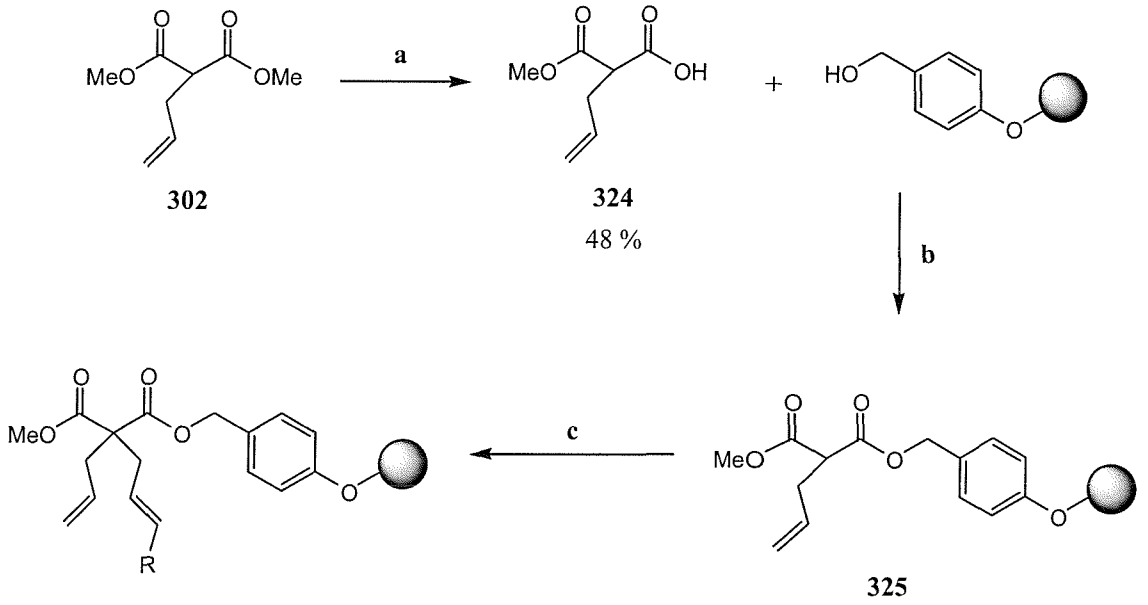


a. 304, KOH (1.0 eq.), MeOH, Δ, 18 h. **b. 305**, KOH (1.0 eq.), MeOH.

Scheme 53

The problem was solved by partial saponification of dimethyl allylmalonate. The mono-acid product did not decarboxylate under the reaction conditions, and was then coupled to Wang

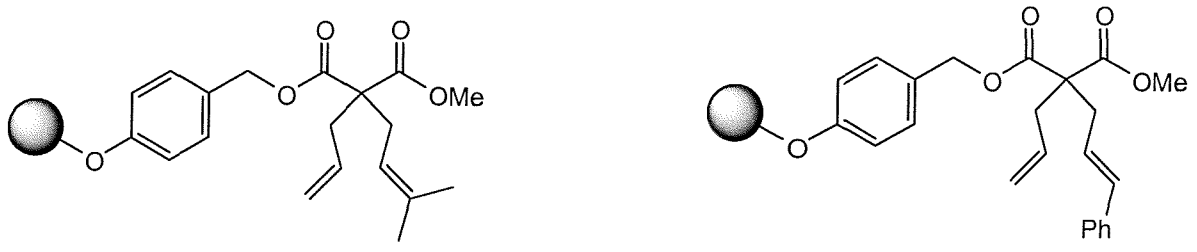
resin. The second alkene was then attached by heating the resin-bound allylmalonate in the presence of the allyl halide and DBU (scheme 54).



a. **302**, KOH (1.0 eq.), MeOH, Δ, 6 h. **b.** Wang resin, **324** (2.0 eq), DIC (2.0 eq.), HOBt (2.0 eq.), DMAP (0.1 eq.), DCM, DMF, 15 h. **c.** **325**, Prenyl / cinnamyl bromide (4.0 eq.), DBU (4.7 eq.), dioxane / acetone (2 : 1), Δ, 36 h.

Scheme 54

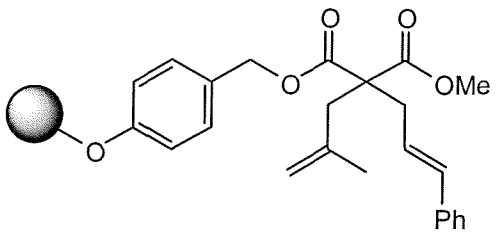
Thus resin-bound 1,6-dienes **326** and **327** were prepared, using this method.



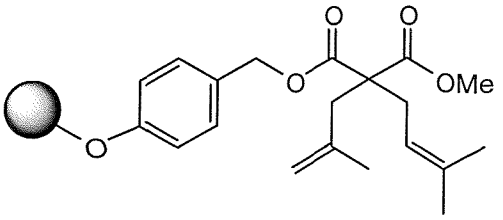
326 **327**

Figure 7

Two more resin-bound dienes, **328** and **329** were prepared by a very similar method, using dimethyl methallylmalonate instead of dimethyl allylmalonate as the starting material.



328

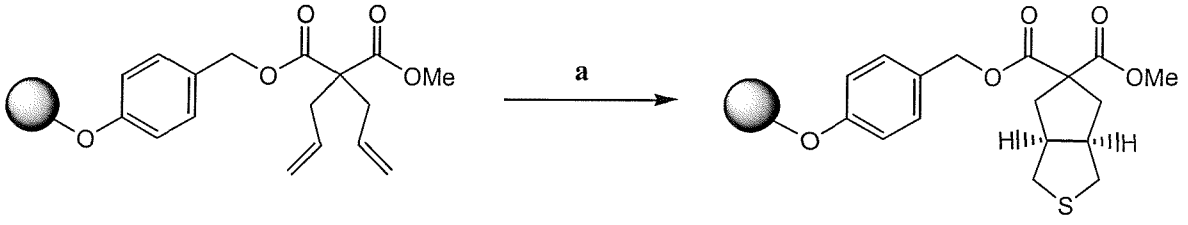


329

Figure 8

3.4 Thiyl Radical Chemistry with *tert*-Butylthiyl Radicals

As discussed previously, *t*-butylthiyl radicals react with 1,6-dienes in the presence of UV light to generate bicyclic systems with *cis* stereochemistry across the ring junction. It was hoped that this observation would be reproduced on resin-bound 1,6-dienes (scheme 55).



318 330

a. $(Bu^tS)_2$, hυ, Toluene, 72 h.

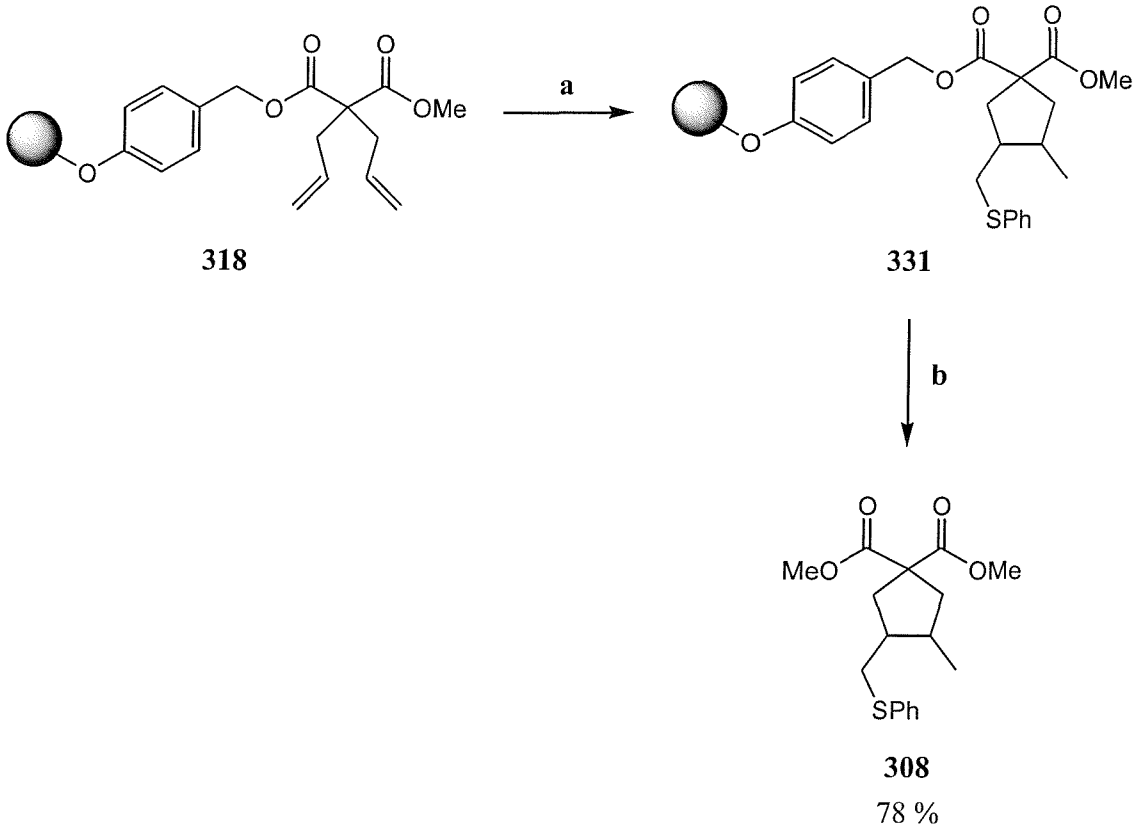
Scheme 55

Unfortunately, despite repeated attempts, no cyclised product was isolated when the malonate was cleaved from the resin using sodium methoxide as described above in scheme 51. The only product isolated after cleavage was dimethyl diallylmalonate. Thus it was decided to discontinue this line of the investigation.

3.5 Thiyl Radical Chemistry Benzenethiyl Radicals

An alternative source of thiyl radicals is thiophenol. The thiol hydrogen is readily abstracted by another radical, generating a highly reactive thiyl radical[50]. The reaction was thus attempted on solid-supported 1,6-diene **318**, tethered to the solid phase using the Wang linker

as shown in scheme 56. The cyclisation proceeded in high yield, giving the product as a 5 : 1 mixture of diastereomers (as determined by n.m.r.) with the *cis* diastereomer as the major product: the same diastereoselectivity shown by the analogous solution phase reaction. This was confirmed by treatment of the resin using sodium methoxide in methanol to cleave the malonate, which was subsequently analysed.



318 **331**

308

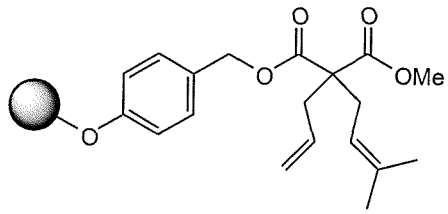
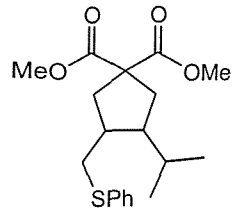
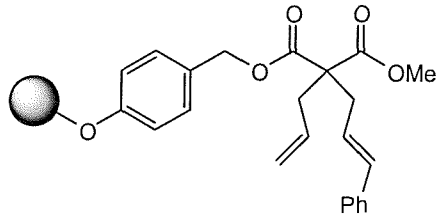
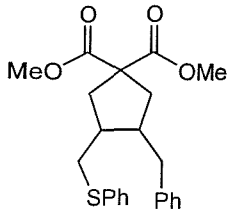
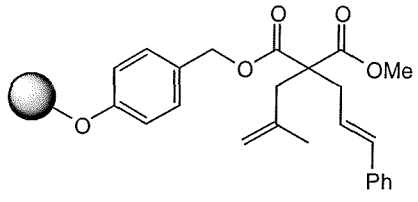
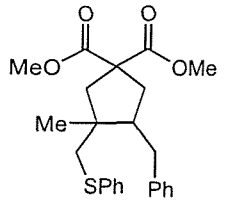
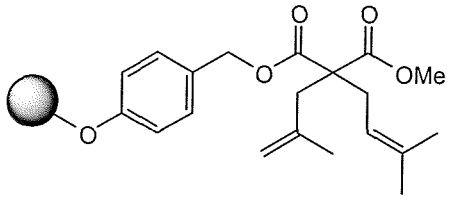
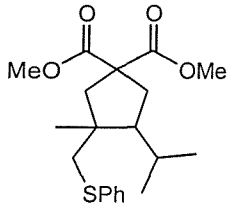
78 %

a. PhSH (5 eq.), AIBN (1.6 eq.), toluene, 80 °C, 8 h. **b.** MeONa (3.0 eq.), MeOH, Δ, 18 h.

Scheme 56

As with the analogous solution phase reaction, portionwise addition of the AIBN was found to greatly increase the yield of cyclised product.

The methodology was then repeated on the other resin-bound substrates described previously. In all cases the cyclised products were subsequently cleaved with sodium methoxide, and the results are displayed in table 10.

Resin-bound 1,6-Diene	Cleaved Cyclised Product
 **326**	 **310** Overall yield: 76 % *cis* : *trans* 3 : 1[a]
 **327**	 **309** Overall yield: 75 % *cis* : *trans* 3.5 : 1[a]
 **328**	 **311** Overall yield: 69 % *cis* : *trans* ~ 1 : 1[a]
 **329**	 **312** Overall yield: 69 % *cis* : *trans* ~ 1 : 1[a]

[a]cis : trans ratio determined by n.m.r.

Table 10

Structures and ratios of diastereomers were determined by comparison of the n.m.r. spectra of the cleaved products with those of the analogous solution phase radical cyclisation reactions. It can be seen that whilst yields are a little lower, diastereoselectivity is unchanged compared to the analogous solution phase reactions.

3.6 Conclusion

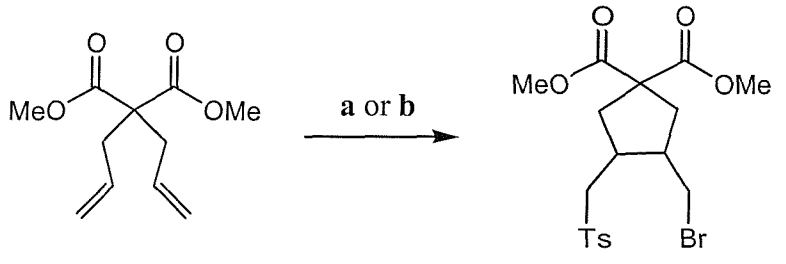
Thiyl radical cyclisations of 1,6-dienes have been developed for 1,6-dienes with two esters at the C4 carbon of the diene. The reaction proceeds in high yield, both in solution and for 1,6-dienes tethered to solid supports *via* malonates. Addition of the thiyl radical to the diene displays excellent regioselectivity, as it will only add to a terminally unsubtituted alkene. Diastereoselectivity is dependent on the substituents on the alkene carbons of the 1,6-diene, but does not differ between a solution phase reaction and its analogous solid phase reaction. Where both alkenes are unsubstituted at both the terminal and internal carbon atoms, diastereoselectivity is very high, with the *cis* isomer predominating. When one alkene bears substituents on the terminal carbon, diastereoselectivity drops significantly, although the *cis* isomer is still predominant. However, substitution at the internal carbon of the thiyl radical accepting alkene gave virtually no diastereoselectivity.

Chapter 4: Results and Discussion 3

Tosyl Radical Cyclisations on the Solid Phase

4.1 Background

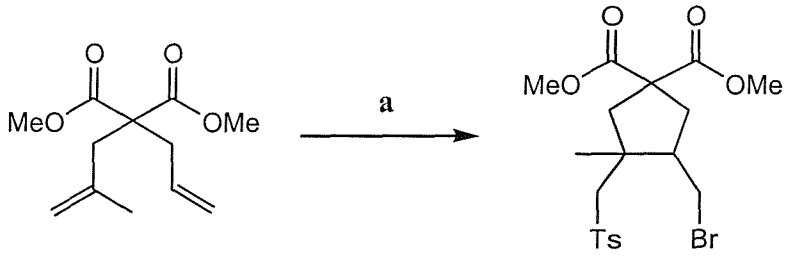
The addition of tosyl radicals to alkenes is a well-known solution phase method for the synthesis of open-chain sulfones[54]. Typically, tosyl halides are used, with the halide adding to the other end of the double bond. The methodology has also been successfully exploited on solid phase, as exemplified by Caddick[19] *et al.* Furthermore, the reaction has been extended by De Riggi[55] and coworkers to induce a 5-*exo*-trig radical cyclisation when the tosyl radical adds to an alkene which is part of a 1,6-diene (scheme 57).



301 **401**

(85%)

a. *cis* : *trans* 93 : 7
b. *cis* : *trans* 79 : 21



301 **402**

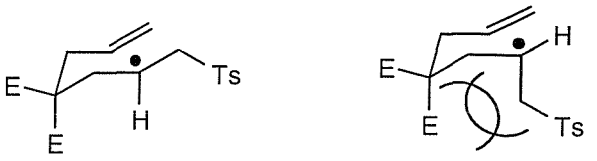
(85%)

a. *cis* : *trans* 63 : 37

a. **301**, TsBr (1.0 eq.), MeCN, hυ, r.t., 14 h. **b.** **301**, TsBr (1.0 eq.), chlorobenzene, 130 °C, 24 h.

Scheme 57: De Riggi's Addition-Cyclisation Reactions of 1,6-Dienes

The reaction can be initiated either thermally or photochemically, and yields for the cyclisation reaction are high. It can be seen from scheme 57 that stereoselectivity is dependant on both the substrate and, to a lesser extent, the conditions. The greater the substitution on the alkene carbons, the lower the stereoselectivity, as discussed in Chapter 3. The relationship between reaction temperature and diastereoselectivity can also be explained using Beckwith's model. At a higher reaction temperature, the radical intermediate can more easily overcome the energy barrier to the bulky group adopting an axial position (figure 9). If the bulky group is axial when cyclisation occurs, the *trans* diastereomer is formed.

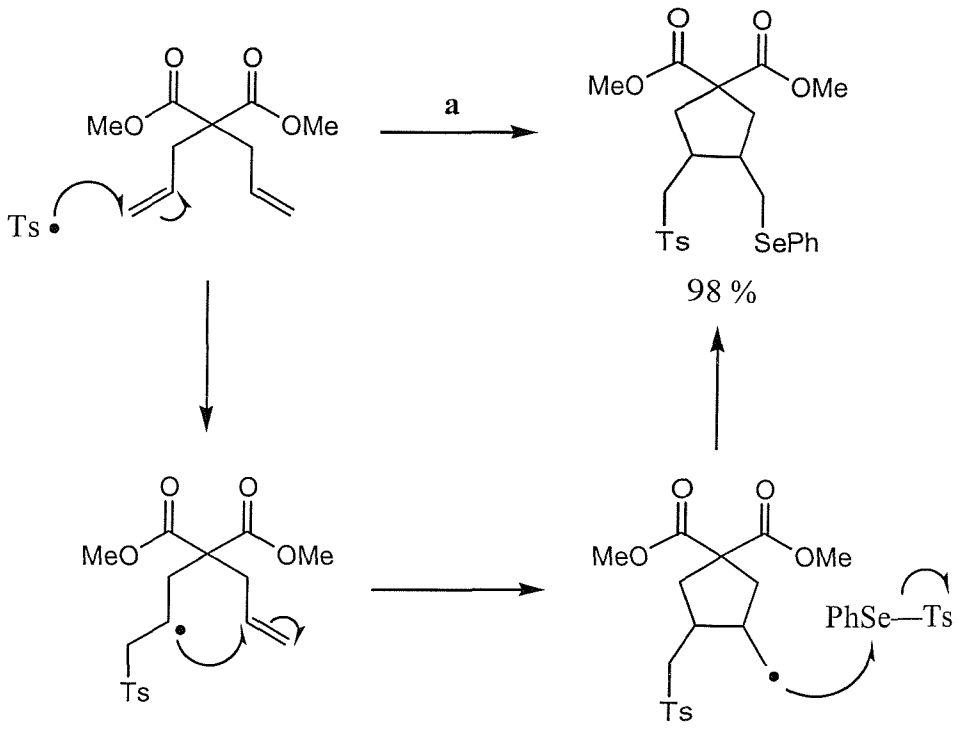


A **B**

(E = CO_2Me)

Figure 9

However, tosyl halides are not the only compounds capable of producing tosyl radicals. Chuang[56] has reported a tosyl-radical induced cyclisation of 1,6-dienes using *p*-tolyl benzeneselenosulfonate (scheme 58). Stereoselectivity is generally high, giving the *cis* isomer as the dominant product. The reaction is relatively fast, and high yielding. In contrast to thiyl radical cyclisations (both in solution and on solid phase), the reaction requires less than an equivalent of AIBN, and the AIBN does not have to be added portionwise. The reaction introduces both tosyl and benzeneselenyl functionalities into the substrate, and the latter functionality is of particular use because of the versatility of organoselenium compounds in organic synthesis[57].



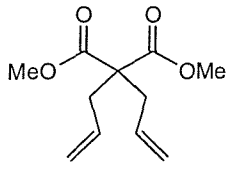
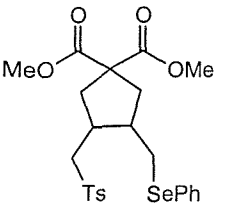
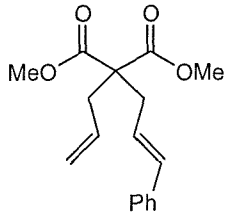
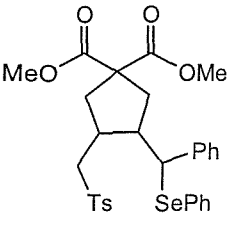
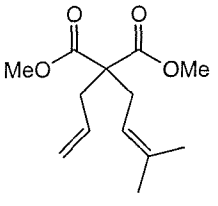
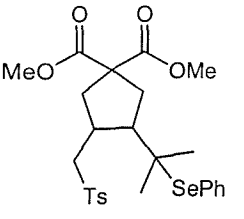
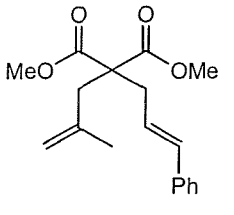
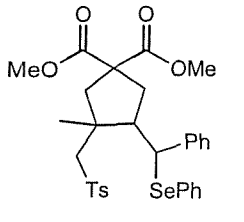
a. **301**, TsSePh (1.3 eq.), $CHCl_3$, Δ, 3 h.

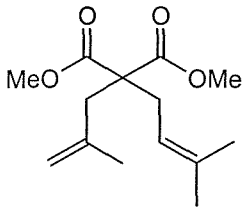
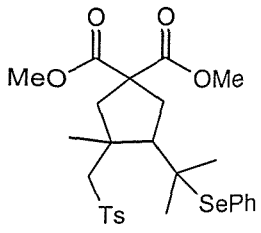
Scheme 58

Thus it was decided to explore further the scope of this methodology in solution phase, and attempt to apply it to the solid phase.

4.2 Solution Phase Tosyl Radical Cyclisations of 1,6-Dienes

In his study into free-radical cyclisations of 1,6-dienes using selenosulfonates, Chuang[56] explored the effect on yield and stereoselectivity of placing different substituents at the 4-position of the 1,6-diene. In only one example was a substituent present on one of the alkene carbons of the 1,6-diene, and thus it was decided that this was an area that warranted further investigation in solution phase before an analogous study was carried out on solid phase. Consequently, the 1,6-dienes synthesised for the thiyl radical cyclisation study discussed in Chapter 3 were also employed for this tosyl radical cyclisation study. The results are shown below.

1,6-Diene	Cyclised Product
 **301**	 **403** Yield: 90 % *cis* : *trans* 7 : 1[a]
 **305**	 **404** Yield: 86 % *diastereomeric ratio:* 3 : 3 : 1 : 1[a]
 **304**	 **405** Yield: 83 % *cis* : *trans* 3.5 : 1[a]
 **306**	 **406** Yield: 84 % *diastereomeric ratio:* ~ 1 : 1 : 1 : 1[a]

 **307**	 **407** Yield: 82 % *cis* : *trans* ~ 1 : 1[a]

[a] cis : trans ratio determined by n.m.r.

Table 11

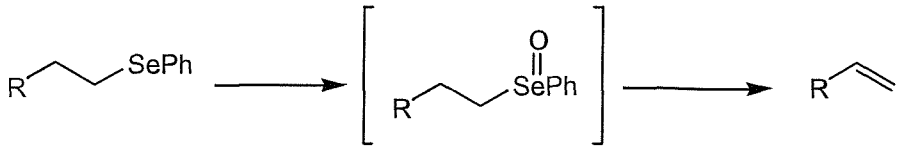
It should be noted that, in all cases, the tosyl radical was totally regioselective for the unsubstituted alkene terminus, mirroring the behaviour of the benzenethiyl radical discussed in Chapter 3. Furthermore, the reaction once again proceeds *via* a 5-*exo*-trig pathway, as is predicted by the Beckwith transition state model.

As can be seen from table 11, the results closely mirror those obtained for the benzenethiyl radical cyclisations. Diastereoselectivity was once again determined using the γ-gauche effect, this time by comparison of the chemical shift of the methylene adjacent to the tosyl group in the two isomers. In all cases, the methylene carbon is readily identified since its chemical shift is at much lower field (δ 55 – 60 ppm) than the other CH_2 carbons in the molecule.

Using this technique, it was observed that once again, stereoselectivity drops significantly when a substituent is placed on the terminal position of one alkene. When one alkene contains a substituent on its terminal position, and the other alkene contains a substituent on its non-terminal carbon (e.g. **306** and **307**), stereoselectivity is very poor indeed. Again, these observations fit very well with the Beckwith transition state model for 5-*exo*-trig radical cyclisations onto 1,6-dienes.

4.3 Attempted Oxidation-Elimination of the Aryl Selenium Species

Organoselenium compounds are often used in organic chemistry because of the ease with which the selenium undergoes an oxidation-elimination reaction, yielding an alkene (scheme 59).



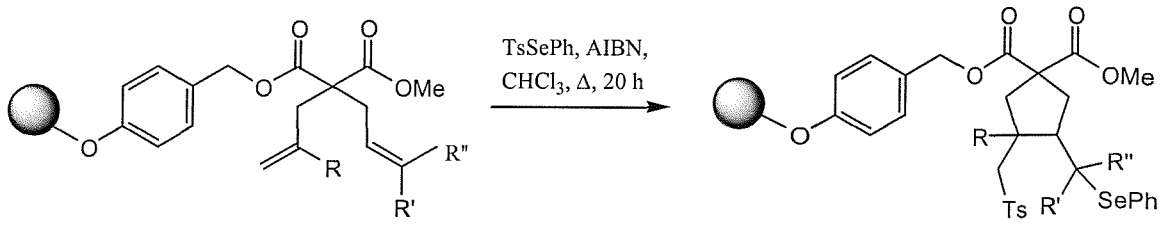
Typical Conditions: H_2O_2, THF, r.t., 2 h.

Scheme 59

It was hoped that oxidative elimination of the selenium moiety from the compounds described above would reduce the number of diastereoisomers in a number of cases, and provide a useful means of re-introducing an alkene functionality into the substrate. *m*CPBA and hydrogen peroxide are two reagents commonly used for oxidative elimination reactions of organoselenides[58], and both were duly used in attempts to oxidise the selenium atom in the cyclised products. Strangely, these attempts to oxidise the selenium failed, and the reason for the failure is not known. This line of investigation was therefore abandoned.

4.4 Tosyl Radical Cyclisations of 1,6-Dienes on the Solid Phase

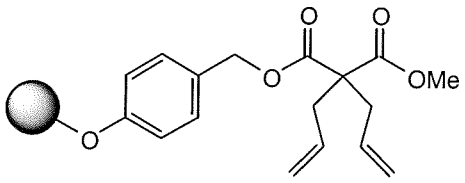
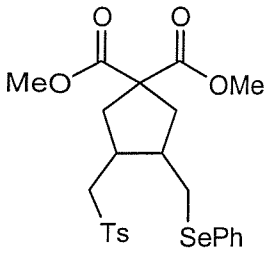
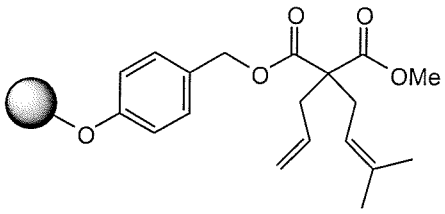
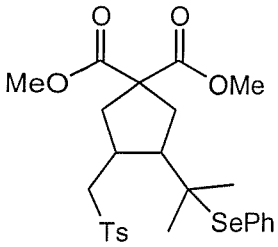
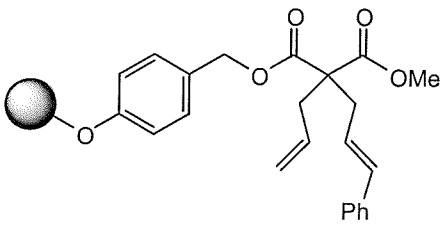
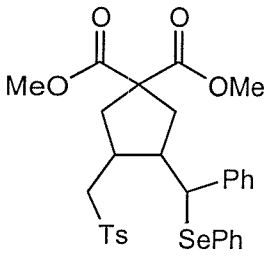
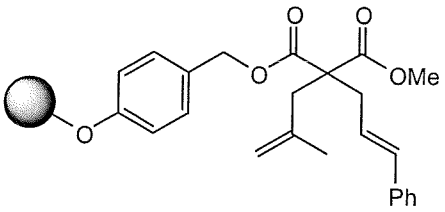
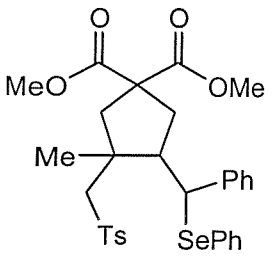
The only example of a tosyl radical reaction on a resin-bound substrate is by Caddick[19] *et al.*, who have reported a tosyl radical addition to an alkene on solid phase, as discussed in Chapter 1. The methodology was not extended to explore cyclisation reactions, and thus tosyl radical cyclisations of resin-bound substrates represent a new class of reactions on the solid phase. The general reaction is shown below, in scheme 60.

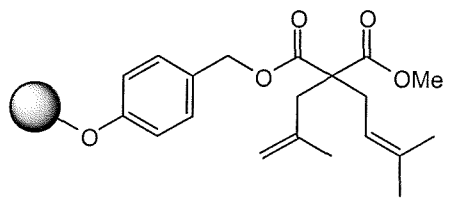
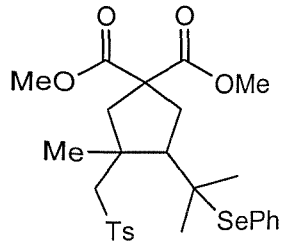


Scheme 60

The same resin-bound 1,6-dienes that were used for the thiyl radical cyclisation studies were employed, and in all cases the reaction was successful. Following cyclisation, the substrates were cleaved from the resin using sodium methoxide. Yields are based on the overall process of loading the substrate onto the resin, performing the cyclisation, and cleaving the resultant cyclised product into solution. The results are shown in table 12. To obtain optimal yields, it was found that an excess of AIBN was required, added in two portions; one at the start of the reaction, and one after 5 hours. The reaction time was also extended relative to the analogous solution-phase reaction, at 20 hours in total.

As can be seen from table 12, the diastereoselectivity of the solid phase radical cyclisations closely mirrors that of the solution phase analogues. Yields are lower than the analogous solution phase reactions, but still good.

Resin-Bound 1,6-Diene	Cyclised Product
 **318**	 **403** Yield: 74 % *cis* : *trans* 8 : 1[a]
 **326**	 **405** Yield: 72 % *cis* : *trans* 3 : 1[a]
 **327**	 **404** Yield: 66 % *diastereomeric ratio:* 3 : 3 : 1 : 1[a]
 **328**	 **406** Yield: 69 % *diastereomeric ratio:* ~ 1 : 1 : 1 : 1[a]

 **329**	 **407** Yield: 68 % *cis* : *trans* ~ 1 : 1[a]

[a]cis : trans ratio determined by n.m.r.

Table 12

4.5 Conclusion

The scope of the solution phase tosyl radical cyclisation methodology, originally demonstrated by Chuang, has been extended by an investigation of the effect of substituents on the terminal carbon atom of the acceptor alkene, and on the internal carbon atom of the other alkene. It has been demonstrated that the reaction is tolerant of substituents at both the aforementioned positions. Regioselectivity is very high, for both the site at which the tosyl radical adds, and the position of the other alkene at which cyclisation occurs. Notably, the tosyl radical only adds to the terminus of a terminally unsubstituted alkene, and cyclisation always follows the 5-*exo*-trig pathway. Diastereoselectivity is dependent on the position of the substituents and ranges from excellent to negligible. Furthermore, the reaction has been successfully carried out on solid-supported 1,6-dienes, achieving similar yields and diastereoselectivities to the analogous solution phase reactions.

Chapter 5

Experimental

General

Infra red spectra of samples were recorded on a Bio Rad FTS 135 FTIR spectrometer. Oils were measured as thin films. Solids were measured neat. Maxima are reported as ν_{max} followed by the signal intensity (described using the abbreviations s, strong; m, medium; w, weak; v, very; br, broad). UV spectra were measured on a Pye Unicam SP8-400 Ultraviolet Spectrophotometer using methanol as a reference sample except where explicitly stated otherwise. Maxima are reported as λ_{max} followed in parentheses by the extinction coefficient ε_{max} ($dm^3\ mol^{-1}\ cm^{-1}$).

^1H n.m.r. spectra were recorded on a Bruker AC300 (300 MHz) or DPX-400 (400 MHz) spectrometer. Chemical shifts (δ_H) are reported as values in parts per million relative to residual $CHCl_3$ (δ 7.27) unless otherwise stated. Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app., apparent. ^{13}C n.m.r. spectra were recorded on a Bruker AM300 (75.5 MHz) or DPX-400 (100 MHz) spectrometer. Chemical shifts (δ_C) are reported as values in parts per million relative to residual $CHCl_3$ (δ 77.2) unless otherwise stated. Multiplicities refer to the signals in the off-resonance spectra, as determined by DEPT 135 experiments. Mass spectroscopic data are reported as values in atomic mass units and are followed in parentheses by the peak intensity relative to the base peak (100 %).

Flash column chromatography was performed using MN Kieselgel 60, 0.04 - 0.063 mm 230 - 400 mesh ASTM silica. Thin layer chromatography was performed on aluminium backed sheets coated with Sil G/UV_{254} 0.25mm Silica gel 60.

Merrifield resin used was 200 - 400 mesh, 1 % cross-linked supplied by NovaBiochem. Loadings varied from batch to batch and the exact loading is specified in each individual procedure. Wang resin was supplied by either Nova-Biochem, or Astra-Zeneca. Bromo-Wang resin used was either supplied by Nova-Biochem, or prepared from hydroxy-Wang by the method of Ngu and Patel[59]. In all cases the beads were 100 - 200 mesh, and 1 % cross-linked. Yields quoted for products cleaved from a resin are for the overall reaction sequence of loading and subsequent cleavage. Where molar quantities for a resin-bound substrate are reported, these indicate the theoretical maximum loading, assuming a 100 % loading of the resin was achieved.

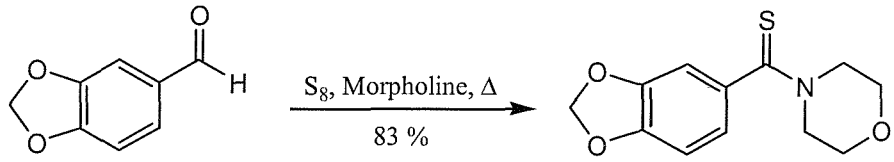
Semi-preparative RP-HPLC was performed using a Hewlett-Packard Series 1100 HPLC System equipped with a Phenomenex Prodigy C18 column (5 μm, 10 x 250 mm). A constant flow rate of 2.500 mL min^{-1} of solvent was used. The mobile phase was composed of 0.1 % TFA in water and 0.042 % TFA in acetonitrile, in the following proportions:

Time	Water / 0.1 % TFA	Acetonitrile / 0.042 % TFA
0 min	100.0 %	0.0 %
40 min	0.0 %	100.0 %
50 min	0.0 %	100.0 %
55 min	100.0 %	0.0 %
60 min	100.0 %	0.0 %

Tetrahydrofuran was dried and degassed by distillation from sodium / benzophenone. Dichloromethane was distilled from calcium hydride. Chloroform was distilled from calcium carbonate. Petroleum ether 40 - 60° was freshly distilled. Toluene was distilled from sodium.

Other solvents were used directly from the bottle as supplied except where stated otherwise. All Grignard, organocuprate, sodium hydride and lithium borohydride reactions, and all radical reactions, were carried out under an atmosphere of nitrogen.

Preparation of Benzo[1,3]dioxol-5-yl-morpholin-4-yl-methanethione **216**



215
$C_8H_6O_3$
Mol. Wt.: 150

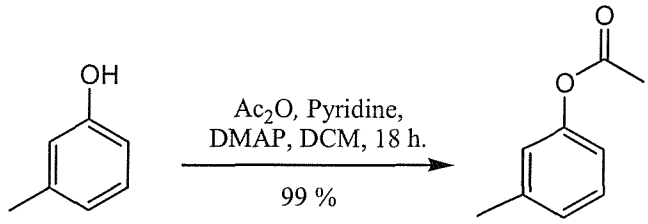
216
$C_{12}H_{13}O_3NS$
Mol. Wt.: 251

Prepared following the procedure of Carayon-Gentil[60]. To a stirred mixture of piperonal (12.5 g, 83.5 mmol) in dry DMF (25 mL) under nitrogen was added sulfur (4.00 g, 125 mmol) followed by morpholine (7.95 g, 8.0 mL, 91.5 mmol). The reaction was heated at 55 °C for 6 hours then cooled. Water (200 mL) was added causing a yellow solid to precipitate. The solid was filtered, washed with petrol and recrystallised from ethanol to give **216** as a pale yellow solid (17.4 g, 69.3 mmol, 83 %).
Spectral and physical data were consistent with literature values[38].

