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# Solid-phase approaches to heterocycles using a sulfur linker cleaved by reduction with samarium (II) iodide

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PhD thesis

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ABSTRACT

SOLID-PHASE APPROACHES TO N-HETEROCYCLES USING A SULFUR LINKER CLEAVED BY SAMARIUM (II) IODIDE

Linker strategies lie at the heart of solid phase and combinatorial chemistry. HASC (α-**H**etero-**A**tom **S**ubstituted **C**arbonyl) linkers have recently been developed and can be cleaved in a traceless manner using $SmI_2$.

My project was concerned with assessing the compatibility of HASC linkers with palladium-catalysed transformations. More specifically, we wished to use the linker system in conjunction with palladium chemistry in the solid-phase synthesis of important heterocyclic systems.

We began by examining palladium-catalysed α-arylations as the basis of a possible solid-phase route to oxindoles and α-aryl carboxylic acids. The second part of my project involved the development of a solid-phase route to tetrahydroquinolones using a microwave-assisted Heck reaction and Michael cyclisation as the key steps. During this work, we also showed the feasibility of a cyclative-cleavage strategy using the HASC linker, where cleavage of the link with $SmI_2$ is followed by cyclisation to give a heterocyclic product directly.

## CONTENTS

The research described in this thesis was carried out under the supervision of Dr David J. Procter in the Loudon laboratory at the University of Glasgow between October 2002 and September 2004 and lab 5.52 at the University of Manchester between September 2004 and September 2005. Research was also conducted on a period of industrial placement at Pfizer Discovery, Sandwich, Kent under the supervision of Mark Stefaniak between May 2004 and July 2004. Part of this thesis has been published previously:

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Special thanks go to my husband Paul who has supported me through the rollercoaster of research and for his considerable emotional and financial support.

| | |
|---|---|
| **Ac** | acetic or acetyl |
| **AIBN** | azobisisobutyronitrile |
| **All** | allyl |
| **Alloc** | allyloxycarbonyl |
| **App** | L-2-amino-5-phenylpentanoic acid |
| **App** | apparent (NMR) |
| **APT** | attached proton test |
| **Ar** | aryl |
| **ATR** | Attenuated total reflection |
| **BBN** | 9-borabicyclo[3.3.1]nonane |
| **Bn** | benzyl |
| **Boc** | *tert*-butoxycarbonyl |
| **BOP-Cl** | bis(2-oxo-3-oxazolidinyl)phosphinic chloride |
| **Bpoc** | (2-(*p*-biphenylyl)-2-propyloxy carbonyl) |
| **18-c-6** | 18-crown-6 |
| **CI** | chemical ionisation |
| **CSA** | camphor sulfonic acid |
| **d** | doublet (NMR) |
| **dba** | dibenzylideneacetone |
| **DBU** | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| **DCC** | dicyclohexyl carbodiimide |
| **DCE** | 1,2-dichloroethane |
| **DEAD** | diethyl azodicarboxylate |
| **DIC** | diisopropyl carbodiimide |
| **DIEA** | diisopropylethylamine |
| **DIPAD** | diisopropyl azodicarboxylate |
| **DMAP** | dimethylaminopyridine |
| **DME** | 1,2-dimethoxyethane |
| **DMF** | N, N-dimethylformamide |
| **DMPU** | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone |
| **DMSO** | dimethyl sulfoxide |
| **Bpoc** | 2-(4-biphenylyl)propyl(2)oxycarbonyl |
| **dppf** | 1,1'-bis(diphenylphosphino)ferrocene |
| **dppp** | 1,3-bis(diphenylphosphino)propane |
| **DTBP** | 2,6-di-*tert*-butyl pyridine |

| | |
|---|---|
| **EDCI** | 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride |
| **ee** | enantiomeric excess |
| **EE** | ethoxy ether |
| **EI** | electron impact |
| **eq.** | equivalents |
| **Et** | ethyl |
| **EWG** | electron withdrawing group |
| **FAB** | fast atom bombardment |
| **FDPP** | pentafluorophenyl diphenylphosphinate |
| **Fmoc** | N-(9-fluorenylmethoxycarbonyl) |
| **g** | gram |
| **GC** | gas chromatography |
| **Gly** | glycine |
| **h** | hour |
| **HATU** | O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexa fluorophosphates |
| **HFIP** | hexafluoro*iso*propanol |
| **HMPA** | hexamethyl phosphoramide |
| **HOBt** | 1-hydroxybenzotriazole |
| **Hz** | Hertz |
| ***i*** | iso |
| **IR** | infrared |
| **KHMDS** | potassium hexamethyldisilazide |
| **LDA** | lithium diiso-propyl amide |
| **LHMDS** | lithium hexamethyldisilazide |
| MAS | magic angle spinning (NMR) |
| ***m*CPBA** | *meta*chloroperoxybenzoic acid |
| **Me** | methyl |
| **mg** | milligram |
| **MHz** | megaHertz |
| **min** | minute |
| **ml** | millilitre |
| **mmol** | millimole |
| **mp** | melting point |
| **MS** | molecular sieves |
| **Mw** | microwave |
| **NaHMDS** | sodium hexamethyldisilazide |

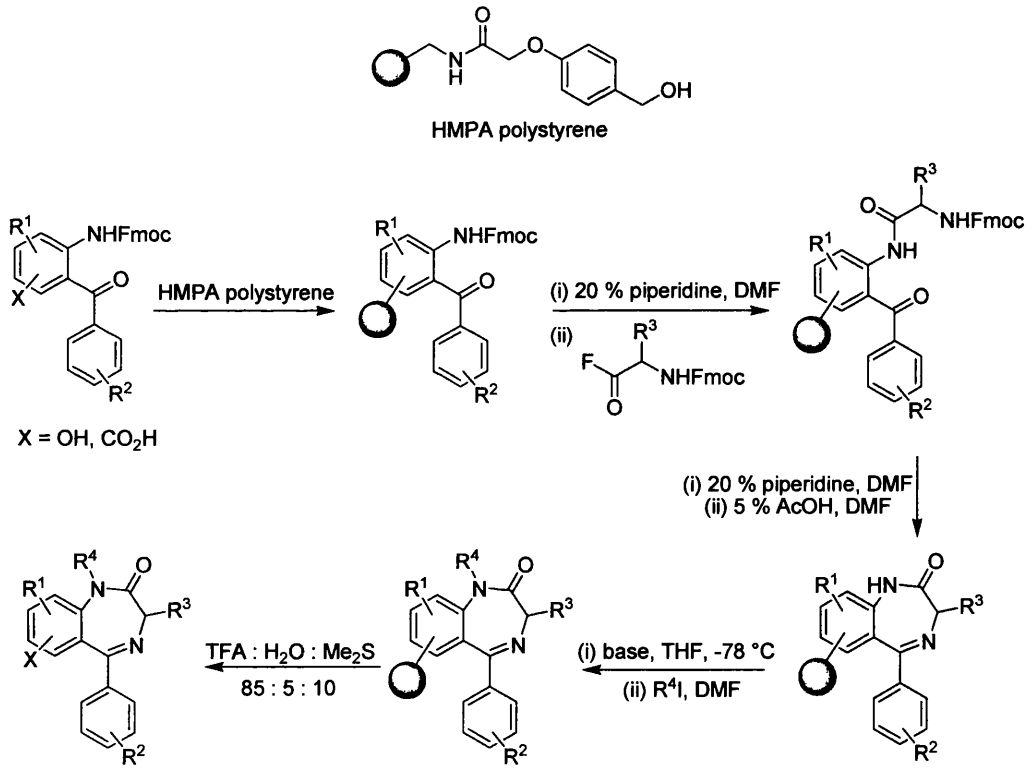
| | |
|---|---|
| **NaO*t*-Bu** | sodium *tert*-butoxide |
| **NBS** | N-bromosuccinimide |
| ***n*-BuLi** | n-butyllithium |
| **$NEt_3$** | triethylamine |
| **NMM** | N-methyl morpholine |
| **NMP** | N-methylpyrollidine |
| **NMR** | nuclear magnetic resonance |
| ***o*** | ortho |
| ***p*** | para |
| **Pbf** | 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl |
| **$PCy_3$** | tricyclohexylphosphine |
| **PEG** | polyethylene glycol |
| **Ph** | phenyl |
| **PMB** | paramethoxy benzyl |
| **Pr** | propyl |
| **Proalloc** | See alloc |
| **PPTS** | pyridinium-*p*-toluenesulfonic acid |
| **$P(t\text{-}Bu)_3$** | tri-*tert*-butylphosphine |
| **PyBOP** | 1-benzotriazolyoxytris(pyrrilodino)phosphinium hexafluorophosphate |
| **q** | quartet (NMR) |
| **rt** | room temperature |
| **s** | singlet |
| **sat.** | saturated |
| **Ser** | serine |
| **SIPr-$BF_4$** | 1,3-bis(2,4-diisopropylphenyl)imidazolinium tetrafluoroborate |
| **SIPr-Cl** | 1,3-bis(2,4-diisopropylphenyl)imidazolinium chloride |
| **SPOS** | Solid-phase organic synthesis |
| **t** | triplet (NMR) |
| **TBAB** | tetrabutylammonium bromide |
| **TBAF** | tetrabutylammonium fluoride |
| **TBDPS** | tert-butyldiphenylsilyl |
| **TBS** | tert-butyldimethylsilyl |
| **Tf** | triflate |
| **TFA** | trifluoroacetic acid |
| **TFAA** | trifluoroacetic anhydride |
| **TFE** | 2,2,2-trifluoro ethanol |
| **TFP** | trifurylphosphine |

| | |
|---|---|
| **THF** | tetrahydrofuran |
| **TLC** | thin layer chromatography |
| **TMEDA** | N,N,N',N'-tetramethyl 1,2-ethanediamine |
| **TMS** | trimethylsilyl |
| **Tol** | tolyl |
| **µl** | microlitre |
| **Val** | valine |

## 1.0 INTRODUCTION TO LINKERS FOR SOLID-PHASE ORGANIC SYNTHESIS

The evolution of solid-phase organic synthesis (SPOS) can be traced back to the solid-phase peptide synthesis first described by Merrifield.[1] His method was revolutionary and solid-phase peptide synthesis is now carried out in automated peptide synthesisers which make full use of the advantages of solid-phase techniques. The major benefits over standard solution-phase techniques include: the ease of product isolation *via* filtration; use of excess reagents to drive reactions to completion and ease of automation.[2, 3]

Solid-phase synthesis remained a tool only for the peptide chemist until the early 1990's when Ellman and Bunin published a convenient and high-yielding solid-phase synthesis of 1,4-diazepines **(scheme 1.1)**.[4] This proved to be a key publication in the area and Ellman later went on to synthesise a library of 192 diazepine analogues using his solid-phase route.[5]




**Scheme 1.1**

SPOS has now become a cornerstone in the combinatorial synthesis of "drug-like" small organic molecule libraries. In the last decade, a great many research groups in academia and industry have made efforts to transfer solution-phase reactions onto solid-phase. As a result SPOS and its application in a combinatorial sense has emerged as an indispensable tool to accelerate drug discovery.