Data for **216:**

ν_{max}/cm^{-1} (neat)	2999 (w), 2860 (w), 1604 (w), 1478 (s), 1432 (s), 1341 (m), 1294 (s), 1224 (s), 1107 (s), 1063 (m), 1029 (s), 830 (s).
δ_H (300 MHz, $CDCl_3$)	6.83 (1H, s, Ar*H*), 6.80 (2H, app s, 2 x Ar*H*), 5.98 (2H, s, OCH_2O), 4.38 (2H, br s, OCH_2), 3.87 (2H, br s, OCH_2), 3.66 (4H, br s, 2 x NCH_2) ppm.
δ_C (75.5 MHz, $CDCl_3$)	200.7 (0, *C*S), 148.4 (0, Ar), 147.8 (0, Ar), 136.4 (0, Ar), 120.2 (1, Ar), 108.3 (1, Ar), 107.7 (1, Ar), 101.7 (2, O*C*H$_2$O), 66.9 (2, O*C*H$_2$), 66.7 (2, O*C*H$_2$), 52.9 (2, N*C*H$_2$), 50.1 (2, N*C*H$_2$) ppm.
LRMS (APCI +ve)	252 ([M+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	284 (4960).
M.P.	164 - 166 °C (ethanol). Lit. 164 - 166 °C (ethanol)[38].

Preparation of Acetic acid *m*-tolyl ester **234**



233
C_7H_8O
Mol. Wt.: 108

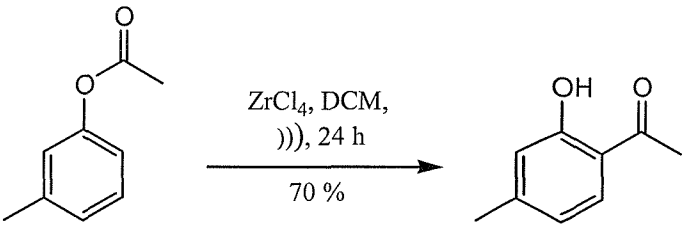
234
$C_9H_{10}O_2$
Mol. Wt.: 150

Prepared by the method of Cullinane and Edwards[61]. A solution of *m*-cresol (20.0 g, 0.19 mol), acetic anhydride (43.2 g, 0.42 mol), pyridine (30 mL) and *N,N*-dimethylaminopyridine (0.60 g, 4.6 mmol) in dichloromethane (320 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was washed successively with dilute HCl (aq., 2 x 100 mL), water (2 x 60 mL) and brine (100 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a pale yellow oil. Column chromatography (silica, 0 - 20 % diethyl ether in petrol) afforded **234** as a clear, colourless oil (28.1 g, 0.19 mol, 99 %).
Spectral data was consistent with literature values[61].

Data for **234:**

ν_{max}/cm^{-1} (thin film)	3032 (m), 2923 (m), 1766 (s), 1614 (s), 1588 (s), 1370 (s), 1207 (s), 1143 (s), 1017 (s), 942 (s), 787 (s), 690 (s).
δ_H (300 MHz, $CDCl_3$)	7.28 (1H, app t, *J* 7.4 Hz, Ar*H*), 7.06 (1H, d, *J* 7.4 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 6.90 (1H, d, *J* 7.4 Hz), 2.38 (3H, s, ArCH_3), 2.31 (3H, s, COCH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	169.8 (0, *C*O), 150.8 (0, Ar), 139.8 (0, Ar), 129.3 (1, Ar), 126.8 (1, Ar), 122.3 (1, Ar), 118.7 (1, Ar), 21.5 (3, ArCH_3), 21.3 (3, COCH_3) ppm.
LRMS (APCI +ve)	149 ([M-H]$^+$, 85 %) amu.
λ_{max}/nm (ε_{max})	259 (380).

1-(2-Hydroxy-4-methyl-phenyl)-ethanone **235**



234
$C_9H_{10}O_2$
Mol. Wt.: 150

235
$C_9H_{10}O_2$
Mol. Wt.: 150

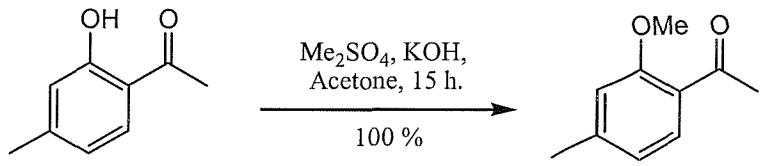
Prepared following the procedure of Harrowven and Dainty[62]. To a solution of 3-methylphenylacetate **234** (26.7 g, 0.18 mol) in dichloromethane (400 mL) was added zirconium tetrachloride (83.9 g, 0.36 mol). The vessel was partially immersed in the water bath of a Decon FS 100 ultrasound cleaner and sonicated for 24 hours, during which the colour of the mixture changed from pale pink to cherry red. The resulting suspension was poured onto ice / water (500 mL) and extracted with dichloromethane (4 x 80 mL). The organic layers were washed with water and brine, dried, filtered and concentrated *in vacuo* to a brown oil. Column chromatography (silica, 10 % diethyl ether in petrol) afforded **235** as a yellow / orange oil (18.6 g, 124 mmol, 70 %).

Spectral data was consistent with literature values[62].

Data for **235:**

ν_{max}/cm^{-1} (thin film)	3500 - 2700 (bs), 1640 (s), 1575 (m), 1507 (m), 1431 (w), 1367 (s), 1303 (m), 1247 (s), 1149 (m), 977 (m), 794 (m).
δ_H (300 MHz, $CDCl_3$)	12.30 (1H, s, ArO*H*), 7.61 (1H, d, *J* 8.1 Hz, Ar*H*), 6.79 (1H, s, Ar*H*), 6.71 (1H, d, *J* 8.1 Hz, Ar*H*), 2.60 (3H, s, ArCOC*H*$_3$), 2.35 (3H, s, ArC*H*$_3$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	204.1 (0, *C*O), 162.6 (0, Ar), 148.2 (0, Ar), 130.8 (1, Ar), 120.4 (1, Ar), 118.5 (1, Ar), 117.7 (0, Ar), 26.6 (3, CO*C*H$_3$), 22.1 (3, Ar*C*H$_3$) ppm.
LRMS (APCI +ve)	151 ([M+H]$^+$) (100 %) amu.
λ_{max}/nm (ε_{max})	321 (5100), 261 (16 500).

1-(2-Methoxy-4-methyl-phenyl)-ethanone **217**



235
$C_9H_{10}O_2$
Mol. Wt.: 150

217
$C_{10}H_{12}O_2$
Mol. Wt.: 164

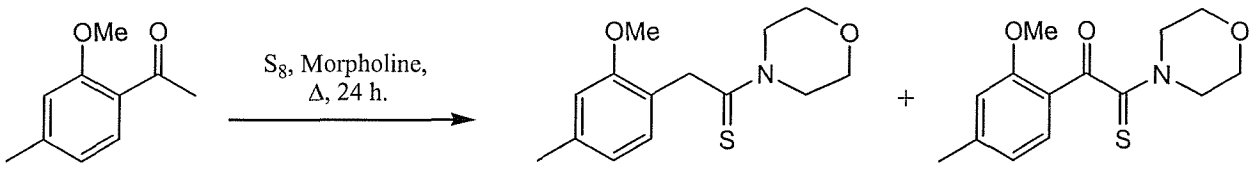
A modified procedure of Jurd[63]. A mixture of 2-hydroxy-4-methylacetophenone **235** (17.9 g, 0.12 mol), dimethyl sulfate (16.4 g, 0.13 mol) and powdered potassium hydroxide (9.0 g, 0.16 mol) was stirred at ambient temperature for 15 hours. The mixture was then partitioned between brine (300 mL) and diethyl ether (100 mL), and the aqueous portion extracted with diethyl ether (3 x 100 mL). The combined organic portions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **217** as a pale yellow solid (19.5 g, 0.12 mmol, Quantitative). The solid was not purified further, since it was deemed to be pure enough already. A sample was recrystallised from petrol for analysis.

Spectral and physical data was consistent with literature values[63].

Data for **217**:

ν_{max}/cm^{-1} (neat)	3003 (w), 1655 (s), 1601 (s), 1495 (m), 1472 (m), 1360 (s), 1256 (s), 1171 (s), 1029 (s), 969 (m), 811 (s), 687 (m).
δ_H (300 MHz, $CDCl_3$)	7.68 (1H, d, *J* 8.1 Hz, Ar*H*), 6.81 (1H, d, *J* 8.1 Hz, Ar*H*), 6.77 (1H, s, Ar*H*), 3.90 (3H, s, ArOCH_3), 2.60 (3H, s, ArCOCH_3), 2.39 (3H, s, ArCH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	199.4 (0, *C*O), 159.3 (0, Ar), 145.0 (0, Ar), 130.7 (1, Ar), 125.6 (0, Ar), 121.5 (1, Ar), 112.4 (1, Ar), 55.5 (3, ArO*C*H$_3$), 32.0 (3, ArCO*C*H$_3$), 22.0 (3, Ar*C*H$_3$) ppm.
LRMS (APCI +ve)	165 ([M+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	302 (3280), 251 (7960).
M.P.	35 - 37 °C (pentane). Lit. 35 - 37 °C (no solvent reported)[63].

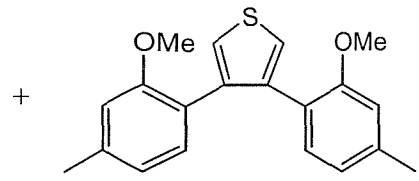
2-(2-Methoxy-4-methyl-phenyl)-1-morpholin-4-yl-ethanethione **218**, 1-(2-Methoxy-4-methyl-phenyl)-2-morpholin-4-yl-2-thioxo-ethanone **219**, 3,4-Bis-(2-methoxy-4-methyl-phenyl)-thiophene **279**



217
$C_{10}H_{12}O_2$
Mol. Wt.: 164

218 (40 %)
$C_{14}H_{19}O_2NS$
Mol. Wt.: 265

219 (7 %)
$C_{14}H_{17}O_3NS$
Mol. Wt.: 279



279 (7 %)
$C_{20}H_{20}O_2S$
Mol. Wt.: 324

Prepared following the procedure of Carmack and Spielman[39]. A stirred mixture of acetophenone **217** (18.9 g, 115 mmol), sulfur (5.70 g, 178 g-atom) and morpholine (15.6 g, 180 mmol) was heated at 100 - 120 °C for 24 hours then allowed to cool to ambient temperature. The resulting red oil was purified by column chromatography (silica, 0 - 40 % diethyl ether in petrol) to yield firstly thiophene **279** (which was recrystallised from diethyl ether / pentane to give a white powder (2.80 g, 8.6 mmol, 7 %)), then thiomorpholide **218** (which was recrystallised from ethyl acetate/pentane to furnish a white powder (12.2 g, 46 mmol, 40 %)), and finally ketothioamide **219** (which was recrystallised from ethyl acetate / pentane to give a yellow powder (2.25 g, 8.1 mmol, 7 %)).

Spectral and physical data were consistent with literature values[38].

Data for **218**:

ν_{max}/cm^{-1} (neat) 3069 (w), 2924 (w), 1656 (s), 1602 (s), 1467 (m), 1414 (m), 1360 (s), 1290 (s), 1256 (s), 1137 (s), 1030 (s), 810 (s).

δ_H (300 MHz, $CDCl_3$) 7.30 (1H, d, *J* 7.4 Hz, Ar*H*), 6.76 (1H, d, *J* 7.4 Hz, Ar*H*), 6.69 (1H, s, Ar*H*), 4.37 (2H, app t, *J* 4.8 Hz, OCH_2), 4.25 (2H, s, CH_2CS), 3.83 (3H, s, ArOCH_3), 3.75 (2H, app t, *J* 5.1 Hz,

	OCH_2), 3.61 (2H, app t, J 4.8 Hz, NCH_2), 3.43 (2H, app t, J 5.1 Hz, NCH_2), 2.35 (3H, s, ArCH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	201.7 (0, *C*S), 155.7 (0, Ar), 138.4 (0, Ar), 128.5 (1, Ar), 121.8 (1, Ar), 121.1 (0, Ar), 111.5 (1, Ar), 66.5 (2, O*C*H_2), 66.4 (2, O*C*H_2), 55.6 (3, O*C*H_3), 50.8 (2, N*C*H_2), 50.3 (2, N*C*H_2), 43.4 (2, *C*H_2CS), 21.7 (3, Ar*C*H_3) ppm.
LRMS (APCI +ve)	266 ($[M+H]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	276 (15 900).
M.P.	63 - 65 °C (ethyl acetate / pentane). Lit. 62 - 64 °C (ethyl acetate / pentane)[38].

Data for **279**:

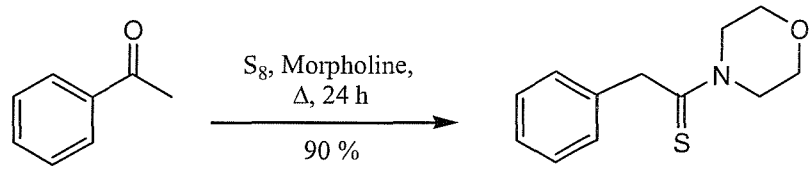
ν_{max}/cm^{-1} (neat)	2971 (w), 2942 (w), 2844 (w), 1604 (w), 1569 (w), 1455 (m), 1405 (m), 1271 (m), 1165 (s), 1031 (s), 857 (s), 813 (s).
δ_H (300 MHz, $CDCl_3$)	7.58 (2H, d, J 7.7 Hz, Ar*H*), 7.46 (2H, s, thiophene), 6.86 (2H, d, J 7.7 Hz, Ar*H*), 6.83 (2H, s, Ar*H*), 3.95 (6H, s, ArOCH_3), 2.40 (6H, s, ArCH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	155.8 (0), 139.1 (0), 138.4 (0), 128.4 (1), 125.4 (1), 121.8 (1), 121.1 (0), 112.6 (1), 55.7 (3), 21.7 (3) ppm.
LRMS (APCI +ve)	325 ($[M+H]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	338 (3900), 236 (2000).
M.P.	84 - 86 °C (diethyl ether / pentane) Lit. 84 - 86 °C (diethyl ether / pentane)[38].

Data for **219**:

ν_{max}/cm^{-1} (neat)	2982 (w), 2860 (m), 1643 (s), 1604 (m), 1517 (s), 1461 (m), 1268 (s), 1230 (m), 1108 (s), 1026 (s), 953 (s), 720 (m).
δ_H (300 MHz, $CDCl_3$)	7.87 (1H, d, J 7.9 Hz, Ar*H*), 6.89 (1H, d, J 7.9 Hz, Ar*H*), 6.77 (1H, s, Ar*H*), 4.24 (2H, app t, J 5.1 Hz, OCH_2), 3.89 (2H, app t, J 5.1 Hz, OCH_2), 3.85 (3H, s, ArOCH_3), 3.74 (2H, app t, J 4.8 Hz, NCH_2), 3.64 (2H, app t, J 4.8 Hz, NCH_2), 2.39 (3H, s, ArCH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	198.7 (*C*S, 0), 186.7 (*C*O, 0), 159.4 (0, Ar), 147.4 (0, Ar), 131.9 (1, Ar), 122.7 (1, Ar), 121.7 (0, Ar), 113.3 (1, Ar), 66.4

	(2, OCH_2), 66.1 (2, OCH_2), 56.2 (3, ArOCH_3), 51.8 (2, NCH_2), 47.0 (2, NCH_2), 22.3 (3, ArCH_3) ppm.
LRMS (APCI +ve)	280 ($[M+H]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	263 (8760).
M.P.	109 - 110 °C (ethyl acetate / pentane). Lit 108 - 110 °C (ethyl acetate / pentane)[38].

1-Morpholin-4-yl-2-phenyl-ethanethione **221**



220
C_8H_8O
Mol. Wt.: 120

221
$C_{12}H_{15}ONS$
Mol. Wt.: 221

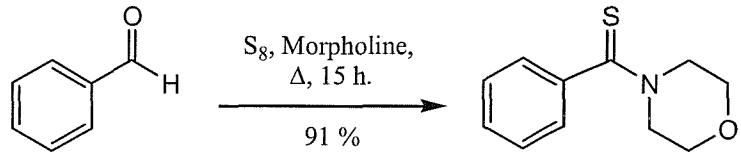
Adapted from a procedure by Carmack and Spielman[39]. Acetophenone (20.0 g, 0.17 mol), morpholine (23.2 g, 0.27 mol) and sulfur (8.6 g, 267 g-atom) were mixed and stirred at 100 °C for 24 hours. After this time the reaction was allowed to cool, and the reaction mixture solidified on standing. Recystallisation from ethanol furnished the product **221** as pale yellow flakes (33.1 g, 0.15 mol, 90 %).

Spectral and physical data were consistent with literature values[64].

Data for **221**:

ν_{max}/cm^{-1} (neat)	2996 (w), 2910 (w), 2852 (m), 1604 (w), 1494 (s), 1430 (m), 1383 (w), 1261 (m), 1110 (s), 1033 (s), 960 (s), 837 (m).
δ_H (300 MHz, $CDCl_3$)	7.34 - 7.32 (5H, m, 5 x Ar*H*), 4.38 - 4.34 (2H, m, OCH_2), 4.36 (2H, s, ArCH_2), 3.76 - 3.73 (2H, m, OCH_2), 3.65 - 3.62 (2H, m, NCH_2), 3.42 - 3.40 (2H, m, NCH_2) ppm.
δ_C (75.5 MHz, $CDCl_3$)	200.1 (0, *C*S), 135.9 (0, Ar), 129.1 (1, Ar), 127.9 (1, Ar), 127.3 (1, Ar), 66.5 (2, O*C*H$_2$), 66.3 (2, O*C*H$_2$), 51.0 (2, N*C*H$_2$), 50.8 (2, Ar*C*H$_2$), 50.3 (2, N*C*H$_2$) ppm.
LRMS (APCI +ve)	222 ([M+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	281 (9370).
M.P.	77 - 78 °C (ethanol). Lit. 80 °C (ethanol)[65].

Morpholin-4-yl-phenyl-methanethione **223**



222

C_7H_6O
Mol. Wt.: 106

223

$C_{11}H_{13}ONS$
Mol. Wt.: 207

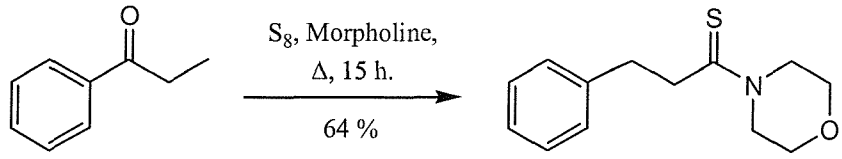
Adapted from a procedure by Carmack and Spielman[39]. Benzaldehyde (21.2 g, 0.20 mol), morpholine (27.7 g, 0.32 mol) and sulfur (10.12 g, 314 g-atom) were mixed together and heated to 100 °C for 15 hours. After this time the reaction was allowed to cool, then the reaction mixture was poured into water (600 mL), causing a brown solid to precipitate. This brown solid was collected by filtration and recrystallised from ethanol to give the thioamide **223** as pale yellow needles (37.7 g, 0.18 mol, 91 %).

Spectral and physical data were consistent with literature values[66].

Data for **223**:

ν_{max}/cm^{-1} (neat)	2984 (w), 2922 (w), 1494 (m), 1476 (s), 1427 (m), 1288 (s), 1254 (m), 1225 (s), 1110 (s), 1024 (s), 870 (m), 756 (s).
δ_H (300 MHz, $CDCl_3$)	7.40 - 7.20 (5H, m, 5 x Ar*H*), 4.42 (2H, t, *J* 5.0 Hz, OC*H*$_2$), 3.86 (2H, t, *J* 4.8 Hz, OC*H*$_2$), 3.59 (4H, app d, *J* 5.1 Hz, 2 x NC*H*$_2$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	201.0 (0, *C*S), 142.6 (0, Ar), 129.0 (1, Ar), 128.7 (1, Ar), 126.0 (1, Ar), 66.9 (2, O*C*H$_2$), 66.6 (2, O*C*H$_2$), 52.7 (2, N*C*H$_2$), 49.7 (2, N*C*H$_2$) ppm.
LRMS (APCI +ve)	208 ([M+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	286 (6210).
M.P.	138 - 139 °C (ethanol) Lit. 137 °C (ethanol)[67].

1-Morpholin-4-yl-3-phenyl-propane-1-thione **225**



224

$C_9H_{10}O$
Mol. Wt.: 134

225

$C_{13}H_{17}ONS$
Mol. Wt.: 235

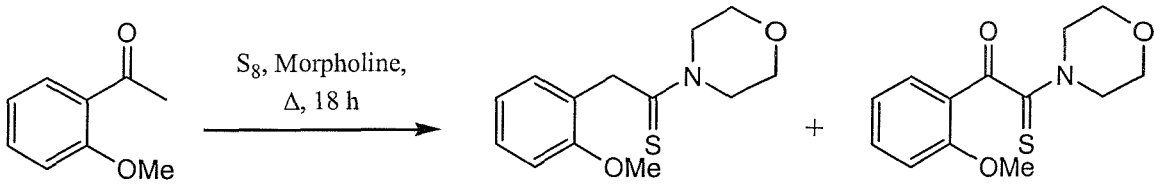
Adapted from a procedure by Carmack and Spielman[39]. Propiophenone (6.00 g, 44.7 mmol), morpholine (6.32 g, 72.5 mmol) and sulfur (2.00 g, 63.0 g-atom) were mixed together and heated to 100 °C for 15 hours. After this time the reaction was allowed to cool, and the resulting brown mixture solidified on standing. Purification by chromatography (silica, 0 - 30 % diethyl ether in petrol) gave the thioamide **225** as a yellow solid (6.72 g, 28.6 mmol, 64 %). A sample was recrystallised from ethanol to give colourless needles.
Spectral and physical data were consistent with literature values[68].

Data for **225**:

ν_{max}/cm^{-1} (neat)	2857 (m), 2920 (m), 2856 (m), 1601 (w), 1487 (s), 1428 (s), 1272 (s), 1246 (s), 1194 (m), 1096 (s), 991 (s), 928 (s), 753 (s).
δ_H (300 MHz, $CDCl_3$)	7.34 - 7.20 (5H, m, Ar*H*), 4.33 (2H, t, *J* 4.9 Hz, OCH_2), 3.71 (2H, t, *J* 4.9 Hz, OCH_2), 3.55 (2H, t, *J* 4.8 Hz, NCH_2), 3.39 (2H, t, *J* 4.8 Hz, NCH_2), 3.13 (4H, s, ArCH_2CH_2) ppm.
δ_C (75.5 MHz, $CDCl_3$)	202.8 (0, *C*S), 140.3 (0, Ar), 128.8 (1, 4 x Ar), 126.8 (1, Ar), 66.6 (2, OCH_2), 66.2 (2, OCH_2), 50.3 (2, NCH_2), 50.1 (2, NCH_2), 44.4 (2, ArCH_2CH_2), 36.0 (2, ArCH_2) ppm.
LRMS (CI)	236 ([M+H]$^+$, 100 %), 91 ([ArCH_2]$^+$, 85 %), 110 ([ArCH_2+NH_4]$^+$, 60 %) amu.
λ_{max}/nm (ε_{max})	276 (6170).
M.P.	131 - 132 °C (ethanol). Lit: 131 - 133 °C (no solvent reported)[68].

2-(2-Methoxy-phenyl)-1-morpholin-4-yl-ethanethione **227** and

1-(2-Methoxy-phenyl)-2-morpholin-4-yl-2-thioxo-ethanone **228**



226
$C_9H_{10}O_2$
Mol. Wt.: 150

227 (41 %)
$C_{13}H_{17}O_2NS$
Mol. Wt.: 251

228 (21 %)
$C_{13}H_{15}O_3NS$
Mol. Wt.: 265

Following the procedure of Carmack and Spielman[39]. 2-Methoxyacetophenone (15.0 g, 0.10 mol), morpholine (13.05 g, 0.15 mol) and sulfur (7.19 g, 150g-atom) were mixed together, stirred and heated to 90 °C for 18 hours. After this time the mixture was allowed to cool, forming a dark red solid. This was purified by chromatography (silica, 10 - 40 % diethyl ether in petrol) to give firstly thioamide **227** as a yellow solid (10.29 g, 0.041 mol, 41 %), and then ketothioamide **228** as a yellow solid (5.57 g, 0.021 mol, 21 %).
Spectral and physical data for **227** were consistent with literature values[69].

Data for **227**:

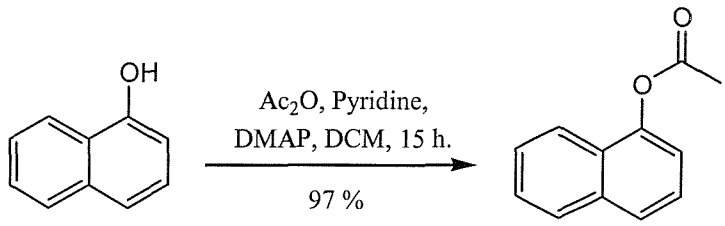
ν_{max}/cm^{-1} (neat)	2971 (w), 2860 (m), 1598 (m), 1491 (s), 1442 (s), 1327 (m), 1249 (s), 1111 (s), 1025 (s), 962 (m), 840 (m), 764 (s).
δ_H (300 MHz, $CDCl_3$)	7.39 (1H, dd, *J* 7.4 Hz, 1.5 Hz, Ar*H*), 7.25 (1H, td, *J* 8.1 Hz, 1.5 Hz, Ar*H*), 6.93 (1H, dt, *J* 1.1 Hz, 7.4 Hz, Ar*H*), 6.86 (1H, d, *J* 8.5 Hz, Ar*H*), 4.36 (2H, app t, *J* 5.0 Hz, OCH_2), 4.27 (2H, s, ArCH_2CS), 3.82 (3H, s, OCH_3), 3.73 (2H, app t, *J* 5.0 Hz, OCH_2), 3.59 (2H, app t, *J* 4.8 Hz, NCH_2), 3.41 (2H, app t, *J* 4.8 Hz, NCH_2) ppm.
δ_C (75.5 MHz, $CDCl_3$)	201.3 (0, *C*S), 155.9 (0, Ar), 128.7 (1, Ar), 128.5 (1, Ar), 124.2 (0, Ar), 121.1 (1, Ar), 110.5 (1, Ar), 66.5 (2, O*C*H_2), 66.4 (2, O*C*H_2), 55.6 (3, O*C*H_3), 50.8 (2, N*C*H_2), 50.3 (2, N*C*H_2), 43.6 (2, Ar*C*H_2CS) ppm.
LRMS (CI)	252 ([M+H]$^+$, 70 %), 222 (M-OCH_2+H]$^+$, 100 %), 165 ([M-N(CH_2CH_2)$_2$O]$^+$, 25 %), 88 ([Morpholine+H]$^+$, 75 %) amu.
λ_{max}/nm (ε_{max})	278 (5580).

M.P.	63 - 65 °C (petrol). Lit. 64 - 65 °C (petrol)[69].

Data for **228**:

ν_{max}/cm^{-1} (neat)	2968 (w), 2859 (m), 1644 (s), 1593 (m), 1514 (s), 1439 (s), 1268 (s), 1110 (s), 1013 (s), 952 (m), 861 (m), 778 (m).
δ_H (300 MHz, $CDCl_3$)	7.96 (1H, dd, *J* 7.7 Hz, 1.8 Hz, Ar*H*), 7.57 - 7.51 (1H, m, Ar*H*), 7.10 - 7.04 (1H, m, Ar*H*), 6.97 (1H, d, *J* 8.3 Hz, Ar*H*), 4.23 (2H, app t, *J* 5.0 Hz, OCH_2), 3.87 (2H, app t, *J* 5.1 Hz, OCH_2), 3.86 (3H, s, OCH_3), 3.77 - 3.71 (2H, m, NCH_2), 3.68 - 3.63 (2H, m, NCH_2) ppm.
δ_C (75.5 MHz, $CDCl_3$)	198.4 (0, *C*S), 186.7 (0, *C*O), 159.3 (0, Ar), 135.8 (1, Ar), 131.9 (1, Ar), 124.4 (0, Ar), 121.6 (1, Ar), 112.7 (1, Ar), 66.4 (2, O*C*H$_2$), 66.1 (2, O*C*H$_2$), 56.3 (3, O*C*H$_3$), 51.9 (2, N*C*H$_2$), 47.1 (2, N*C*H$_2$) ppm.
LRMS (APCI +ve)	266 ([M+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	260 (3770).
CHN	Found: C, 58.50; H, 5.68; N, 5.22. $C_{13}H_{15}NO_3S$ requires C, 58.85; H, 5.70; N, 5.28.
M.P.	137 - 139 °C (petrol / diethyl ether).

Acetic acid naphthalen-1-yl ester **238**



237
$C_{10}H_8O$
Mol. Wt.: 144

238
$C_{12}H_{10}O_2$
Mol. Wt.: 186

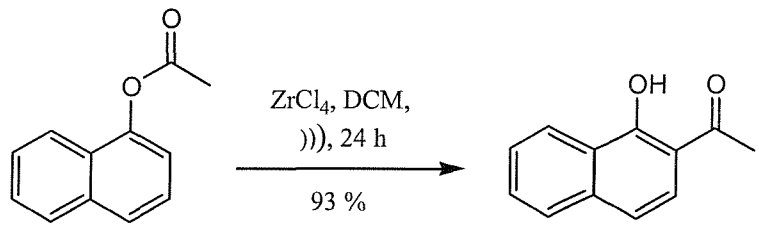
Following the procedure of Cullinane and Edwards[61]. 1-Naphthol (14.4 g, 0.10 mol), acetic anhydride (21.6 g, 20.0 mL, 0.21 mol), pyridine (14.8 g, 15.0 mL, 0.19 mol), N,N-dimethylaminopyridine (DMAP) (0.3 g, 2.3 mmol) and dichloromethane (160 mL) were mixed together and stirred for 15 hours. The resulting cherry red reaction mixture was washed successively with dilute HCl (aq., 2 x 100 mL), water (2 x 60 mL) and brine (100 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a red oil. Column chromatography (silica, 0 - 30 % diethyl ether in petrol) afforded **238** as a red oil (18.0 g, 0.097 mol, 97 %).

Spectral data was consistent with literature values[70].

Data for **238**:

ν_{max}/cm^{-1} (neat)	3060 (m), 1755 (s), 1597 (m), 1509 (m), 1367 (s), 1193 (s), 1076 (m), 1012 (m), 915 (m), 867 (w), 795 (m), 769 (s).
δ_H (300 MHz, $CDCl_3$)	7.97 - 7.91 (2H, m, Ar*H*), 7.80 (1H, d, *J* 8.1 Hz, Ar*H*), 7.61 - 7.49 (3H, m, Ar*H*), 7.32 (1H, d, *J* 7.5 Hz, Ar*H*), 2.50 (3H, s, C*H*$_3$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	169.8 (0, *C*O), 146.8 (0, Ar), 134.9 (0, Ar), 128.3 (1, Ar), 127.0 (0, Ar), 126.7 (1, 2 x Ar), 126.3 (1, Ar), 125.6 (1, Ar), 121.4 (1, Ar), 118.3 (1, Ar), 21.2 (3, *C*H$_3$) ppm.
LRMS (CI)	204 ([M+NH_4]$^+$, 100 %), 186 (M$^+$, 5 %), 144 ([M-CH_3CO+H]$^+$, 75 %) amu.
λ_{max}/nm (ε_{max})	266 (4200).

1-(1-Hydroxy-naphthalen-2-yl)-ethanone **239**



238
$C_{12}H_{10}O_2$
Mol. Wt.: 186

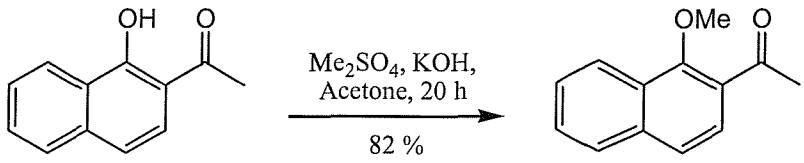
239
$C_{12}H_{10}O_2$
Mol. Wt.: 186

Following the procedure of Harrowven and Dainty[62]. **238** (16.8 g, 0.09 mol) was dissolved in dichloromethane (200 mL) and zirconium tetrachloride (42.0 g, 0.18 mol) was added. The mixture was then sonicated for 24 hours, and after this period the resulting brown suspension was poured onto ice / water (500 mL) and extracted with dichloromethane (4 x 80 mL). The combined organic phases were washed with water (50 mL) and brine (100 mL), dried, filtered and concentrated *in vacuo* to a brown oil. Column chromatography (silica, 0 - 20 % diethyl ether in petrol) afforded **239** as a yellow solid (15.6 g, 0.084 mol, 93 %). A sample was recrystallised from ethanol to give white flakes.
Spectral and physical data were consistent with literature values[71].

Data for **239:**

ν_{max}/cm^{-1} (neat)	2971 (w), 2850 (w), 1644 (s), 1595 (s), 1469 (m), 1362 (w), 1272 (s), 1112 (m), 1019 (m), 953 (m), 858 (s), 797 (m).
δ_H (300 MHz, $CDCl_3$)	14.03 (1H, s, O*H*), 8.47 (1H, d, *J* 8.3 Hz, Ar*H*), 7.76 (1H, d, *J* 8.1 Hz, Ar*H*), 7.66-7.60 (2H, m, Ar*H*), 7.54 (1H, app. t, *J* 7.3 Hz, Ar*H*), 7.26 (1H, d, *J* 8.8 Hz, Ar*H*), 2.68 (3H, s, CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	204.5 (0, *C*O), 162.6 (0, Ar), 137.5 (0, Ar), 130.2 (1, Ar), 127.6 (1, Ar), 126.1 (1, Ar), 125.4 (0, Ar), 125.1 (1, Ar), 124.6 (1, Ar), 118.5 (1, Ar), 113.4 (0, Ar), 27.0 (3, *C*H_3) ppm.
LRMS (CI)	187 ([M+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	368 (3440), 258 (18,600).
M.P.	101 - 102 °C (ethanol). Lit: 102 °C (no solvent reported)[72].

1-(1-Methoxy-naphthalen-2-yl)-ethanone **229**



239

$C_{12}H_{10}O_2$
Mol. Wt.: 186

229

$C_{13}H_{12}O_2$
Mol. Wt.: 200

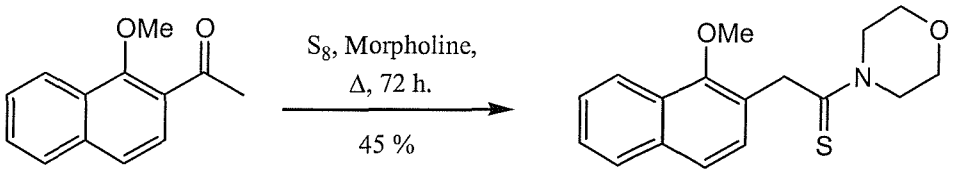
Following a modified procedure of Jurd[63]. To a stirred solution of **239** (15.2 g, 0.082 mol) and dimethyl sulfate (11.4 g, 0.09 mol) in acetone (300 mL) was added powdered potassium hydroxide (6.8 g, 0.12 mol). The reaction was stirred at room temperature for 20 hours, and then partitioned between water (50 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL), then the organic phases were combined, extracted with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* at room temperature to a yellow solid. Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) gave the product **229** as a yellow solid (13.4 g, 0.067 mol, 82 %). A sample was recrystallised from ethanol to give a white powder.

Spectral and physical data were consistent with literature values[73].

Data for **229**:

ν_{max}/cm^{-1} (neat)	2969 (w), 2851 (w), 1662 (s), 1620 (m), 1566 (m), 1445 (m), 1360 (s), 1242 (s), 1070 (m), 1112 (s), 825 (s), 757 (s).
δ_H (300 MHz, $CDCl_3$)	8.26 - 8.22 (1H, m, Ar*H*), 7.89 - 7.85 (1H, m, Ar*H*), 7.77 - 7.74 (1H, m, Ar*H*), 7.65 - 7.57 (3H, m, Ar*H*), 4.02 (3H, s, OCH_3), 2.79 (3H, s, $COCH_3$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	200.3 (0, *C*O), 174.0 (0, Ar), 157.7 (0, Ar), 137.1 (0, Ar), 128.4 (1, Ar), 128.2 (1, Ar), 128.0 (0, Ar), 126.8 (1, Ar), 125.7 (1, Ar), 124.3 (1, Ar), 123.5 (1, Ar), 64.0 (3, OCH_3), 31.0 (3, $COCH_3$) ppm.
LRMS (CI)	201 ($[M+H]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	334 (1250), 284 (4100), 249 (19, 650), 244 (19, 850).
M.P.	49 - 50 °C (ethanol). Lit. 50 °C (ethanol)[73].