## 1.1 TRACELESS LINKERS

New interest in using SPOS for the synthesis of libraries of drug-like molecules found limitations in the use of conventional linkers which were designed for the synthesis of peptides. Conventionally, the link to polymer was at the C-terminus of the peptide meaning traditional linkers such as Merrifield, Rink and Wang resins required carboxylic acid functionality in the substrate for loading onto resin.[6, 7] **Fig. 1.1** shows some traditional resins originally used in peptide synthesis. They now form the basis of new SPOS resins.

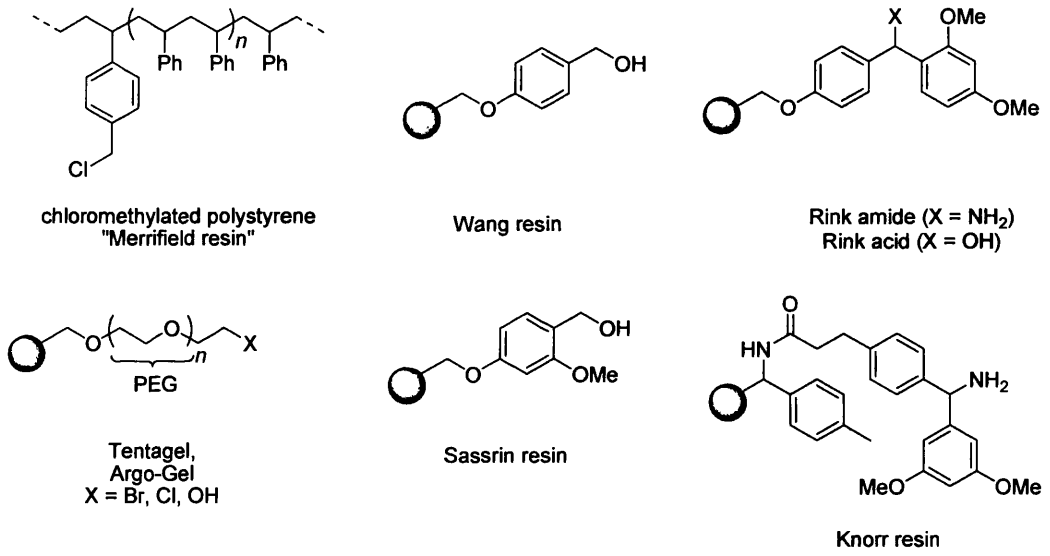


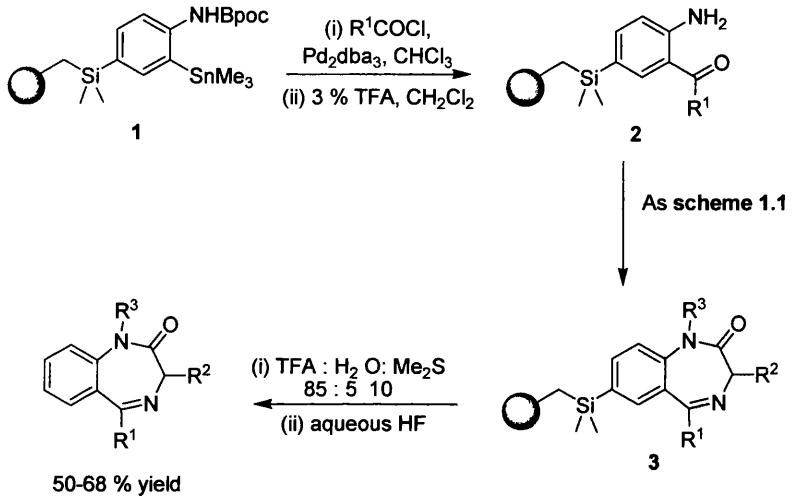

**Fig. 1.1**

Following the synthesis, the carboxylic acid functionality is regenerated after conventional cleavage from the polymer support. In Ellman's pioneering synthesis of 1,4-benzodiazapines **(scheme 1.1)**, the molecules are linked *via* a phenolic or carboxylic acid residue and after cleavage these functionalities were unmasked.

Functional groups have a dramatic outcome on the potential medicinal efficacy of the final products. The use of linkers that dictate the type of functionality present in a

substrate has limited the utility of SPOS for drug discovery. With this in mind, solid-phase chemists set about designing new linkers that were termed "traceless" linkers, where the point of attachment is not apparent in the final molecule.

Ellman was again a pioneer in this field and he developed the use of a silicon-based traceless linker for the synthesis of 1,4-benzodiazepine derivatives **(scheme 1.2)**.[8, 9]




**Scheme 1.2**

The resin bound stannane **1** was coupled with acid chlorides using the Stille reaction and deprotection of the Bpoc group gave supported aniline **2**. Following the procedure outlined in **scheme 1.1**, the functionalised, supported 1,4-benzodiazepines **3** were synthesised. Any protecting groups that remained in the side chains $R^1$-$R^3$ were removed with TFA and the molecules cleaved from the support using aqueous HF. No trace of the point of attachment to the support is found in the cleaved molecule and the functionality of the aryl ring could be adapted to access different target molecules. This was a significant step in SPOS however the linker **4**, used in Ellman's strategy **(Fig. 1.2)** was laborious to synthesise from aminomethylpolystyrene (5 steps).

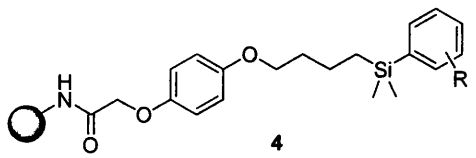


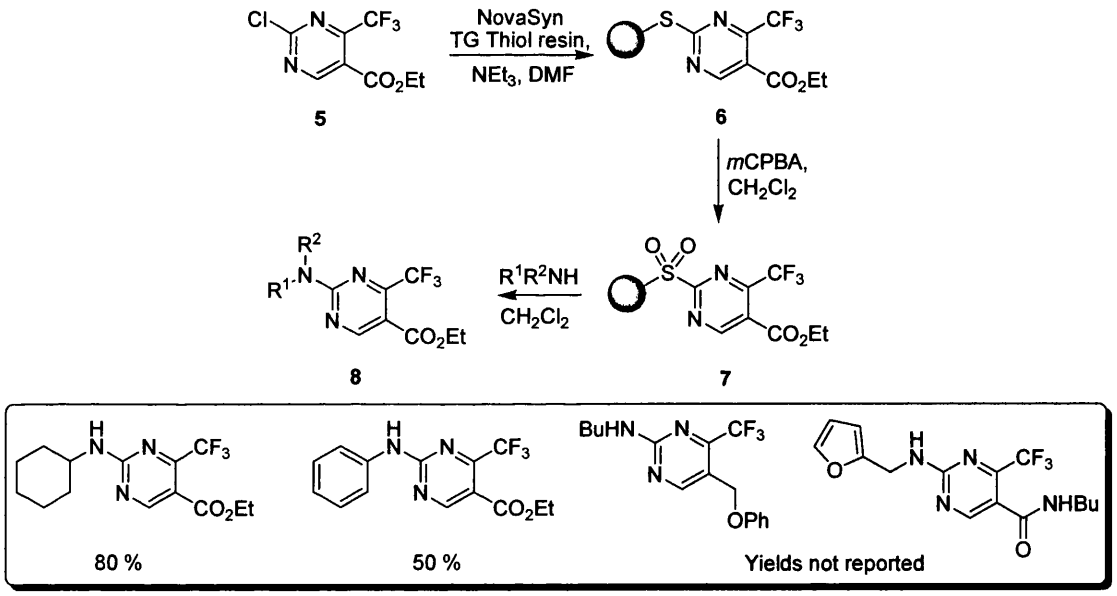

**Fig. 1.2**

Since this early work on traceless linkers there have been many contributions to the area with many heteroatom based linkers (Si, Ge, S, Se, N, P, B, O and Cr) used in SPOS.[10] Protecting group- and auxiliary-based linkers have also been developed as well as target-specific traceless linkers. Such is the growth in the field, the meaning of the term traceless has become somewhat vague. Perhaps the best definition of a traceless linker is a linker that, when cleaved, leaves an aliphatic or aromatic hydrogen at what was the point of attachment to the support.[11]

## 1.2 INTRODUCTION TO SULFUR AND SELENIUM LINKERS.

### 1.2.1 Sulfur linkers

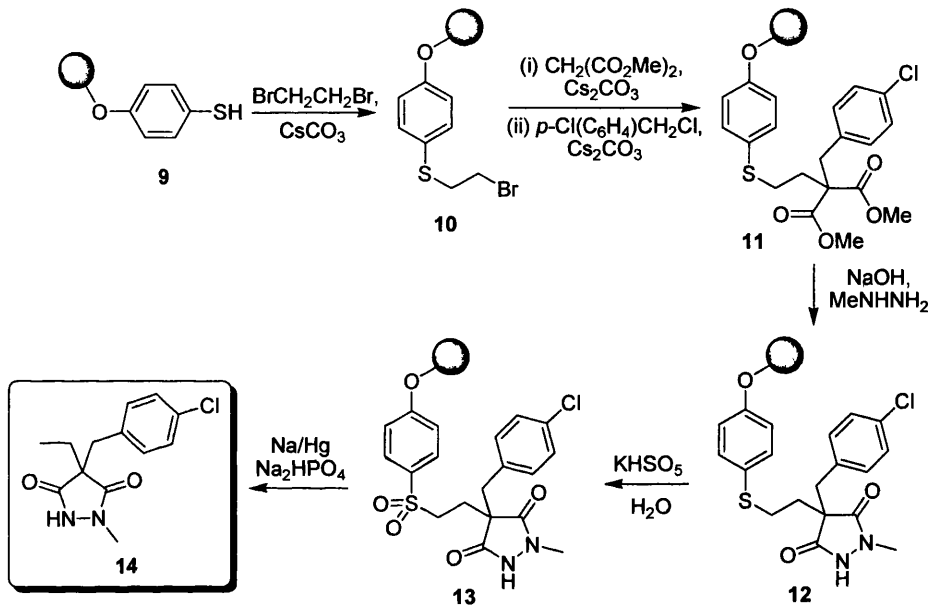
The first example of a sulfur-based linker was reported by Suto *et al.* in 1997 **(scheme 1.3)**.[12] Oxidative activation of a sulfide linker allowed nucleophilic displacement of the sulfone, introducing further diversity into the final compound.




**Scheme 1.3**

The 2-chloropyrimidine **5** was loaded onto Tentagel thiol resin (a PEG based resin) and the resulting immobilised sulfide **6** oxidised to the sulfone **7** with *m*CPBA. Cleavage from the support using primary and secondary amines gave pyrimidines **8** in 50-93 % yield. The purity of the final compounds was excellent (> 90 %) and the ester group in intermediates such as **7** could also be manipulated to synthesise amides and ethers.