2-(1-Methoxy-naphthalen-2-yl)-1-morpholin-4-yl-ethanethione **230**



229

$C_{13}H_{12}O_2$
Mol. Wt.: 200

230

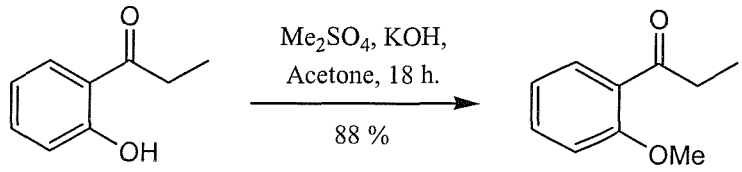
$C_{17}H_{19}O_2NS$
Mol. Wt.: 301

Following a modified procedure of Carmack and Spielman[39]. Acetonaphthone **229** (8.20 g, 0.041 mol), sulfur (2.00 g, 63.5 g-atom) and morpholine (5.60 g, 0.064 mol) were mixed together and heated to 100 °C with stirring for 72 hours. On cooling, the now dark red mixture solidified. Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) yielded thiomorpholide **230** as a dark-coloured solid (5.55 g, 0.018 mol, 45 %). A sample was recrystallised from ethanol / water to give a pale yellow powder.

Data for **230**:

ν_{max}/cm^{-1} (neat)	2969 (w), 2860 (w), 1596 (w), 1571 (w), 1491 (s), 1371 (m), 1307 (m), 1276 (m), 1110 (s), 1032 (s), 814 (s), 741 (m).
δ_H (300 MHz, $CDCl_3$)	8.11 - 7.39 (6H, m, Ar*H*), 4.55 (2H, s, ArCH_2CS), 4.31 (2H, app t, *J* 5.3 Hz, OCH_2), 3.89 (3H, s, OCH_3), 3.72 - 3.55 (4H, m, OCH_2 & NCH_2), 3.23 (2H, app t, *J* 5.2 Hz, NCH_2) ppm.
δ_C (75.5 MHz, $CDCl_3$)	200.2 (0, *C*S), 152.2 (0, Ar), 134.4 (0, Ar), 128.3 (1, Ar), 127.9 (0, Ar), 126.5 (1, Ar), 126.4 (1, Ar), 126.1 (1, Ar), 124.9 (1, Ar), 124.4 (0, Ar), 122.1 (1, Ar), 66.5 (2, O*C*H$_2$), 66.3 (2, O*C*H$_2$), 62.4 (3, O*C*H$_3$), 50.8 (2, N*C*H$_2$), 50.5 (2, N*C*H$_2$), 44.2 (2, Ar*C*H$_2$CS) ppm.
LRMS (CI)	302 ([M+H]$^+$, 5 %), 270 ([M-OCH$_3$]$^+$, 10 %), 88 ([O(CH$_2$CH$_2$)$_2$NH+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	280 (14 300).
M.P.	120 - 122 °C (ethanol / water).
CHN	Found: C, 68.12; H, 6.19; N, 4.53. $C_{17}H_{19}NO_2S$ requires C, 67.78; H, 6.31; N, 4.65.

1-(2-Methoxy-phenyl)-propan-1-one **231**



280

$C_9H_{10}O_2$
Mol. Wt.: 150

231

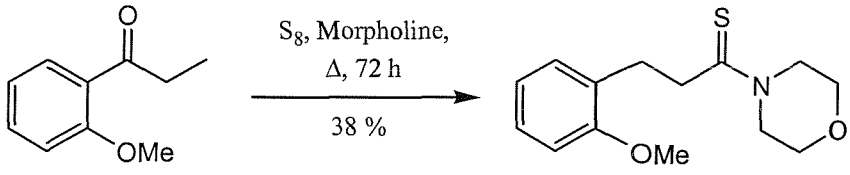
$C_{10}H_{12}O_2$
Mol. Wt.: 164

A modified procedure of Jurd[63]. To a stirred solution of 2'-hydroxypropiophenone (5.00 g, 0.033 mol) and dimethyl sulfate (5.04 g, 0.034 mol) in acetone (100 mL) was added powdered potassium hydroxide (2.80 g, 0.051 mol). The reaction mixture was stirred at room temperature for 18 hours, then partitioned between brine (100 mL) and diethyl ether (100 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* at ambient temperature to a yellow oil. This was purified by chromatography (silica, petrol) to give **231** as a yellow oil (4.83 g, 0.029 mol, 88 %).
Data was consistent with literature values[74].

Data for **231**:

ν_{max}/cm^{-1} (neat)	2973 (w), 2939 (w), 1673 (s), 1596 (s), 1484 (s), 1436 (s), 1349 (m), 1242 (s), 1162 (m), 1020 (m), 805 (m), 754 (s).
δ_H (300MHz, $CDCl_3$)	7.69 (1H, dd, *J* 7.5 Hz, 2.0 Hz, Ar*H*), 7.46 - 7.39 (1H, ddd, *J* 8.3 Hz, 7.4 Hz, 1.9 Hz, Ar*H*), 7.01 - 6.92 (2H, m, Ar*H*), 3.88 (3H, s, OCH_3), 2.98 (2H, q, *J* 7.3 Hz, CH_2CH_3), 1.20 (3H, t, *J* 7.3 Hz, CH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	203.6 (0, *C*O), 158.6 (0, Ar), 133.3 (1, Ar), 130.3 (1, Ar), 128.6 (0, Ar), 120.7 (1, Ar), 111.7 (1, Ar), 55.6 (3, OCH_3), 37.1 (2, CH_2CH_3), 8.6 (3, CH_2CH_3) ppm.
LRMS (CI)	165 ($[M+H]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	302 (5100), 244 (2310).

3-(2-Methoxy-phenyl)-1-morpholin-4-yl-propane-1-thione **232**



231

$C_{10}H_{12}O_2$
Mol. Wt.: 164

232

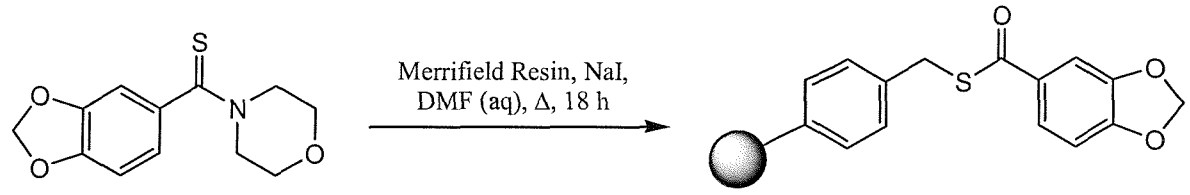
$C_{14}H_{19}O_2NS$
Mol. Wt.: 265

Following a modified procedure of Carmack and Spielman[39]. 2'-Methoxypropiophenone **231** (4.83 g, 29.5 mmol), morpholine (3.79 g, 43.5 mmol) and sulfur (1.39 g, 43.5 g-atom) were mixed together, stirred and heated at 90 °C for 72 hours. After this time the reaction was allowed to cool to ambient temperature. The dark-coloured solid that formed on standing was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to give the thiomorpholide **232** as a yellow solid (2.98 g, 11.2 mmol, 38 %). A sample was recrystallised from petrol / diethyl ether to give colourless plates.

Data for **232**:

ν_{max}/cm^{-1} (neat)	2991 (w), 2900 (w), 1599 (m), 1490 (s), 1424 (s), 1279 (s), 1239 (s), 1091 (s), 1036 (m), 987 (s), 877 (m), 747 (m).
δ_H (300MHz, $CDCl_3$)	7.32 - 7.19 (2H, m, Ar*H*), 6.96 - 6.82 (2H, m, Ar*H*), 4.33 (2H, t, *J* 4.6 Hz, CH_2CS), 3.85 (3H, s, OCH_3), 3.73 (4H, t, *J* 4.6 Hz, 2 x OCH_2), 3.49 (2H, t, *J* 4.6 Hz, CH_2CH_2CS), 3.24 - 3.01 (4H, m, 2 x NCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	203.4 (0, *C*S), 157.5 (0, Ar), 130.7 (1, Ar), 128.4 (0, Ar), 128.2 (1, Ar), 121.0 (1, Ar), 110.3 (1, Ar), 66.6 (2, OCH_2CH_2), 66.5 (2, OCH_2CH_2), 55.4 (3, OCH_3), 50.3 (2, NCH_2CH_2), 50.1 (2, NCH_2CH_2), 43.3 (2, CH_2CS), 31.1 (ArCH_2CH_2CS) ppm.
LRMS (CI)	266 ($[M+H]^+$, 15 %), 179 ($[M-N(CH_2CH_2)_2O]^+$, 20 %), 88 ($[H_2N(CH_2CH_2)_2O]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	277 (13 600).
M.P.	94 - 96 °C (petrol / diethyl ether).
CHN	Found: C, 62.99; H, 7.34; N, 5.24. $C_{14}H_{19}NO_2S$ requires C, 63.39; H, 7.22; N, 5.28.

Preparation of Resin-Bound Thioester **240**



216

$C_{12}H_{13}O_3NS$
Mol. Wt.: 251

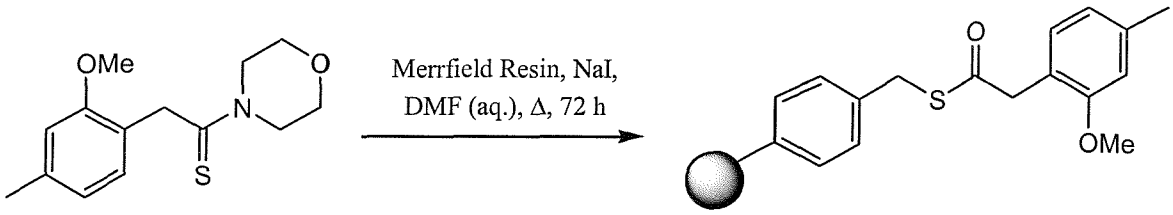
240

Merrifield resin (3.00 g, 3.72 mmol active sites) was swollen in DMF (6 mL) for 30 minutes. After this time, a pre-formed solution of **216** (3.73 g, 14.9 mmol) and sodium iodide (5.58 g, 37.2 mmol) in DMF (18 mL) with water (4 mL) was added. The reaction was heated at 100 °C for 48 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **240**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2914 (w), 2849 (w), 1658 (m), 1600 (w), 1485 (m), 1439 (m), 1249 (m), 1037 (m), 847 (m), 737 (m), 696 (s).

Preparation of Resin-Bound Thioester **241**



218

$C_{14}H_{19}O_2NS$
Mol. Wt.: 265

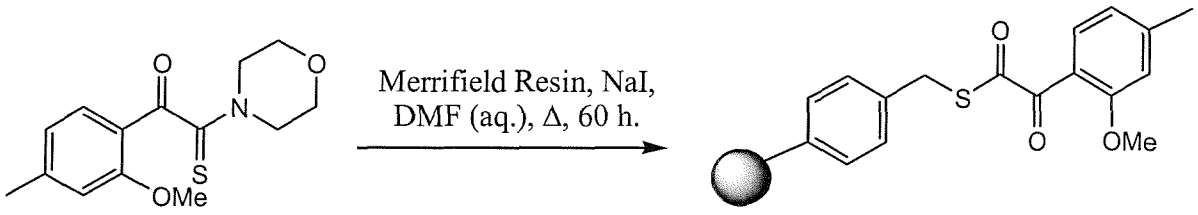
241

Merrifield resin (1.00 g, 1.48 mmol active sites) was swollen in DMF (3 mL) for 30 minutes. After this time, a pre-formed solution of **218** (1.20 g, 4.48 mmol) and sodium iodide (2.24 g, 14.8 mmol) in DMF (8 mL) with water (2 mL) was added. The reaction was heated at 100 °C for 72 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **241**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2919 (m), 2848 (w), 1685 (m), 1601 (w), 1583 (w), 1508 (w), 1493 (m), 1452 (m), 1269 (w), 1154 (w), 1119 (w), 757 (m), 696 (s).

Preparation of Resin-Bound Thioester **242**



219

$C_{14}H_{17}O_3NS$
Mol. Wt.: 279

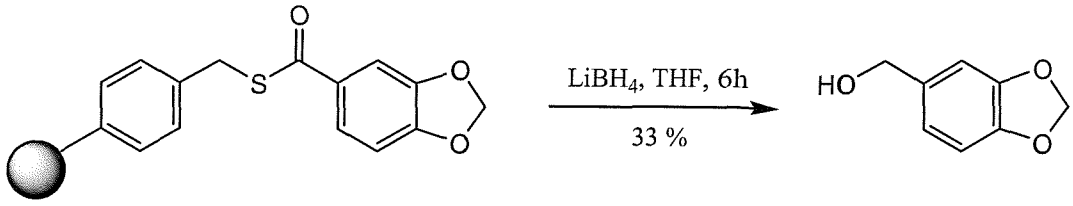
242

Merrifield resin (0.50 g, 0.75 mmol active sites) was swollen in DMF (3 mL) for 30 minutes. After this time, a pre-formed solution of **219** (0.84 g, 3.00 mmol) and sodium iodide (1.12 g, 7.5 mmol) in DMF (8 mL) with water (2 mL) was added. The reaction was heated at 100 °C for 60 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **242**:

ν_{max}/cm^{-1} (solid phase) 3057 (w), 3026 (m), 2919 (m), 2848 (w), 1725 (w), 1676 (w), 1602 (m), 1492 (s), 1450 (s), 1152 (w), 1027 (m), 905 (w).

Benzo[1,3]dioxol-5-yl-methanol **243**



240 **243**

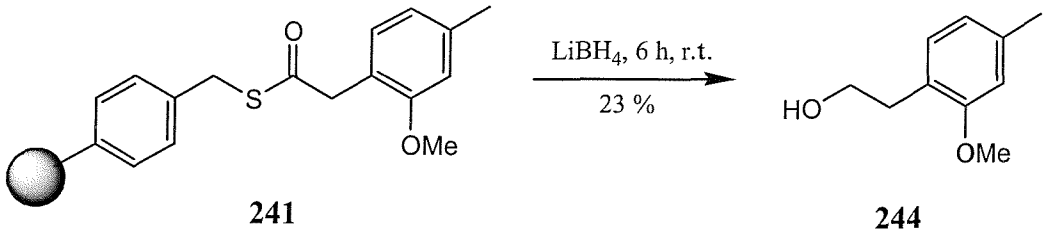
$C_8H_8O_3$
Mol. Wt.: 152

Adapted from a reported procedure by Kobayashi[31] *et al.* **240** (0.40 g, 0.60 mmol) was pre-swollen in THF (2 mL) for 10 minutes, before lithium borohydride (2M solution in THF, 1.5 mL, 3.0 mmol) was added *via* syringe. The reaction was then left to stand for 6 hours at room temperature. After this time, the reaction was worked up by the slow addition of 10 % HCl (aq., 10 mL). The reaction mixture was then filtered to trap the beads, and after removal of the filtrate the beads were washed with water (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL) before drying *in vacuo*. The filtrate was extracted with diethyl ether (3 x 25 mL), and the organic portions combined and dried ($MgSO_4$). The solution was then concentrated *in vacuo,* and purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield **243** as a colourless solid (0.030 g, 0.20 mmol, 33 %).
Data was consistent with literature values[75].

Data for **243**:

ν_{max}/cm^{-1} (neat)	3500 - 3000 (bs), 2910 (w), 1502 (m), 1445 (m), 1372 (w), 1249 (s), 1042 (m), 1015 (m), 921 (w), 805 (m), 766 (w).
δ_H (300 MHz, $CDCl_3$)	6.87 (1H, s, Ar*H*), 6.78 (2H, m, Ar*H*), 5.95 (2H, s, OCH_2O), 4.58 (2H, s, $ArCH_2OH$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	148.0 (0, Ar), 147.2 (0, Ar), 135.0 (0, Ar), 120.7 (1, Ar), 108.4 (1, Ar), 108.1 (1, Ar), 101.2 (2, OCH_2O), 65.4 (2, CH_2OH) ppm.
LRMS (APCI +ve)	152 ($[M]^+$, 40 %), 135 ($[M\text{-}OH]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	284 (3310), 234 (3580).
M.P.	53 - 55 °C (ethanol). Lit. 53 - 55 °C (ethanol)[76].

2-(2-Methoxy-4-methyl-phenyl)-ethanol **244**



241

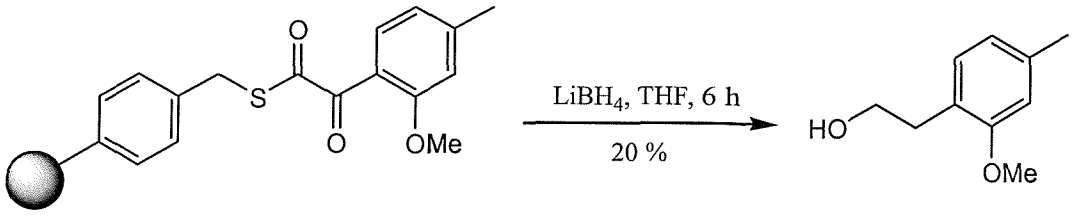
244
$C_{10}H_{14}O_2$
Mol. Wt.: 166

Adapted from a reported procedure by Kobayashi *et al.*[31]. **241** (0.80 g, 0.96 mmol) was swollen in THF (5 mL) for 10 minutes, then lithium borohydride (2M solution in THF, 2.4 mL, 4.8 mmol) was added *via* syringe. The reaction was allowed to stand for 6 hours, then worked up with deionised water (10 mL). The beads were collected by filtration, and washed with 1:1 THF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL) before being dried *in vacuo*. Water (10 mL) was added to the filtered reaction mixture, which was then extracted with diethyl ether (3 x 30 mL). The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo* to a pale yellow oil. The crude product was purified by chromatography (silica, 0 - 40 % diethyl ether in petrol) to yield **244** as a colourless oil (0.037 g, 0.22 mmol, 23 %).

Data for **244**:

ν_{max}/cm^{-1} (neat)	3600-3100 (bs), 2933 (m), 2865 (w), 1613 (m), 1582 (m), 1508 (m), 1464 (m), 1263 (s), 1126 (s), 1040 (s), 925 (w).
δ_H (300 MHz, $CDCl_3$)	7.05 (1H, d, *J* 7.5 Hz, Ar*H*), 6.74 (1H, d, *J* 7.5 Hz, Ar*H*), 6.71 (1H, s, Ar*H*), 3.83 (3H, s, OCH_3), 3.82 (2H, t, *J* 6.4 Hz, CH_2OH), 2.88 (2H, t, *J* 6.4 Hz, ArCH_2CH_2OH), 2.35 (3H, s, ArCH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	157.6 (0, Ar), 137.9 (0, Ar), 130.8 (1, Ar), 124.0 (0, Ar), 121.3 (1, Ar), 111.6 (1, Ar), 63.2 (2, CH_2OH), 55.4 (3, OCH_3), 33.9 (2, ArCH_2), 21.6 (3, ArCH_3) ppm.
LRMS (APCI +ve):	166 ([M^+], 55 %) amu.
λ_{max}/nm (ε_{max})	276 (2860).

2-(2-Methoxy-4-methyl-phenyl)-ethanol **244**



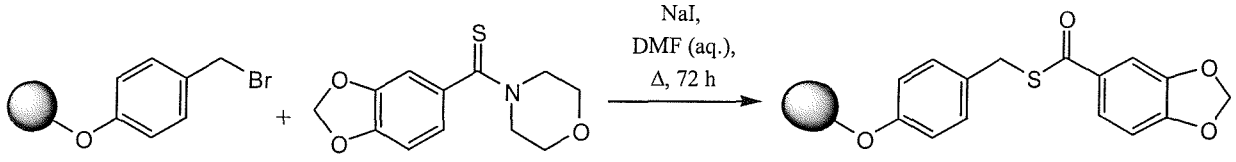
242 **244**

$C_{10}H_{14}O_2$
Mol. Wt.: 166

Adapted from a reported procedure by Kobayashi *et al.*[31]. **242** (0.60 g, 0.61 mmol) was swollen in THF (5 mL) for 10 minutes, then lithium borohydride (2M solution in THF, 1.5 mL, 3 mmol) was added *via* syringe. The reaction was allowed to stand for 6 hours, then worked up with deionised water (10 mL). The beads were collected by filtration, and washed with 1:1 THF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL) before being dried *in vacuo*. Water (10 mL) was added to the filtered reaction mixture, which was then extracted with diethyl ether (3 x 30 mL). The organic portions were combined, dried ($MgSO_4$), and concentrated *in vacuo* to a pale yellow oil. The crude product was purified by chromatography (silica, 0 - 40 % diethyl ether in petrol) to yield **244** as a colourless oil (0.020 g, 0.12 mmol, 20 %).

^{1}H n.m.r. and LRMS (CI) spectra were in accordance with those reported for this compound earlier in this report.

Preparation of Resin-Bound Thioester **245**



216

$C_{12}H_{13}O_3NS$
Mol. Wt.: 251

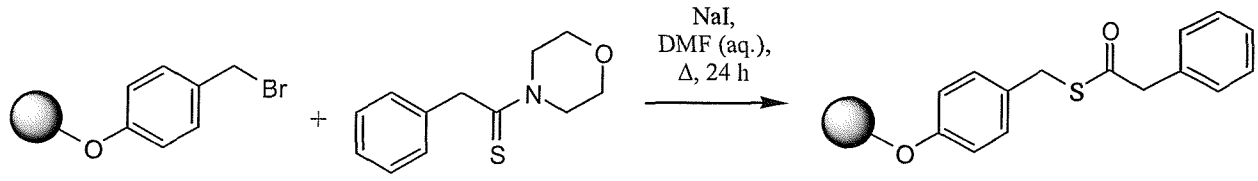
245

Bromo-Wang resin (0.50 mmol g^{-1} active sites, 3.10 g, 1.55 mmol) was swollen in DMF (6 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **216** (1.92 g, 7.75 mmol) and sodium iodide (2.29 g, 15.5 mmol) in 20 mL DMF with 3 mL water was added. The reaction was heated to 100 °C for 72 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF / H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **245**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2917 (w), 1657 (w), 1602 (w), 1491 (m), 1251 (m), 1032 (m), 848 (w), 749 (w), 696 (s).

Preparation of Resin-Bound Thioester **246**



221

$C_{12}H_{15}ONS$
Mol. Wt.: 221

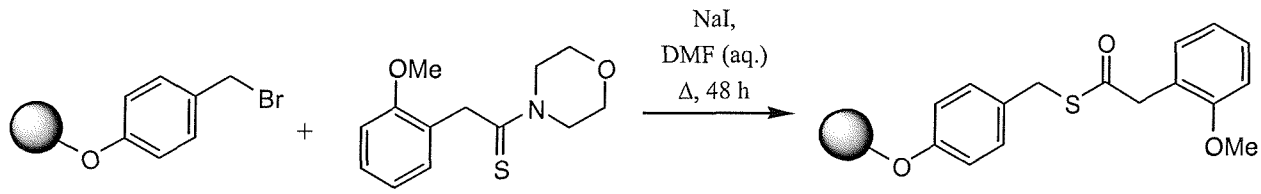
246

Bromo-Wang resin (0.50 mmol g^{-1} active sites, 2.00 g, 1.00 mmol) was swollen in DMF (4 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **221** (1.11 g, 5.00 mmol) and sodium iodide (1.50 g, 10.0 mmol) in DMF (10 mL) with water (2 mL) was added. The reaction was heated to 100 °C for 24 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **246**:

ν_{max}/cm^{-1} (solid phase) 3025 (m), 2921 (m), 2852 (w), 1687 (m), 1601 (m), 1510 (m), 1492 (m), 1450 (m), 1226 (w), 1114 (m), 1026 (m), 756 (w).

Preparation of Resin-Bound Thioester **252**



227

$C_{13}H_{17}O_2NS$
Mol. Wt.: 251

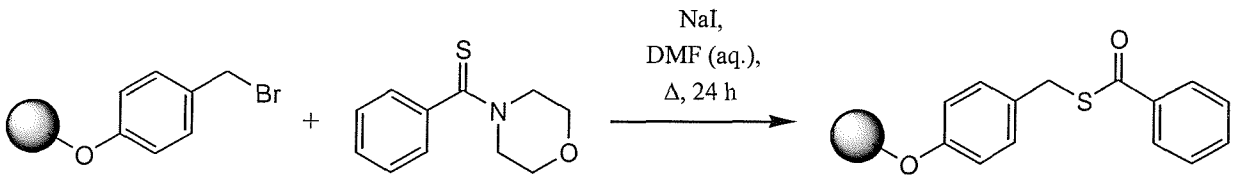
252

Bromo-Wang resin (0.50 mmol g^{-1} active sites, 1.00 g, 0.50 mmol) was swollen in DMF (3 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **227** (0.62 g, 2.48 mmol) and sodium iodide (0.74 g, 5.00 mmol) in DMF (8 mL) with water (2 mL) was added. The reaction was heated to 100 °C for 48 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **252**:

ν_{max}/cm^{-1} (solid phase) 3024 (w), 2919 (m), 1680 (m), 1602 (m), 1509 (m), 1493 (m), 1451 (w), 1244 (m), 1174 (m), 1014 (m), 824 (m), 752 (s).

Preparation of Resin-Bound Thioester **247**



223

$C_{11}H_{13}ONS$

Mol. Wt.: 207

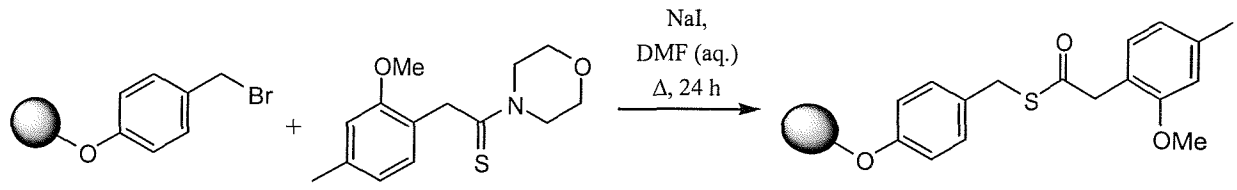
247

Bromo-Wang resin (0.50 mmol g^{-1} active sites, 1.00 g, 0.50 mmol) was swollen in DMF (3 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **223** (0.52 g, 2.50 mmol) and sodium iodide (0.74 g, 5.00 mmol) in DMF (8 mL) with water (2 mL) was added. The reaction was heated to 100 °C for 24 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **247**:

ν_{max}/cm^{-1} (solid phase) 3024 (w), 2919 (m), 2848 (m), 1658 (m), 1601 (m), 1510 (m), 1492 (m), 1450 (m), 1206 (m), 1174 (m), 1026 (w), 910 (m), 750 (m), 696 (s).

Preparation of Resin-Bound Thioester **248**



218

$C_{14}H_{19}O_2NS$

Mol. Wt.: 265

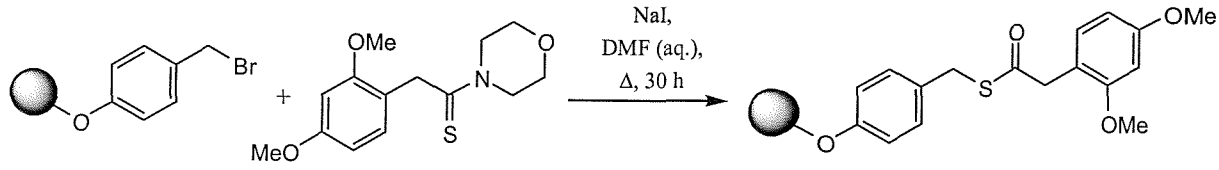
248

Bromo-Wang resin (0.50 mmol g^{-1} active sites, 1.00 g, 0.50 mmol) was swollen in DMF (3 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **218** (0.60 g, 2.26 mmol) and sodium iodide (0.74 g, 5.00 mmol) in DMF (8 mL) with water (2 mL) was added. The reaction was heated to 100 °C for 24 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **248**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 2849 (w), 1687 (w), 1601 (w), 1510 (m), 1492 (m), 1450 (m), 1226 (w), 1114 (w), 1026 (w), 906 (w), 750 (m), 696 (s).

Preparation of Resin-Bound Thioester **250**



249

$C_{14}H_{19}O_3NS$
Mol. Wt.: 281

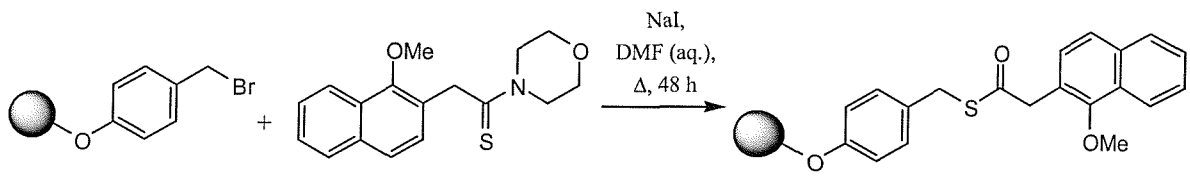
250

Bromo-Wang resin (1.1 mmol g^{-1} active sites, 2.00 g, 2.2 mmol) was swollen in DMF (4 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **249** (2.47 g, 8.8 mmol) (sample kindly supplied by M. Lucas) and sodium iodide (1.35 g, 9.0 mmol) in DMF (20 mL) with water (3 mL) was added. The reaction was heated to 100 °C for 30 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **250**:

ν_{max}/cm^{-1} (solid phase) 3024 (w), 2920 (m), 2845 (w), 1681 (m), 1601 (m), 1509 (s), 1492 (m), 1451 (m), 1209 (s), 1156 (m), 1030 (s), 830 (m), 735 (m).

Preparation of Resin-Bound Thioester **253**



230

$C_{17}H_{19}O_2NS$
Mol. Wt.: 301

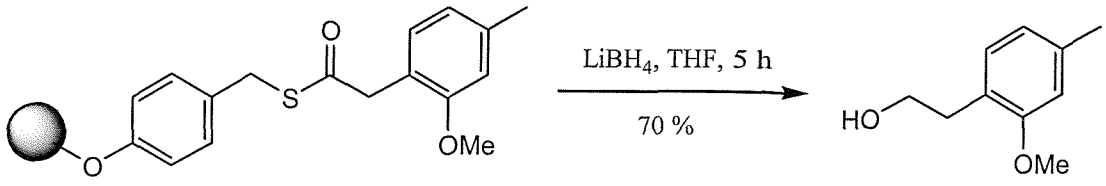
253

Bromo-Wang resin (1.1 mmol g^{-1} active sites, 0.80 g, 0.88 mmol) was swollen in DMF (3 mL) for 30 minutes. After this time, a pre-formed solution of thioamide **230** (0.96 g, 3.2 mmol) and sodium iodide (0.66 g, 4.4 mmol) in DMF (12 mL) with water (2 mL) was added. The reaction was heated to 100 °C for 48 hours, then allowed to cool. The beads were isolated by filtration, washed with 1:1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*.

Data for **253**:

ν_{max}/cm^{-1} (solid phase) 3024 (w), 2920 (m), 2844 (w), 1681 (m), 1602 (m), 1509 (s), 1492 (m), 1451 (s), 1221 (s), 1010 (m), 826 (m), 734 (s).

2-(2-Methoxy-4-methyl-phenyl)-ethanol **244**



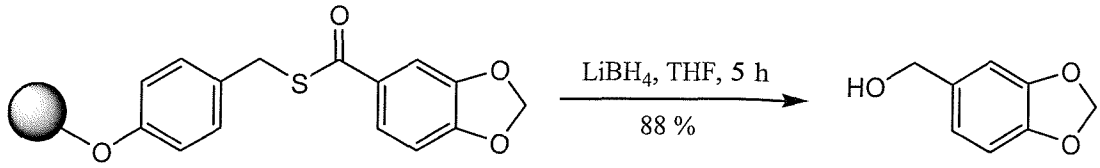
248 **244**

$C_{10}H_{14}O_2$
Mol. Wt.: 166

Adapted from a reported procedure by Kobayashi *et al.*[31]. **248** (0.64 g, 0.30 mmol) was swollen in THF (3 mL) for 20 minutes, then THF (6 mL) and lithium borohydride (2M solution in THF, 0.8 mL, 1.6 mmol) were added. The reaction was allowed to stand at room temperature, with occasional agitation, for 5 hours before work-up with 2M HCl (aq., 10 mL). The beads were then collected by filtration, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with water (20 mL) then brine (20 mL), and dried ($MgSO_4$) before concentration *in vacuo*. The resin beads were washed with 1:1 THF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL) then dried *in vacuo*. Purification of the crude product by chromatography (silica, 0 - 30 % diethyl ether in petrol) gave alcohol **244** as a colourless oil (0.035 g, 0.21 mmol, 70 %).

^{1}H n.m.r. and LRMS (CI) spectra were in accordance with those reported for this compound earlier in this report.

Benzo[1,3]dioxol-5-yl-methanol **243**



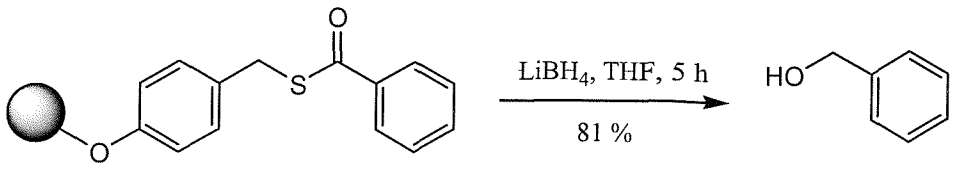
245 **243**

$C_8H_8O_3$
Mol. Wt.: 152

Adapted from a reported procedure by Kobayashi *et al.*[31]. **245** (1.00 g, 0.48 mmol) was swollen in THF (4 mL) for 20 minutes, then further THF (10 mL) was added, followed by lithium borohydride (2M solution in THF, 1.5 mL, 3.0 mmol). The reaction was allowed to stand at room temperature, with occasional agitation, for 5 hours before work-up with 2M HCl (aq., 10 mL). The reaction mixture was then filtered to trap the beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with water (20 mL) then brine (20 mL), and dried ($MgSO_4$) before concentration *in vacuo*. The resin beads were washed with 1 : 1 THF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo*. Purification of the crude product by chromatography (silica, 0 - 20 % diethyl ether in petrol) afforded alcohol **243** as a pale yellow solid (0.064 g, 0.42 mmol, 88 %).

^{1}H n.m.r. and LRMS (CI) spectra were in accordance with those reported for this compound earlier in this report.

Phenyl-methanol **254**



247 **254**

C_7H_8O
Mol. Wt.: 108

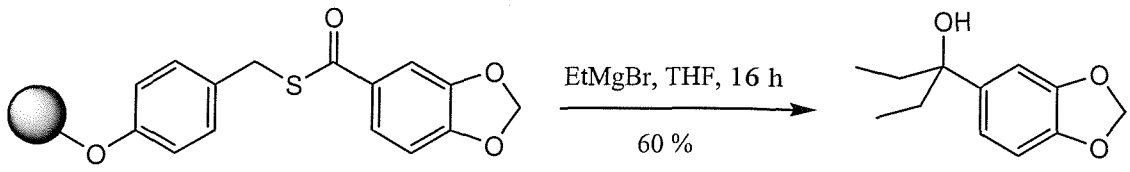
Adapted from a reported procedure by Kobayashi *et al.*[31]. **247** (0.97 g, 1.09 mmol) was swollen in THF (3 mL) for 20 minutes, then further THF (20 mL) was added, followed by lithium borohydride (2M solution in THF, 4.0 mL, 8.0 mmol). The reaction was allowed to stand at room temperature, with occasional agitation, for 5 hours before work-up with 2M HCl (aq., 10 mL). The reaction mixture was then filtered to trap the beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with water (20 mL), then brine (20 mL), and dried ($MgSO_4$) before concentration *in vacuo*. The resin beads were washed with 1:1 THF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and diethyl ether (3 x 10 mL) then dried *in vacuo*. Purification of the crude product by chromatography (silica, 0 - 20 % diethyl ether in petrol) afforded alcohol **254** as a colourless liquid (0.095 g, 0.88 mmol, 81 %).

Spectroscopic and physical data were in accordance with literature values[77].

Data for **254**:

ν_{max}/cm^{-1} (neat)	3500-3100 (bs), 3030 (m), 2872 (w), 1496 (m), 1454 (s), 1365 (w), 1208 (m), 1079 (w), 1037 (m), 1013 (s), 912 (w), 734 (s), 696 (s).
δ_H (300 MHz, $CDCl_3$)	7.43-7.29 (5H, m, Ar*H*), 4.68 (2H, s, ArCH_2), 2.12 (1H, s, O*H*) ppm.
δ_C (75.5 MHz, $CDCl_3$)	141.0 (0, Ar), 128.7 (1, 2 x Ar), 127.8 (1, Ar), 127.2 (1, 2 x Ar), 65.5 (2, ArCH_2) ppm.
LRMS (CI)	108 ($[M]^+$, 100 %), 91 $(M-OH]^+$, 65 %) amu.
λ_{max}/nm (ε_{max})	253 (4500).

3-Benzo[1,3]dioxol-5-yl-pentan-3-ol **255**



245 **255**

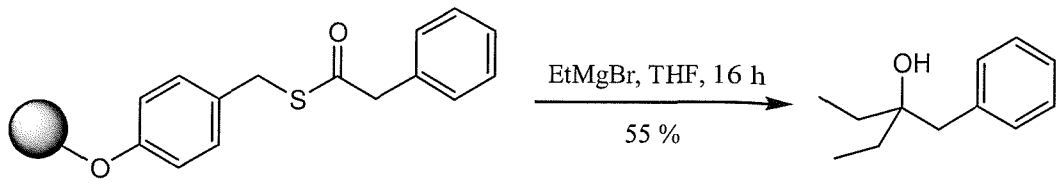
$C_{12}H_{16}O_3$
Mol. Wt.: 208

245 (1.40 g, 0.67 mmol) was pre-swollen for 20 minutes in THF (5 mL) before ethylmagnesium bromide (3M solution in diethyl ether, 6.0 mmol, 2.0 mL) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL), followed by 2M HCl (aq., 3 mL). The reaction mixture was filtered to trap the resin beads, then the filtrate was extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.99 g, 0.48 mmol, 71 %.) This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **255** as a colourless oil (0.083 g, 0.40 mmol, 60 %).

Data for **255**:

ν_{max}/cm^{-1} (neat)	3600-3250 (bs), 2968 (m), 2879 (m), 1605 (w), 1502 (m), 1486 (s), 1345 (w), 1234 (s), 1109 (m), 1038 (s), 928 (s), 858 (m), 691 (w).
δ_H (300 MHz, C_6D_6)	6.95 (1H, s, Ar*H*), 6.73-6.67 (2H, m, Ar*H*), 5.36 (2H, s, OCH_2O), 1.62-1.46 (4H, m, 2 x CH_2CH_3), 1.26 (1H, s, O*H*), 0.70 (6H, t, *J* 7.4 Hz, 2 x CH_2CH_3) ppm.
δ_C (75.5 MHz, C_6D_6)	148.2 (0, Ar), 146.5 (0, Ar), 140.6 (0, Ar), 119.1 (1, Ar), 108.0 (1, Ar), 107.1 (1, Ar), 101.0 (2, OCH_2O), 77.2 (0, *C*OH), 35.8 (2, 2 x CH_2CH_3), 8.1 (3, 2 x CH_3) ppm.
LRMS (CI)	208 ([M]$^+$, 5 %), 191 ([M-OH]$^+$, 100 %) amu.
HRMS	Found M$^+$: 208.1099. $C_{12}H_{16}O_3$ requires M$^+$: 208.1099.
λ_{max}/nm (ε_{max})	282 (10 600).

3-Benzyl-pentan-3-ol **256**



246 **256**

$C_{12}H_{18}O$
Mol. Wt.: 178

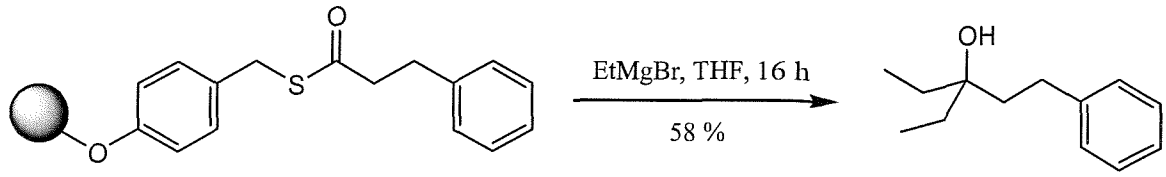
246 (0.90 g, 0.92 mmol) was pre-swollen for 20 minutes in THF (5 mL), before ethylmagnesium bromide (3M solution in diethyl ether, 2.0 mL, 6.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL), followed by 2M HCl (aq., 3 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.115 g, 0.65 mmol, 71 %). This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **256** as a colourless oil (0.091 g, 0.51 mmol, 55 %).

Spectroscopic and physical data were in accordance with literature values[78].

Data for **256**:

ν_{max}/cm^{-1} (neat)	3600 - 3300 (bs), 2966 (m), 2938 (m), 2879 (m), 1600 (w), 1495 (m), 1453 (s), 1377 (w), 1123 (m), 964 (s), 757 (s).
δ_H (300 MHz, C_6D_6)	7.09-7.00 (5H, m, Ar*H*), 2.50 (2H, s, ArCH_2), 1.23 (4H, q, *J* 5.6 Hz, 2 x CH_2CH$_3$), 0.73 (6H, t, *J* 5.6 Hz, 2 x CH_3) ppm.
δ_C (75.5 MHz, C_6D_6)	138.6 (0, Ar), 131.3 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.7 (1, Ar), 74.6 (1, *C*OH), 45.5 (2, Ar*C*H$_2$), 31.3 (2, 2 x *C*H$_2$CH$_3$), 8.4 (3, 2 x *C*H$_3$) ppm.
LRMS (CI)	196 ([M+NH$_4$]$^+$, 40 %), 178 ([M-H$_2$O+NH$_4$]$^+$, 30 %), 161 ([M-OH]$^+$, 70 %), 91 ([ArCH$_2$]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	259 (5100).

3-Ethyl-1-phenyl-pentan-3-ol **257**



251 **257**

$C_{13}H_{20}O$
Mol. Wt.: 192

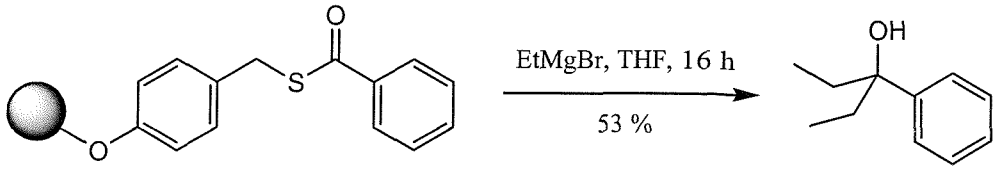
251 (0.90 g, 0.89 mmol) was pre-swollen for 20 minutes in THF (5 mL), before ethylmagnesium bromide (3M solution in diethyl ether, 2.0 mL, 6.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL), followed by 2M HCl (aq., 3 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed brine, (30 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.127 g, 0.66 mmol, 73 %). This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **257** as a colourless oil (0.10 g, 0.52 mmol, 58 %).

Spectroscopic and physical data were in accordance with literature values[79].

Data for **257**:

ν_{max}/cm^{-1} (neat)	3450 - 3120 (br s), 3026 (w), 2964 (s), 2937 (s), 1602 (w), 1453 (s), 1258 (w), 1121 (m), 1031 (m), 973 (m), 923 (s), 696 (s).
δ_H (300 MHz, C_6D_6)	7.21 - 7.04 (5H, m, Ar*H*), 2.55 (2H, t, *J* 7.9 Hz, ArCH_2), 1.60 (2H, t, *J* 8.2 Hz, ArCH$_2$CH_2), 1.34 (4H, q, *J* 7.7 Hz, 2 x CH_2CH$_3$), 0.79 (4H, t, *J* 7.4 Hz, 2 x CH$_2$CH_3) ppm.
δ_C (75.5 MHz, C_6D_6)	143.4 (0, Ar), 129.0 (1, 2 x Ar), 128.8 (1, 2 x Ar), 126.1 (1, Ar), 74.2 (0, *C*OH), 41.0 (2, ArCH$_2$*C*H$_2$), 31.3 (2, 2 x *C*H$_2$CH$_3$), 30.5 (2, Ar*C*H$_2$), 8.2 (3, 2 x *C*H$_3$) ppm.
LRMS (CI)	210 ([M+NH$_4$]$^+$, 60 %), 192 ([M-H$_2$O+NH$_4$]$^+$, 60 %), 174 ([M-H$_2$O]$^+$, 90 %), 163 ([M-CH$_2$CH$_3$]$^+$, 80 %), 145 ([M-CH$_2$CH$_3$-H$_2$O]$^+$, 90 %), 105 ([PhCH$_2$CH$_2$]$^+$, 65 %), 91 ([PhCH$_2$]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	258 (4200).

3-Phenyl-pentan-3-ol **258**



247 **258**

$C_{11}H_{16}O$
Mol. Wt.: 164

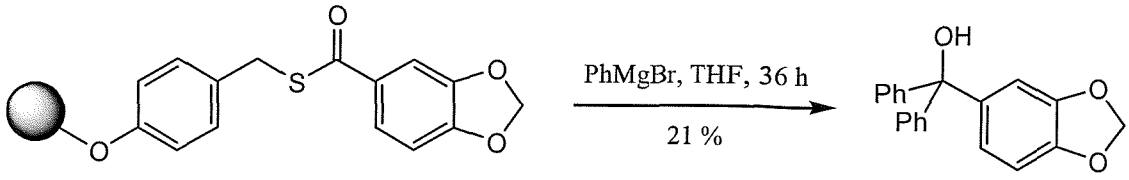
247 (0.90 g, 1.00 mmol) was pre-swollen for 20 minutes in THF (5 mL), before ethylmagnesium bromide (3M solution in diethyl ether, 2.0 mL, 6.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL), followed by 2M HCl (aq., 3 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.119 g, 0.73 mmol, 73 %). This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **258** as a colourless oil (0.087 g, 0.53 mmol, 53 %).

Spectroscopic and physical data were in accordance with literature values[78].

Data for **258**:

ν_{max}/cm^{-1} (neat)	3500 - 3200 (bs), 2967 (s), 2934 (m), 1602 (w), 1493 (m),1446 (s), 1375 (w), 1264 (w), 1160 (m), 1030 (m), 959 (s), 893 (s), 756 (s).
δ_H (300 MHz, C_6D_6)	7.33 - 7.04 (5H, m, Ar*H*), 1.71 - 1.50 (4H, complex, 2 x CH_2), 1.17 (1H, s, O*H*), 0.69 (6H, t, *J* 7.4 Hz, 2 x CH_3) ppm.
δ_C (75.5 MHz, C_6D_6)	146.3 (0, Ar), 128.3 (1, 2 x Ar), 126.5 (1, Ar), 126.0 (1, 2 x Ar), 77.2 (0, *C*OH), 35.8 (2, 2 x *C*H_2CH_3), 8.1 (3, 2 x CH_2CH_3) ppm.
LRMS (CI)	164 ([M-H_2O+NH_4]$^+$, 50 %), 147 ([M-OH]$^+$, 100 %), 135 ([M-CH_2CH_3]$^+$, 90 %) amu.
λ_{max}/nm (ε_{max})	254 (5200).

Benzo[1,3]dioxol-5-yl-diphenyl-methanol **259**



245 **259**

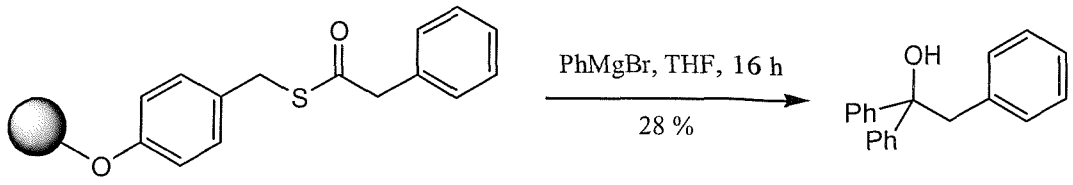
$C_{20}H_{16}O_3$
Mol. Wt.: 304

245 (1.00 g, 0.48 mmol) was pre-swollen for 20 minutes in THF (5 mL), before phenyl magnesium bromide (1M solution in THF, 7.0 mL, 7.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 36 hours, then worked up with water (20 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, extracted with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.108 g, 0.36 mmol, 74 %) This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **259** as a pale yellow oil (0.031 g, 0.10 mmol, 21 %).

Data for **259**:

ν_{max}/cm^{-1} (neat)	3650 - 3100 (bs), 2891 (w), 1598 (w), 1485 (s), 1446 (m), 1237 (s), 1036 (m), 935 (m), 812 (m), 758 (m), 700 (s)
δ_H (300 MHz, C_6D_6)	7.34 - 7.27 (4H, m, Ar*H*), 7.17 - 6.96 (7H, m, Ar*H*), 6.67 (1H, dd, *J* 8.1 Hz, 1.8 Hz, Ar*H*), 6.52 (1H, d, *J* 8.5 Hz, Ar*H*), 5.26 (2H, s, OCH_2O) ppm.
δ_C (75.5 MHz, C_6D_6)	148.1 (0, Ar), 147.8 (0, Ar), 147.2 (0, Ar), 142.1 (0, Ar), 130.1 (1, Ar), 129.3 (1, Ar), 127.5 (1, Ar), 122.2 (1, Ar), 109.5 (1, Ar), 107.7 (1, Ar), 101.2 (2, OCH_2O), 82.1 (0, Ph_2C(OH)Ar) ppm.
LRMS (APCI +ve)	304 ([M]$^+$, 10 %), 287 ([M-OH]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	244 (10 300)

1,1,2-Triphenyl-ethanol **260**



246 **260**

$C_{20}H_{18}O$
Mol. Wt.: 274

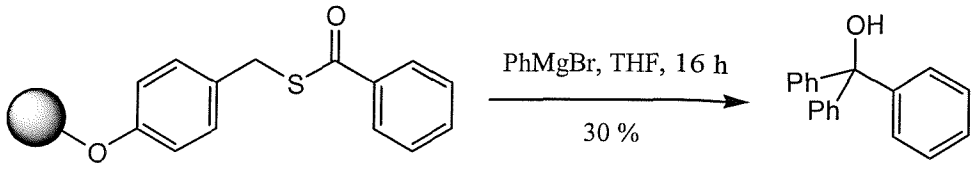
246 (0.90 g, 0.88 mmol) was pre-swollen for 20 minutes in THF (5 mL), phenyl magnesium bromide (1M solution in THF, 5.0 mL, 5.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, extracted with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.123 g, 0.45 mmol, 51 %.) This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **260** as a white solid (0.069 g, 0.25 mmol, 28 %). A sample was recrystallised from petrol to give white flakes.

Spectroscopic and physical data were in accordance with literature values[80].

Data for **260**:

ν_{max}/cm^{-1} (neat)	3540 (m), 3056 (w), 3025 (w), 1579 (w), 1492 (s), 1444 (s), 1321 (w), 1262 (m), 1157 (m), 1025 (s), 954 (w), 910 (w), 837 (m), 753 (s)
δ_H (300 MHz, C_6D_6)	7.43 - 7.34 (3H, m, Ar*H*), 7.19 - 6.92 (10H, m, Ar*H*), 6.88 - 6.82 (3H, m, Ar*H*), 3.40 (2H, s, ArCH_2), 1.91 (1H, s, CO*H*) ppm.
δ_C (75.5 MHz, C_6D_6)	147.5 (0, 2 x Ar), 136.8 (0, Ar), 131.4 (1, Ar), 128.5 (1, 4 x Ar), 128.3 (1, 4 x Ar), 128.2 (1, 2 x Ar), 127.9 (1, 2 x Ar), 126.8 (1, 2 x Ar), 78.1 (0, *C*OH), 48.4 (2, ArCH_2) ppm.
LRMS (CI)	257 ([M-H_2O+H]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	254 (5780)
M.P.	88 - 89 °C (petrol) Lit: 91 °C (petrol)[81].

Triphenyl-methanol **261**



247 **261**

$C_{19}H_{14}O$
Mol. Wt.: 258

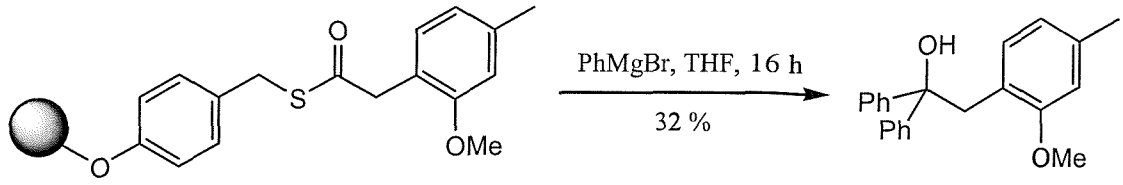
247 (0.80 g, 0.89 mmol) was pre-swollen for 20 minutes in THF (3 mL), before phenyl magnesium bromide (1M solution in THF, 5.0 mL, 5.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, extracted with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.17 g, 0.66 mmol, 74 %) This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **261** as a white solid (0.069 g, 0.27 mmol, 30 %). A sample was recrystallised from petrol to give white flakes.

Spectroscopic and physical data were in accordance with literature values[82].

Data for **261**:

ν_{max}/cm^{-1} (neat)	3540 (m), 3056 (w), 3022 (w), 1596 (w), 1579 (w), 1492 (s), 1444 (s), 1263 (m), 1157 (m), 1025 (s), 837 (m), 738 (s)
δ_H (300 MHz, C_6D_6)	7.48 - 7.37 (6H, m, Ar*H*), 7.04 - 6.96 (9H, m, Ar*H*), 2.87 (1H, s, O*H*) ppm.
δ_C (75.5 MHz, C_6D_6)	145.2 (0, 3 x Ar), 129.3 (1, 6 x Ar), 127.6 (1, 6 x Ar), 127.2 (1, 3 x Ar), 83.5 (0, *C*OH) ppm.
LRMS (CI)	243 ([M-OH]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	256 (4460)
M.P.	163 - 164 °C (petrol) Lit: 163 - 164 °C (petrol)[83].

2-(2-Methoxy-4-methyl-phenyl)-1,1-diphenyl-ethanol **262**



248 **262**

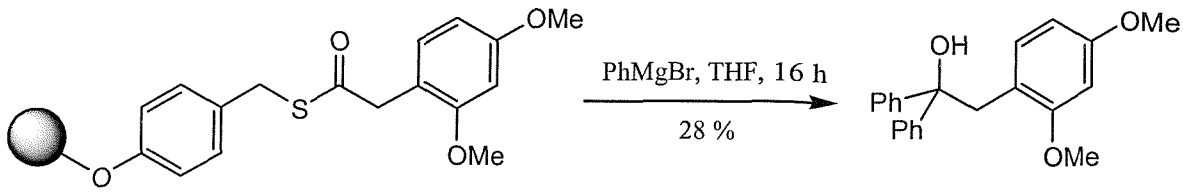
$C_{22}H_{22}O_2$
Mol. Wt.: 318

248 (0.57 g, 0.55 mmol) was pre-swollen for 20 minutes in THF (3 mL), before phenyl magnesium bromide (1M solution in THF, 3.0 mL, 3.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, extracted with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.124 g, 0.39 mmol, 71 %) This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **262** as a white solid (0.056 g, 0.18 mmol, 32 %). A portion was recrystallised from ethanol to give colourless needles.

Data for **262**:

ν_{max}/cm^{-1} (neat)	3478 (s), 3026 (w), 2925 (w), 1613 (m), 1579 (m), 1492 (s), 1253 (s), 1126 (s), 1034 (s), 909 (m), 813 (s), 750 (s), 695 (s)
δ_H (300 MHz, C_6D_6)	7.61 - 7.55 (3H, m, Ar*H*), 7.16 - 6.97 (7H, m, Ar*H*), 6.51 - 6.33 (3H, m, Ar*H*), 3.99 (1H, s, O*H*), 3.67 (2H, s, ArCH_2), 3.08 (3H, s, OCH_3), 2.04 (3H, s, ArCH_3) ppm.
δ_C (75.5 MHz, C_6D_6)	158.0 (0, Ar), 148.5 (0, Ar), 137.7 (0, Ar), 132.9 (1, Ar), 128.1 (1, 4 x Ar), 127.1 (1, 4 x Ar), 126.8 (1, 2 x Ar), 122.6 (0, Ar), 121.7 (1, Ar), 111.6 (1, Ar), 78.9 (0, *C*OH), 54.9 (3, O*C*H$_3$), 42.7 (2, ArCH$_2$), 21.6 (3, ArCH$_3$) ppm.
LRMS (CI)	301 ([M-OH]$^+$, 100 %), 136 ([M-HOC(Ph)$_2$+H]$^+$, 80 %) amu.
λ_{max}/nm (ε_{max})	273 (6300)
M.P.	98 - 100°C (ethanol)
CHN	Found: C, 82.84; H, 7.14. $C_{22}H_{22}O_2$ requires C, 82.99; H, 6.96.

2-(2,4-Dimethoxy-phenyl)-1,1-diphenyl-ethanol **263**



250 **263**

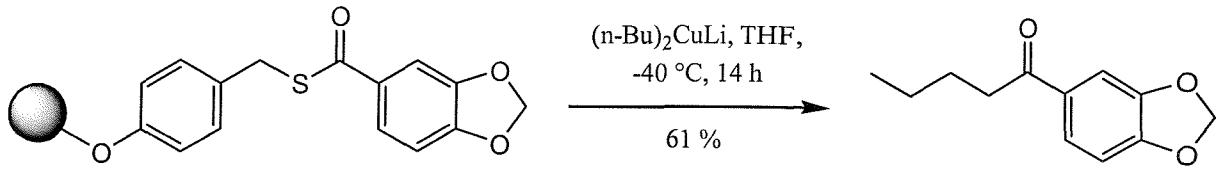
$C_{22}H_{22}O_3$
Mol. Wt.: 334

250 (0.80 g, 0.77 mmol) was pre-swollen for 20 minutes in THF (5 mL), before phenyl magnesium bromide (1M solution in THF, 5.0 mL, 5.0 mmol) was added *via* syringe. The reaction was left to stand at room temperature for 16 hours, then worked up with water (20 mL). The reaction mixture was filtered to trap the resin beads, and the filtrate extracted with diethyl ether (3 x 20 mL). The organic portions were combined, extracted with brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil. (Crude yield: 0.154 g, 0.46 mmol, 60 %). This was purified by chromatography (silica, 0 - 30 % diethyl ether in petrol) to yield alcohol **263** as a white solid (0.072 g, 0.22 mmol, 28 %). A portion was recrystallised from ethanol to give colourless needles.

Data for **263**:

ν_{max}/cm^{-1} (neat)	3499 (s), 2922 (w), 1612 (m), 1586 (s), 1506 (s), 1445 (s), 1289 (s), 1207 (s), 1126 (s), 1004 (m), 910 (m), 829 (m)
δ_H (400 MHz, C_6D_6)	7.72 - 7.68 (4H, m, Ar*H*), 7.28 - 7.23 (4H, m, Ar*H*), 7.17 - 7.13 (2H, m, Ar*H*), 6.63 (1H, d, *J* 6.2 Hz, Ar*H*), 6.43 (1H, d, *J* 1.9 Hz, Ar*H*), 6.22 (1H, dd, *J* 6.3 Hz, 1.9 Hz, Ar*H*), 3.89 (1H, s, O*H*), 3.77 (2H, s, ArCH_2), 3.37 (3H, s, OCH_3), 3.15 (3H, s, OCH_3)
δ_C (100 MHz, C_6D_6)	160.6 (0, Ar), 159.4 (0, Ar), 148.8 (0, 2 x Ar), 133.6 (1, 2 x Ar), 129.0 (1, Ar), 127.3 (1, 4 x Ar), 127.0 (1, 4 x Ar), 118.0 (0, Ar), 104.8 (1, Ar), 99.3 (1, Ar), 79.2 (0, *C*OH), 55.1 (3, 2 x OCH_3), 42.5 (2, ArCH_2)
LRMS (CI)	317 ([M-OH]$^+$, 100 %)
λ_{max}/nm (ε_{max})	274 (10 500)
CHN	Found: C, 78.76; H, 6.56. $C_{22}H_{22}O_3$ requires C, 79.02; H, 6.63.
M.P.	107 - 109 °C (ethanol)

1-Benzo[1,3]dioxol-5-yl-pentan-1-one **266**



245 **266**

$C_{12}H_{14}O_3$
Mol. Wt.: 206

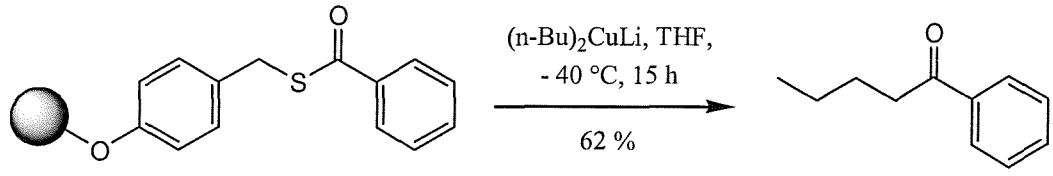
n-Butyllithium (1.23 M in hexane, 2.0 mL, 2.46 mmol) was added to a suspension of copper (I) iodide (0.24 g, 1.23 mmol) in THF (20 mL) at -40 °C and the mixture stirred for 2 hours. **245** (1.00 g, 0.47 mmol), swollen in dichloromethane (3 mL) for 30 minutes was added and the reaction stirred at -40 °C for a further 14 hours. Ammonium chloride (aq., sat., 20 mL) and then diethyl ether (20 mL) were added and the reaction mixture was allowed to warm to room temperature. The beads were collected by filtration, and washed with THF (3 x 10 mL). The filtrate was removed and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave ketone **266** as a pale yellow oil (0.059 g, 0.29 mmol, 61 %).

Spectroscopic and physical data were in accordance with literature values[84].

Data for **266**:

ν_{max}/cm^{-1} (neat)	2958 (m), 2925 (m), 2873 (m), 1674 (s), 1604 (m), 1503 (m), 1487 (s), 1439 (s), 1244 (s), 1034 (s), 934 (m), 808 (m)
δ_H (300 MHz, $CDCl_3$)	7.57 (1H, dd, *J* 8.2 Hz, 1.7 Hz, Ar*H*), 7.45 (1H, d, *J* 1.7 Hz, Ar*H*), 6.85 (1H, d, *J* 8.2 Hz), 6.05 (2H, s, OCH_2O), 2.89 (2H, t, *J* 7.2 Hz, COH_2), 1.70 (2H, m, COH_2CH_2), 1.40 (2H, m, $COH_2CH_2CH_2$), 0.95 (3H, t, *J* 7.4 Hz, CH_2CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	199.8 (0, *C*O), 151.7 (0, Ar), 148.3 (0, Ar), 132.1 (0, Ar), 124.4 (1, Ar), 108.1 (1, Ar), 108.0 (1, Ar), 101.9 (2, OCH_2O), 38.3 (2, $COCH_2$), 26.9 (2, COH_2CH_2), 22.7 (2, $COH_2CH_2CH_2$), 14.1 (3, CH_2CH_3) ppm.
LRMS (APCI +ve)	207 ($[M+H]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	306 (4350), 273 (4120)

1-Phenyl-pentan-1-one **267**



247 **267**

$C_{11}H_{14}O$
Mol. Wt.: 162

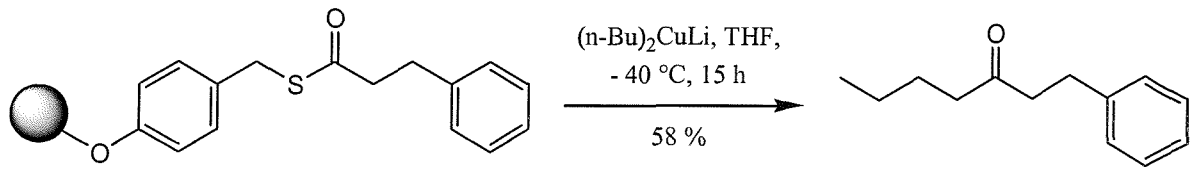
n-Butyllithium (1.76 M in hexane, 2.3 mL, 4.05 mmol) was added to a suspension of copper (I) iodide (0.38 g, 2.00 mmol) in THF (20 mL) at -40 °C and the mixture stirred for 2 hours. **247** (0.97 g, 1.09 mmol), swollen in dichloromethane (3 mL) for 30 minutes was added and the reaction stirred at -40 °C for a further 15 hours. Ammonium chloride (aq., sat., 20 mL) and then diethyl ether (20 mL) were added and the reaction mixture was allowed to warm to room temperature. The beads were collected by filtration, and washed with THF (3 x 10 mL). The filtrate was removed and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave ketone **267** as a colourless oil (0.11 g, 0.68 mmol, 62 %).

Spectroscopic and physical data were in accordance with literature values[85].

Data for **267**:

ν_{max}/cm^{-1} (neat)	2957 (m), 2931 (m), 2872 (w), 1684 (s), 1597 (m), 1581 (w), 1448 (m), 1321 (w), 1265 (m), 1207 (m), 1013 (w), 751 (m).
δ_H (300 MHz, $CDCl_3$)	7.97 - 7.92 (2H, m, Ar*H*), 7.57 - 7.50 (1H, m, Ar*H*), 7.47 - 7.41 (2H, m, Ar*H*), 2.95 (2H, t, *J* 7.4 Hz, $COCH_2$), 1.71 (2H, quin, *J* 7.4 Hz, $CH_2CH_2CH_3$), 1.40 (2H, sext, *J* 7.4 Hz, CH_2CH_3), 0.95 (3H, t, *J* 7.2 Hz, CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	200.1 (0, *C*O), 137.2 (0, Ar), 133.0 (1, Ar), 128.7 (1, 2 x Ar), 128.2 (1, 2 x Ar), 38.5 (2, $COCH_2$), 26.6 ($CH_2CH_2CH_3$), 22.6 (2, CH_2CH_3), 14.1 (3, CH_3) ppm.
LRMS (CI)	180 ($[M+NH_4]^+$, 35 %), 163 ($[M+H]^+$, 100 %), 105 ($[ArCO]^+$, 95 %) amu.
λ_{max}/nm (ε_{max})	255 (3850), 239 (10 700).

1-Phenyl-heptan-3-one **268**



251 **268**

$C_{13}H_{18}O$
Mol. Wt.: 190

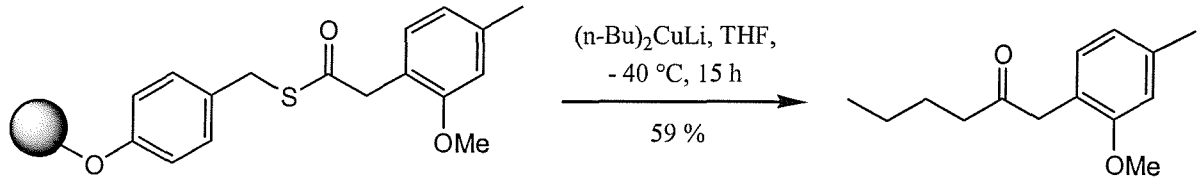
n-Butyllithium (1.38 M in hexane, 5.8 mL, 8.00 mmol) was added to a suspension of copper (I) iodide (0.76 g, 4.00 mmol) in THF (20 mL) at -40 °C and the mixture stirred for 2 hours. **251** (0.80 g, 0.81 mmol), swollen in dichloromethane (3 mL) for 30 minutes was added and the reaction stirred at -40 °C for a further 15 hours. Ammonium chloride (aq., sat., 20 mL) and then diethyl ether (20 mL) were added and the reaction mixture was allowed to warm to room temperature. The beads were collected by filtration, and washed with THF (3 x 10 mL). The filtrate was removed and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave ketone **268** as a colourless oil (0.089 g, 0.47 mmol, 58 %).

Spectroscopic and physical data were in accordance with literature values[85].

Data for **268**:

ν_{max}/cm^{-1} (neat)	3027 (w), 2956 (m), 2930 (m), 2871 (w), 1710 (s), 1603 (w), 1496 (m), 1453 (m), 1369 (m), 1126 (m), 1061 (m), 746 (s).
δ_H (300 MHz, $CDCl_3$)	7.33 - 7.28 (2H, m, Ar*H*), 7.23 - 7.18 (3H, m, Ar*H*), 2.92 (2H, t, *J* 7.5 Hz, CH_2CO), 2.75 (2H, t, *J* 7.9 Hz, CH_2CO), 2.40 (2H, t, *J* 7.5 Hz, ArCH_2), 1.62 - 1.51 (2H, m, CH_2CH$_2$CH$_3$), 1.37 - 1.25 (2H, m, CH_2CH$_3$), 0.91 (3H, t, *J* 7.4 Hz, CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	210.5 (0, *C*O), 141.4 (0, Ar), 128.6 (1, 2 x Ar), 128.5 (1, 2 x Ar), 126.2 (1, Ar), 44.4 (2, ArCH$_2$*C*H$_2$C(O)), 42.9 (2, C(O)*C*H$_2$), 30.0 (2, Ar*C*H$_2$), 26.0 (2, *C*H$_2$CH$_2$CH$_3$), 22.5 (2, *C*H$_2$CH$_3$), 14.0 (3, *C*H$_3$) ppm.
LRMS (CI)	191 ([M+H]$^+$, 100 %), 91 ([ArCH$_2$]$^+$, 90 %), 105 ([ArCH$_2$CH$_2$]$^+$, 70 %), 208 ([M+NH$_4$]$^+$, 50 %) amu.
λ_{max}/nm (ε_{max})	256 (3210).

1-(2-Methoxy-4-methyl-phenyl)-hexan-2-one **269**



248 **269**

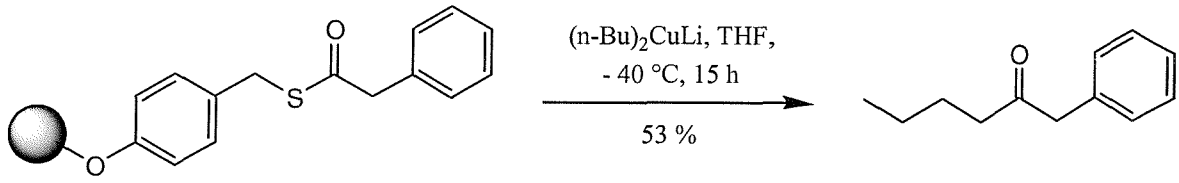
$C_{14}H_{20}O_2$
Mol. Wt.: 220

n-Butyllithium (1.46 M in hexane, 4.4 mL, 6.42 mmol) was added to a suspension of copper (I) iodide (0.61 g, 3.20 mmol) in THF (20 mL) at -40 °C and the mixture stirred for 2 hours. **248** (0.65 g, 0.63 mmol), swollen in dichloromethane (3 mL) for 30 minutes was added and the reaction stirred at -40 °C for a further 15 hours. Ammonium chloride (aq., sat., 20 mL) and then diethyl ether (20 mL) were added and the reaction mixture was allowed to warm to room temperature. The beads were collected by filtration, and washed with THF (3 x 10 mL). The filtrate was removed and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave ketone **269** as a colourless oil (0.082 g, 0.37 mmol, 59 %).

Data for **269**:

ν_{max}/cm^{-1} (neat)	2957 (m), 2933 (m), 2872 (w), 1713 (s), 1614 (m), 1584 (m), 1509 (s), 1464 (m), 1266 (s), 1154 (m), 1040 (s), 925 (w).
δ_H (300 MHz, $CDCl_3$)	7.01 (1H, d, *J* 7.5 Hz, Ar*H*), 6.75 (1H, d, *J* 7.4 Hz, Ar*H*), 6.71 (1H, s, Ar*H*), 3.80 (3H, s, OCH_3), 3.64 (2H, s, ArCH_2), 2.44 (2H, *t*, *J* 7.4 Hz, C(O)CH_2), 2.37 (3H, s, ArCH_3), 1.57 (2H, quin., *J* 7.4 Hz, C(O)CH$_2$CH_2), 1.30 (2H, sext., *J* 7.4 Hz, C(O)CH$_2$CH$_2$CH_2), 0.90 (3H, t, *J* 7.3 Hz, CH$_2$CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	209.6 (0, *C*O), 157.3 (0, Ar), 138.5 (0, Ar), 131.1 (1, Ar), 121.3 (1, Ar), 120.8 (0, Ar), 111.6 (1, Ar), 55.4 (3, OCH_3), 44.5 (2, *C*H$_2$CH$_2$CH$_2$CH$_3$), 41.7 (2, ArCH_2C(O)), 26.1 (2, *C*H$_2$CH$_2$CH$_3$), 22.5 (2, *C*H$_2$CH$_3$), 21.7 (3, ArCH_3), 14.1 (3, CH$_2$CH_3) ppm.
LRMS (CI)	221 ([M+H]$^+$, 100 %), 135 ([M-C_4H_9CO]$^+$, 95 %) amu.
HRMS	Found M$^+$: 220.1467. $C_{14}H_{20}O_2$ requires M$^+$: 220.1463.
λ_{max}/nm (ε_{max})	273 (8200).

1-Phenyl-hexan-2-one **270**



246 **270**

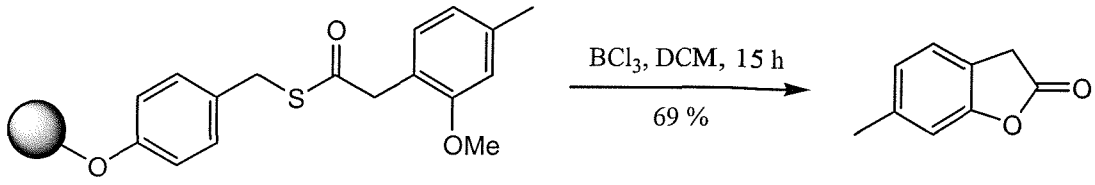
$C_{12}H_{16}O$
Mol. Wt.: 176

n-Butyllithium (1.90 M in hexane, 2.1 mL, 3.99 mmol) was added to a suspension of copper (I) iodide (0.38 g, 2.00 mmol) in THF (20 mL) at -40 °C and the mixture stirred for 2 hours. **246** (0.90 g, 0.88 mmol), swollen in dichloromethane (3 mL) for 30 minutes was added and the reaction stirred at -40 °C for a further 15 hours. Ammonium chloride (aq., sat., 20 mL) and then diethyl ether (20 mL) were added and the reaction mixture was allowed to warm to room temperature. The beads were collected by filtration, and washed with THF (3 x 10 mL). The filtrate was removed and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave ketone **270** as a colourless oil (0.082 g, 0.47 mmol, 53 %).
Spectroscopic and physical data were in accordance with literature values[86].

Data for **270**:

ν_{max}/cm^{-1} (neat)	2957 (m), 2932 (m), 2872 (m), 1711 (s), 1602 (w), 1496 (m), 1454 (m), 1365 (w), 1125 (m), 1051 (m), 726 (m), 698 (s).
δ_H (300 MHz, $CDCl_3$)	7.39 - 7.20 (5H, m, Ar*H*), 3.69 (2H, s, ArCH_2), 2.47 (2H, t, *J* 7.4 Hz, COCH_2), 1.56 (2H, quin., *J* 7.4 Hz, $CH_2CH_2CH_3$), 1.30 (2H, sext., *J* 7.3 Hz, CH_2CH_3), 0.88 (3H, t, *J* 7.5 Hz, CH_2CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	208.7 (*C*O), 134.6 (0, Ar), 129.6 (1, 2 x Ar), 128.8 (1, 2 x Ar), 127.1 (1, Ar), 50.3 (2, ArCH_2), 41.8 (2, COCH_2), 26.0 ($CH_2CH_2CH_3$), 22.4 (CH_2CH_3), 14.0 (CH_2CH_3) ppm.
LRMS (CI)	194 ($[M+NH_4]^+$, 75 %), 177 ($[M+H]^+$, 100 %), 85 ($[C(O)CH_2CH_2CH_2CH_3]^+$, 90 %) amu.
λ_{max}/nm (ε_{max})	255 (4170).