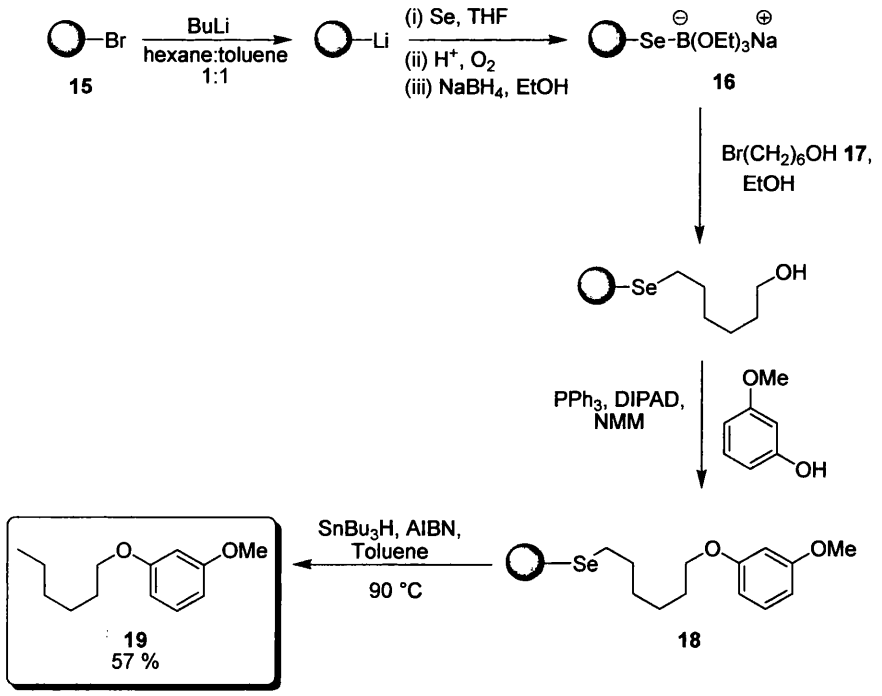
Janda and co-workers have reported the use of a "soluble" PEG based resin using a sulfur linker in the synthesis of a 3,5-pyrazolidinedione.[13] Alkylation of the thiophenol resin **9** with a symmetrical dihalide gave the supported bromoalkane **10 (scheme 1.4)**. Alkylation with dimethyl malonate, followed by alkylation with a benzylic halide provided the cyclisation substrate **11**. Treatment of **11** with base and methyl hydrazine resulted in cyclisation to give the supported 3,5-pyrazolidinedione **12**. Chemoselective sulfide oxidation gave the sulfone **13** which was reductively cleaved with Na/Hg to release the free heterocycle **14**. The polymer support is soluble in most organic solvents enabling the reactions to be carried out in a solution-like environment but can be conveniently precipitated with *i*-PrOH to facilitate isolation and washing.




**Scheme 1.4**

## 1.2.2 Selenium linkers

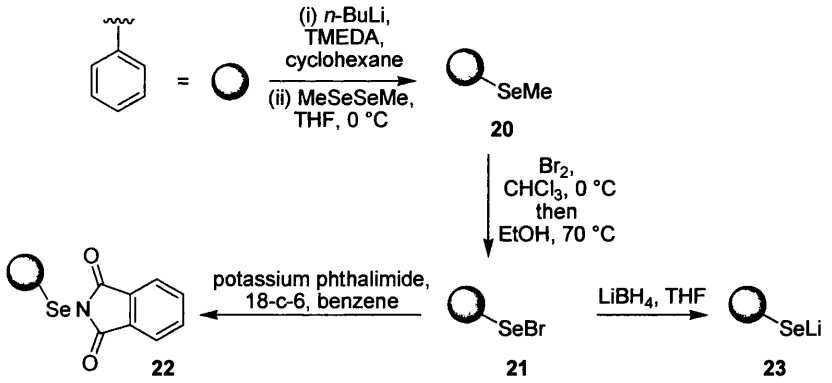
Selenium has proved to be a useful element for traceless SPOS, attracting much recent interest. The first example of the use of a selenium-based traceless linker was in the solid-phase synthesis of a library of phenolic ethers described by Ruhland and co-workers **(scheme 1.5)**.[14]




**Scheme 1.5**

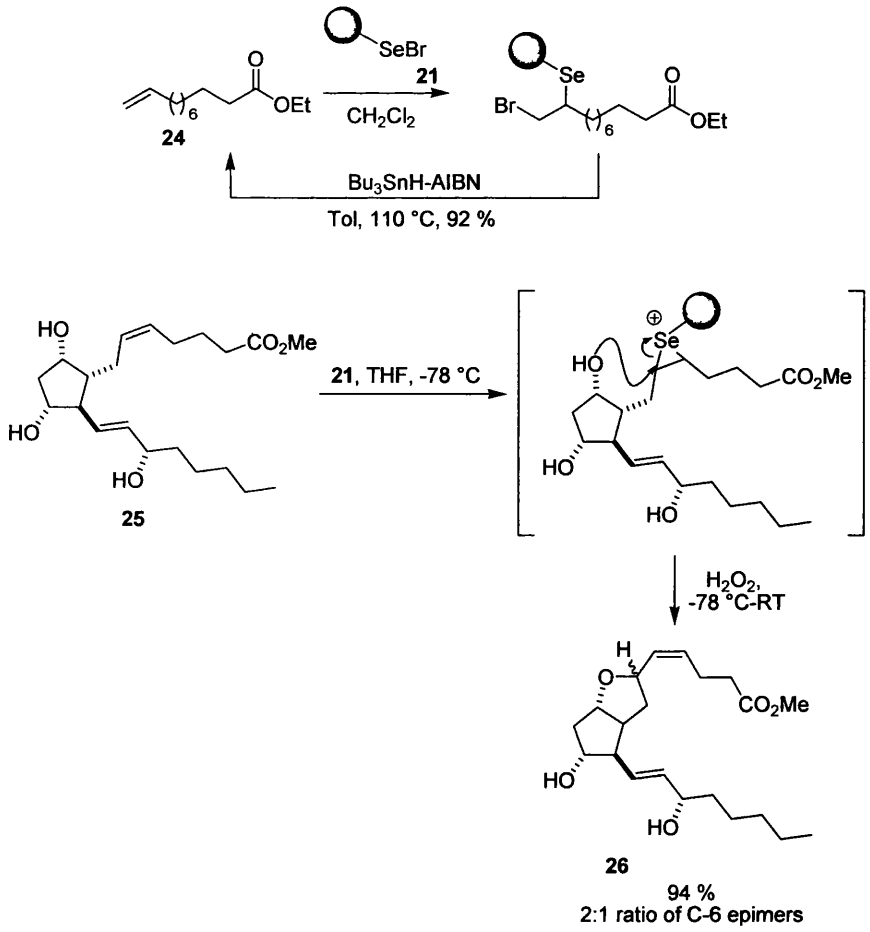
Commercial bromopolystyrene **15** was lithiated and treated with selenium powder. Air oxidation gave a diselenide resin, which was reduced using sodium borohydride to give the resin-bound sodium(triethyl)borate complex **16**. Halo alcohols such as **17** were then immobilised and reacted with phenols under Mitsonobu conditions to give supported phenolic ethers such as **18**. Cleavage *via* a radical reduction gave a library of phenolic ethers such as **19** in good yield **(scheme 1.5)**.

At around the same time, Nicolaou carried out a more extensive study of the use of selenium linkers.[15] A series of solid-phase resins were prepared from readily available starting materials. Polystyrene beads suspended in cyclohexane were treated with *n*-BuLi and TMEDA and the lithiated species quenched with dimethyldiselenide to give resin **20 (scheme 1.6)**. Exposure of **20** to bromine gave the polymer supported selenyl bromide resin **21**. Selenium phthalimide reagent **22** was prepared from **21** by displacement with potassium phthalimide in the presence of 18-crown-6. The lithium selenide resin **23** was prepared by $LiBH_4$ reduction of **21**.



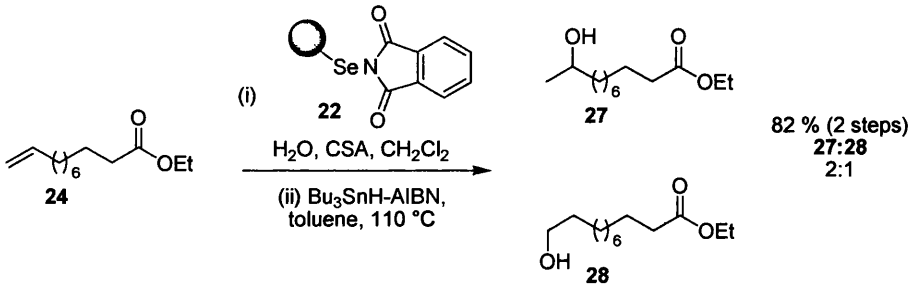

**Scheme 1.6**

The use of resins **21-23** as polymer supports and as polymer supported reagents was then illustrated. Olefin **24** was immobilised using the selenium bromide resin **21** and subsequently released reductively upon treatment with $Bu_3SnH$-AIBN. The starting olefin was recovered in 92 % yield. The polymer supported selenium bromide **21** was also found to be as effective as the corresponding solution-phase reagent, phenyl selenium bromide, for the transformation of $PGF_{2\alpha}$ methyl ester **25** to the $PGI_2$ analogue **26 (scheme 1.7)**. In this case, immobilisation using **21** triggers cyclisation to form the tetrahydrofuran ring. Oxidation of the linking selenium atom to the selenoxide and elimination releases **26** from the support.




**Scheme 1.7**

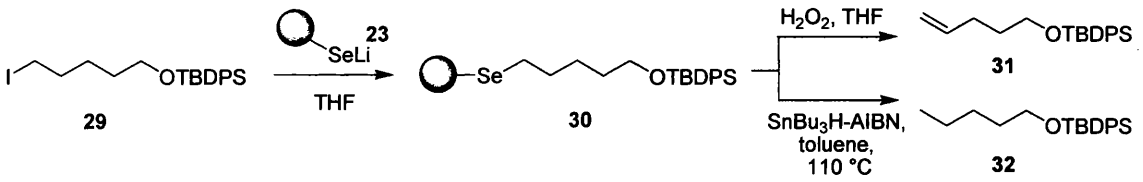
Phthalimide selenium resin **22** also proved to be a useful polymer bound reagent. Terminal olefin **24** was converted to the regioisomeric alcohols **27** and **28** in 82 % overall yield after reductive cleavage of the selenide linker **(scheme 1.8)**.




**Scheme 1.8**

The protected iodo alcohol **29** was loaded onto lithium selenide resin **23** to give **30**. Oxidation followed by spontaneous cleavage released the terminal alkene **31**.