6-Methyl-3*H*-benzofuran-2-one **272**



248 **272**

$C_9H_8O_2$
Mol. Wt.: 148

248 (0.72 g, 0.70 mmol) was swollen in dichloromethane (3 mL) for 30 minutes, before dichloromethane (15 mL) and boron trichloride (1.0M solution in heptane, 4.2 mL, 4.2 mmol) were added. The reaction was left to stand for 15 hours, and then the resin beads were collected by filtration. The resin beads were swollen for 20 minutes with THF (3 mL), and then THF : 2M HCl (aq., 15 mL) (1:1) was added. The beads were left to stand for a further 1 hour, collected by filtration, and washed with THF (10 mL). The filtrate was extracted with diethyl ether (3 x 10 mL), and the combined organic phases washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange solid.

The beads were swollen in dichloromethane (4 mL) for 30 minutes, before the addition of dichloromethane (10 mL) and triethylamine (2 mL). The reaction was left to stand, with occasional agitation, for 15 hours before the beads were collected by filtration, washed with dichloromethane (3 x 10 mL) and dried *in vacuo*. The filtrate was washed with 2M HCl (aq., 10 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a brown solid.

Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) of both portions gave lactone **272** as a yellow solid, in the following proportions:

Post-acid wash: 0.016 g, 0.11 mmol, 15 %

Post-base wash: 0.056 g, 0.38 mmol, 54 %

Overall: 0.072 g, 0.49 mmol, 69 %

A portion was recrystallised from petroleum to give colourless needles.

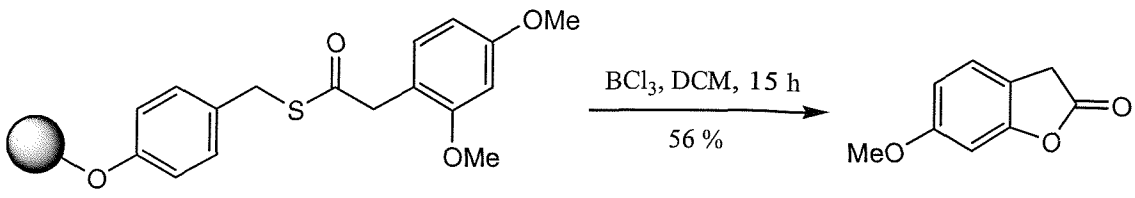
Spectroscopic and physical data were in accordance with literature values[87].

Data for **272**:

ν_{max}/cm^{-1} (neat) 2921 (w), 1801 (s), 1629 (m), 1500 (w), 1426 (w), 1224 (w), 1152 (m), 1056 (s), 946 (m), 866 (w), 835 (w), 682 (w).

δ_H (300 MHz, $CDCl_3$)	7.18 (1H, d, *J* 7.5 Hz, Ar*H*), 6.93 (1H, d, *J* 7.5 Hz, Ar*H*), 6.91 (1H, s, Ar*H*), 3.70 (2H, s, CH_2CO), 2.38 (3H, s, $ArCH_3$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	174.7 (0, *C*O), 155.0 (0, Ar), 139.5 (0, Ar), 124.9 (1, Ar), 124.3 (1, Ar), 120.0 (0, Ar), 111.6 (1, Ar), 33.0 (2, $ArCH_2CO$), 21.8 (3, $ArCH_3$) ppm.
LRMS (APCI +ve)	189 ($[M+MeCN]^+$, 60 %), 146 ($[M-CO_2+MeCN]^+$, 88 %), 105 $[M-CO_2]^+$ (95 %) amu.
λ_{max}/nm (ε_{max})	269 (1740).
M.P.	67 - 69 °C (petrol). Lit. 68 - 70 °C (petrol)[38].

6-Methoxy-3*H*-benzofuran-2-one **273**



250 **273**

$C_9H_8O_3$
Mol. Wt.: 164

250 (0.85 g, 0.82 mmol) was swollen in dichloromethane (3 mL) for 30 minutes, before dichloromethane (15 mL) and boron trichloride (1.0M solution in heptane, 4.8 mL, 4.8 mmol) were added. The reaction was left to stand for 15 hours, and then the resin beads were collected by filtration. The resin beads were swollen for 20 minutes with THF (3 mL), and then THF : 2M HCl (aq., 15 mL) (1:1) was added. The beads were left to stand for a further 1 hour, collected by filtration, and washed with THF (10 mL). The filtrate was extracted with diethyl ether (3 x 10 mL), and the combined organic phases washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil.

The beads were swollen in dichloromethane (4 mL) for 30 minutes, before the addition of dichloromethane (10 mL) and triethylamine (2 mL). The reaction was left to stand, with occasional agitation, for 15 hours before the beads were collected by filtration, washed with dichloromethane (3 x 10 mL) and dried *in vacuo*. The filtrate was washed with 2M HCl (aq., 10 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a brown oil.

Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) of both portions gave lactone **273** as a yellow solid, in the following proportions:

Post-acid wash: 0.020 g, 0.12 mmol, 16 %

Post-base wash: 0.056 g, 0.34 mmol, 41 %

Overall: 0.076 g, 0.46 mmol, 56 %

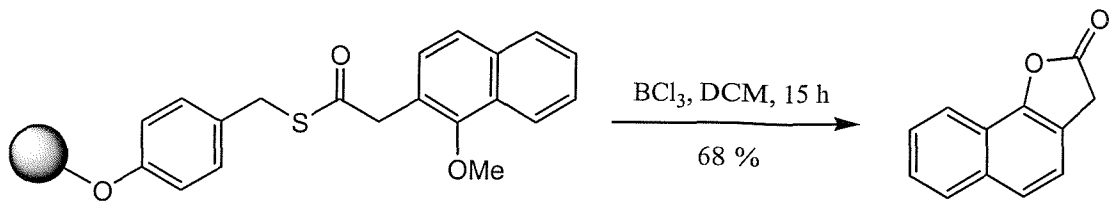
Spectroscopic and physical data were in accordance with literature values[88].

Data for **273**:

ν_{max}/cm^{-1} (neat)	3011 (w), 2948 (w), 2834 (w), 1794 (s), 1631 (s), 1600 (m), 1498 (s), 1342 (m), 1256 (m), 1155 (s), 942 (s), 852 (m).
δ_H (300 MHz, $CDCl_3$)	7.24 (1H, d, *J* 7.7 Hz, Ar*H*), 6.73 - 6.68 (2H, m, Ar*H*), 3.80 (3H, s, OCH_3), 3.74 (2H, s, $ArCH_2$) ppm.

δ_C (75.5 MHz, $CDCl_3$)	175.0 (0, *C*O), 161.0 (0, Ar), 156.2 (0, Ar), 125.8 (1, Ar), 116.1 (0, Ar), 110.0 (0, Ar), 97.6 (1, Ar), 55.7 (3, O*C*H_3), 32.4 (2, Ar*C*H_2) ppm.
LRMS (CI)	182 ($[M+NH_4]^+$, 100 %), 164 ($[M]^+$, 75 %) amu.
λ_{max}/nm (ε_{max})	276 (11 200).
M.P.	54 - 56 °C Lit: 55 - 56 °C (diethyl ether)[89].

3*H*-Naphtho[1,2-*b*]furan-2-one **274**



253 **274**

$C_{12}H_8O_2$
Mol. Wt.: 184

253 (0.79 g, 0.75 mmol) was swollen in dichloromethane (3 mL) for 30 minutes, before dichloromethane (15 mL) and boron trichloride (1.0M solution in heptane, 4.5 mL, 4.5 mmol) were added. The reaction was left to stand for 15 hours, and then the resin beads were collected by filtration. The resin beads were swollen for 20 minutes with THF (3 mL), and then THF : 2M HCl (aq., 15 mL) (1:1) was added. The beads were left to stand for a further 1 hour, collected by filtration, and washed with THF (10 mL). The filtrate was extracted with diethyl ether (3 x 10 mL), and the combined organic phases washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil.

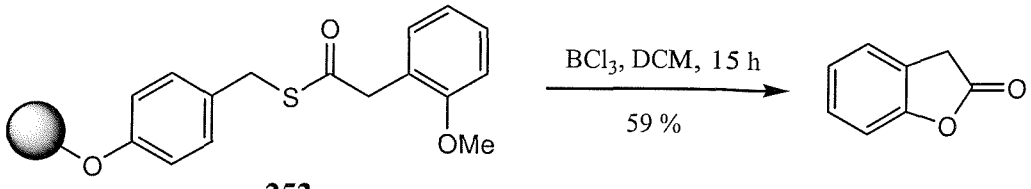
Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) gave lactone **274** as a yellow solid (0.094 g, 0.51 mmol, 68 %)

Spectroscopic and physical data were in accordance with literature values[90].

Data for **274**:

ν_{max}/cm^{-1} (neat)	3065 (w), 1799 (s), 1600 (w), 1520 (m), 1442 (m), 1387 (s), 1288 (m), 1113 (s), 1044 (s), 935 (m), 887 (s), 797 (s).
δ_H (300MHz, $CDCl_3$)	7.98 (1H, m, Ar*H*), 7.85 (1H, m, Ar*H*), 7.62 (1H, d, *J* 8.3 Hz, Ar*H*), 7.58 - 7.49 (2H, m, Ar*H*), 7.33 (1H, d, *J* 8.3 Hz, Ar*H*), 3.84 (2H, s, CH_2CO) ppm.
δ_C (75.5MHz, $CDCl_3$)	174.8 (0, *C*O), 150.2 (0, Ar), 133.9 (0, Ar), 128.3 (1, Ar), 126.9 (1, Ar), 126.8 (1, Ar), 124.1 (1, Ar), 121.4 (1, Ar), 121.0 (1, Ar), 119.9 (0, Ar), 117.5 (0, Ar), 34.1 (2, CH_2CO) ppm.
LRMS (APCI +ve)	184 ([M]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	327 (5460), 287 (6950).
M.P.	110-112 °C (pentane / ether). Lit. 108-109 °C (no solvent given)[90].

3*H*-Benzofuran-2-one **275**



252 **275**

$C_8H_6O_2$
Mol. Wt.: 134

252 (0.35 g, 0.44 mmol) was swollen in dichloromethane (3 mL) for 30 minutes, before dichloromethane (15 mL) and boron trichloride (1.0M solution in heptane, 4.0 mL, 4.0 mmol) were added. The reaction was left to stand for 15 hours, and then the resin beads were collected by filtration. The resin beads were swollen for 20 minutes with THF (3 mL), and then THF : 2M HCl (aq., 15 mL) (1:1) was added. The beads were left to stand for a further 1 hour, collected by filtration, and washed with THF (10 mL). The filtrate was extracted with diethyl ether (3 x 10 mL), and the combined organic phases washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil.

The beads were swollen in dichloromethane (4 mL) for 30 minutes, before the addition of dichloromethane (10 mL) and triethylamine (2 mL). The reaction was left to stand, with occasional agitation, for 15 hours before the beads were collected by filtration, washed with dichloromethane (3 x 10 mL) and dried *in vacuo*. The filtrate was washed with 2M HCl (aq., 10 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a brown oil.

Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) of both portions gave lactone **275** as a yellow solid, in the following proportions:

Post-acid wash: 0.005 g, 0.035 mmol, 8 %

Post-base wash: 0.030 g, 0.22 mmol, 51 %

Overall: 0.035 g, 0.26 mmol, 59 %

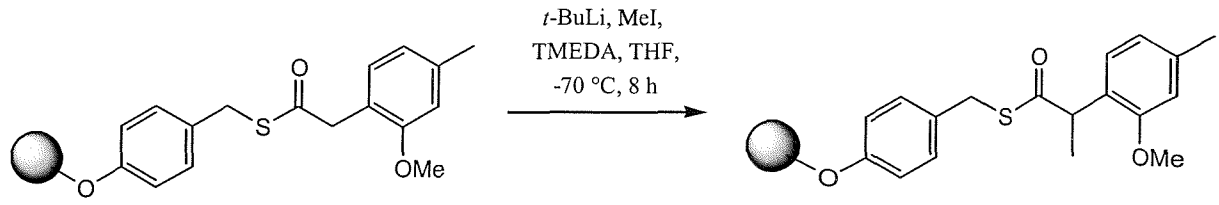
Spectroscopic and physical data were in accordance with literature values[76].

Data for **275**:

ν_{max}/cm^{-1} (neat)	3066 (w), 2930 (w), 1805 (s), 1620 (m), 1598 (s), 1479 (m), 1463 (s), 1230 (s), 1119 (m), 1058 (s), 891 (s), 754 (s).
δ_H (300MHz, $CDCl_3$)	7.35 - 7.27 (2H, m, Ar*H*), 7.18 - 7.09 (2H, m, Ar*H*), 3.75 (2H, s, ArCH_2) ppm.

δ_C (75.5MHz, $CDCl_3$)	174.3 (0, *C*O), 154.8 (0, Ar), 129.0 (1, Ar), 124.8 (1, Ar), 124.3 (1, Ar), 123.2 (0, Ar), 110.9 (1, Ar), 33.1 (2, *C*H_2CO) ppm.
LRMS (CI)	152 ($[M+NH_4]^+$, 25 %), 134 ($[M]^+$, 100 %), 106 ($[M-CO]^+$, 30 %) amu.
λ_{max}/nm (ε_{max})	266 (9400).
M.P.	48 - 50 °C (pentane / ether). Lit. 49 °C (no solvent given)[76].

Preparation of Resin-Bound Thioester **276**



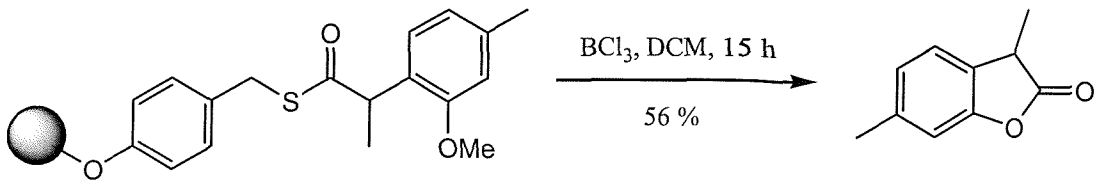
248 **276**

248 (0.90 g, 0.88 mmol) was swollen in THF (3 mL) for 30 minutes, then further THF (15 mL) was added, followed by methyl iodide (0.19 g, 1.32 mmol) and TMEDA (0.15 g, 1.32 mmol). The reaction was stirred, and cooled to -70 °C, then *t*-butyllithium (1.03 M solution in pentane, 0.9 mL, 0.9 mmol) was added dropwise. The reaction was kept at -70 °C for 8 hours, then 2M HCl (aq., 3 mL) was added and the reaction allowed to warm to room temperature. The beads were collected by filtration, washed with 1:1 THF : H_2O (3 x 10 mL), THF (3 x 10 mL) and methanol (3 x 10 mL), then dried *in vacuo*.

Data for **276**:

ν_{max}/cm^{-1} (solid phase) 2918 (m), 2847 (w), 1685 (m), 1602 (m), 1509 (s), 1451 (m), 1220 (s), 1173 (m), 1010 (s), 828 (m), 754 (m), 697 (s).

3,6-Dimethyl-3*H*-benzofuran-2-one **277**



276 **277**

$C_{10}H_{10}O_2$
Mol. Wt.: 162

276 (0.80 g, 0.77 mmol) was swollen in dichloromethane (3 mL) for 30 minutes, then further dichloromethane (15 mL) was added, followed by boron trichloride (1M solution in heptane, 4.6 mL, 4.6 mmol). The reaction was left to stand for 15 hours, then the resin beads were collected by filtration. The resin beads were then swollen for 30 minutes in THF (3 mL), and after this time 1:1 THF : 2M HCl (aq., 15 mL) was added and the beads were left to stand for a further 1 hour. The beads were then collected again by filtration, and washed with THF (10 mL). At this point the filtrate was removed, and extracted with diethyl ether (3 x 10 mL). The organic portions were combined, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil.

Meanwhile, the beads were swollen in dichloromethane (4 mL) for 30 minutes, then dichloromethane (10 mL) followed by triethylamine (2 mL) were added, and the reaction was left to stand, with occasional agitation, for 6 hours. After this time, the beads were collected by filtration and washed with dichloromethane (3 x 10 mL), then dried *in vacuo*. The filtrate was removed and washed with 2M HCl (aq., 10 mL), water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a brown oil.

Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) of both oils gave lactone **277** as a yellow solid, in the following proportions:

Post-acid wash: 0.013 g, 0.08 mmol, 10 %.

Post-base wash: 0.057 g, 0.35 mmol, 46 %.

Overall yield: 0.070 g, 0.43 mmol, 56 %.

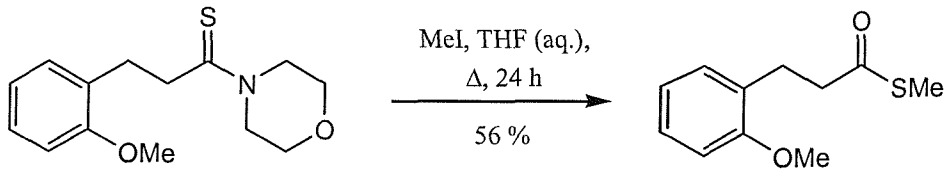
Spectroscopic and physical data were in accordance with literature values[87].

Data for **277**:

ν_{max}/cm^{-1} (neat) 2978 (w), 2934 (w), 1800 (s), 1629 (m), 1499 (m), 1328 (w), 1258 (m), 1153 (m), 1093 (s), 1025 (s), 940 (s), 814 (m).

δ_H (300MHz, $CDCl_3$)	7.14 (1H, d, *J* 7.5 Hz, Ar*H*), 6.96 (1H, d, *J* 7.5 Hz, Ar*H*), 6.94 (1H, s, Ar*H*), 3.70 (1H, q, *J* 7.5 Hz, C*H*CH_3), 2.39 (3H, s, ArCH_3), 1.55 (3H, d, *J* 7.5 Hz, $CHCH_3$) ppm.
δ_H (300MHz, $CDCl_3$)	178.6 (0, *C*O), 153.7 (0, Ar), 139.4 (0, Ar), 125.9 (0, Ar), 124.9 (1, Ar), 123.6 (1, Ar), 111.5 (1, Ar), 38.4 (1, Ar*C*H), 21.8 (3, ArCH_3), 16.2 (3, CHCH_3) ppm.
LRMS (CI)	162 ($[M]^+$, 100 %), 134 ($[M-CO]^+$, 90 %), 180 ($[M+NH_4]^+$, 90 %) amu.
λ_{max}/nm (ε_{max})	270 (8700).
M.P.	35 - 37 °C (petrol). Lit. 35 - 37 °C (petrol)[87].

3-(2-Methoxy-phenyl)-thiopropionic acid *S*-methyl ester **278**



232

$C_{14}H_{19}O_2NS$
Mol. Wt.: 265

278

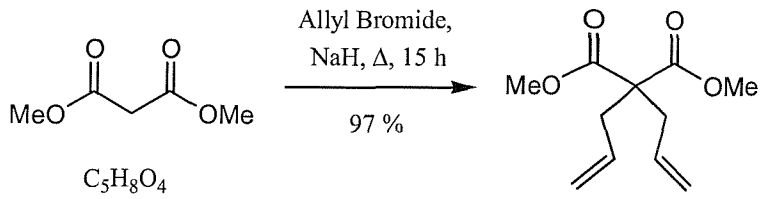
$C_{11}H_{14}O_2S$
Mol. Wt.: 210

232 (2.28 g, 8.60 mmol) and methyl iodide (1.70 g, 12.0 mmol) were dissolved in THF (45 mL) with water (5 mL), and the reaction was heated to reflux for 24 hours. After this time the reaction was allowed to cool to ambient temperature, then partitioned between diethyl ether (30 mL) and water (30 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL), then the organic phases were combined, washed with sodium thiosulfate solution (aq., sat.), washed with brine (sat.), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography gave **278** as a pale yellow oil (1.01 g, 4.81 mmol, 56 %).

Data for **278**:

ν_{max}/cm^{-1} (neat)	3002 (w), 2931 (m), 1686 (s), 1600 (m), 1587 (w), 1493 (s), 1461 (m), 1438 (m), 1241 (s), 1112 (m), 1044 (m), 750 (s).
δ_H (300MHz, $CDCl_3$)	7.26 - 7.15 (2H, m, Ar*H*), 6.93 - 6.86 (2H, m, Ar*H*), 3.85 (3H, s, OCH_3), 3.01 (2H, t, *J* 7.2 Hz, ArCH_2), 2.90 (2H, t, *J* 7.2 Hz, CH_2C(O)), 2.32 (3H, s, SCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	199.7 (0, *C*O), 157.6 (0, Ar), 130.1 (1, Ar), 128.6 (0, Ar), 127.8 (1, Ar), 120.6 (1, Ar), 110.4 (1, Ar), 55.3 (3, O*C*H$_3$), 43.8 (2, *C*H$_2$CO), 26.9 (2, Ar*C*H$_2$), 11.7 (3, S*C*H$_3$) ppm.
LRMS (CI)	211 ([M+H]$^+$, 55 %), 180 ([M+H-OCH$_3$]$^+$, 55 %), 163 ([M-SCH$_3$]$^+$, 90 %), 121 ([M-CH$_2$C(O)SCH$_3$]$^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	273 (3080).

Preparation of 2,2-Diallyl-malonic acid dimethyl ester **301**



$C_5H_8O_4$
Mol. Wt.: 132

301
$C_{11}H_{16}O_4$
Mol. Wt.: 212

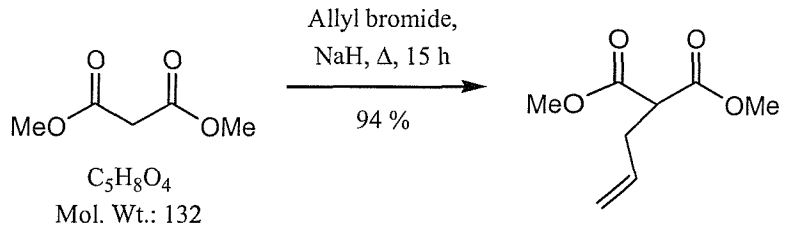
Prepared following a modified procedure of Semmelhack[91] *et al.* To a stirred suspension of sodium hydride (3.12 g, 13.0 mmol) at 0 °C, was added dropwise a solution of dimethyl malonate (8.18 g, 62.0 mol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of allyl bromide (15.7 g, 13.0 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **301** as a pale yellow oil (12.7 g, 5.99 mmol, 97 %).

Spectroscopic and physical data were in accordance with literature values[92].

Data for **301**:

ν_{max}/cm^{-1} (neat)	2982 (w), 2954 (w), 1735 (s), 1642 (w), 1438 (m), 1326 (w), 1288 (m), 1219 (s), 1205 (s), 1145 (m), 995 (w), 922 (m), 857 (w).
δ_H (300 MHz, $CDCl_3$)	5.63 (2H, ddt, *J* 19.3 Hz, 9.6 Hz, 7.4 Hz, 2 x C*H*=CH_2), 5.13-5.06 (4H, m, 2 x =CH_2), 3.70 (6H, s, 2 x OCH_3), 2.62 (4H, d, *J* 7.4 Hz, 2 x CH_2CH=) ppm.
δ_C (75.5 MHz, $CDCl_3$)	171.3 (0, 2 x *C*O), 132.4 (1, 2 x =*C*H), 119.4 (2, 2 x =CH_2), 57.8 (0, CO*C*CO), 52.5 (3, 2 x O*C*H_3), 37.0 (2, 2 x *C*H_2) ppm.
LRMS (CI)	213 ([M+H]$^+$, 100 %) amu.

Preparation of 2-Allyl-malonic acid dimethyl ester **302**



$C_5H_8O_4$
Mol. Wt.: 132

302
$C_8H_{12}O_4$
Mol. Wt.: 172

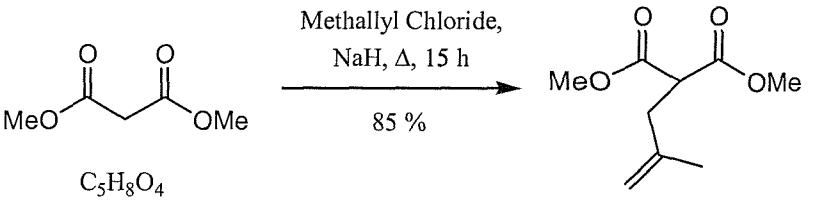
Prepared following a modified procedure of Semmelhack[91] *et al.* To a stirred suspension of sodium hydride (1.51 g, 62.9 mmol) at 0 °C , was added dropwise a solution of dimethyl malonate (8.18 g, 62.0 mmol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of allyl bromide (7.62 g, 63.0 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **302** as a pale yellow oil (10.0 g, 58.1 mmol, 94 %).

Spectroscopic and physical data were in accordance with literature values[93].

Data for **302**:

ν_{max}/cm^{-1} (neat)	3005 (w), 2956 (w), 1735 (s), 1643 (w), 1436 (m), 1341 (m), 1274 (m), 1238 (m), 1197 (m), 1156 (m), 1026 (w), 923 (w), 748 (w).
δ_H (300 MHz, $CDCl_3$)	5.71 (1H, ddt, *J* 17.1 Hz, 10.3 Hz, 7.0 Hz, C*H*=CH_2), 5.12-4.98 (2H, m, =CH_2), 3.69 (6H, s, 2 x OCH_3), 3.42 (1H, t, *J* 7.5 Hz, COC*H*CO), 2.63-2.56 (2H, m, CH_2CH=) ppm.
δ_C (75.5 MHz, $CDCl_3$)	169.3 (0, 2 x *C*O), 134.0 (1, =*C*H), 117.7 (2, =CH_2), 52.6 (3, 2 x OCH_3), 51.4 (1, C(O)*C*HC(O)), 33.0 (2, =CH*C*H_2) ppm.
LRMS (CI)	173 ([M+H]$^+$, 100 %), 190 ([M+NH_4]$^+$, 70 %) amu.

Preparation of 2-(2-Methyl-allyl)-malonic acid dimethyl ester **303**



$C_5H_8O_4$
Mol. Wt.: 132

303

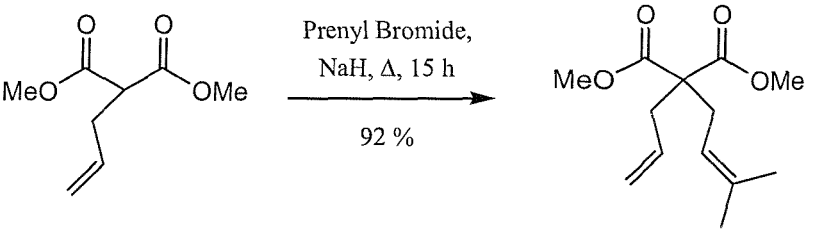
$C_9H_{14}O_4$
Mol. Wt.: 186

Prepared following a modified procedure of Semmelhack[91] *et al.* The reaction was carried out under nitrogen. To a stirred suspension of sodium hydride (0.50 g, 2.08 mmol) at 0 °C , was added dropwise a solution of dimethyl malonate (2.77 g, 2.10 mmol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of methallyl chloride (2.00 g, 2.21 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **303** as a pale yellow oil (3.32 g, 17.8 mmol, 85 %).
Spectroscopic and physical data were in accordance with literature values[94].

Data for **303**:

ν_{max}/cm^{-1} (neat)	3080 (w), 2955 (w), 2847 (w), 1737 (s), 1651 (w), 1436 (m), 1341 (w), 1274 (w), 1228 (w), 1153 (m), 1049 (w), 898 (w), 749 (w).
δ_H (300 MHz, $CDCl_3$)	4.74 (2H, d, *J* 19.5 Hz, =C*H*$_2$), 3.71 (6H, s, 2 x OC*H*$_3$), 3.60 (1H, t, *J* 7.8 Hz, COC*H*CO), 2.60 (2H, d, *J* 7.7 Hz, CHC*H*$_2$), 1.73 (3H, s, =CC*H*$_3$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	169.6 (0, 2 x *C*O), 141.7 (0, *C*(CH$_3$)=), 112.5 (2, =*C*H$_2$), 52.6 (3, 2 x OCH$_3$), 50.4 (1, COCCO), 36.7 (2, *C*H$_2$), 22.4 (3, =*C*CH$_3$) ppm.
LRMS (CI)	187 ([M+H]$^+$, 100 %), 127 ([M-CO_2Me]$^+$, 55 %) amu.

2-Allyl-2-(3-methyl-but-2-enyl)-malonic acid dimethyl ester **304**



302
$C_8H_{12}O_4$
Mol. Wt.: 172

304
$C_{13}H_{20}O_4$
Mol. Wt.: 240

Prepared following a modified procedure of Semmelhack[91] *et al.* To a stirred suspension of sodium hydride (0.57 g, 14.3 mmol) at 0 °C, was added dropwise a solution of allyl dimethyl malonate **302** (2.40 g, 14.0 mmol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of prenyl bromide (2.13 g, 14.3 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **304** as a pale yellow oil (3.08 g, 12.8 mmol, 92 %).

Spectroscopic and physical data were in accordance with literature values[95].

Data for **304**:

ν_{max}/cm^{-1} (neat) 2953 (w), 2928 (w), 1736 (s), 1642 (w), 1437 (m), 1288 (m), 1224 (m), 1208 (m), 1176 (w), 1064 (w), 995 (w), 923 (w), 749 (w).

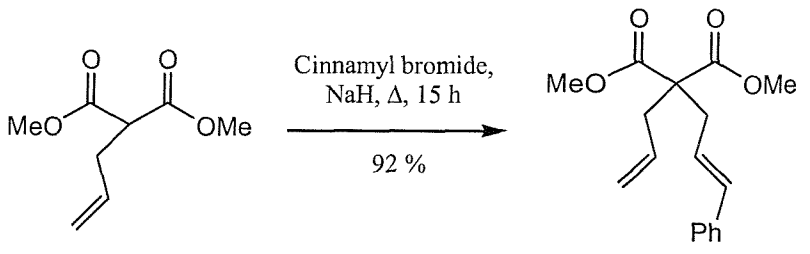
δ_H (300 MHz, $CDCl_3$) 5.61 (1H, ddt, *J* 17.5 Hz, 9.5 Hz, 7.4 Hz, C*H*=CH_2), 5.08-4.99 (2H, m, CH=CH_2), 4.91 (1H, tt, *J* 7.5 Hz, 1.5 Hz, C*H*=$C(CH_3)_2$), 3.66 (6H, s, 2 x OCH_3), 2.59-2.53 (4H, m, 2 x CH_2CH=), 1.65 (3H, d, *J* 1.1 Hz, =C(CH_3)), 1.56 (3H, s, =C(CH_3)) ppm.

δ_C (75.5 MHz, $CDCl_3$) 171.6 (0, *C*O), 135.8 (0, =*C*$(CH_3)_2$), 132.7 (1, =*C*H), 119.0 (2, =*C*H_2), 117.6 (1, =*C*H), 58.0 (0, CO*C*CO), 52.4 (3, 2 x O*C*H_3),

37.0 (2, CH_2C=), 31.2 (2, CH_2C=), 26.1 (3, =CCH_3), 18.0 (3, =CCH_3) ppm.

LRMS (CI) 241 ($[M+H]^+$, 100 %), 199 ($[M-CH_2CH=CH_2]^+$, 55 %) amu.

2-Allyl-2-(3-phenyl-allyl)-malonic acid dimethyl ester **305**



302
$C_8H_{12}O_4$
Mol. Wt.: 172

305
$C_{17}H_{20}O_4$
Mol. Wt.: 288

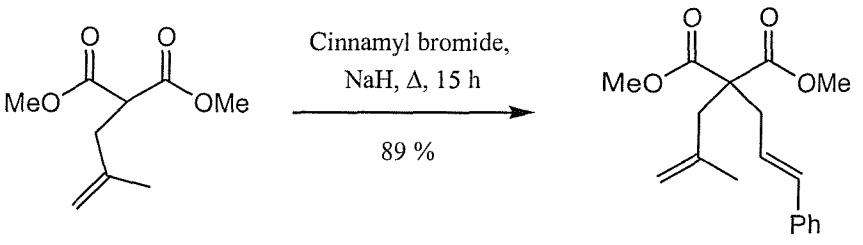
Prepared following a modified procedure of Semmelhack[91] *et al.* The reaction was carried out under nitrogen. To a stirred suspension of sodium hydride (0.60 g, 15.0 mmol) at 0 °C, was added dropwise a solution of allyl dimethyl malonate (2.41 g, 14.0 mmol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of cinnamyl bromide (2.96 g, 15.0 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **305** as a pale yellow oil (3.71 g, 12.9 mmol, 92 %).
Spectroscopic and physical data were in accordance with literature values[95].

Data for **305**:

ν_{max}/cm^{-1} (neat)	3027 (w), 2952 (w), 1732 (s), 1641 (w), 1598 (w), 1436 (m), 1288 (w), 1212 (m), 1142 (w), 969 (m), 924 (w), 742 (m), 693 (m).
δ_H (300 MHz, $CDCl_3$)	7.36-7.21 (5H, m, Ar*H*), 6.46 (1H, d, *J* 15.6 Hz, ArC*H*), 6.04 (1H, dt, *J* 15.6 Hz, 7.5 Hz, ArCH=C*H*), 5.71 (1H, ddt, *J* 17.3 Hz, 9.5 Hz, 7.5 Hz, C*H*=CH_2), 5.19-5.11 (2H, m, CH=CH_2), 3.74 (6H, s, 2 x OCH_3), 2.84 (2H, dd, *J* 7.7 Hz, 1.3 Hz, CH_2CH=), 2.70 (2H, dt, *J* 7.4 Hz, 1.1 Hz, CH_2CH=) ppm.
δ_C (75.5 MHz, $CDCl_3$)	171.4 (0, *C*O). 137.2 (0, Ar), 134.3 (1, ArCH_2=), 132.4 (1, *C*H=CH_2), 128.7 (1, 2 x Ar), 127.6 (1, Ar), 126.4 (1, 2 x Ar), 123.9

	(1, *C*H=CH_2), 119.5 (2, =*C*H_2), 58.1 (0, C(O)*C*C(O)), 52.6 (3, 2 x O*C*H_3), 37.4 (2, *C*H_2CH=), 36.5 (2, *C*H_2CH=) ppm.
LRMS (CI)	289 ($[M+H]^+$, 100 %), 257 ($[M-OMe]^+$, 55 %), 215 ($[M-CO_2Me-Me+H]^+$, 75 %), 117 ($[M-CH_2CH=CHAr]^+$, 90 %) amu.
λ_{max}/nm (ε_{max})	247 (6200).

2-(2-Methyl-allyl)-2-(3-phenyl-allyl)-malonic acid dimethyl ester **306**



303

$C_9H_{14}O_4$
Mol. Wt.: 186

306

$C_{18}H_{22}O_4$
Mol. Wt.: 302

Prepared following a modified procedure of Semmelhack[91] *et al.* The reaction was carried out under nitrogen. To a stirred suspension of sodium hydride (0.28 g, 7.00 mmol) at 0 °C , was added dropwise a solution of methallyl dimethyl malonate **303** (1.28 g, 6.89 mmol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of cinnamyl bromide (1.39 g, 7.10 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **306** as a colourless oil (1.85 g, 6.13 mmol, 89 %).

Data for **306**:

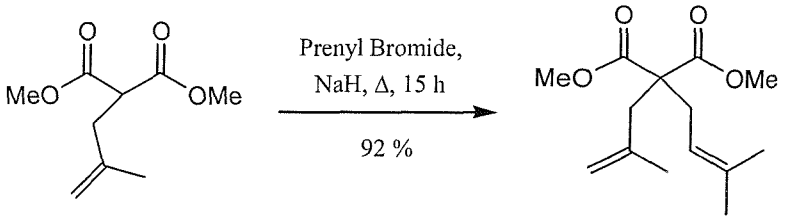
ν_{max}/cm^{-1} (neat) 3027 (w), 2952 (w), 1735 (s), 1495 (w), 1436 (m), 1377 (w), 1267 (w), 1203 (m), 1074 (w), 969 (w), 901 (w), 744 (m), 693 (w).

δ_H (300 MHz, $CDCl_3$) 7.36-7.19 (5H, m, Ar*H*), 6.44 (1H, d, *J* 15.6 Hz, ArC*H*=), 6.07 (1H, dt, *J* 15.6 Hz, 7.5 Hz, ArCH=C*H*), 4.92 (1H, s, =C*H*H), 4.81 (1H, s, =CH*H*), 3.72 (6H, s, 2 x OCH_3), 2.83 (2H, d, *J* 7.5 Hz, CH_2CH=), 2.78 (2H, s, CH_2C(CH_3)=), 1.70 (3H, s, CH_3) ppm.

δ_C (75.5 MHz, $CDCl_3$) 171.8 (0, *C*O), 140.6 (0), 137.3 (0), 134.1 (1, Ar*C*H=), 128.7 (1, 2 x Ar), 127.6 (1, Ar), 126.4 (1, 2 x Ar), 124.4 (1, ArCH=*C*H), 116.1 (2, =CH_2), 57.4 (0, COCCO), 52.6 (3, 2 x OCH_3), 40.9 (2, *C*H_2), 36.6 (2, *C*H_2), 23.3 (3, *C*H_3) ppm.

LRMS (CI)	303 ([M+H]$^+$, 100 %), 271 ([M-OCH_3]$^+$, 70 %), 243 ([M-CO_2Me]$^+$, 100 %), 183 ([M-CH_2CH=$CHPh$+H]$^+$, 80 %) amu.
HRMS	Found [M+H]$^+$: 303.1596. $C_{18}H_{22}O_4$ requires [M+H]$^+$: 303.1596.
λ_{max}/nm (ε_{max})	247 (5300).

2-(2-Methyl-allyl)-2-(3-methyl-but-2-enyl)-malonic acid dimethyl ester **307**



303

$C_9H_{14}O_4$

Mol. Wt.: 186

307

$C_{14}H_{22}O_4$

Mol. Wt.: 254

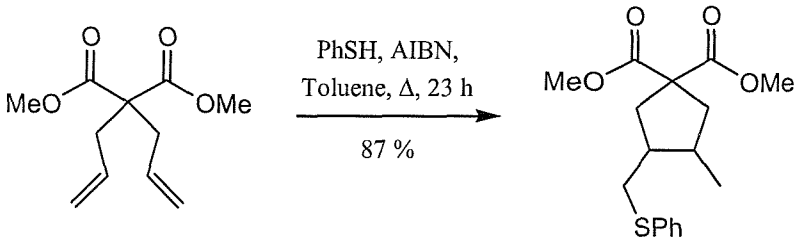
Prepared following a modified procedure of Semmelhack[91] *et al.* To a stirred suspension of sodium hydride (0.38 g, 9.60 mmol) at 0 °C, was added dropwise a solution of methallyl dimethyl malonate **303** (1.75 g, 9.41 mmol) in THF (10 mL). The reaction was allowed to warm to room temperature, then a solution of prenyl bromide (1.43 g, 9.60 mmol) in THF (10 mL) was added dropwise, after which the reaction was heated to reflux for 15 hours. It was then allowed to cool, and water (30 mL) followed by diethyl ether (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 10 % diethyl ether in petrol) gave **307** as a colourless oil (2.20 g, 8.66 mmol, 92 %).

Spectroscopic and physical data were in accordance with literature values[55].

Data for **307**:

ν_{max}/cm^{-1} (neat)	2952 (m), 2917 (w), 1731 (s), 1646 (w), 1435 (s), 1377 (m), 1274 (m), 1219 (s), 1170 (s), 1114 (w), 1055 (s), 983 (w), 899 (s).
δ_H (300 MHz, $CDCl_3$)	4.95 (1H, t, *J* 7.4 Hz, CH_2CH=), 4.84 (1H, s, =C*H*H), 4.68 (1H, s, =CH*H*), 3.67 (6H, s, 2 x OCH_3), 2.66 (2H, s, $CH_2C(CH_3)$=), 2.60 (2H, d, *J* 7.4 Hz, CH_2CH=), 1.66 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.56 (3H, s, CH_3) ppm.
δ_C (75.5 MHz, $CDCl_3$)	172.0 (0, 2 x *C*O), 140.7 (0, *C*=), 135.6 (0, *C*=), 117.9 (*C*H=), 115.6 (=*C*H_2), 57.5 (0, CO*C*CO), 52.4 (3, 2 x O*C*H_3), 40.2 (2, *C*H_2), 31.2 (2, *C*H_2), 26.1 (3, *C*H_3), 23.3 (3, *C*H_3), 18.0 (3, *C*H_3) ppm.
LRMS (CI)	255 ($[M+H]^+$, 100 %), 195 ($[M-CO_2Me]^+$, 70 %) amu.

3-Methyl-4-(phenylsulfanylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **308**



301
$C_{11}H_{16}O_4$
Mol. Wt.: 212

308
$C_{17}H_{22}O_4S$
Mol. Wt.: 322

Diallyl dimethyl malonate (0.55 g, 2.59 mmol) and thiophenol (1.14 g, 10.4 mmol) were dissolved in toluene (50 mL), and the reaction was heated to 90 °C. AIBN (0.51 g, 3.11 mmol) was added portionwise over 8 hours, then the reaction was left at 90 °C for a further 15 hours before allowing to cool to room temperature. The reaction mixture was concentrated *in vacuo* to an orange oil. Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) gave **308**, a pale yellow oil (0.73 g, 2.27 mmol, 87 %), as a mixture of diastereomers (*cis* : *trans* 5 : 1) which could not be separated by chromatography.

Data for **308** (recorded on mixture of diastereoisomers):

ν_{max}/cm^{-1} (neat)	2953 (m), 2877 (w), 1729 (s), 1583 (w), 1480 (m), 1435 (s), 1253 (s), 1153 (m), 1087 (w), 1025 (m), 941 (w), 740 (s), 690 (s)
LRMS (CI)	323 ([M+H]$^+$, 95 %), 291 ([M-OCH$_3$]$^+$, 100 %), 213 ([M-SPh]$^+$, 50 %)
HRMS	Found [M+Na]$^+$: 345.1128. $C_{17}H_{22}O_4S$ requires [M+Na]$^+$: 345.1131
λ_{max}/nm (ε_{max})	252 (6000)

***cis* isomer:**

δ_H (400 MHz, CDCl$_3$)	7.22 - 7.13 (4H, m, 4 x Ar*H*), 7.07 - 7.03 (1H, m, Ar*H*), 3.59 (3H, s, OC*H*$_3$), 3.58 (3H, s, OC*H*$_3$), 2.85 (1H, dd, *J* 12.3 Hz, 6.3 Hz, PhSC*H*H), 2.68 (1H, dd, *J* 12.3 Hz, 8.0 Hz, PhSCH*H*), 2.38 (1H, dd, *J* 12.8 Hz, 6.3 Hz, C*H*HCH), 2.34 (1H, dd, *J* 13.8 Hz, 7.0 Hz, C*H*HCH), 2.20 - 2.12 (2H, m, 2 x C*H*), 2.07 (1H, dd, *J* 12.8 Hz,

8.8 Hz, CH*H*CH), 1.92 (1H, dd, *J* 13.8 Hz, 5.2 Hz, C*H*), 0.81 (3H, d, *J* 6.8 Hz, CHCH_3) ppm + other peaks due to ca. 20 % *trans* isomer.

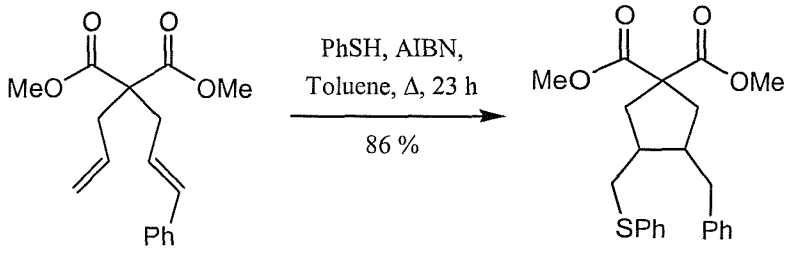
δ_C (100 MHz, $CDCl_3$) 173.3 (0, 2 x *C*O), 136.8 (0, Ar), 129.4 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.1 (1, Ar), 58.9 (0, CO*C*CO), 52.9 (3, 2 x O*C*H_3), 41.9 (1, *C*H), 41.5 (2, C*C*H_2CH), 38.4 (2, C*C*H_2CH), 35.9 (1, C*H*), 34.8 (2, PhS*C*H_2), 14.9 (3, CH*C*H_3) ppm + other peaks due to ca 20 % *trans* isomer.

***trans* isomer:**

δ_H (400 MHz, $CDCl_3$) 3.05 (1H, dd, *J* 12.3 Hz, 3.8 Hz, PhSC*H*H), 0.90 (3H, d, *J* 5.8 Hz) ppm + other peaks, obscured by dominant *cis* isomer.

δ_C (100 MHz, $CDCl_3$) 173.3 (0, 2 x *C*O), 136.8 (0, Ar), 129.2 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.0 (1, Ar), 58.3 (0, CO*C*CO), 52.9 (3, 2 x O*C*H_3), 46.1 (1, *C*H), 42.9 (2, C*C*H_2CH), 40.3 (2, C*C*H_2CH), 39.8 (1, *C*H), 37.6 (2, PhS*C*H_2), 18.0 (3, CH*C*H_3) ppm + other peaks due to dominant *cis* isomer.

3-Benzyl-4-(phenylsulfanylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **309**



305

$C_{17}H_{20}O_4$
Mol. Wt.: 288

309

$C_{23}H_{26}O_4S$
Mol. Wt.: 398

The reaction was carried out under nitrogen. Malonate **305** (1.10 g, 3.82 mmol) and thiophenol (1.98 g, 18.0 mmol) were dissolved in toluene (50 mL), and the reaction was heated to 90 °C. AIBN (0.72 g, 4.40 mmol) was added portionwise over 8 hours, then the reaction was left at 90 °C for a further 15 hours before allowing to cool to room temperature. The reaction mixture was concentrated *in vacuo* to an orange oil. Purification by chromatography (silica, 0-20 % diethyl ether in petrol) gave **309**, a pale yellow oil (1.31 g, 3.29 mmol, 86 %), as a mixture of diastereomers (*cis* : *trans* 3.5 : 1). Partial separation of the diastereoisomers was achieved by RP-HPLC.

Data for **309**:

***cis* isomer:**

ν_{max}/cm^{-1} (neat) 3026 (w), 2951 (w), 1731 (s), 1601 (w), 1583 (w), 1481 (m), 1437 (m), 1260 (s), 1197 (m), 1164 (m), 1025 (w), 740 (m), 700 (m)

δ_H (400 MHz, $CDCl_3$) 7.35 - 7.19 (10H, m, 10 x Ar*H*), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.17 (1H, dd, *J* 12.8 Hz, 5.8 Hz, PhSC*H*H), 2.88 (1H, dd, *J* 12.8 Hz, 9.0 Hz, PhSCH*H*), 2.91 - 2.81 (1H, obs., C*H*), 2.62 - 2.50 (3H, m, 3 x C*H*), 2.47 - 2.36 (2H, m, 3 x C*H*), 2.33 (1H, dd, *J* 14.0 Hz, 6.5 Hz, PhC*H*HC), 2.21 (1H, dd, *J* 13.9 Hz, 6.8 Hz, PhCH*H*C) ppm.

δ_C (100 MHz, $CDCl_3$) 173.6 (0, *C*O), 173.4 (0, *C*O), 140.9 (0, Ar), 136.7 (0, Ar), 129.7 (1, 2 x Ar), 129.3 (1, 4 x Ar), 128.9 (1, 2 x Ar), 126.5 (1, Ar), 126.4 (1, Ar), 58.9 (0, CO*C*CO), 53.2 (3, 2 x O*C*H$_3$), 43.7 (1, ring-

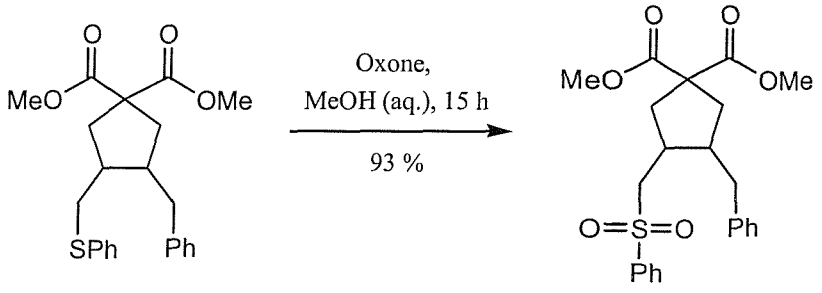
	*C*H), 41.6 (1, ring-*C*H), 38.9 (2, C*C*H_2CH), 38.6 (2, Ph*C*H_2), 35.3 (2, C*C*H_2CH), 34.5 (2, PhS*C*H_2) ppm.
LRMS (CI)	399 ([M+H]$^+$, 100 %), 367 ([M-OCH_3]$^+$, 85 %), 289 ([M-SPh]$^+$, 50 %), 91 ([PhCH_2]$^+$, 95 %)
λ_{max}/nm (ε_{max})	253 (10 100)

***trans* isomer (contains c. 20 % residual *cis* isomer):**

ν_{max}/cm^{-1} (neat)	3025 (w), 2951 (m), 1731 (s), 1583 (w), 1481 (w), 1437 (m), 1266 (s), 1197 (m), 1164 (m), 1105 (w), 1025 (w), 740 (s).
δ_H (400 MHz, $CDCl_3$)	7.37 - 7.15 (10H, m, 10 x Ar*H*), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.17 (1H, dd, *J* 12.8 Hz, 6.0 Hz, PhSC*H*H), 2.93 - 2.86 (1H, obs., PhSCH*H*), 2.62 - 2.51 (3H, m, 3 x C*H*), 2.47 - 2.39 (2H, m, 2 x C*H*), 2.34 (1H, dd, *J* 13.8 Hz, 6.2 Hz, PhC*H*HC), 2.21 (1H, dd, *J* 13.8 Hz, 6.8 Hz, PhCH*H*C), 2.01 (1H, dd, *J* 13.6 Hz, 9.8 Hz, C*H*) ppm + other peaks due to residual *cis* isomer.
δ_C (100 MHz, $CDCl_3$)	173.2 (0, 2 x *C*O), 140.7 (0, Ar), 137.0 (0, Ar), 129.9 (1, Ar), 129.7 (1, 2 x Ar), 129.3 (1, 4 x Ar), 128.8 (1, 2 x Ar), 126.5 (1, Ar), 58.7 (0, CO*C*CO), 53.2 (3, O*C*H_3), 52.9 (3, O*C*H_3), 46.4 (1, ring-*C*H), 44.6 (1, ring-*C*H), 40.7 (2, *C*H_2), 40.3 (2, *C*H_2), 35.3 (2, *C*H_2), 34.5 (2, *C*H_2) ppm + other peaks due to residual *cis* isomer.
LRMS (CI)	399 ([M+H]$^+$, 100 %), 367 ([M-OCH_3]$^+$, 75 %), 289 ([M-SPh]$^+$, 55 %), 91 ([PhCH_2]$^+$, 70 %)
λ_{max}/nm (ε_{max})	254 (8600)

HRMS (recorded on mixture of diastereomers)	Found M$^+$: 398.1550. $C_{23}H_{26}O_4S$ requires M$^+$: 398.1552

Derivatisation to 3-Benzenesulfonylmethyl-4-benzyl-cyclopentane-1,1-dicarboxylic acid dimethyl ester **332**:



309

$C_{23}H_{26}O_4S$
Mol. Wt.:398

332

$C_{23}H_{26}O_6S$
Mol. Wt.: 430

Prepared following a modified procedure of Booker-Milburn[96] *et al.* To a stirred solution of **309** (0.50 g, 1.26 mmol, mixture of stereoisomers in *cis* : *trans* ratio 3.5 : 1) in methanol (25 mL) at 0 °C, was added dropwise a solution of Oxone® (2.37 g, 3.85 mmol) in water (25 mL). The reaction was allowed to warm to room temperature and stirred for 15 hours, before being extracted into chloroform (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 50% ethyl acetate in petrol) gave **332**, a pale yellow oil (0.50 g, 1.16 mmol, 93%), as a mixture of diastereoisomers (*cis* : *trans* 3.5 : 1) which could not be separated by chromatography.

Data for **332** (recorded on a mixture of diastereomers):

ν_{max}/cm^{-1} (neat)	3027 (w), 2953 (w), 1730 (s), 1602 (w), 1447 (m), 1307 (m), 1270 (s), 1149 (s), 1086 (m), 883 (w), 745 (w), 718 (m), 618 (w)
LRMS (CI)	448 ($[M+NH_4]^+$, 30 %), 431 ($[M+H]^+$, 20 %), 399 ($[M-OCH_3]^+$, 25 %), 289 ($[M-Ts]^+$, 25 %), 257 ($[M-Ts-H-OCH_3]^+$, 70%), 91 ($[PhCH_2]^+$, 100%) amu.
HRMS	Found $[M+H]^+$: 431.1525. $C_{23}H_{26}O_6S$ requires $[M+H]^+$: 431.1528
λ_{max}/nm (ε_{max})	254 (9200)
***cis* isomer:**	
δ_H (300 MHz, $CDCl_3$)	7.71 - 7.63 (2H, m, 2 x Ar*H*), 7.49 - 7.43 (1H, m, Ar*H*), 7.38 - 7.32 (1H, m, Ar*H*), 7.07 - 6.80 (6H, m, 6 x Ar*H*), 3.54 (3H, s, OCH_3),

3.48 (3H, s, OC*H*$_3$), 3.09 (1H, dd, *J* 14.0 Hz, 5.5 Hz, $PhSO_2CHH$), 2.97 (1H, dd, *J* 14.0 Hz, 8.6 Hz, $PhSO_2CHH$), 2.49 (1H, dd, *J* 13.3 Hz, 5.5 Hz, CC*H*HC), 2.43 - 2.25 (3H, m, 3 x C*H*), 2.15 (1H, dd, *J* 13.3 Hz, 8.0 Hz, C*H*), 2.10 (1H, dd, *J* 13.0 Hz, 11.0 Hz, C*H*), 2.01 (1H, dd, *J* 14.6 Hz, 7.0 Hz, C*H*), 1.89 (1H, dd, *J* 14.6 Hz, 6.0 Hz, C*H*) ppm + other peaks due to *trans* isomer.

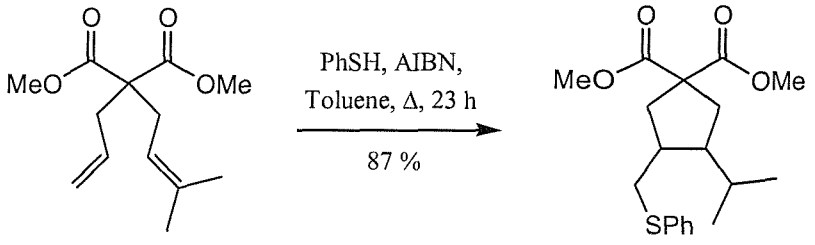
δ_C (75.5 MHz, $CDCl_3$) 173.2 (0, *C*O), 172.8 (0, *C*O), 139.8 (0, Ar), 134.0 (1, Ar), 129.6 (1, 2 x Ar), 129.0 (1, 2 x Ar), 128.7 (0, Ar), 128.6 (1, 2 x Ar), 128.1 (1, 2 x Ar), 126.4 (1, Ar), 58.2 (0, CO*C*CO), 56.3 (2, $PhSO_2CH_2$), 53.1 (3, 2 x O*C*H$_3$), 43.8 (ring-*C*H), 38.4 (2, *C*H$_2$), 37.8 (2, *C*H$_2$), 37.1 (ring-*C*H), 34.8 (2, *C*H$_2$) ppm + other peaks due to *trans* isomer.

***trans* isomer:**

δ_H (400 MHz, $CDCl_3$) All peaks obscured by dominant *cis* isomer.

δ_C (100 MHz, $CDCl_3$) 174.2 (0, *C*O), 173.2 (0, *C*O), 139.7 (0, Ar), 134.0 (1, Ar), 129.6 (1, 2 x Ar), 129.0 (1, 2 x Ar), 128.7 (1, 2 x Ar), 128.6 (0, Ar), 128.1 (1, 2 x Ar), 126.4 (1, Ar), 60.4 (2, $PhSO_2CH_2$), 58.8 (0, CO*C*CO), 53.1 (3, 2 x OCH$_3$), 46.4 (1, ring-*C*H), 39.9 (2, *C*H$_2$), 39.8 (2, *C*H$_2$), 39.6 (2, *C*H$_2$), 38.9 (1, ring-*C*H) ppm + other peaks due to *cis* isomer.

3-Isopropyl-4-(phenylsulfanylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **310**



304
$C_{13}H_{20}O_4$
Mol. Wt.: 240

310
$C_{19}H_{26}O_4S$
Mol. Wt.: 350

The reaction was carried out under nitrogen. Malonate **304** (0.80 g, 3.33 mmol) and thiophenol (1.65 g, 15.0 mmol) were dissolved in toluene (50 mL), and the reaction was heated to 90 °C. AIBN (0.66 g, 4.00 mmol) was added portionwise over 8 hours, and the reaction was left at 90 °C for a further 15 hours before allowing to cool to room temperature. The reaction mixture was concentrated *in vacuo* to an orange oil. Purification by chromatography (silica, 0-20 % diethyl ether in petrol) gave **310**, a pale yellow oil (1.02 g, 2.93 mmol, 87 %), as a mixture of diastereomers (*cis* : *trans* 3: 1) which could not be separated by chromatography.

Data for **310** (recorded on a mixture of diastereomers):

ν_{max}/cm^{-1} (neat)	2955 (m), 2872 (w), 1731 (s), 1583 (w), 1437 (m), 1368 (w), 1252 (s), 1196 (m), 1166 (m), 1089 (m), 1025 (w), 742 (m), 692 (m)
LRMS (CI)	368 ($[M+NH_4]^+$, 20 %), 351 ($[M+H]^+$, 90 %), 319 ($[M-OCH_3]$, 241 ($[M-SPh]^+$, 25 %)
HRMS	Found $[M+Na]^+$: 373.1448. $C_{19}H_{26}O_4S$ requires $[M+Na]^+$: 373.1444
λ_{max}/nm (ε_{max})	252 (5700)
***cis* isomer:**	
δ_H (400 MHz, $CDCl_3$)	7.42 - 7.37 (2H, m, 2 x Ar*H*), 7.34 - 7.30 (2H, m, 2 x Ar*H*), 7.25 - 7.20 (1H, m, Ar*H*), 3.77 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 3.10 (1H, dd, *J* 12.5 Hz, 3.3 Hz, PhSC*H*H), 2.71 (1H, dd, *J* 14.5 Hz, 1.3 Hz, CC*H*HCH), 2.57 (1H, t, *J* 12.5 Hz, PhSCH*H*), 2.49 - 2.41 (2H, m, 2 x C*H*), 2.35 - 2.27 (1H, m, CCH_2CH), 2.04 (1H, app. t, *J* 13.0 Hz, C*H*), 1.78 - 1.68 (1H, m, CCH_2CH), 1.67 - 1.59 (1H, m,

C*H*$(CH_3)_2$), 0.97 (3H, d, *J* 6.3 Hz, CHC*H*$_3$), 0.91 (3H, d, *J* 6.3 Hz, CHC*H*$_3$) ppm.

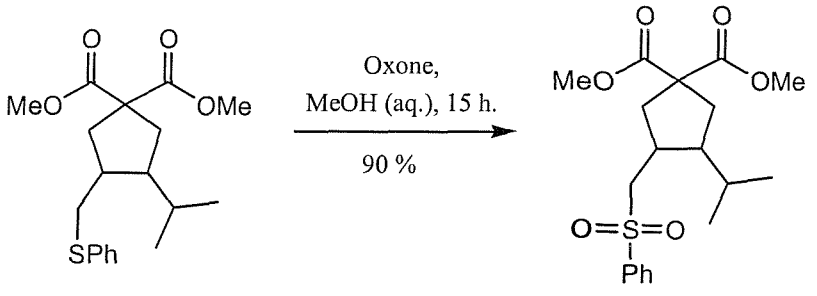
δ_C (100 MHz, $CDCl_3$) 173.6 (0, *C*O), 173.5 (0, *C*O), 136.5 (0, Ar), 130.2 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.4 (1, Ar), 58.5 (0, CO*C*CO), 53.0 (3, 2 x O*C*H_3), 51.6 (1, CCH_2*C*H), 40.0 (1, CCH_2*C*H), 38.2 (2, C*C*H_2CH), 37.5 (2, C*C*H_2CH), 33.9 (2, PhS*C*H_2), 28.5 (1, *C*H$(CH_3)_2$), 22.2 (3, *C*H_3), 21.9 (3, *C*H_3) ppm.

***trans* isomer:**

δ_H (400 MHz, $CDCl_3$) 7.42 - 7.36 (2H, m, 2 x Ar*H*), 7.34 - 7.29 (2H, m, 2 x Ar*H*), 7.25 - 7.21 (1H, m, Ar*H*), 3.77 (3H, s, OC*H*$_3$), 3.75 (3H, s, OCH_3), 3.20 (1H, dd, *J* 12.4 Hz, 4.0 Hz, PhSC*H*H), 2.77 (1H, dd, *J* 12.5 Hz, 9.8 Hz, PhSCH*H*), 2.61 (1H, dd, *J* 13.6 Hz, 8.0 Hz, CC*H*HCH), 2.49 - 2.41 (1H, m, C*H*), 2.34 - 2.27 (1H, m, CCH_2C*H*), 2.19 (1H, dd, *J* 13.5 Hz, 8.5 Hz, C*H*), 1.77 - 1.66 (2H, m, CCH_2C*H* & C*H*$(CH_3)_2$), 0.94 (3H, d, *J* 6.8 Hz, CHC*H*$_3$), 0.85 (3H, d, *J* 6.5 Hz, CHC*H*$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 173.6 (0, *C*O), 173.5 (0, *C*O), 136.5 (0, Ar), 129.6 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.2 (1, Ar), 58.5 (0, CO*C*CO), 52.9 (3, 2 x O*C*H_3), 50.8 (1, CCH_2*C*H), 41.4 (1, CCH_2*C*H), 39.8 (2, C*C*H_2CH), 38.9 (2, PhS*C*H_2), 36.2 (2, C*C*H_2CH), 29.4 (1, *C*H$(CH_3)_2$), 22.1 (3, *C*H_3), 17.9 (3, *C*H_3) ppm.

Derivatisation to 3-Benzenesulfonylmethyl-4-isopropyl-cyclopentane-1,1-dicarboxylic acid dimethyl ester **333**:



310
$C_{19}H_{26}O_4S$
Mol. Wt.: 350

333
$C_{19}H_{26}O_6S$
Mol. Wt.: 382

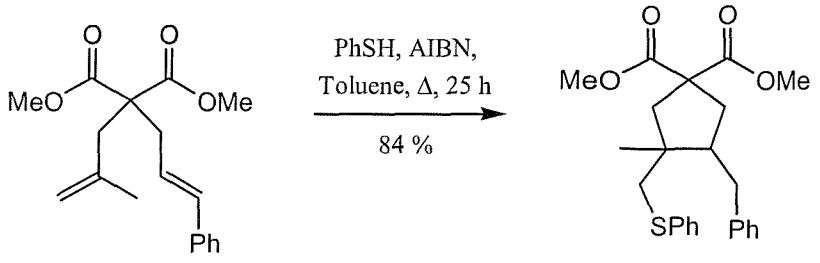
Prepared following a modified procedure of Booker-Milburn[96] *et al.* To a stirred solution of **310** (0.53 g, 1.51 mmol) as a mixture of stereoisomers (*cis* : *trans* 3: 1) in methanol (25 mL) at 0 °C, was added dropwise a solution of Oxone® (2.37 g, 3.85 mmol) in water (25 mL). The reaction was allowed to warm to room temperature and stirred for 15 hours, before being extracted into chloroform (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 50% ethyl acetate in petrol) gave **333**, a pale yellow oil (0.52 g, 1.36 mmol, 90%), as a mixture of stereoisomers (*cis* : *trans* 3 : 1) that could not be separated by chromatography.

Data for **333** (recorded on a mixture of diastereomers):

ν_{max}/cm^{-1} (neat)	2955 (m), 2877 (w), 1730 (s), 1447 (m), 1307 (m), 1258 (s), 1201 (m), 1148 (s), 1086 (m), 868 (w), 751 (w), 717 (w), 689 (w)
LRMS (CI)	400 ($[M+NH_4]^+$, 10 %), 368 ($[M-CH_3+H]^+$, 20 %), 351 ($[M-OCH_3]^+$, 50 %), 241 ($[M-PhSO_2]^+$, 70 %), 181 ($[M-PhSO_2-CO_2Me-H]^+$, 100 %) amu.
HRMS	Found $[M+NH_4]^+$: 400.1796. $C_{19}H_{26}O_6S$ requires $[M+NH_4]^+$: 400.1794
λ_{max}/nm (ε_{max})	253 (8700)
***cis* isomer:**	
δ_H (400 MHz, $CDCl_3$)	3.18 - 3.00 (2H, m, PhSOC*H*$_2$), 2.69 - 2.53 (2H, m, 2 x C*H*), 2.49 - 2.36 (2H, m, 2 x C*H*), 2.22 - 2.15 (1H, m, C*H*), 1.81 (1H, t, *J* 13.0

	Hz, C*H*), 1.73 - 1.63 (1H, m, C*H*), 0.93 (3H, d, *J* 6.5 Hz, CHCH_3), 0.81 (3H, d, *J* 6.6 Hz, CHCH_3) ppm + other peaks obscured by *trans* isomer.
δ_C (100 MHz, $CDCl_3$)	58.3 (0, CO*C*CO), 54.4 (2, PhSO_2*C*H_2), 53.2 (3, O*C*H_3), 53.1 (3, O*C*H_3), 51.8 (1, ring-*C*H), 38.4 (2, ring-*C*H_2), 37.8 (2, ring-*C*H_2), 35.7 (1, ring-*C*H), 28.6 (1, *C*H(CH_3)$_2$), 21.9 (3, *C*H_3), 21.2 (3, *C*H_3) ppm + other peaks obscured by *trans* isomer.
***trans* isomer:**	
δ_H (400 MHz, $CDCl_3$)	All peaks obscured by dominant *cis* isomer.
δ_C (100 MHz, $CDCl_3$)	61.0 (2, PhSO_2*C*H_2), 58.9 (0, CO*C*CO), 52.9 (3, 2 x O*C*H_3), 50.8 (1, ring-*C*H), 38.2 (2, ring-*C*H_2), 37.4 (2, ring-*C*H_2), 36.1 (1, ring-*C*H), 29.3 (1, *C*H(CH_3)$_2$), 21.8 (3, *C*H_3), 17.8 (3, *C*H_3) ppm + other peaks obscured by dominant *cis* isomer.

4-Benzyl-3-methyl-3-(phenylsulfanylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **311**



306

$C_{18}H_{22}O_4$
Mol. Wt.: 302

311

$C_{24}H_{28}O_4S$
Mol. Wt.: 412

The reaction was carried out under nitrogen. Malonate **306** (0.72 g, 2.38 mmol) and thiophenol (1.21 g, 11.0 mmol) were dissolved in toluene (50 mL) and the reaction was heated to 90 °C. AIBN (0.59 g, 3.60 mmol) was added portionwise over 10 hours, then the reaction was left at 90 °C for a further 15 hours before allowing to cool to room temperature. The reaction mixture was concentrated *in vacuo* to an orange oil. Purification by chromatography (silica, 0 - 20 % diethyl ether in petrol) gave **311**, a pale yellow oil (0.82 g, 2.00 mmol, 84 %), as a mixture of diastereomers (*cis* : *trans* 1 : 1), which were separated by RP-HPLC.

Data for **311**:

***cis* isomer:**

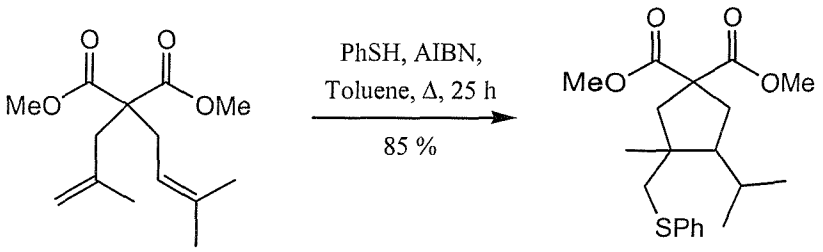
ν_{max}/cm^{-1} (neat) 3025 (w), 2952 (w), 1732 (s), 1583 (w), 1481 (w), 1437 (m), 1380 (w), 1265 (s), 1201 (m), 1165 (m), 1025 (w), 740 (m), 692 (m)

δ_H (400 MHz, $CDCl_3$) 7.31 - 7.08 (10H, m, 10 x Ar*H*), 3.59 (6H, s, 2 x OCH_3), 2.93 (1H, d, *J* 11.8 Hz, SC*H*H), 2.88 (1H, d, *J* 11.9 Hz, SCH*H*), 2.78 (1H, dd, *J* 13.3 Hz, 3.8 Hz, CC*H*HCH), 2.67 (1H, d, *J* 14.3 Hz, CC*H*HC), 2.32 (1H, dd, *J* 13.0 Hz, 11.6 Hz, CCH*H*CH), 2.22 (1H, dd, *J* 14.1 Hz, 11.3 Hz, PhC*H*H), 2.15 (1H, d, *J* 14.3 Hz, CCH*H*C), 2.14 (1H, dd, *J* 14.2 Hz, 7.5 Hz, PhCH*H*), 2.14 - 1.96 (1H, m, C*H*), 1.13 (3H, CCH_3) ppm

δ_C (100 MHz, $CDCl_3$) 173.5 (0, 2 x *C*O), 141.2 (0, Ar), 138.1 (0, Ar), 130.1 (1, 2 x Ar), 129.3 (1, 2 x Ar), 129.1 (1, 2 x Ar), 128.9 (1, 2 x Ar), 126.4 (1, 2 x

	Ar), 57.8 (0, CO*C*CO), 53.3 (3, O*C*H$_3$), 53.2 (3, O*C*H$_3$), 52.5 (1, *C*HCH$_2$Ph), 46.2 (0, *C*CH$_3$), 45.4 (2, C*C*H$_2$C), 41.6 (2, *C*H$_2$SPh), 38.8 (2, Ph*C*H$_2$), 35.8 (2, C*C*H$_2$CH), 25.8 (3, C*C*H$_3$) ppm.
LRMS (CI)	412 ([M]$^+$, 35 %), 381 ([M-OCH$_3$]$^+$, 40 %), 91 ([PhCH$_2$]$^+$, 100 %)
λ_{max}/nm (ε_{max})	252 (9400)
***trans* isomer:**	
ν_{max}/cm^{-1} (neat)	2953 (m), 1731 (s), 1651 (w), 1587 (w), 1480 (w), 1435 (m), 1270 (s), 1201 (m), 1163 (m), 1025 (w), 952 (w), 688 (w)
δ_H (400 MHz, CDCl$_3$)	7.40 - 7.09 (10H, m, 10 x Ar*H*), 3.77 (3H, s, OC*H*$_3$), 3.71 (3H, s, OC*H*$_3$), 3.09 (1H, d, *J* 12.3 Hz, SC*H*H), 3.00 (1H, d, *J* 12.3 Hz, SCH*H*), 2.80 (1H, dd, *J* 13.3 Hz, 4.0 Hz, CC*H*HCH), 2.54 (1H, d, *J* 14.3 Hz, C*H*HC), 2.42 (1H, dd, *J* 13.3 Hz, 10.0 Hz, CCH*H*CH), 2.36 (1H, d, *J* 14.3 Hz, CH*H*C), 2.38 - 2.24 (2H, m, 3 x C*H*), 2.16 (1H, dd, *J* 12.3 Hz, 11.3 Hz, CCH*H*CH), 1.11 (3H, s, CC*H*$_3$) ppm.
δ_C (100 MHz, CDCl$_3$)	173.2 (0, 2 x *C*O), 140.8 (0, Ar), 137.9 (0, Ar), 129.4 (1, 2 x Ar), 129.1 (1, 2 x Ar), 128.9 (1, 2 x Ar), 128.6 (1, 2 x Ar), 126.1 (1, Ar), 126.0 (1, Ar), 57.2 (0, CO*C*CO), 53.0 (3, 2 x O*C*H$_3$), 49.0 (1, *C*HCH$_2$Ph), 46.4 (2, C*C*H$_2$C), 45.8 (0, *C*CH$_3$), 45.6 (2, *C*H$_2$SPh), 39.0 (2, C*C*H$_2$CH), 36.0 (2, C*C*H$_2$CH), 20.9 (3, C*C*H$_3$) ppm.
LRMS (CI)	412 ([M]$^+$, 70 %), 381 ([M-OCH$_3$]$^+$, 100 %), 91 ([PhCH$_2$]$^+$, 85 %)
λ_{max}/nm (ε_{max})	253 (8100)
HRMS (recorded on mixture of diastereomers)	Found [M+H]$^+$: 413.1792. $C_{24}H_{28}O_4S$ requires [M+H]$^+$: 413.1781

4-Isopropyl-3-methyl-3-(phenylsulfanylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **312**



307
$C_{14}H_{22}O_4$
Mol. Wt.: 254

312
$C_{20}H_{28}O_4S$
Mol. Wt.: 364

The reaction was carried out under nitrogen. Malonate **307** (0.83 g, 3.27 mmol) and thiophenol (1.45 g, 13.0 mmol) were dissolved in toluene (50 mL), and the reaction was heated to 90 °C. AIBN (0.81 g, 4.94 mmol) was added portionwise over 10 hours, then the reaction was left at 90 °C for a further 15 hours before being cooled to room temperature. The reaction mixture was concentrated *in vacuo* to an orange oil. Purification by chromatography (silica, 0-20 % diethyl ether in petrol) gave **312**, a pale yellow oil (1.01 g, 2.78 mmol, 85 %), as a mixture of diastereomers (*cis* : *trans* 1 : 1) which were separated by RP-HPLC.