Alternatively, radical cleavage of selenide **30** gave alkane **32**. Moderate to good yields of product were reported (48-94 %) for a diverse range of substrates.



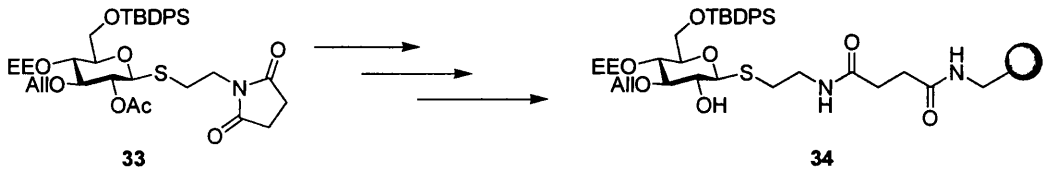

**Scheme 1.9**

## 1.3 PALLADIUM-CATALYSED TRANSFORMATIONS ON SUBSTRATES IMMOBILISED THROUGH SULFUR AND SELENIUM LINKERS.

Any new type of linker for use in solid-phase synthesis must be compatible with palladium mediated transformations such is the importance of this methodology in both academia and industry.[16] The main advantage of solid-phase techniques is the avoidance of tedious work up procedures and this is particularly important for palladium-catalysed reactions as the soluble palladium catalyst can be easily removed by washing processes. In recent years, an increasing number of reports have appeared describing well-established palladium-mediated processes being performed on solid-phase substrates.[16] In this short review I will concentrate on palladium-catalysed transformations carried out on supported substrates immobilised through a sulfur or selenium linker.

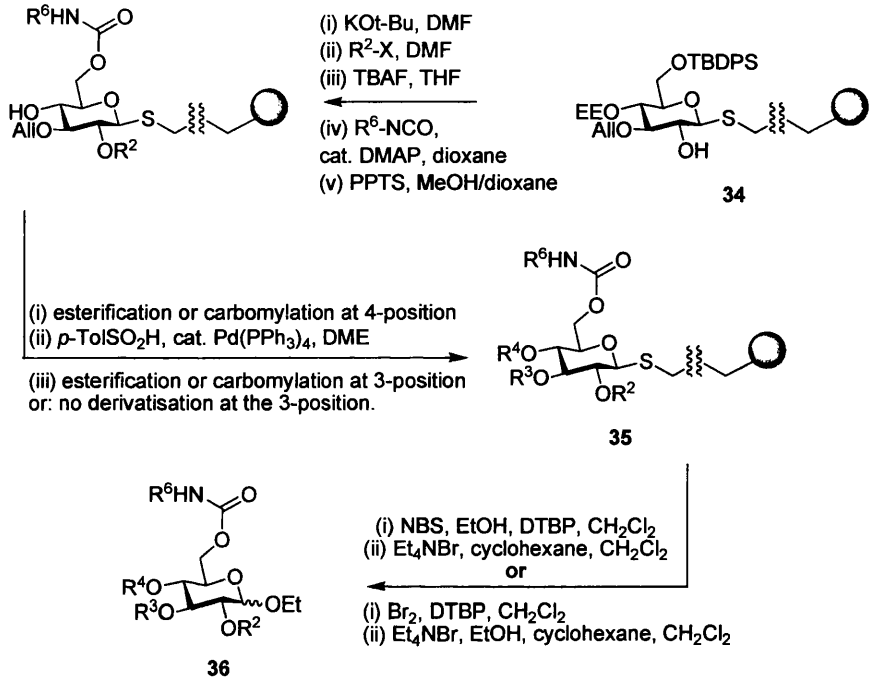
### 1.3.1 Sulfide linkers

Kunz *et al.* have illustrated the use of the palladium-catalysed removal of allyl protecting groups in the synthesis of a library of compounds from the orthogonally protected monosaccharide template **34** immobilised *via* a sulfur link to the support.[17] The template is synthesised in three steps from succinimide **33 (scheme 1.10)**.




**Scheme 1.10**

Derivatisation was first carried out at the 2-position followed by deprotection of the silyl ether and carbamoylation **(scheme 1.11)**. Deprotection of the ethoxy ether group was followed by esterification or carbamoylation. Palladium-catalysed deprotection of the acid and base stable allyl ether group was then carried out using *p*-toluene-sulfinic acid as the proton source and allyl acceptor. The deprotected hydroxyl group at C-3 was carbamoylated, esterified or left underivatised to give the resin-bound glucoside intermediates **35 (scheme 1.11)**.




**Scheme 1.11**

Cleavage from the solid-support was achieved by addition of bromine or NBS with a hindered base and led to the formation of reactive 1-bromo sugars which were converted into the corresponding 1-O-ethyl glycosides **36** by Lemieux activation with tetraethyl ammonium bromide and reaction with ethanol **(scheme 1.11)**. A range of structurally diverse glucose derivatives was synthesised using this approach, some of which are shown in **Fig. 1.3**, in moderate to good yields and high purity illustrating the efficiency of each reaction on solid-phase.

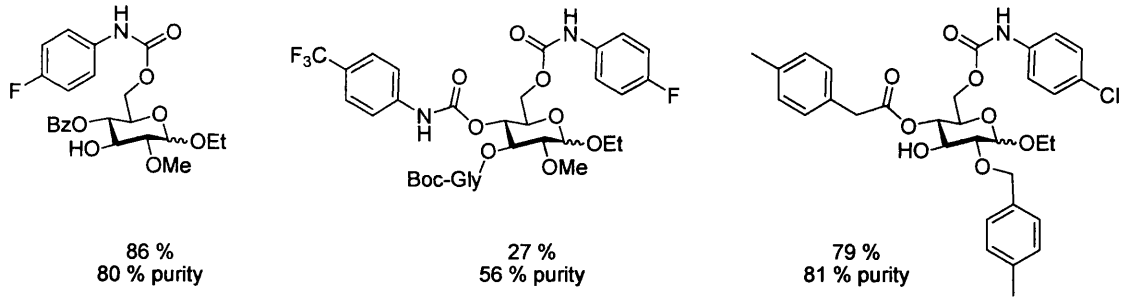
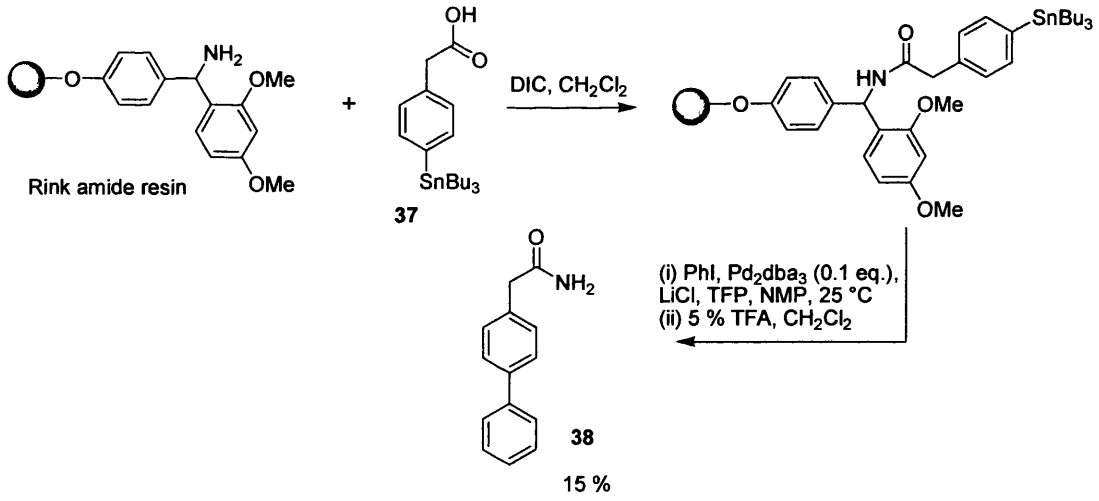



**Fig. 1.3**

The group of Sucholeiki at Eli Lilly described the use of a sulfur linker in a solid-phase synthesis of biaryls using the Stille reaction.[18] The use of both a nitrogen and sulfur-based linker was investigated and their utilities compared.

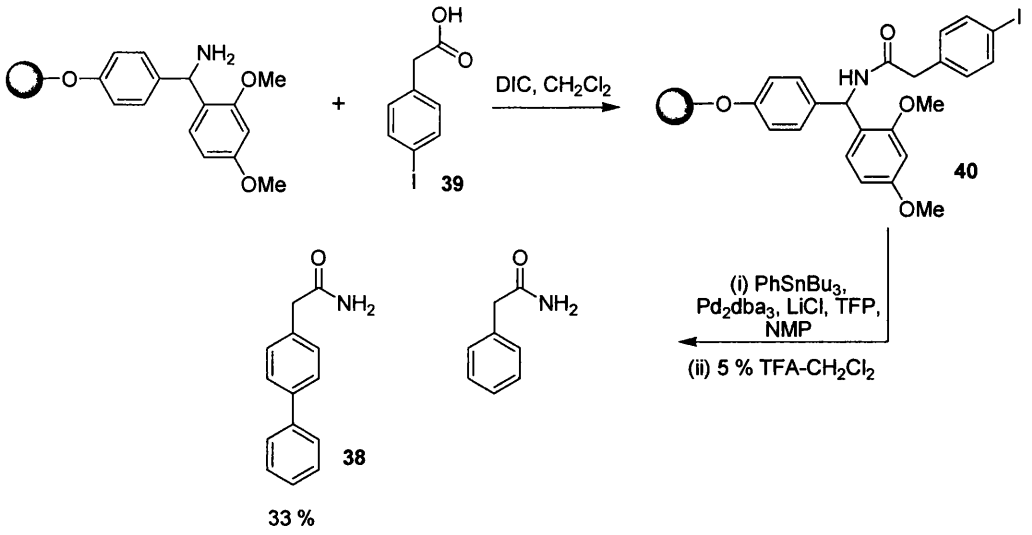
Initial work concentrated on the immobilisation of the aryl stannane **37** using the Rink amide resin. Stille coupling was carried out with phenyl iodide to give biphenyl **38** after cleavage from the support **(scheme 1.12)**. The intermediate resin-bound biaryl was characterised by gel-phase $^{13}C$ NMR. Unfortunately, the maximum yield of **38** achieved was only 15 %.