Data for **312**:

***cis* isomer:**

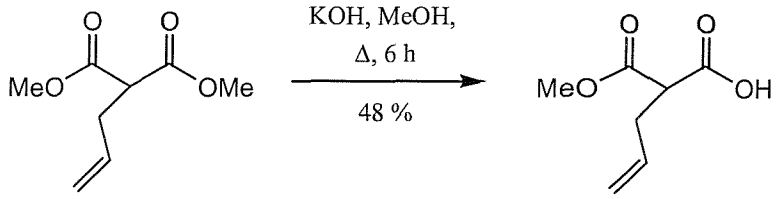
ν_{max}/cm^{-1} (neat) 2955 (m), 2872 (w), 1732 (s), 1583 (w), 1436 (m), 1382 (w), 1252 (s), 1199 (m), 1069 (w), 1025 (w), 867 (w), 740 (m), 691 (m)

δ_H (400 MHz, $CDCl_3$) 7.29 - 7.05 (5H, m, Ar*H*), 3.66 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 2.91 (1H, dd, *J* 11.8 Hz, 1.5 Hz, SC*H*H), 2.86 (1H, d, *J* 11.8 Hz, SCH*H*), 2.66 (1H, d, *J* 14.5 Hz, CC*H*HC), 2.34 (1H, dd, *J* 13.8 Hz, 7.3 Hz, CHC*H*HC), 2.19 (1H, dd, *J* 13.8 Hz, 12.8 Hz, CHCH*H*C), 2.12 (1H, dd, *J* 14.5 Hz, CCH*H*C), 1.66 - 1.58 (1H, m, C*H*$(CH_3)_2$), 1.46 (1H, ddd, *J* 12.8 Hz, 7.3 Hz, 5.52 Hz, C*H*CH$(CH_3)_2$), 1.16 (3H, s, CCH_3), 0.93 (3H, d, *J* 6.5 Hz, CHCH_3), 0.85 (3H, d, *J* 6.5 Hz, CHCH_3) ppm.

δ_C (100 MHz, $CDCl_3$) 173.5 (0, *C*O), 173.3 (0, *C*O), 138.0 (0, Ar), 129.5 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.0 (1, Ar), 57.1 (1, ring *C*H), 56.9 (0, CO*C*CO), 53.0 (3, 2 x O*C*H_3), 46.1 (2, *C*H_2), 45.7 (0, *C*CH_3), 41.1

	(2, PhSCH_2), 38.8 (2, CH_2), 28.8 ($CH(CH_3)_2$, 27.6 (3, CH_3), 23.2 (3, CHCH_3), 23.1 (3, CHCH_3) ppm.
LRMS (CI)	382 ($[M+NH_4]^+$, 10 %), 365 ($[M+H]^+$, 90 %), 333 ($[M-OCH_3]^+$, 100 %)
λ_{max}/nm (ε_{max})	251 (4600)
***trans* isomer:**	
ν_{max}/cm^{-1} (neat)	2954 (m), 2872 (w), 1732 (s), 1583 (w), 1436 (m), 1382 (w), 1252 (s), 1199 (m), 1144 (w), 1069 (w), 866 (w), 746 (m), 691 (m)
δ_H (400 MHz, $CDCl_3$)	7.31 - 7.09 (5H, m, Ar*H*), 3.63 (6H, s, 2 x OCH_3), 3.09 (1H, d, *J* 12.0 Hz, SC*H*H), 2.95 (1H, d, *J* 12.0 Hz, SCH*H*), 2.45 (1H, d, *J* 14.3 Hz, CC*H*HC), 2.44 (1H, dd, *J* 13.5 Hz, 6.5 Hz, CC*H*HCH), 2.17 (1H, d, *J* 14.3 Hz, CCH*H*C), 1.98 (1H, dd, *J* 13.5 Hz, 12.3 Hz, CCH*H*CH), 1.64 - 1.50 (2H, m, C*HCH*), 0.95 (3H, s, CCH_3), 0.88 (3H, d, *J* 6.3 Hz, CHCH_3), 0.84 (3H, d, *J* 6.3 Hz, CHCH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	173.4 (0, *C*O), 173.3 (0, *C*O), 138.1 (0, Ar), 129.5 (1, 2 x Ar), 129.0 (1, 2 x Ar), 126.0 (1, Ar), 56.8 (0, CO*C*CO), 53.6 (1, ring *C*H), 52.9 (3, 2 x OCH_3), 47.2 (2, PhSCH_2), 47.2 (2, CH_2), 45.8 (0, *C*CH_3), 38.4 (2, CH_2), 28.8 ($CH(CH_3)_2$), 23.0 (3, CHCH_3), 22.6 (3, CHCH_3), 21.2 (3, CH_3) ppm.
LRMS (CI)	382 ($[M+NH_4]^+$, 5 %), 364 ($[M]^+$, 90 %), 333 ($[M-OCH_3]^+$, 100 %)
λ_{max}/nm (ε_{max})	254 (6200)
HRMS (recorded on mixture of diastereomers)	Found $[M+Na]^+$: 387.1596. $C_{20}H_{28}O_4S$ requires $[M+Na]^+$: 387.1600

2-Allyl-malonic acid monomethyl ester **324**



302
$C_8H_{12}O_4$
Mol. Wt.: 172

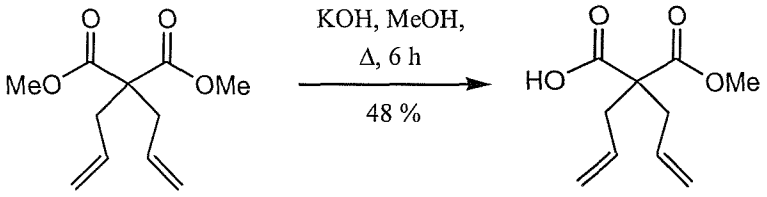
324
$C_7H_{10}O_4$
Mol. Wt.: 158

Prepared following a modified procedure of Semmelhack[91] *et al.* **302** (2.35 g, 13.7 mmol) and potassium hydroxide (0.77 g, 13.7 mmol) were dissolved in methanol (50 mL), and heated to reflux for 6 hours, then allowed to cool. 2M HCl (aq, 15 mL) was added, followed by water (20 mL) and diethyl ether (30 mL). The aqueous phase was then extracted into diethyl ether (4 x 20 mL). The organic portions were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 5 % methanol in dichloromethane) gave **324** as a pale yellow oil (1.04 g, 6.58 mmol, 48 %).

Data for **324**:

ν_{max}/cm^{-1} (neat)	3400 - 3100 (bs), 2957 (w), 1715 (s), 1644 (w), 1438 (m), 1340 (w), 1240 (m), 1164 (m), 1054 (w), 923 (m), 792 (w), 714 (m)
δ_H (300 MHz, $CDCl_3$)	10.63 - 10.42 (1H, bs, COO*H*), 5.78 (1H, ddt, *J* 16.9 Hz, 10.3 Hz, 7.0 Hz, C*H*=CH_2), 5.18-5.07 (2H, m, CH=CH_2), 3.76 (3H, s, OCH_3), 3.51 (1H, t, *J* 7.7 Hz, COC*H*CO), 2.67 (2H, t, *J* 7.2 Hz, CH_2CH=CH_2)
δ_C (75.5 MHz, $CDCl_3$)	174.8 (0, *C*O), 169.3 (0, *C*O), 133.6 (1, *C*H=CH_2), 118.2 (2, CH=*C*H_2), 52.9 (3, O*C*H_3), 51.5 (1, CO*C*HCO), 32.9 (*C*H_2CH=)
LRMS (ES-)	157 ([M-H]$^-$, 100 %)
HRMS	Found M^+: 158.0584. $C_7H_{10}O_4$ requires M^+: 158.0579

2,2-Diallyl-malonic acid monomethyl ester **317**



301
$C_{11}H_{16}O_4$
Mol. Wt.: 212

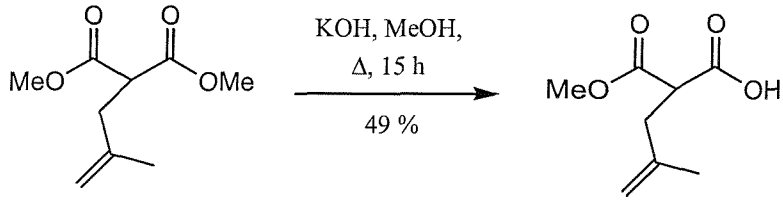
317
$C_{10}H_{14}O_4$
Mol. Wt.: 198

Prepared following a modified procedure of Semmelhack[91] *et al.* **301** (2.50 g, 11.8 mmol) and potassium hydroxide (0.66 g, 11.8 mmol) was dissolved in methanol (50 mL). The reaction was heated to reflux for 6 hours, then allowed to cool. 2M HCl (aq, 15 mL) was added, followed by water (20 mL) and diethyl ether (30 mL). The aqueous phase was then extracted into diethyl ether (4 x 20 mL). The organic portions were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 5 % methanol in dichloromethane) gave **317** as a colourless oil (1.12 g, 5.66 mmol, 48 %).

Data for **317**:

ν_{max}/cm^{-1} (neat)	3400-3100 (bs), 3080 (w), 2955 (w), 1711 (s), 1642 (m), 1438 (m), 1293 (w), 1214 (s), 1143 (m), 994 (w), 922 (m), 800 (w), 714 (w)
δ_H (300 MHz, $CDCl_3$)	9.71-9.45 (1H, br s, COO*H*), 5.72-5.56 (2H, m, 2 x C*H*=CH_2), 5.16-5.04 (4H, m, 2 x CH=CH_2), 3.71 (3H, s, OCH_3), 2.61 (4H, d, *J* 7.2 Hz, 2 x CH_2CH=)
δ_C (75.5 MHz, $CDCl_3$)	176.2 (0, *C*O), 171.5 (0, *C*O), 132.0 (1, 2 x *C*H=CH_2), 119.7 (2 x CH=*C*H_2), 57.8 (0, CO*C*CO), 52.8 (3, O*C*H_3), 37.2 (2, 2 x *C*H_2CH=)
LRMS (ES-)	197 ([M-H]$^-$, 100 %)
HRMS	Found [M+Na]$^+$: 221.0783. $C_{10}H_{14}O_4Na$ requires [M+Na]$^+$: 221.0784

2-(2-Methyl-allyl)-malonic acid monomethyl ester **334**



303
$C_9H_{14}O_4$
Mol. Wt.: 186

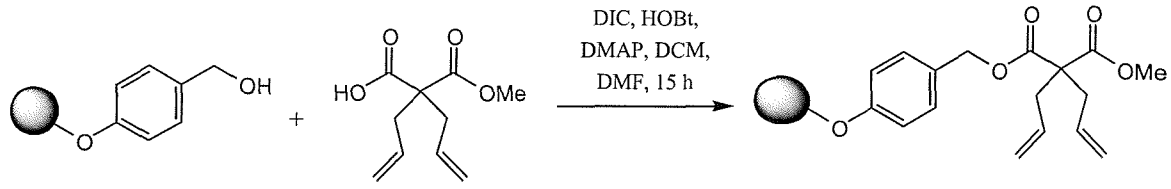
334
$C_8H_{12}O_4$
Mol. Wt.: 172

Prepared following a modified procedure of Semmelhack[91] *et al.* **303** (1.50 g, 8.10 mmol) and potassium hydroxide (0.45 g, 8.10 mmol) were dissolved in methanol (50 mL). The reaction was heated to reflux for 15 hours, then allowed to cool. 2M HCl (aq, 4 mL) was added, followed by water (20 mL) and diethyl ether (20 mL). The aqueous phase was then extracted into diethyl ether (4 x 20 mL). The organic portions were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 5 % methanol in dichloromethane) gave **334** as a pale yellow oil (0.68 g, 3.95 mmol, 49 %).

Data for **334**:

ν_{max}/cm^{-1} (neat)	3400-3100 (bs), 2957 (w), 1717 (s), 1651 (w), 1504 (w), 1437 (m), 1282 (w), 1158 (m), 1049 (w), 897 (m), 788 (w), 714 (m)
δ_H (300 MHz, $CDCl_3$)	11.15-10.97 (1H, br s, COO*H*), 4.80 (1H, s, =C*H*H), 4.73 (1H, s, =CH*H*), 3.75 (3H, s, OCH_3), 3.65 (1H, t, *J* 7.7 Hz, COC*H*CO), 2.62 (2H, d, *J* 7.6 Hz), 1.74 (3H, s, CH_3)
δ_C (75.5 MHz, $CDCl_3$)	175.2 (0, *C*O), 169.4 (0, *C*O), 141.3 (0, *C*(CH_3)=CH_2), 112.7 (2, =*C*H_2), 52.9 (3, O*C*H_3), 50.4 (1, CO*C*HCO), 36.5 (2, *C*H_2), 22.4 (3, *C*H_3)
LRMS (ES-)	171 ([M-H]$^-$, 70 %), 343 (2M-H]$^-$, 100 %)
HRMS	Found [M+Na]$^+$: 195.0628. $C_8H_{12}O_4Na$ requires [M+Na]$^+$: 195.0628

Preparation of Resin-Bound Diene **318**



317
$C_{10}H_{14}O_4$
Mol. Wt.: 198

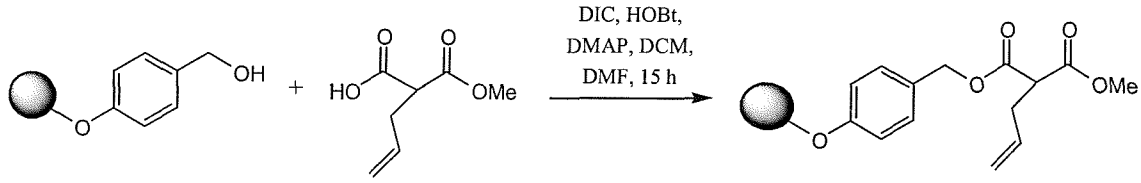
318

Prepared following the procedure of Bennet[97] *et al.* **317** (0.95 g, 4.80 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (0.65 g, 4.81 mmol) were dissolved in DMF (3 mL), and added to Wang resin (1.70 mmol g^{-1} active sites, 1.40 g, 2.38 mmol) swollen in DCM (14 mL) with DMF (2 mL) for 30 minutes. Diisopropylcarbodiimide (DIC) (0.61 g, 4.83 mmol) was then added to the reaction mixture, and finally, in a separate flask, 4-dimethylaminopyridine (DMAP) (0.061 g, 0.50 mmol) was dissolved in DMF (2 mL) then added to the resin. The reaction was shaken at room temperature for 15 hours, then the beads were collected by filtration and washed with dichloromethane (3 x 10 mL), THF / H_2O (3 x 10 mL 1:1), methanol (3 x 10mL) and diethyl ether (3 x 10 mL) before drying *in vacuo*.

Data for **318**:

ν_{max}/cm^{-1} (solid phase) 3026 (w), 2920 (m), 1732 (s), 1602 (m), 1584 (w), 1510 (s), 1452 (s), 1220 (s), 1155 (m), 1009 (m), 825 (m), 755 (s), 698 (s)

Preparation of Resin-Bound Alkene **325**



324

$C_7H_{10}O_4$

Mol. Wt.: 158

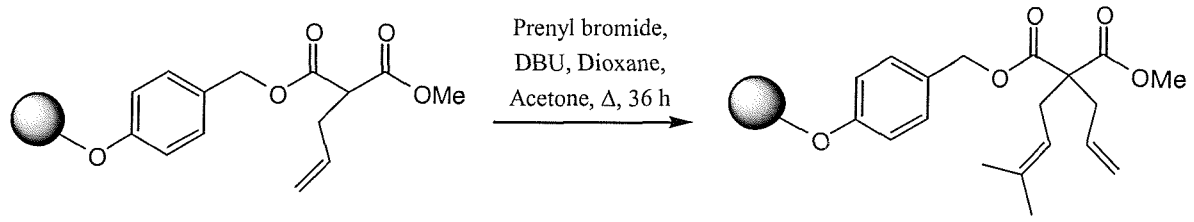
325

Prepared following the procedure of Bennet[97] *et al.* Wang resin (1.70 mmol g^{-1} active sites, 1.60 g, 2.72 mmol) was swollen in DCM (20 mL) with DMF (2 mL) for 30 minutes before **324** (0.85 g, 5.38 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (0.73 g, 5.40 mmol) dissolved in DMF (3 mL) were added. Diisopropylcarbodiimide (DIC) (0.68 g, 5.39 mmol) was then added, followed by 4-dimethylaminopyridine (DMAP) (0.037 g, 0.30 mmol) in DMF (2 mL). The reaction mixture was then shaken at room temperature for 15 hours, before the beads were collected by filtration and washed with dichloromethane (3 x 10 mL), 1:1 THF / H_2O (3 x 10 mL), methanol (3 x 10mL) and diethyl ether (3 x 10 mL) then dried *in vacuo*.

Data for **325**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 2852 (w), 1734 (s), 1602 (m), 1584 (w), 1510 (s), 1451 (s), 1376 (w), 1220 (s), 1172 (m), 1015 (s), 823 (m)

Preparation of Resin-Bound Diene **326**



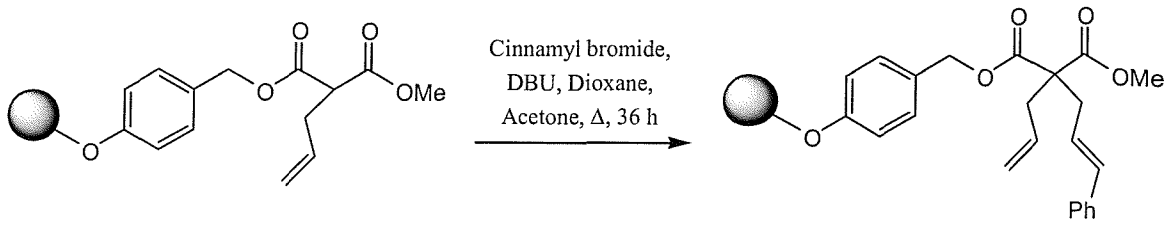
325 **326**

325 (0.80 g, 1.10 mmol) was swollen in dioxane (4 mL) for 30 minutes, then prenyl bromide (0.66 g, 4.4 mmol) in dioxane (16 mL) was added, followed by DBU (0.79 g, 5.2 mmol) in acetone (10 mL). The reaction was heated to 90 °C and stirred for 36 hours, then allowed to cool. The beads were trapped by filtration and washed with 1:1 acetone / dioxane (3 x 10 mL), dioxane (3 x 10 mL), dichloromethane (3 x 10 mL) and methanol (3 x 10 mL), then dried *in vacuo*.

Data for **326**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 2847 (w), 1732 (s), 1610 (m), 1585 (m), 1510 (s), 1451 (s), 1375 (w), 1219 (m), 1009 (s), 823 (m), 697 (s)

Preparation of Resin-Bound Diene **327**



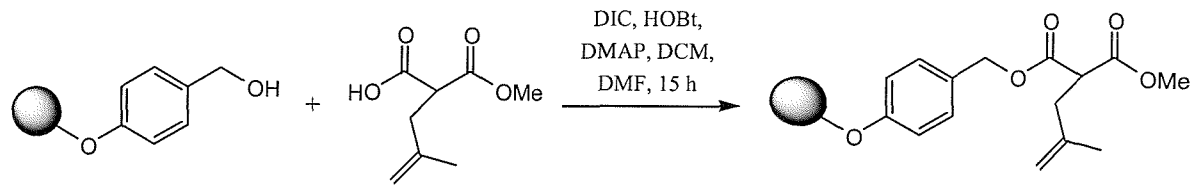
325 **327**

325 (1.40 g, 1.93 mmol) was swollen in dioxane (4 mL) for 30 minutes, then cinnamyl bromide (1.52 g, 7.71 mmol) in dioxane (16 mL) was added, followed by DBU (1.39 g, 9.13 mmol) in acetone (10 mL). The reaction was heated to 90 °C and stirred for 36 hours, then allowed to cool. The beads were collected by filtration and washed with 1:1 acetone / dioxane (3 x 10 mL), dioxane (3 x 10 mL), dichloromethane (3 x 10 mL) and methanol (3 x 10 mL), then dried *in vacuo*.

Data for **327**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 1731 (s), 1601 (m), 1510 (w), 1492 (s), 1451 (s), 1370 (w), 1153 (w), 1025 (w), 907 (w), 751 (m), 697 (s)

Preparation of Resin-Bound Alkene **335**



334

$C_8H_{12}O_4$
Mol. Wt.: 172

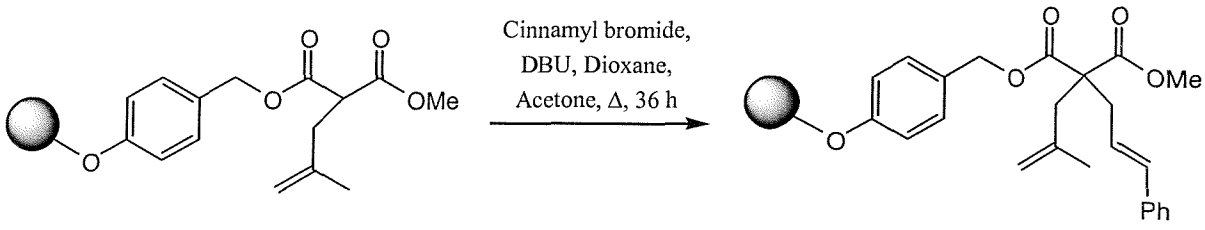
335

Prepared following the procedure of Bennet[97] *et al.* Wang resin (1.70 mmol g^{-1} active sites, 1.70 g, 2.89 mmol) was swollen in DCM (20 mL) with DMF (5 mL) for 30 minutes before **334** (0.75 g, 4.34 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (0.39 g, 2.89 mmol) dissolved in DMF (3 mL) were added. Diisopropylcarbodiimide (DIC) (0.36 g, 2.89 mmol) was then added, followed by 4-dimethylaminopyridine (DMAP) (0.016 g, 0.13 mmol) dissolved in DMF (2 mL). The reaction mixture was shaken at room temperature for 15 hours, before the beads were collected by filtration and washed with dichloromethane (3 x 10 mL), 1:1 THF / H_2O (3 x 10 mL), methanol (3 x 10mL) and diethyl ether (3 x 10 mL) then dried *in vacuo*.

Data for **335**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 1731 (s), 1606 (m), 1510 (s), 1492 (m), 1451 (s), 1376 (w), 1220 (s), 1008 (m), 824 (m), 756 (s), 697 (s)

Preparation of Resin-Bound Diene **328**



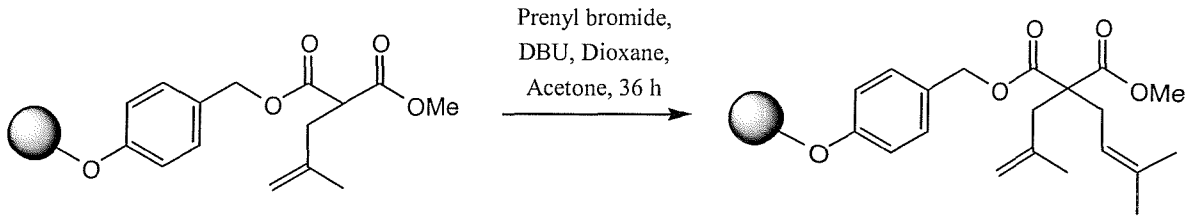
335 **328**

335 (1.00 g, 1.35 mmol) was swollen in dioxane (4 mL) for 30 minutes, then cinnamyl bromide (1.06 g, 5.38 mmol) in dioxane (16 mL) was added, followed by DBU (0.97 g, 6.37 mmol) in acetone (10 mL). The reaction was heated to 90 °C and stirred for 36 hours, then allowed to cool. The beads were collected by filtration and washed with 1:1 acetone / dioxane (3 x 10 mL), dioxane (3 x 10 mL), dichloromethane (3 x 10 mL) and methanol (3 x 10 mL), then dried *in vacuo*.

Data for **328**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 1731 (s), 1610 (m), 1585 (w), 1510 (s), 1492 (m), 1451 (s), 1219 (s), 1172 (m), 1009 (s), 756 (m), 697 (s)

Preparation of Resin-Bound Alkene **329**



335 **329**

335 (1.00 g, 1.35 mmol) was swollen in dioxane (4 mL) for 30 minutes, then prenyl bromide (0.80 g, 5.37 mmol) in dioxane (16 mL) was added, followed by DBU (0.97 g, 6.37 mmol) in acetone (10 mL). The reaction was heated to 90 °C and stirred for 36 hours, then allowed to cool. The beads were collected by filtration and washed with 1:1 acetone / dioxane (3 x 10 mL), dioxane (3 x 10 mL), dichloromethane (3 x 10 mL) and methanol (3 x 10 mL), then dried *in vacuo*.

Data for **329**:

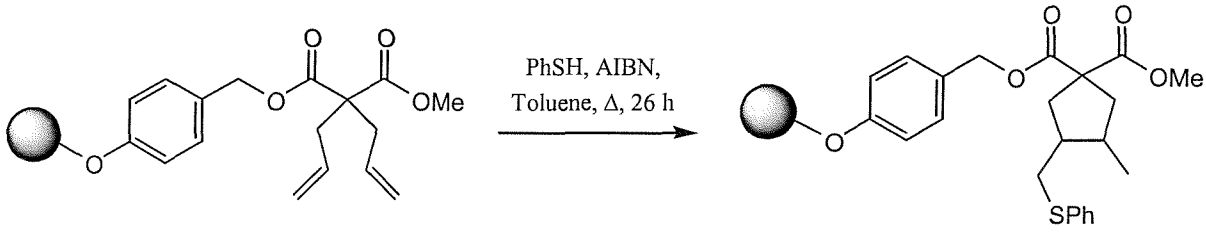
ν_{max}/cm^{-1} (solid phase) 3025 (w), 2920 (m), 2847 (w), 1735 (s), 1610 (m), 1584 (w), 1510 (s), 1492 (s), 1451 (s), 1376 (w), 1218 (s), 1172 (s), 1009 (s), 908 (w), 822 (s), 756 (s), 697 (s)

General Procedure for Benzenethiyl Radical Cyclisation of Resin-Bound 1,6-Dienes

In all cases, the reaction was carried out under nitrogen. The resins were swollen for 30 minutes in 4 mL toluene, then a further 20 mL of toluene was added, followed by thiophenol. The reactions were heated, with stirring, to 90 °C, and the AIBN was added portionwise over 14 hours. The reaction was then left at 90 °C for a further 12 hours before cooling to ambient temperature. The beads were then collected by filtration and washed with 3 x 10 mL toluene, 3 x 10 mL dichloromethane and 3 x 10 mL methanol, before being dried *in vacuo*.

Cyclisations carried out using the above procedure:

Preparation of Resin-Bound Cyclised Product **331**



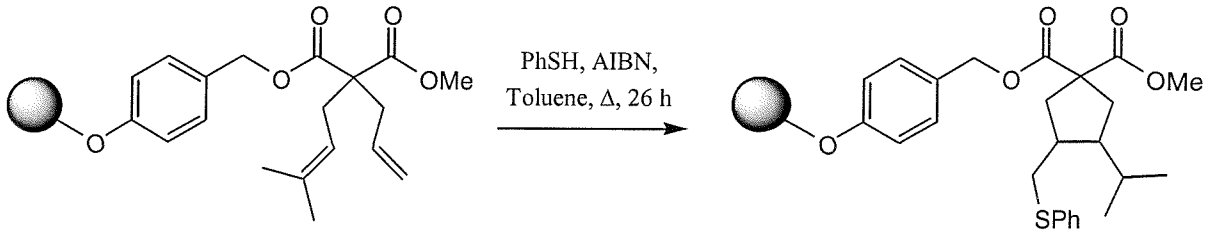
318 **331**

Typical experimental conditions: 0.80 g (1.30 mmol) **318**, 0.66 g (6.0 mmol) thiophenol, 0.49 g (3.0 mmol) AIBN.

Data for **331:**

ν_{max}/cm^{-1} (solid phase) 3026 (w), 2920 (m), 2852 (w), 1732 (s), 1602 (m), 1585 (w), 1511 (s), 1492 (s), 1452 (s), 1377 (w), 1220 (s), 1172 (m), 1113 (w), 1009 (s), 909 (w), 825 (m), 755 (m), 697 (s)

Preparation of Resin-Bound Product **336**



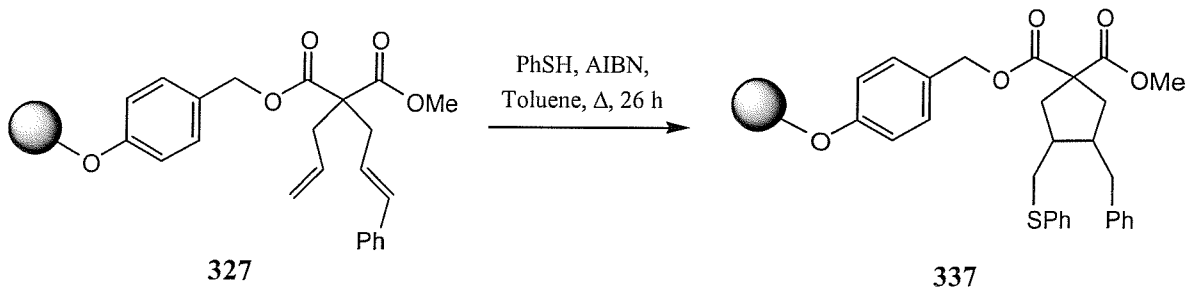
326 **336**

Typical experimental conditions: 0.80 g (1.00 mmol) **326**, 0.77 g (7.0 mmol) thiophenol, 0.49 g (3.0 mmol) AIBN.

Data for **336:**

ν_{max}/cm^{-1} (solid phase) 3025 (m), 2921 (m), 2847 (w), 1730 (s), 1601 (s), 1584 (m), 1510 (s), 1492 (m), 1451 (s), 1376 (w), 1219 (s), 1172 (m), 1018 (s), 824 (s), 758 (m), 698 (s)

Preparation of Resin-Bound Product **337**



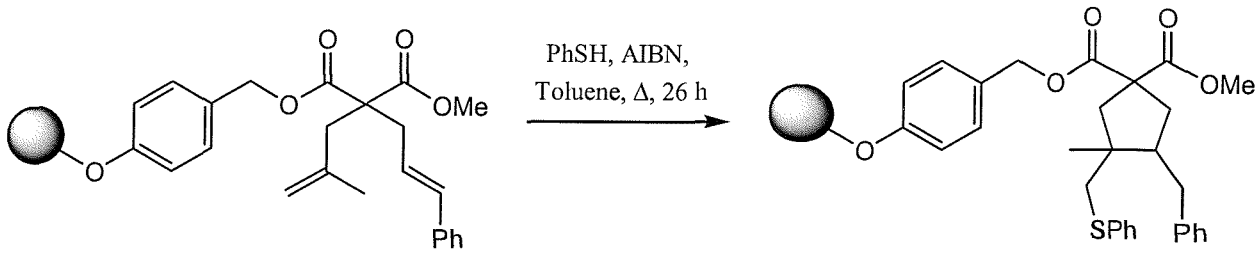
327 **337**

Typical experimental conditions: 0.90 g (1.07 mmol) **327**, 0.66 g (6.0 mmol) thiophenol, 0.49 g (3.0 mmol) AIBN.

Data for **337:**

ν_{max}/cm^{-1} (solid phase) 3024 (w), 2920 (m), 2847 (w), 1726 (m), 1602 (m), 1510 (s), 1492 (s), 1450 (s), 1376 (w), 1218 (s), 1172 (m), 1010 (s), 825 (m), 755 (s), 697 (s)

Preparation of Resin-Bound Product **338**



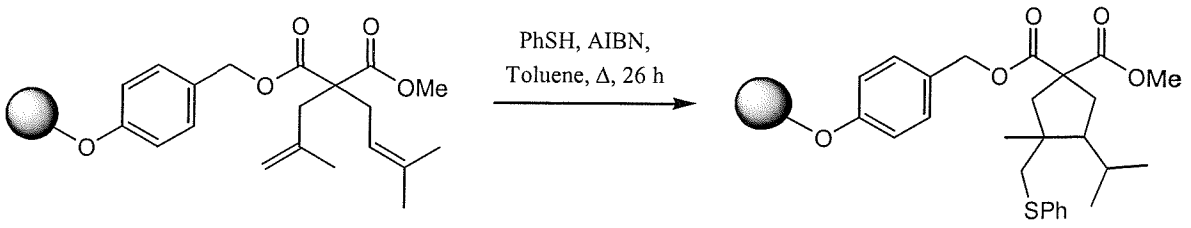
328 **338**

Typical experimental conditions: 0.90 g (1.05 mmol) **328**, 0.66 g (6.0 mmol) thiophenol, 0.66 g (4.0 mmol) AIBN.

Data for **338**:

ν_{max}/cm^{-1} (solid phase) 3024 (w), 2920 (m), 2847 (w), 1726 (s), 1601 (s), 1584 (m), 1510 (s), 1492 (s), 1451 (s), 1376 (w), 1299 (w), 1218 (s), 1172 (m), 1015 (s), 824 (m), 755 (m), 697 (s)

Preparation of Resin-Bound Product **339**



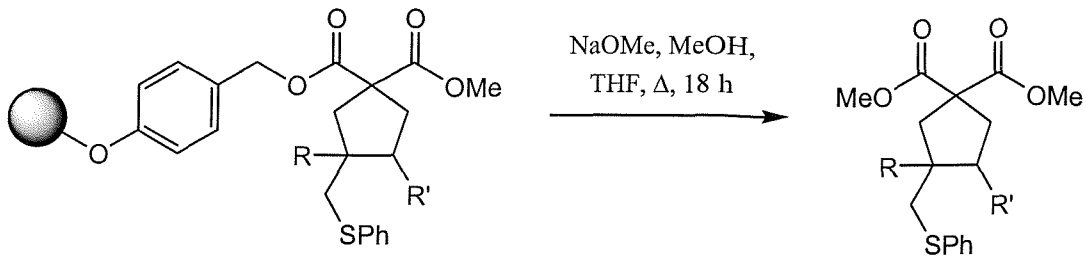
329 **339**

Typical experimental conditions: 0.90 g (1.11 mmol) **329**, 0.66 g (6.0 mmol) thiophenol, 0.66 g (4.0 mmol) AIBN.

Data for **339**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2921 (m), 2847 (w), 1730 (s), 1601 (s), 1584 (m), 1510 (s), 1492 (m), 1451 (s), 1376 (w), 1219 (s), 1160 (m), 1017 (s), 825 (m), 757 (m), 698 (s)

General Procedure for the Methoxide Cleavage of Resin-Bound Cyclised Products **331**, **336**, **337**, **338**, and **339**



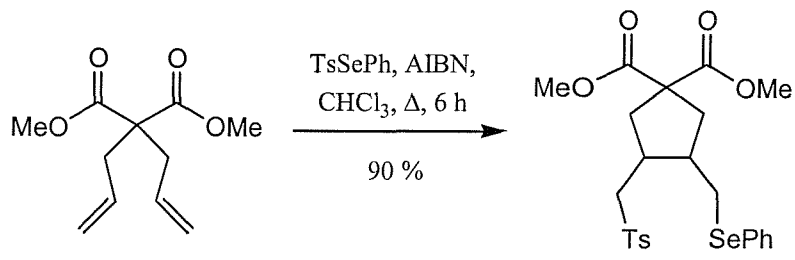
In all cases, the reaction was carried out under nitrogen. The resin was swollen for 30 minutes in 4 mL THF, during which time sodium methoxide (0.16 g, 3.0 mmol) was freshly prepared by the addition of sodium to anhydrous methanol. The sodium methoxide was then dissolved in 5 mL of anhydrous methanol, and the sodium methoxide solution added to the resin along with a further 20 mL of THF. The reaction was heated to reflux for 18 hours, then allowed to cool. The beads were collected by filtration, and washed with 3 x 10 mL THF followed by 3 x 10 mL methanol, then dried *in vacuo*. The filtrate was collected and partitioned between 20 mL water and 30 mL diethyl ether. 10 mL HCl (aq, 2M) was added, then the aqueous layer was extracted with 3 x 20 mL diethyl ether. The organic portions were combined, washed with brine (sat.), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0-30% diethyl ether in petrol) gave the products as pale yellow oils.

For each product, ^1H n.m.r., ^{13}C n.m.r. and LRMS (CI) spectra were in accordance with those reported for the compound earlier in this report. In all cases, cis / trans stereoselectivity was found to be the same as for the analogous solution phase reaction.

Substrate Cleaved	Experimental Conditions and Overall Yield* of Cyclised Product
308	**331** (0.95 g, 1.08 mmol). Yield: 0.27 g (0.84 mmol, 78 %)
310	**336** (0.85 g, 0.94 mmol). Yield: 0.25 g (0.71 mmol, 76 %)
309	**337** (0.95 g, 1.00 mmol). Yield: 0.30 g (0.75 mmol, 75 %)
311	**338** (0.95 g, 0.98 mmol). Yield: 0.28 g (0.68 mmol, 69 %)
312	**339** (0.95 g, 1.03 mmol). Yield: 0.26 g (0.71 mmol, 69 %)

*Yields are for the overall process of loading the substrate onto the resin, cyclising it, and then cleaving it.

3-Phenylselanylmethyl-4-(toluene-4-sulfonylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **403**



301

$C_{11}H_{16}O_4$
Mol. Wt.: 212

403

$C_{24}H_{28}O_6SSe$
Mol. Wt.: 524

Following the modified procedure of Chuang[56] *et al.* Dimethyl diallylmalonate (1.00 g, 4.72 mmol) and *p*-tolyl benzeneselenosulfonate (1.62 g, 5.21 mmol) were dissolved in chloroform (50 mL), then AIBN (0.41 g, 2.50 mmol) was added and the reaction was heated to reflux for 6 hours, then allowed to cool. The reaction mixture was concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 0 - 30 % ethyl acetate in petrol) gave the product **403**, a viscous yellow oil, as a mixture of stereoisomers (*cis* : *trans* 7 : 1) inseparable by chromatography (2.22 g, 4.24 mmol, 90 %).
Spectroscopic and physical data were in accordance with literature values[56].

Data for **403**:

ν_{max}/cm^{-1} (neat) 2953 (m), 1729 (s), 1596 (w), 1478 (w), 1436 (m), 1403 (w), 1261 (s), 1145 (s), 1087 (m), 889 (w), 742 (m), 690 (w).