**Scheme 1.12**

The "sense" of the Stille reaction was then reversed. Immobilisation of iodo-substituted carboxylic acid **39** was achieved through a coupling onto the free amine of the linker to give the resin-bound aryl iodide **40 (scheme 1.13)**. Stille coupling with phenyltributyltin gave a 33 % yield of the desired biphenyl **38** after acid cleavage. The authors highlighted the possibility that the resin-bound tin species in **scheme 1.12** was

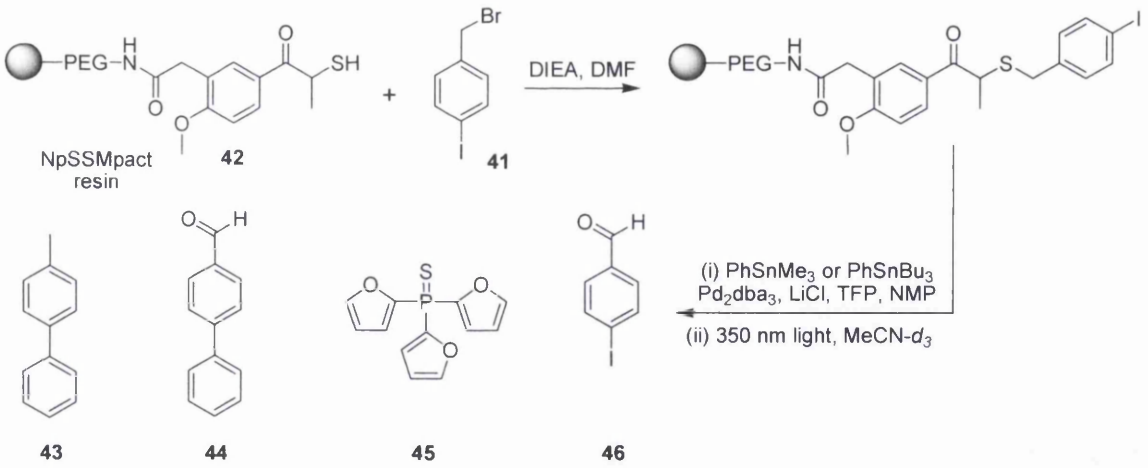
changing the expansion-contraction properties of the cross-linked resin, restricting the access of the reagents to the interior of the support thus an improved yield was obtained when coupling a resin bound iodide with a solution-phase trialkylphenyltin.




**Scheme 1.13**

The use of a traceless sulfide linker was then investigated and 4-iodobenzylbromide **41** was immobilised using thiol resin **42**. NpSSMpact resin is a photoactive support developed by the group. Stille coupling and photolytic cleavage in deuterated acetonitrile resulted in a mixture of products **(scheme 1.14)** which was analysed by $^1$H NMR.

When the conditions optimised using the Rink amide resin were used in the Stille coupling with the sulfur linker system, only a very small amount of the corresponding biaryls **43** and **44** were isolated **(table 1.1)**. In addition to the expected biaryls, unreacted aryl iodide **46** and trifurylphosphine sulfide **45** were produced **(scheme 1.14)**. The production of this sulfide by product was suppressed by reducing the number of equivalents of TFP used **(table 1.1)**. It was found that much higher quantities of palladium catalyst and trialkylphenylstannane were needed with the sulfur linker system. It was proposed that this was due to chelation of the palladium catalyst to unreacted thiol on the resin.




**Scheme 1.14**

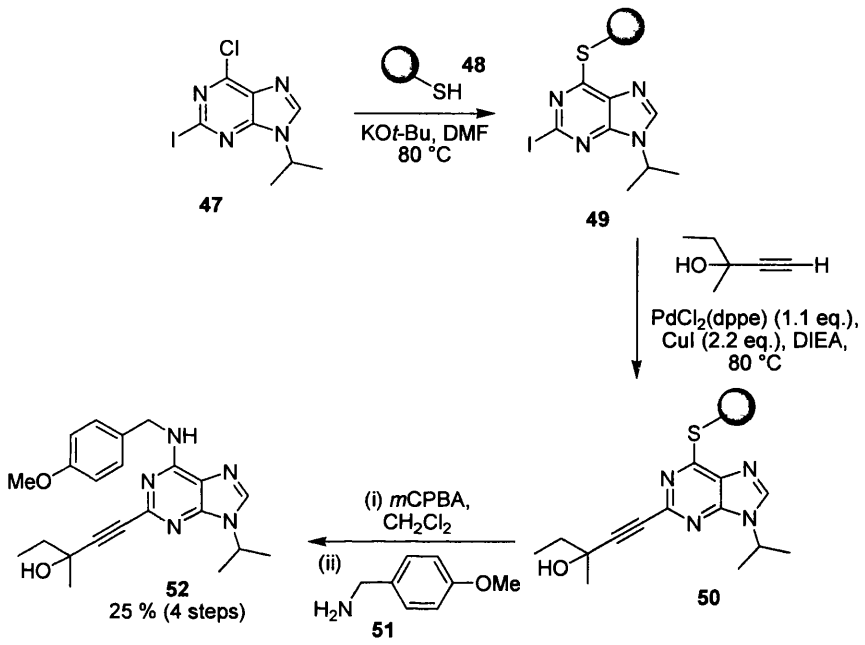
Adjusting the number of equivalents of each of the various reagents **(entry 6, table 1.1)** gave a moderate yield of the desired product **43** (27 %).

| Entry | $PhSnR_3$, equiv | TFP, equiv | $Pd_2dba_3$, equiv | LiCl, equiv | Equiv | | | | % yield of **43** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **43** | **44** | **45** | **46** | |
| 1 | $CH_3$, 1.5 | 0.21 | 0.11 | 1.4 | 1 | 0.25 | 1.67 | 0.29 | 3 |
| 2 | $CH_3$, 2.9 | 0.43 | 0.23 | 1.4 | 1 | 0.20 | 0.57 | 0 | 10 |
| 3 | $CH_3$, 2.9 | 0.12 | 0.21 | 1.4 | 1 | 0.7 | 0 | 0 | 4.5 |
| 4 | $CH_3$, 4.9 | 0.22 | 0.29 | 2.6 | 1 | 0.1 | 0.12 | 0 | 10 |
| 5 | Butyl, 4.3 | 0.23 | 0.28 | 2.8 | 1 | 0.7 | <0.05 | 0 | 3 |
| 6 | $CH_3$, 12 | 0.18 | 0.23 | 2.0 | 1 | 0.1 | 0 | 0 | 27 |

**Table 1.1**

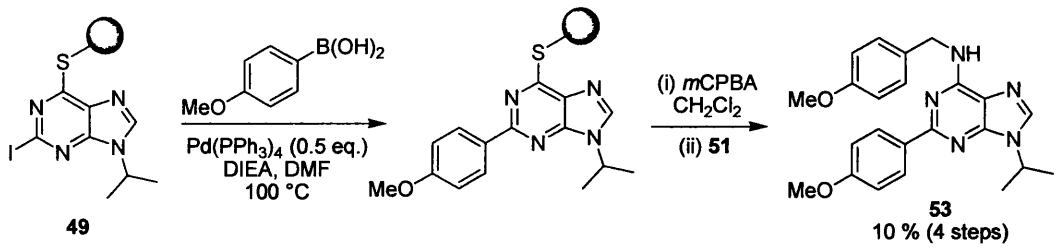
The compatibility of a sulfur linker with Suzuki and Sonogashira cross coupling conditions has been reported by the group of Legraverand in a solid-phase synthesis of 2,6,9-trisubstituted purines **(scheme 1.15)**.[19] The route was first validated in solution-phase studies employing benzyl thiol as a model for a Merrifield-derived thiol resin. 6-Chloro-2-iodo-9-*iso*propylpurine **47** was stirred together with thiol resin **48** and potassium *tert*-butoxide to give the immobilised purine **49**. Sonogashira coupling with a stoichiometric quantity of $PdCl_2$(dppe) and CuI gave the 6-alkynyl derivative **50**. Oxidative activation of the link with *m*CPBA followed by displacement with 4-methoxy benzylamine **51** gave the trisubstituted purine **52** in a 25 % yield after 4 steps. The conditions employed for the Sonogashira coupling on the solid-phase are different to those optimised in solution. The solution-phase route used $(PPh_3)_2PdCl_2$ as the

stoichiometric catalyst and $NEt_3$ as the base however when these conditions were transferred to solid-phase no reaction occurred. The use of a stoichiometric amount of palladium is an obvious disadvantage of this route. The need for a greater quantity of palladium may be due to chelation from remaining free thiol sites after immobilisation of **47**. This would not have caused any problems in the solution-phase optimisation of the route since purification would have been carried out following each reaction.




**Scheme 1.15**

The Suzuki reaction of **49** was less successful. Treatment of the resin bound 2-iodopurine **49** with 4-methoxyphenyl boronic acid and 50 mol % of $Pd(PPh_3)_4$ followed by oxidation and displacement with **51** gave only 10 % of the cleaved product **53**. The low yield was attributed to steric crowding and catalyst destruction through "irreversible" coordination of palladium to purine N-7 and the sulfur atom at position 6.




**Scheme 1.16**

To confirm that steric crowding was contributing to the low yield, both the Suzuki and Sonogashira reactions were investigated using a resin bound purine **54** with a "spacer" between the sulfur atom linkage and the resin backbone **(Fig. 1.4)**. The results showed an increased yield of the products **52** (64 % with the "spacer", compared to 25 % without) and **53** (35 % with the "spacer", compared to 10 % without). This clearly suggests that steric crowding rather than "poisoning" of the palladium due to coordination to sulfur was the main problem.

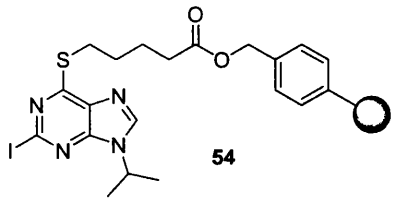
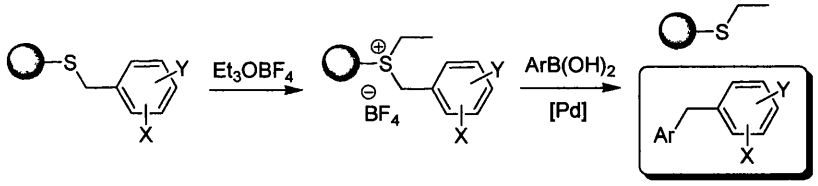