LRMS (ES) 547 ([M+Na]$^+$, 100 %) amu.

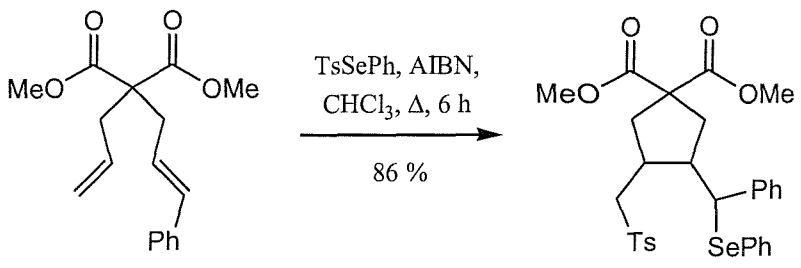
λ_{max}/nm (ε_{max}) 257 (9700).

***cis* isomer:**

δ_H (300 MHz, $CDCl_3$) 7.76 (2H, dd, *J* 7.2 Hz, 1.8 Hz, Ar*H*), 7.48 - 7.41 (2H, m, Ar*H*), 7.36 (2H, d, *J* 6.6 Hz), 7.28 - 7.20 (4H, m, Ar*H*), 3.71 (6H, s, 2 x OC*H*$_3$), 3.22 (1H, dd, *J* 13.8 Hz, 4.2 Hz, TsC*H*H), 3.09 (1H, dd, *J* 13.8 Hz, 9.0 Hz, TsCH*H*), 2.90 (1H, dd, *J* 11.8 Hz, 5.8 Hz, PhSeC*H*H), 2.69 (1H, dd, *J* 11.8 Hz, 9.8 Hz, PhSeCH*H*), 2.62 - 2.48 (2H, m, 2 x C*H*), 2.59 - 2.54 (1H, m, CCH$_2$C*H*), 2.50 (1H, dd, *J* 13.3 Hz, 6.5 Hz, CC*H*HCH), 2.48 (3H, s,

	ArC*H*$_3$), 2.45 - 2.38 (1H, m, CCH$_2$C*H*), 2.31 (1H, dd, *J* 13.6 Hz, 6.5 Hz, CCH*H*CH) ppm.
δ_C (75.5 MHz, $CDCl_3$)	173.0 (0, *C*O), 172.6 (0, *C*O), 145.0 (0, Ar), 136.5 (0, Ar), 133.2 (1, 2 x Ar), 130.2 (1, 2 x Ar), 129.3 (1, 2 x Ar), 128.4 (0, Ar), 128.2 (1, 2 x Ar), 127.4 (1, Ar), 58.4 (0, CO*C*CO), 56.1 (2, Ts*C*H$_2$), 53.2 (3, OCH$_3$), 53.1 (3, O*C*H$_3$), 42.3 (1, CCH$_2$*C*H), 39.0 (2, C*C*H$_2$CH), 38.1 (2, C*C*H$_2$CH), 37.0 (1, CCH$_2$*C*H), 28.1 (2, PhSe*C*H$_2$), 21.8 (3, SO$_2$ArC*H*$_3$) ppm.
***trans* isomer:**	
δ_H (300 MHz, $CDCl_3$)	3.31 (1H, dd, *J* 13.6 Hz, 5.1 Hz, TsC*H*H) ppm + other peaks, all obscured by dominant *cis* isomer.
δ_C (75.5 MHz, $CDCl_3$)	60.5 (2, Ts*C*H$_2$), 58.9 (0, CO*C*CO), 45.3 (1, CCH$_2$*C*H), 40.3 (2, C*C*H$_2$CH), 40.2 (2, C*C*H$_2$CH), 39.8 (1, CCH$_2$*C*H), 31.3 (2, PhSe*C*H$_2$) ppm + other peaks obscured by dominant *cis* isomer.

3-(Phenyl-phenylselanyl-methyl)-4-(toluene-4-sulfonylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **404**



305
$C_{17}H_{20}O_4$
Mol. Wt.: 288

404
$C_{30}H_{32}O_6SSe$
Mol. Wt.: 600

Following the modified procedure of Chuang[56] *et al.* **305** (1.00 g, 3.47 mmol) and *p*-tolyl benzeneselenosulfonate (1.56 g, 5.02 mmol) were dissolved in chloroform (60 mL), then AIBN (0.61 g, 3.71 mmol) was added and the reaction was heated to reflux for 6 hours, then allowed to cool. The reaction mixture was concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 0 - 30 % ethyl acetate in petrol) gave the product **404**, a viscous yellow oil (1.79 g, 2.98 mmol, 86 %), as a mixture of four diastereoisomers (3 : 3 : 1 : 1). Partial separation of the diastereoisomers was achieved by RP-HPLC, and n.m.r. data for two of the four diastereomers are presented below. It is believed that one of the diastereomers is *cis* across the ring junction, and the other *trans*, by consideration of the γ-gauche effect.

Data for **404**:

***cis* isomer:**

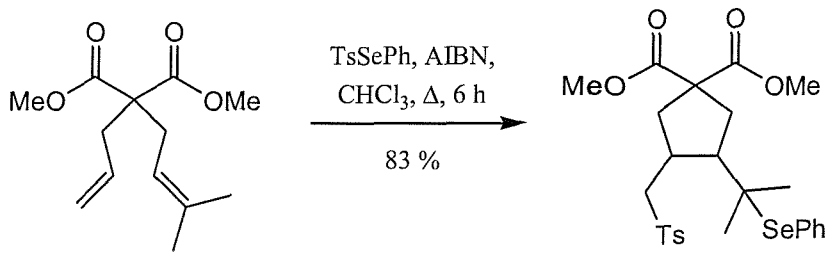
ν_{max}/cm^{-1} (neat) 2952 (w), 1730 (s), 1597 (w), 1452 (m), 1436 (m), 1302 (m), 1267 (s), 1136 (s), 1022 (w), 817 (w), 745 (m), 699 (m)

δ_H (400 MHz, $CDCl_3$) 7.94 - 7.00 (13H, m, 13 x Ar*H*), 6.80 - 6.77 (1H, m, Ar*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.80 - 3.70 (1H, m, C*H*), 3.08 - 2.55 (6H, m, 6 x C*H*), 2.41 (3H, s, ArCH_3), 2.34 (1H, app. t, *J* 13.3 Hz, C*H*), 2.19 - 2.08 (1H, m, C*H*) ppm + peaks due to other diastereomers.

δ_C (100 MHz, $CDCl_3$) 173.1 (0, *C*O), 172.8 (0, *C*O), 144.4 (0, Ar), 141.0 (0, Ar), 137.4 (1, 2 x Ar), 136.3 (0, Ar), 131.9 (0, Ar), 130.3 (1, 2 x Ar), 130.1 (1, 2 x Ar), 129.6 (1, Ar), 128.8 (1, 2 x Ar), 128.6 (1, 2 x Ar), 127.9 (1, 2 x Ar), 127.4 (1, Ar), 58.4 (0, CO*C*CO),

	54.2 (2, Ts*C*H_2), 53.5 (3, O*C*H_3), 53.4 (3, O*C*H_3), 49.5 (1, *C*H), 47.3 (1, *C*H), 39.8 (2, C*C*H_2CH), 37.7 (2, C*C*H_2CH), 36.4 (1, *C*H), 21.9 (3, Ar*C*H_3) ppm + peaks due to other diastereomers.
LRMS (ES)	623 ($[M+Na]^+$, 100 %), 465 ($[M-SePhH+Na]^+$, 60 %) amu.
λ_{max}/nm (ε_{max})	252 (10 400)
***trans* isomer:**	
ν_{max}/cm^{-1} (neat)	2954 (m), 1731 (s), 1597 (w), 1435 (m), 1387 (w), 1303 (w), 1263 (m), 1149 (s), 1066 (w), 1021 (w), 821 (m), 746 (m).
δ_H (400 MHz, $CDCl_3$)	7.95 - 6.95 (14H, m, 14 x Ar*H*), 3.79 - 3.66 (7H, m, 2 x O*C*H_3 & TsCH*H*), 3.06 - 2.56 (4H, m, 4 x C*H*), 2.50 (3H, s, Ar*C*H_3), 2.46 - 2.30 (3H, m, C*H*), 2.05- 1.87 (1H, m, C*H*) ppm + peaks due to other diastereomers.
δ_C (100 MHz, $CDCl_3$)	172.9 (0, *C*O), 172.7 (0, *C*O), 145.1 (0, Ar), 141.9 (0, Ar), 37.4 (0, Ar), 136.3 (1, Ar), 135.8 (1, Ar), 130.4 (0, Ar), 130.1 (1, 2 x Ar), 129.3 (1, 2 x Ar), 129.2 (1, 2 x Ar), 129.1 (1, 2 x Ar), 128.9 (1, 2 x Ar), 128.7 (1, 2 x Ar), 60.7 (2, Ts*C*H_2), 59.0 (0, CO*C*CO), 53.4 (3, O*C*H_3), 53.3 (3, O*C*H_3), 49.9 (1, *C*H), 48.6 (1, *C*H), 38.5 (2, C*C*H_2CH), 38.1 (2, C*C*H_2CH), 37.0 (1, *C*H), 22.1 (3, Ar*C*H_3) ppm + peaks due to other diastereomers.
LRMS (ES)	623 ($[M+Na]^+$, 100 %), 481 ($[M-SePhH+K]^+$, 60 %) amu.
λ_{max}/nm (ε_{max})	254 (8700)
HRMS (recorded on mixture of diastereomers)	Found $[M+Na]^+$: 623.0983. $C_{30}H_{32}O_6SSe$ requires $[M+Na]^+$: 623.0977

3-(1-Methyl-1-phenylselanyl-ethyl)-4-(toluene-4-sulfonylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **405**



304

$C_{13}H_{20}O_4$
Mol. Wt.: 240

405

$C_{26}H_{32}O_6SSe$
Mol. Wt.: 552

Following the modified procedure of Chuang[56] *et al.* **304** (0.60 g, 2.50 mmol) and *p*-tolyl benzeneselenosulfonate (1.16 g, 3.75 mmol) were dissolved in chloroform (40 mL), then AIBN (0.44 g, 2.68 mmol) was added and the reaction was heated to reflux for 6 hours, then allowed to cool. The reaction mixture was concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 0 - 30 % ethyl acetate in petrol) gave the product **405**, a viscous yellow oil (1.15 g, 2.08 mmol, 83 %), as a mixture of stereoisomers (*cis* : *trans* 3.5 : 1). Partial separation of the diastereoisomers was achieved by RP-HPLC.

Data for **405**:

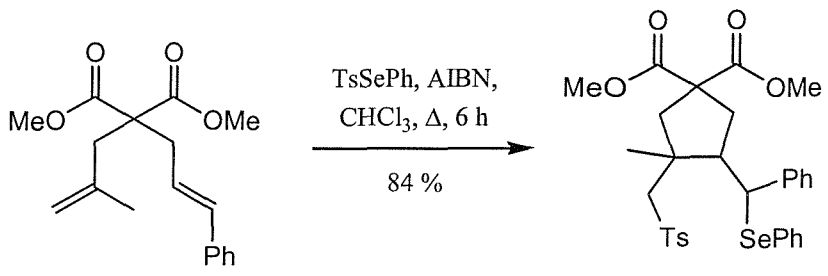
***cis* isomer:**

ν_{max}/cm^{-1} (neat) 2954 (m), 2927 (w), 1730 (s), 1597 (m), 1436 (s), 1369 (w), 1260 (s), 1147 (s), 1087 (s), 818 (w), 746 (s), 695 (m).

δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.2 Hz, 2 x Ar*H*), 7.56 - 7.52 (2H, m, 2 x Ar*H*), 7.42 - 7.39 (3H, m, 3 x Ar*H*), 7.34 - 7.29 (2H, m, 2 x Ar*H*), 3.80 (1H, dd, *J* 13.8 Hz, 7.2 Hz, TsC*H*H), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.24 (1H, dd, *J* 13.8 Hz, 12.0 Hz, TsCH*H*), 2.75 (1H, d, *J* 14.8 Hz, $TsCH_2CHCHH$), 2.73 - 2.68 (1H, m, $TsCH_2CH$), 2.54 (1H, dd, *J* 13.3 Hz, 6.0 Hz, C*H*HCH), 2.48 (3H, s, ArCH_3), 2.41 (1H, dd, *J* 14.8 Hz, 6.5 Hz, $TsCH_2CHCHH$), 2.29 (1H, app t, *J* 13.3 Hz, CH*H*CH), 2.13 (1H, dt, *J* 12.8 Hz, 6.3 Hz, C*H*CSePh), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3) ppm.

δ_C (100 MHz, $CDCl_3$)	173.6 (0, *C*O), 173.0 (0, *C*O), 145.1 (0, Ar), 138.8 (1, 2 x Ar), 137.3 (0, Ar), 130.4 (1, 2 x Ar), 129.3 (1, Ar), 129.2 (1, 2 x Ar), 128.5 (1, 2 x Ar), 127.3 (0, Ar), 57.8 (0, CO*C*CO), 56.0 (2, TsCH_2), 54.4 (1, ring-*C*H), 53.5 (3, OCH_3), 53.3 (3, OCH_3), 47.0 (0, *C*SePh), 38.2 (2, ring-CH_2), 36.7 (1, ring-*C*H), 35.4 (2, ring-CH_2), 30.3 (3, C(CH_3)(CH_3)SePh), 30.2 (3, C(CH_3)(CH_3)SePh), 22.0 (ArCH_3) ppm.
LRMS (ES)	591 ($[M+K]^+$, 25 %), 575 ($[M+Na]^+$, 100 %), 417 ($[M-SePh+H_2O]^+$, 35 %) amu.
λ_{max}/nm (ε_{max})	258 (6100)
***trans* isomer:**	
ν_{max}/cm^{-1} (neat)	2954 (w), 1730 (s), 1597 (w), 1455 (m), 1436 (m), 1301 (m), 1197 (w), 1138 (m), 1259 (s), 1087 (m), 1006 (w), 821 (m).
δ_H (400 MHz, $CDCl_3$)	7.87 - 7.81 (2H, m, 2x Ar*H*), 7.58 - 7.53 (2H, m, 2 x Ar*H*), 7.43 - 7.38 (3H, m, 3 x Ar*H*), 7.34 - 7.28 (2H, m, 2 x Ar*H*), 3.85 - 3.78 (1H, m, TsC*H*H), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.35 (2H, m, TsCH*H* & C*H*), 2.77 - 2.68 (2H, m, 2 x C*H*), 2.56 (1H, app. dd, *J* 13.1 Hz, 7.1 Hz, C*H*), 2.49 (3H, s, ArCH_3), 2.20 - 2.10 (1H, m, C*H*), 1.98 (1H, dt, *J* 10.8 Hz, 7.5 Hz, C*H*C(CH_3)$_2$) 1.27 (3H, s, CCH_3), 1.23 (3H, s, CCH_3) ppm + peaks due to dominant *cis* isomer.
δ_C (100 MHz, $CDCl_3$)	173.6 (0, *C*O), 173.0 (0, *C*O), 145.1 (0, Ar), 138.7 (1, 2 x Ar), 137.3 (0, Ar), 130.4 (1, 2 x Ar), 129.3 (1, 2 x Ar), 129.2 (1, Ar), 128.5 (1, 2 x Ar), 128.1 (0, Ar), 62.7 (2, TsCH_2), 56.0 (0, CO*C*CO), 55.4 (1, ring-*C*H), 53.3 (3, OCH_3), 53.2 (3, OCH_3), 49.9 (0, *C*SePh), 39.7 (2, ring-CH_2), 38.2 (2, ring-CH_2), 34.9 (1, ring-*C*H), 30.3 (3, C(CH_3)(CH_3)SePh), 30.2 (3, C(CH_3)(CH_3)SePh), 22.1 (3, ArCH_3) ppm + peaks due to dominant *cis* isomer.
LRMS (ES)	575 ($[M+Na]^+$, 100 %), 417 ($[M-SePh+H_2O]^+$, 45 %) amu.
λ_{max}/nm (ε_{max})	254 (7300)
HRMS (recorded on mixture of diastereomers)	Found $[M+Na]^+$: 575.0977. $C_{26}H_{32}O_6SSe$ requires $[M+Na]^+$: 575.0992.

3-Methyl-4-(phenyl-phenylselanyl-methyl)-3-(toluene-4-sulfonylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **406**



306

$C_{18}H_{22}O_4$
Mol. Wt.: 302

406

$C_{31}H_{34}O_6SSe$
Mol. Wt.: 614

Following the modified procedure of Chuang *et al.* **306** (0.45 g, 1.49 mmol) and *p*-tolyl benzeneselenosulfonate (0.78 g, 2.51 mmol) were dissolved in chloroform (40 mL), then AIBN (0.40 g, 2.44 mmol) was added and the reaction was heated to reflux for 6 hours, then allowed to cool. The reaction mixture was concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 0 - 30 % ethyl acetate in petrol) gave the product **406**, a viscous yellow oil, as a mixture of four stereoisomers (3 : 3 : 1 : 1) inseparable by chromatography (0.77 g, 1.25 mmol, 84 %). Partial separation of the diastereoisomers was achieved by RP-HPLC, and n.m.r. data for two of the four diastereomers are presented below. It is believed that one of the diastereomers is *cis* across the ring junction, and the other *trans*, by consideration of the γ-gauche effect.

Data for **406**:

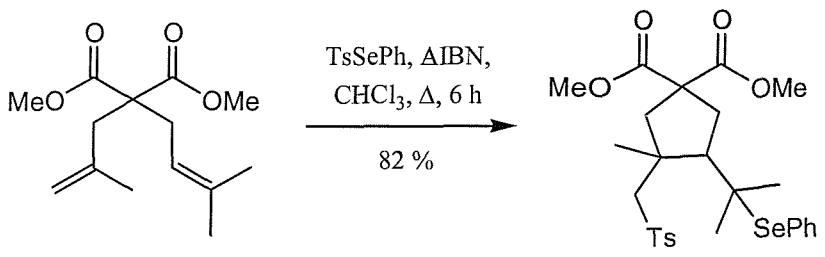
***cis* isomer:**

ν_{max}/cm^{-1} (neat) 2952 (w), 1730 (s), 1597 (w), 1454 (m), 1436 (m), 1315 (m), 1257 (s), 1147 (s), 1087 (m), 742 (m), 702 (m), 670 (w).

δ_H (400 MHz, $CDCl_3$) 7.76 - 6.89 (14H, m, 14 x Ar*H*), 3.75 (1H, d, *J* 12.0 Hz, PhSeC*H*), 3.68 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 3.48 (1H, d, *J* 13.1 Hz, TsC*H*H), 3.28 (1H, d, *J* 15.0 Hz, CC*H*HC), 3.21 (1H, d, *J* 13.3 Hz, TsCH*H*), 2.43 - 2.33 (2H, m, CCH_2CH & CCH*H*C), 2.41 (3H, s, ArCH_3), 2.05 (1H, dd, *J* 14.3 Hz, 12.6 Hz, CC*H*HCH), 1.87 (1H, dd, *J* 14.5 Hz, 7.3 Hz, CCH*H*CH), 1.62 (3H, s, CCH_3) ppm.

δ_C (100 MHz, $CDCl_3$)	173.4 (0, *C*O), 173.0 (0, *C*O), 144.8 (0, Ar), 142.2 (0, Ar), 139.6 (0, Ar), 136.3 (1, 2 x Ar), 130.3 (1, 2 x Ar), 129.1 (1, 2 x Ar), 128.7 (1, 2 x Ar), 128.6 (1, 2 x Ar), 128.1 (1, 2 x Ar), 127.9 (1, Ar), 127.6 (0, Ar), 127.3 (1, Ar), 59.1 (2, CH_2Ts), 57.1 (1, CCH_2CH), 56.8 (0, CO*C*CO), 53.5 (3, OCH_3), 53.3 (3, OCH_3), 49.9 (1, PhSe*C*H), 45.7 (2, CCH_2C), 45.6 (0, CCH_3), 40.1 (2, CCH_2CH), 28.3 (3, CH_3), 22.1 (3, ArCH_3) ppm.
LRMS (ES)	653 ($[M+K]^+$, 90 %), 637 ($[M+Na]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	253 (9900)
***trans* isomer:**	
ν_{max}/cm^{-1} (neat)	3031 (w), 2952 (w), 1730 (s), 1494 (w), 1453 (m), 1257 (s), 1201 (m), 1147 (s), 1087 (m), 875 (w), 742 (m), 670 (w).
δ_H (400 MHz, $CDCl_3$)	7.29 - 6.87 (14H, m, 14 x Ar*H*), 3.71 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.61 (1H, m, TsC*H*H), 2.80 (1H, m, TsCH*H*), 2.47 - 2.34 (5H, m, C*H*), 2.33 (3H, s, ArCH_3), 2.18 - 2.12 (1H, m, C*H*), 1.05 (3H, s, CCH_3) ppm + other peaks due to *cis* isomer.
δ_C (100 MHz, $CDCl_3$)	173.8 (0, *C*O), 173.1 (0, *C*O), 144.2 (0, Ar), 141.7 (0, Ar), 138.6 (0, Ar), 136.3 (1, 2 x Ar), 130.1 (0, Ar), 129.6 (1, 2 x Ar), 128.8 (1, 2 x Ar), 128.6 (1, 2 x Ar), 128.4 (1, 2 x Ar), 128.3 (1, 2 x Ar), 127.3 (1, 2 x Ar), 67.3 (2, TsCH_2), 57.3 (0, CO*C*CO), 54.8 (1, *C*H), 53.7 (3, OCH_3), 53.5 (3, OCH_3), 51.0 (1, *C*H), 47.6 (2, $CH_2C(CH_3)(CH_2Ts)$-ring), 39.4 (2, ring-CH_2), 30.0 (0, ring-$C(CH_3)(CH_2Ts)$), 22.2 (3, ArCH_3), 20.0 (3, CH_3) ppm.
LRMS (ES)	637 ($[M+Na]^+$, 60 %), 495 ($[M-PhSeH+K]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	254 (8300)
HRMS (recorded on mixture of diastereomers)	Found $[M+Na]^+$: 637.1126. $C_{31}H_{34}O_6SSe$ requires $[M+Na]^+$: 637.1133

3-Methyl-4-(1-methyl-1-phenylselanyl-ethyl)-3-(toluene-4-sulfonylmethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester **407**



307

$C_{14}H_{22}O_4$
Mol. Wt.: 254

407

$C_{27}H_{34}O_6SSe$
Mol. Wt.: 566

Following the modified procedure of Chuang[56] *et al.* **307** (0.63 g, 2.48 mmol) and *p*-tolyl benzeneselenosulfonate (1.16 g, 3.75 mmol) were dissolved in chloroform (50 mL), then AIBN (0.66 g, 4.00 mmol) was added and the reaction was heated to reflux for 6 hours, then allowed to cool. The reaction mixture was concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 0 - 30 % ethyl acetate in petrol) gave the product **407**, a viscous yellow oil (1.15 g, 2.03 mmol, 82 %), as a mixture of stereoisomers (*cis* : *trans* 1 : 1). Separation of the diastereoisomers was achieved by RP-HPLC.

Data for **407**:

***cis* isomer:**

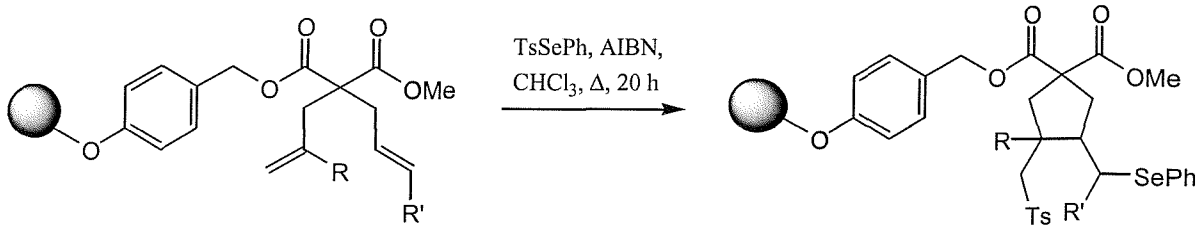
ν_{max}/cm^{-1} (neat) 2954 (w), 1731 (s), 1597 (w), 1436 (m), 1315 (m), 1263 (s), 1200 (m), 1149 (s), 1087 (m), 1021 (w), 746 (m), 664 (w).

δ_H (400 MHz, $CDCl_3$) 7.74 - 7.69 (2H, m, 2 x Ar*H*), 7.47 - 7.43 (2H, m, 5 x Ar*H*), 7.31 - 7.17 (5H, m, 5 x Ar*H*), 3.73 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.35 (1H, d, *J* 13.5 Hz, SC*H*H), 3.28 (1H, d, *J* 14.8 Hz, CC*H*HC), 3.25 (1H, d, *J* 13.5 Hz, SCH*H*), 2.66 (1H, app t, *J* 14.0 Hz, C*H*HCH), 2.53 (1H, dd, *J* 14.2 Hz, 7.0 Hz, CH*H*CH), 2.36 (3H, s, ArCH_3), 2.25 (1H, d, *J* 14.8 Hz, CCH*H*C), 1.80 (1H, dd, *J* 13.3 Hz, 7.0 Hz, C*H*), 1.45 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.30 (3H, s, CH_3) ppm.

δ_C (100 MHz, $CDCl_3$) 173.6 (0, *C*O), 173.1 (0, *C*O), 144.5 (0, Ar), 139.4 (0, Ar), 138.6 (1, 2 x Ar), 130.1 (1, 2 x Ar), 129.1 (1, Ar), 129.0 (1, 2 x Ar), 129.0 (0, Ar), 127.6 (1, 2 x Ar), 62.1 (1, *C*H), 60.1 (2,

	CH_2SO_2Ar), 55.3 (0, COCCO), 53.3 (3, OCH_3), 53.1 (3, OCH_3), 48.7 (0), 46.4 (0), 45.3 (2, CCH_2C), 36.9 (2, CCH_2CH), 32.4 (3, CH_3), 29.1 (3, CH_3), 28.3 (3, CH_3), 21.8 ($ArCH_3$) ppm.
LRMS (ES)	589 ($[M+Na]^+$, 65 %), 431 ($[M-PhSeH+Na]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	258 (8700)
***trans* isomer:**	
ν_{max}/cm^{-1} (neat)	2954 (w), 1731 (s), 1597 9w), 1435 (m), 1314 (w), 1263 (s), 1200 (m), 1149 (s), 1021 (w), 821 (w), 746 (m), 695 (w).
δ_H (400 MHz, $CDCl_3$)	7.74 - 7.69 (2H, m, Ar*H*), 7.49 - 744 (2H, m, Ar*H*), 7.31 - 7.17 (5H, m, Ar*H*), 3.69 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.61 (1H, d, *J* 13.8 Hz, SC*H*H), 3.00 (1H, d, 13.8 Hz, SCH*H*), 2.83 (1H, d, *J* 14.8 Hz, CC*H*HC), 2.63 (1H, dd, *J* 13.8 Hz, 6.8 Hz, C*H*HCH), 2.52 (1H, app t, *J* 13.8 Hz, CH*H*CH), 2.47 (1H, d, *J* 14.8 Hz, CCH*H*C), 2.37 (3H, s, $ArCH_3$), 1.95 (1H, dd, *J* 12.8 Hz, 6.8 Hz, C*H*), 1.38 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.28 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	173.2 (0, *C*O), 172.7 (0, *C*O), 144.6 (0, Ar), 139.0 (0, Ar), 138.5 (1, 2 x Ar), 130.1 (1, 2 x Ar), 129.1 (1, Ar), 129.0 (1, 2 x Ar), 129.0 (0, Ar), 127.7 (1, 2 x Ar), 68.1 (2, CH_2SO_2Ar), 58.4 (1, *C*H), 56.1 (0, COCCO), 53.2 (3, OCH_3), 53.1 (3, OCH_3), 49.1 (0), 47.5 (2, CCH_2C), 45.6 (0), 35.6 (2, CCH_2CH), 31.0 (3, $C(SePh)CH_3$), 28.7 (3, $C(SePh)CH_3$), 22.7 (3, CH_3), 21.8 ($ArCH_3$) ppm.
LRMS (ES)	589 ($[M+Na]^+$, 85 %), 431 ($[M-PhSeH+Na]^+$, 100 %) amu.
λ_{max}/nm (ε_{max})	254 (9400)
HRMS (recorded on mixture of diastereomers)	Found $[M+Na]^+$: 589.1124. $C_{27}H_{34}O_6SSe$ requires $[M+Na]^+$: 589.1133

General Procedure for Tosyl Radical Cyclisation of Resin-Bound 1,6-Dienes



In all cases, the reaction was carried out under nitrogen. The resin was swollen for 20 minutes in 3 mL chloroform, then the *p*-tolyl benzeneselenosulfonate was dissolved in 20 mL of chloroform and added to the resin beads. The reaction was then heated to reflux, and the AIBN was added in two portions: one at the start, and one after 5 hours. After the second portion had been added, the reaction was refluxed for 15 hours before cooling to ambient temperature. The beads were then collected by filtration and washed with 3 x 10 mL chloroform, 3 x 10 mL dichloromethane and 3 x 10 mL methanol, before being dried *in vacuo*.

Preparation of Resin-Bound Selenide **408**

318 **408**

318 (0.86 g, 1.10 mmol), TsSePh (0.68 g, 2.20 mmol), AIBN (0.36 g, 2.20 mmol).

Data for **408**:

ν_{max}/cm^{-1} (solid phase) 3027 (w), 2922 (m), 2852 (w), 1731 (m), 1602 (m), 1509 (s), 1492 (m), 1451 (m), 1370 (w), 1302 (w), 1218 (m), 1165 (m), 1089 (m), 1010 (m), 823 (m), 756 (s), 697 (s)

Preparation of Resin-Bound Selenide **409**

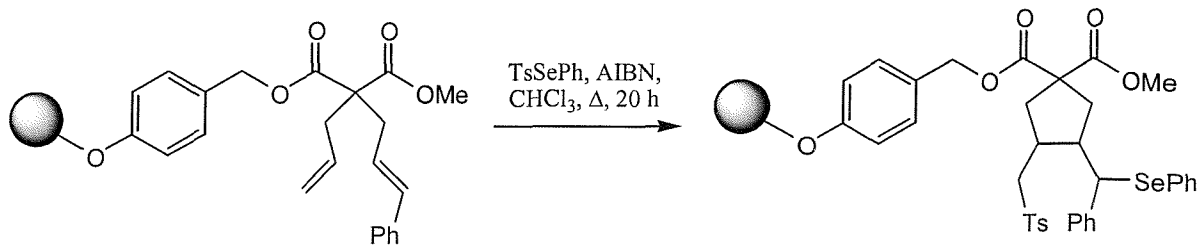
326 **409**

326 (0.85 g, 1.07 mmol), TsSePh (0.93 g, 3.0 mmol), AIBN (0.39 g, 2.40 mmol).

Data for **409**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2921 (m), 2851 (w), 1731 (w), 1602 (m), 1585 (w), 1509 (s), 1492 (s), 1451 (s), 1302 (w), 1218 (s), 1170 (m), 1089 (m), 1011 (m), 906 (w), 821 (s), 757 (s), 697 (s).

Preparation of Resin-Bound Selenide **410**



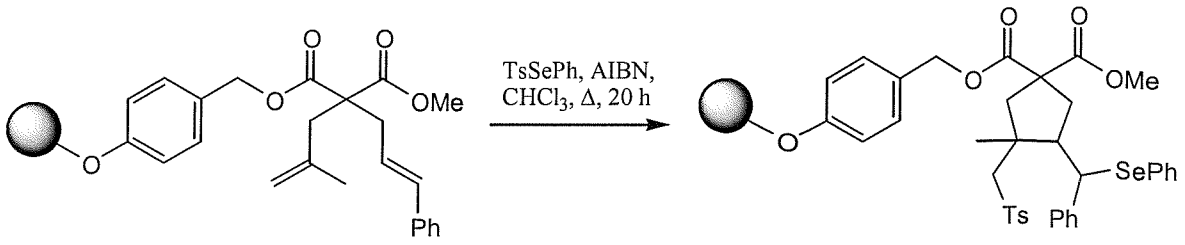
327 **410**

327 (0.90 g, 1.07 mmol), TsSePh (1.16 g, 3.75 mmol), AIBN (0.36 g, 2.2 mmol).

Data for **410**:

ν_{max}/cm^{-1} (solid phase) 3025 (w), 2921 (m), 2847 (w), 1731 (m), 1602 (m), 1510 (s), 1492 (m), 1451 (s), 1302 (m), 1218 (s), 1171 (m), 1089 (m), 1005 (m), 756 (m), 697 (s)

Preparation of Resin-Bound Selenide **411**



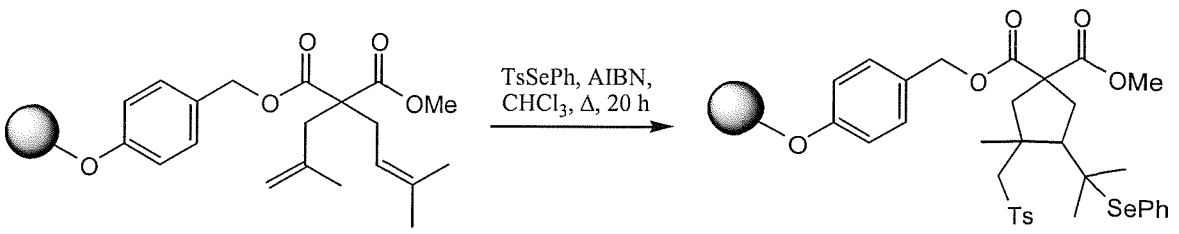
328 **411**

328 (0.95 g, 1.12 mmol), TsSePh (1.16 g, 3.75 mmol), AIBN (0.49 g, 3.0 mmol).

Data for **411**:

ν_{max}/cm^{-1} (solid phase) 3026 (w), 2921 (m), 2852 (w), 1736 (w), 1602 (m), 1510 (s), 1492 (s), 1451 (s), 1302 (m), 1219 (s), 1170 (m), 1089 (s), 1010 (m), 823 (m), 756 (s), 697 (s).

Preparation of Resin-Bound Selenide **412**



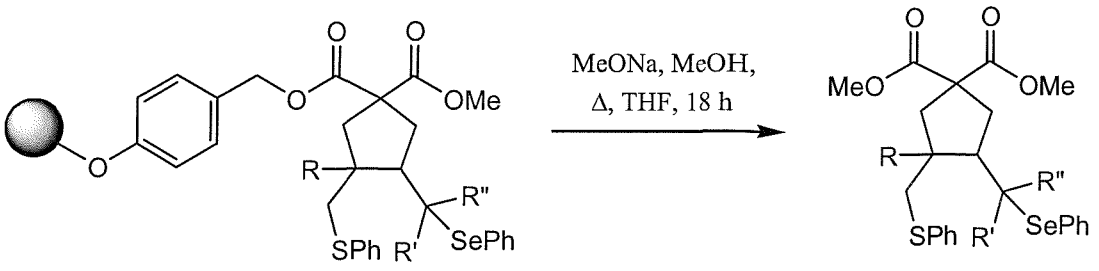
329 **412**

329 (0.90 g, 1.11 mmol), TsSePh (1.03 g, 3.31 mmol), AIBN (0.54 g, 3.29 mmol).

Data for **412**:

ν_{max}/cm^{-1} (solid phase) 3022 (w), 2921 (m), 2851 (w), 1731 (m), 1602 (m), 1584 (w), 1509 (s), 1492 (s), 1451 (s), 1371 (w), 1219 (s), 1171 (m), 1089 (s), 1012 (m), 905 (w), 822 (m), 756 (s), 697 (s)

General Procedure for the Methoxide Cleavage of Resin-Bound Cyclised Products **408**, **409**, **410**, **411** and **412**



In all cases, the reaction was carried out under nitrogen. The resin was swollen for 30 minutes in 4 mL THF, during which time sodium methoxide (0.16 g, 3.0 mmol) was freshly prepared by the addition of sodium to anhydrous methanol. The sodium methoxide was then dissolved in 5 mL of anhydrous methanol, and the sodium methoxide solution added to the resin along with a further 20 mL of THF. The reaction was heated to reflux for 18 hours, then allowed to cool. The beads were collected by filtration, and washed with THF (3 x 10 mL) followed by methanol (3 x 10 mL), then dried *in vacuo*. The filtrate was collected and partitioned between water (20 mL) and diethyl ether (30 mL). 2M HCl (10 mL, aq) was added, then the aqueous layer was extracted with diethyl ether (3 x 20 mL). The organic portions were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 - 40% ethyl acetate in petrol) gave the products as yellow oils.

For each product, ^1H n.m.r., ^{13}C n.m.r. and LRMS (CI) spectra were in accordance with those reported for the compound earlier in this report. In all cases, cis / trans stereoselectivity was found to be the same as for the analagous solution phase reaction.

Substrate Cleaved	Experimental Conditions and Overall Yield* of Cyclised Product
403	**408** (1.11 g, 1.00 mmol). Yield: 0.39 g (0.74 mmol, 74 %)
404	**410** (1.05 g, 0.91 mmol). Yield: 0.36 g (0.60 mmol, 66 %)
405	**409** (0.95 g, 0.86 mmol). Yield: 0.34 g (0.62 mmol, 72 %)
406	**411** (1.05 g, 0.90 mmol). Yield: 0.38 g (0.62 mmol, 69 %)
407	**412** (1.10 g, 0.98 mmol). Yield: 0.38 g (0.67 mmol, 68 %)

*Yields are for the overall process of loading the substrate onto the resin, cyclising it, and then cleaving it.

Chapter 6

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