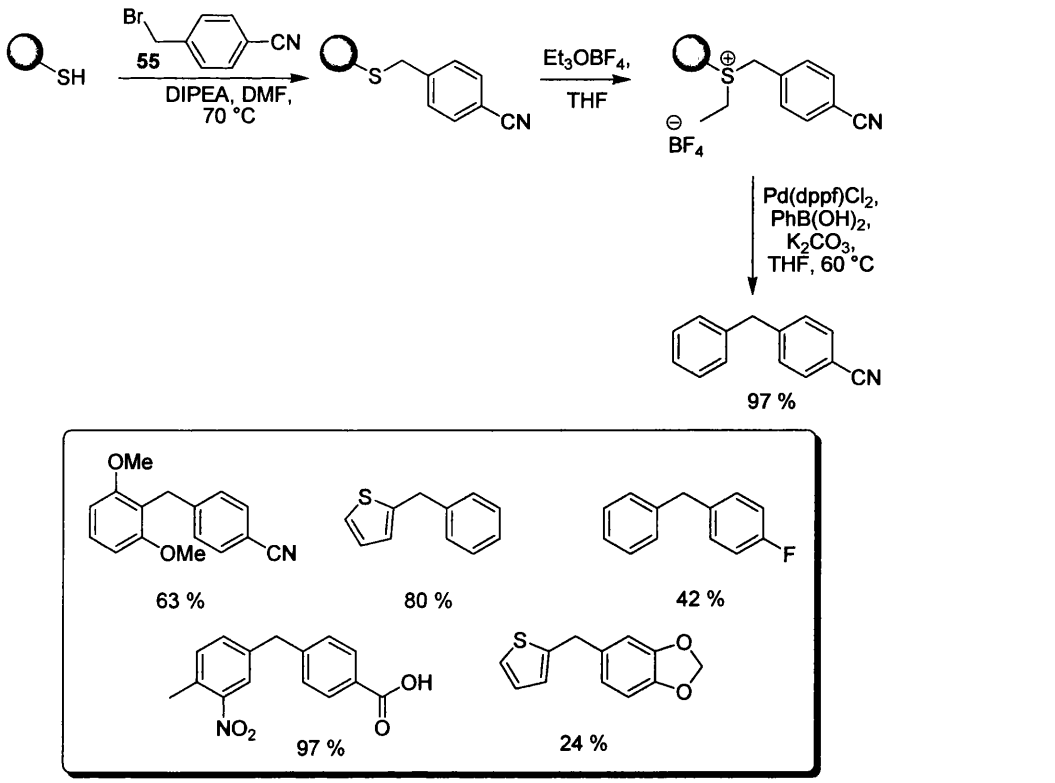

**Fig. 1.4**

A Suzuki coupling-release strategy has been developed by Vanier *et al.* and used in a traceless, solid-phase synthesis of biarylmethanes **(scheme 1.17)**.[20] Solution-phase studies indicated that acyclic benzyl sulfonium salts should give the best yields of biarylmethane products in the Suzuki cross-coupling and attachment to resin was therefore carried out through a benzylic bond to an alkyl thiol resin.



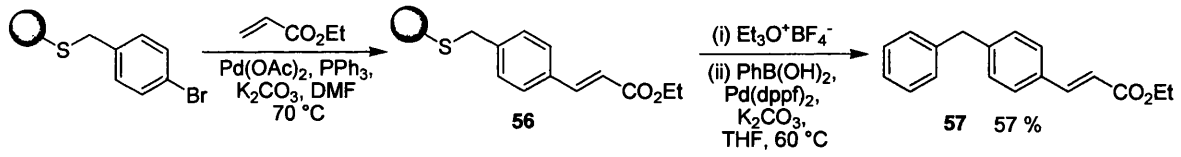

**Scheme 1.17**

Benzyl bromide derivative **55** was immobilised using a thiol resin and the sulfur atom linkage was activated by alkylation. A Suzuki coupling release was then carried out using optimised conditions involving $Pd(dppf)_2$ and $K_2CO_3$ to give a range of biarylmethanes in good yields. **Scheme 1.18** shows an illustrative sequence and a selection of biarylmethanes synthesised using the approach.




**Scheme 1.18**

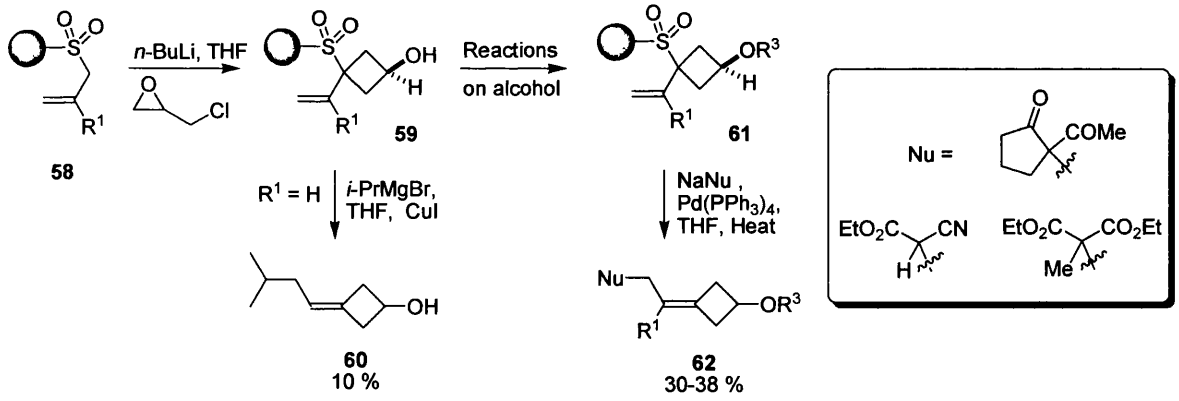
The versatility of the activation/cleavage sequence was illustrated by the synthesis of the biaryl cinnamate derivative **57 (scheme 1.19)**. Two successive palladium-catalysed reactions were carried out: Heck reaction to give the supported cinnamate **56** followed by the Suzuki coupling-release to give **57** in 57 % yield.




**Scheme 1.19**

### 1.3.2 Sulfone linkers

The chemistry of allylic sulfone derivatives has been used by Kurth *et al.* as the basis for a solid-phase synthesis of cyclobutylidenes **(scheme 1.20)**.[21]

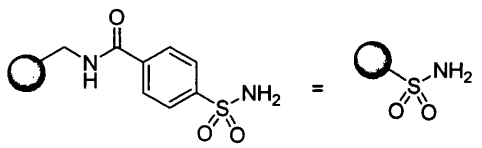



**Scheme 1.20**

The allyl sulfone resins **58** were synthesised in 2 steps from commercial polystyrene resin, the sulfone being linked directly to the aromatic backbone of the polymer. Reaction of the lithiated sulfone with epichlorohydrin gave the supported cyclobutanol **59**. When $R^1$ = H, cleavage with *i*-PrMgBr gave the cyclobutylidene derivative **60** *via* allylic attack of the Grignard with displacement of the phenyl sulfinate resin. Alternatively, the alcohol was derivatised and cleaved using palladium-catalysed allylic alkylation with sodium carbanions to give cyclobutylidene derivatives **62**. The copper-assisted Grignard displacements occurred in poor yield on the solid-phase while the palladium-catalysed allylic alkylations were found to be a more efficient method for the cleavage of products.

### 1.3.3 Sulfonamide linkers

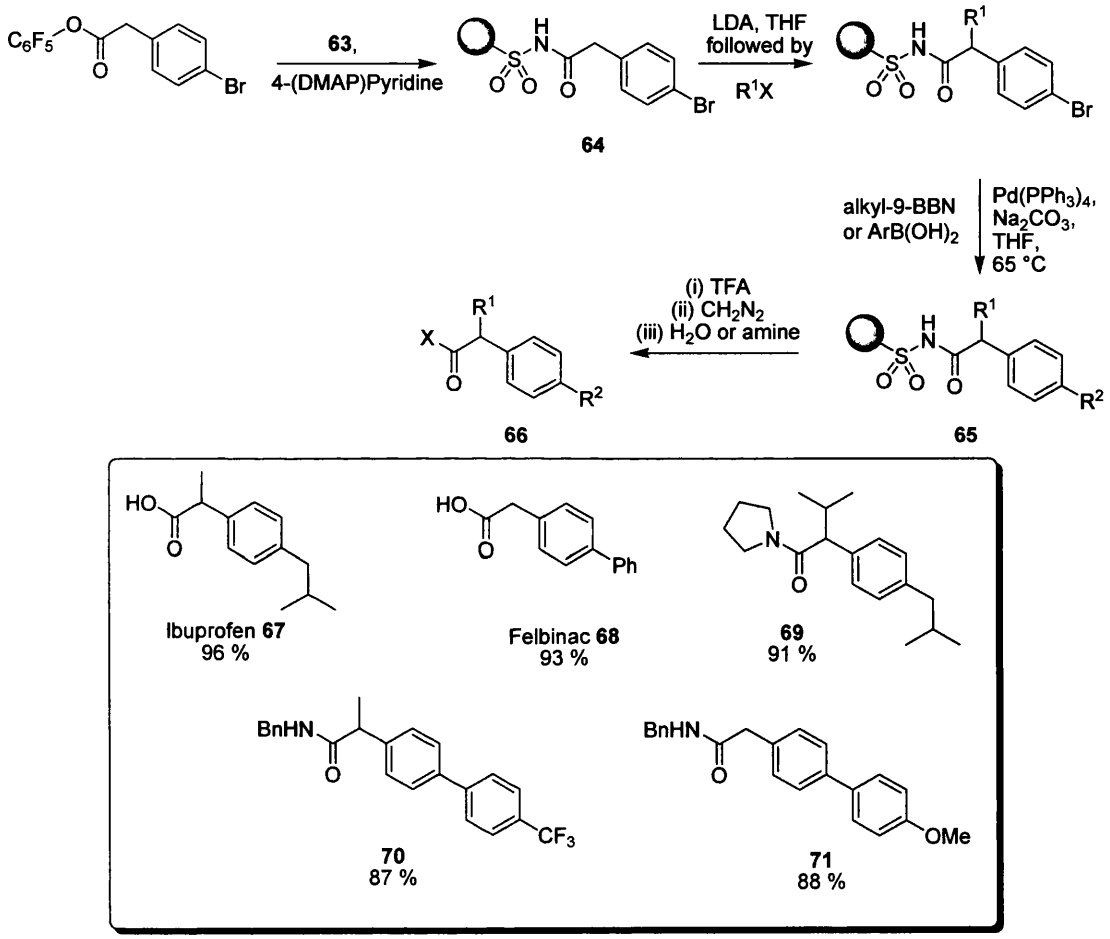
An early paper by Ellmann and Backes describes the use of a sulfonamide "safety-catch" linker, which was originally developed by Kenner **(Fig. 1.5)** for peptide chemistry, in a synthesis of substituted aryl acetic acid derivatives.[22] This report assesses the compatibility of the linker with carbon-carbon bond forming reactions including enolate alkylation and Suzuki coupling.




Kenner's acylsulfonamide linker
**63**

**Fig. 1.5**

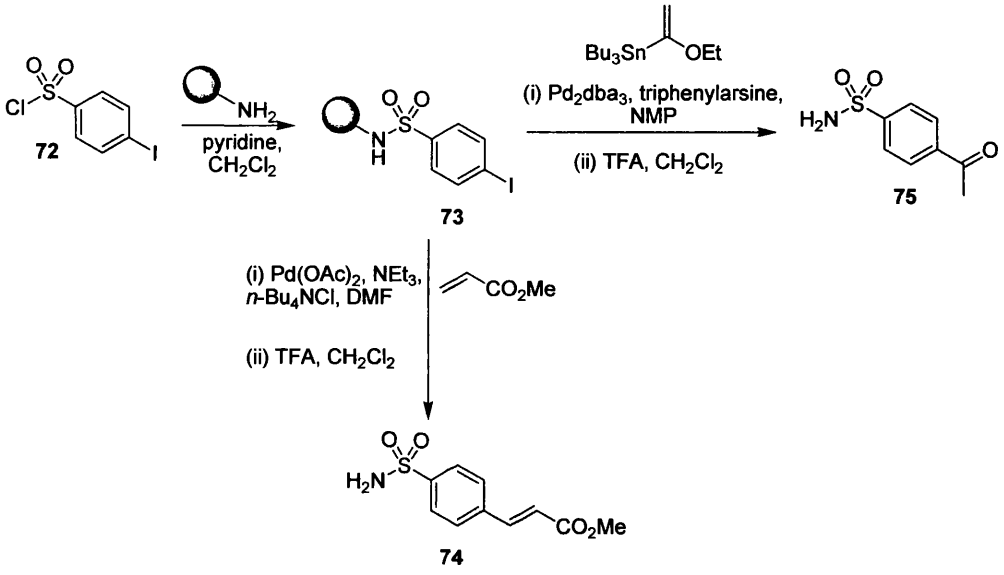
Pentafluorophenyl 4-bromophenyl acetate was immobilised using the sulfonamide resin **63** to give a supported acyl sulfonamide **64**. Alkylation could then be carried out using LDA and an alkyl halide **(scheme 1.21)**. Suzuki coupling was then investigated with a range of electronically varied aryl boronic acids and alkyl boranes. Linker activation was then accomplished by first rinsing the acylsulfonamide **65** with TFA to ensure complete protonation, followed by treatment with $CH_2N_2$ to alkylate the sulfonamide nitrogen. The substituted acylacetic acid derivatives were then cleaved from the support by treatment with a nucleophilic amine or water.




**Scheme 1.21**

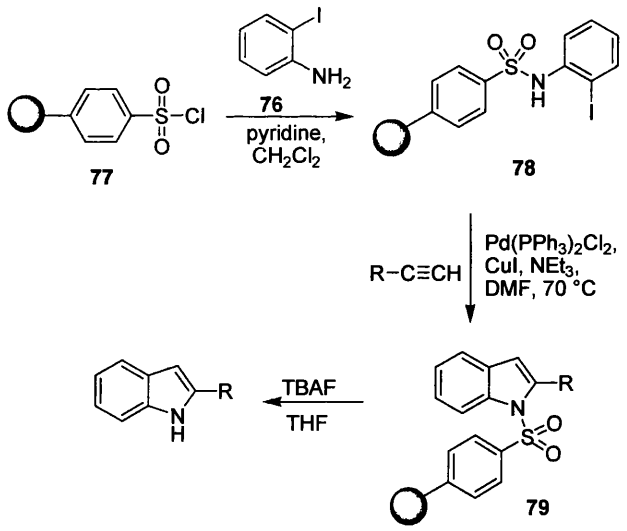
As shown by the excellent yields, hydrolysis cleanly provided carboxylic acid derivatives such as ibuprofen **67** and feblinac **68**. Cleavage with nucleophilic amines such as benzylamine and pyrrolidine gave excellent yields of amides such as **69**, **70** and **71**. The Suzuki coupling was very successful and no proto dehalogenation products were isolated.

In another early report, the group of Spear reported the compatibility of a sulfonamide linker with Stille and Heck couplings.[23] 4-Iodobenzene sulfonyl chloride **72** was immobilised using Rink amide resin **(scheme 1.22)**. Treatment of the supported aryl iodide **73** with palladium (II) and methyl acrylate followed by cleavage with TFA gave **74**. A Stille coupling was achieved by treating **73** with 1-(ethoxyvinyl)tributyltin in the presence of palladium (0) and triphenylarsine and this gave the 4-acetyl sulfonamide **75** after cleavage with TFA.




**Scheme 1.22**

The solid-phase synthesis of indoles facilitated by an activating sulfonamide linker has been described by Zhang and co-workers.[24] Immobilisation of 2-iodoaniline **76** onto a commercially available polystyrene sulfonyl chloride resin **77** gave supported aryl iodide **78 (scheme 1.23)**. Palladium-catalysed Sonogashira coupling under standard conditions with $Pd(PPh_3)_2Cl_2$ and CuI gave an alkyne intermediate which underwent cyclisation to give the supported indole **79**. The process was facilitated by the electron withdrawing nature of the linker which activates the amide nitrogen.




**Scheme 1.23**

The synthesis was also successful when a Merrifield based sulfonamide linker **80** was employed. The excellent yields obtained demonstrate that the palladium-mediated $sp^2$-sp coupling of the aryl iodide derivatives of **80** with different acetylenes and the sulfonamide linker-activated indole cyclisation occur efficiently, in one pot, under relatively mild conditions **(Fig. 1.6)**.

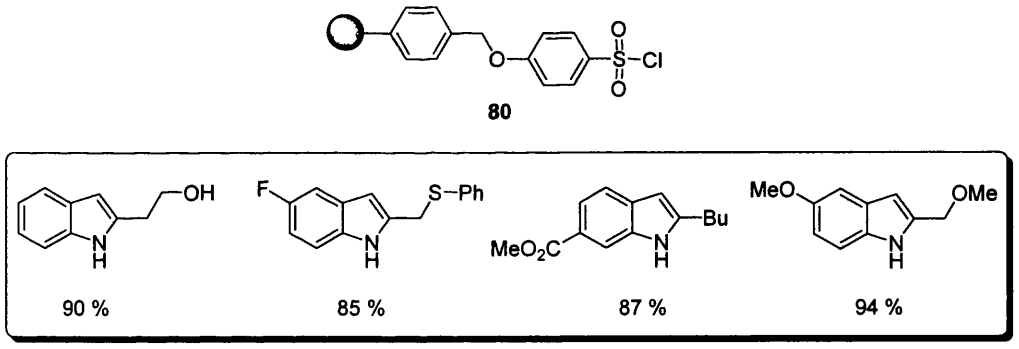
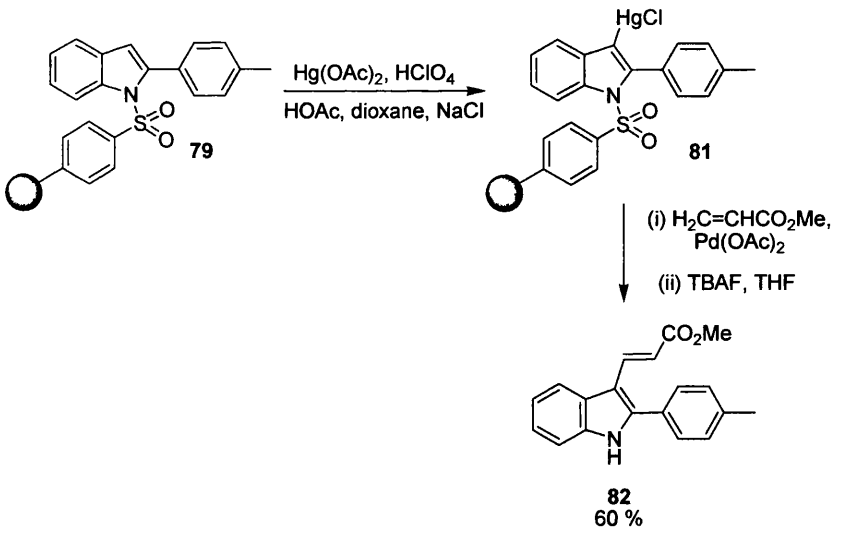


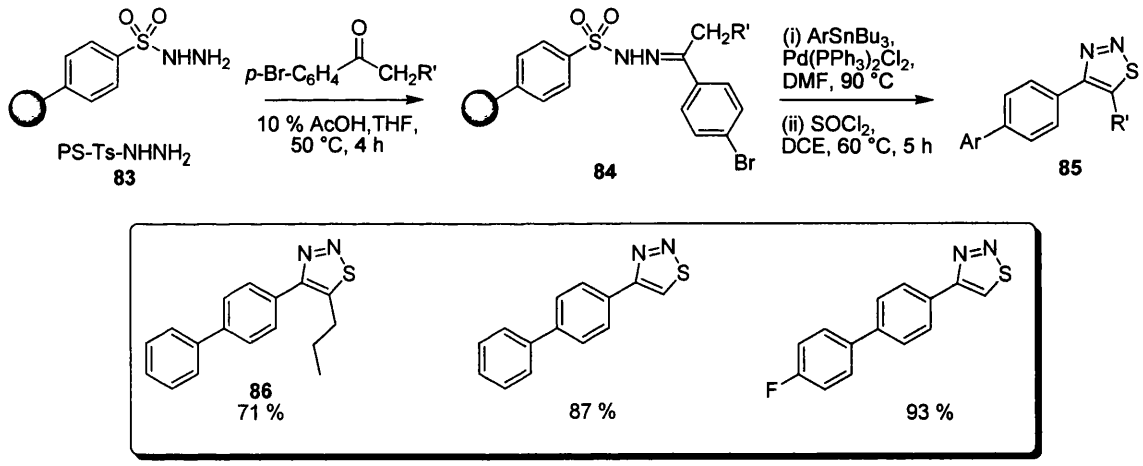

**Fig. 1.6**

Further evidence of the compatibility of this linker system with palladium chemistry is shown in the further functionalisation of the supported indole **79** (R = 4-$MeC_6H_4$-) **(scheme 1.24)**. Treatment of **79** with mercury(II) acetate and a catalytic amount of $HClO_4$ gave the resin bound organomercurial **81**. This was coupled with methyl acrylate using $Pd(OAc)_2$ and the substituted indole **82** was isolated in 60 % yield after cleavage **(scheme 1.24)**.




**Scheme 1.24**

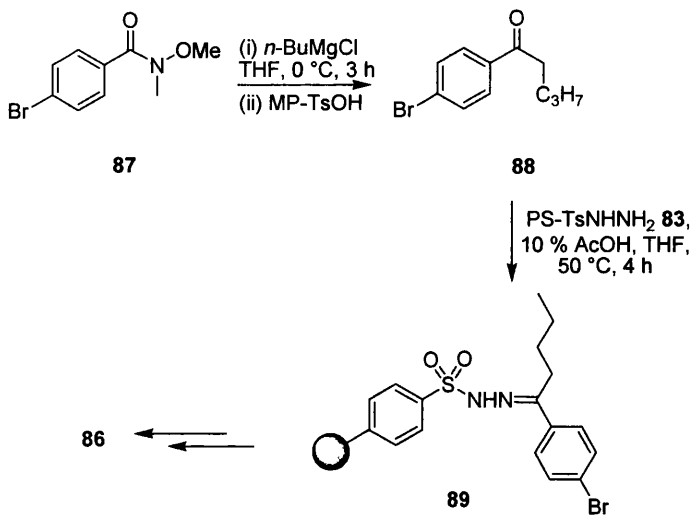
A sulfonyl hydrazide link **83** has been used by Porco *et al.* in a solid-phase "catch and release" synthesis of 1,2,3-thiadiazoles utilising a Stille coupling **(scheme 1.25)**.[25]




**Scheme 1.25**

Polymer-bound sulfonyl hydrazones **84** generated from ketones and sulfonylhydrazine resin **83** were reacted with aryl stannanes using $Pd(PPh_3)Cl_2$ as a catalyst (10 mol %) in DMF. 1,2,3-Thiadiazoles **85** were then formed by treatment with thionyl chloride **(scheme 1.25)**. Non-commercially available *p*-bromophenyl ketones were prepared by reacting *N*-methoxy-*N*-methyl-*p*-bromobenzamide **87** with Grignard reagents such as *n*-BuMgCl. The reaction mixture was quenched with a macroporous polystyrene-sulfonic acid resin (MP-TsOH) to decompose the tetrahedral intermediate. Acetic acid (10 % v/v) was added and the ketone solution **88** was then directly transferred by cannula into

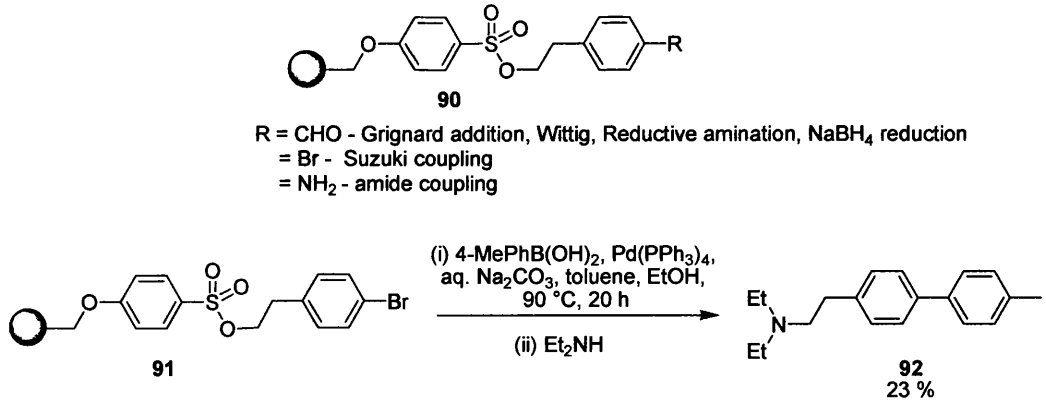
a reaction vessel containing PS-Ts-$NHNH_2$ **83 (scheme 1.26)**. The synthesis is described by the authors as a hybrid solution/solid-phase sequence.




**Scheme 1.26**

## 1.3.4 Sulfonate linkers

The use of an aryl sulfonate link in SPOS and the compatibility of the linker with a wide range of reaction conditions was investigated by Reitz and co-workers.[26] Resins such as **90** were synthesised from the requisite 4-substituted phenethyl alcohols and a sulfonyl chloride resin. A number of reaction conditions were then investigated depending on the functional group on the aromatic ring **(scheme 1.27)**.

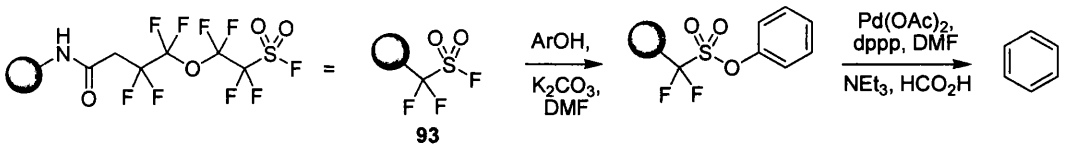



**Scheme 1.27**

Good yields were obtained for most transformations with the exception of the Suzuki coupling on the aryl bromide substrate **91**. Substrate **91** was reacted with 4-methylphenyl boronic acid and $Pd(PPh_3)_4$ at 90 °C for 20 h but the product **92** was only isolated in 23 % yield after nucleophilic cleavage with diethylamine. The authors state that the reaction proceeded very cleanly and the product was isolated in excellent purity even though the overall yield was disappointing.

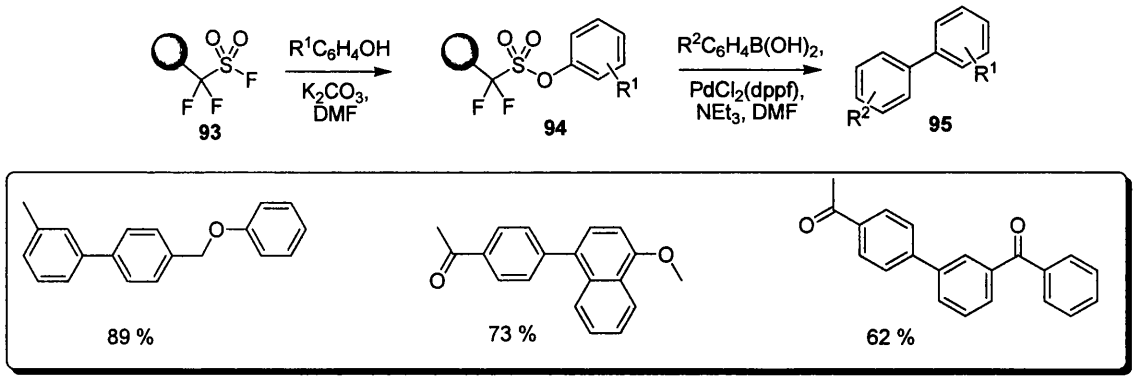
### 1.3.5 Perfluoroalkyl-sulfonate linkers

Holmes and co-workers have reported the preparation of a perfluoroalkyl-sulfonyl (PFS) fluoride resin and its application in the traceless synthesis of arenes using a palladium-mediated reductive deoxygenation **(scheme 1.28)**.[27]



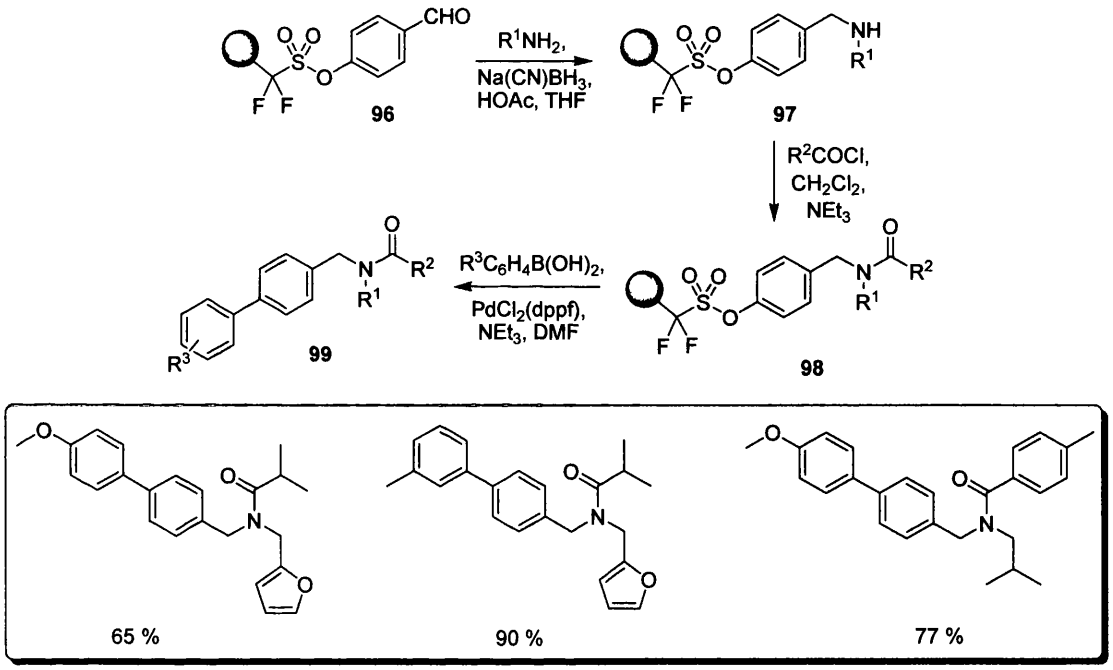

**Scheme 1.28**

The application of this linker was also extended to a cross-coupling release strategy **(scheme 1.29)**.[28] Phenols were directly coupled to the electrophilic sulfonyl fluoride resin **93** using $K_2CO_3$ to create a perfluoroalkylsulfonate species **94**. Treatment with a variety of arylboronic acids in the presence of $PdCl_2(dppf)$ and $NEt_3$ in DMF at 80 °C for 8 h gave the desired biaryl compounds **95** in good yield **(scheme 1.29)**.




**Scheme 1.29**

The generality of the traceless Suzuki cross-coupling release strategy was then explored in the synthesis of a small library of biarylamides **99** employing reductive amination and acylation steps in the sequence **(scheme 1.30)**. 4-Hydroxybenzaldehyde was tethered to the PFS support **93** to generate the resin bound aldehyde **96**. Aldehyde **96** was split into 3 batches which were separately subjected to reductive amination with isobutylamine, furfurylamine, and isopropylamine in the presence of $Na(CN)BH_3$ and acetic acid. The resulting benzylamines **97** were further split and treated with four acid chlorides (benzoyl chloride, *p*-toluoyl chloride, isobutyryl chloride, 2-furoyl chloride) to give the N-acylated products **98**. Each product resin was then individually cleaved with an arylboronic acid to liberate the biarylamides **99**, some of which are also shown in **scheme 1.30**.



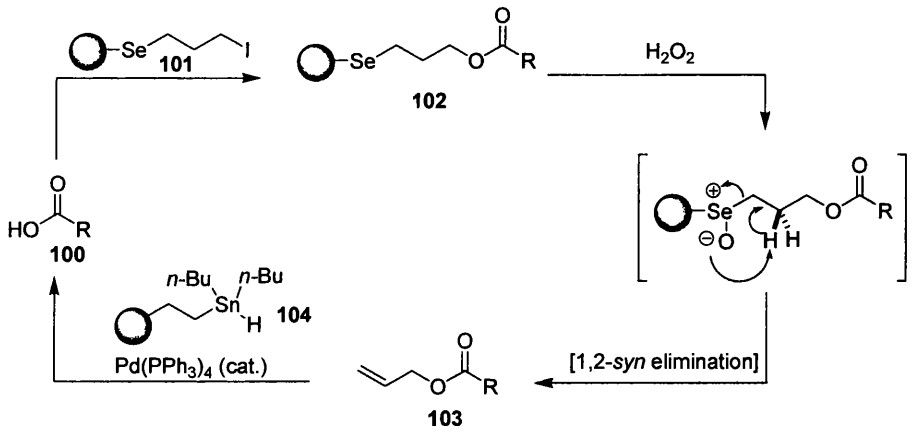

**Scheme 1.30**

### 1.3.6 Selenide linkers

Nicolaou has made use of a palladium-catalysed deallylation strategy to cleave a selenium safety-catch linker under mild, specific conditions.[29] This strategy has been illustrated in the solid-phase semisynthesis of Vancomycin.

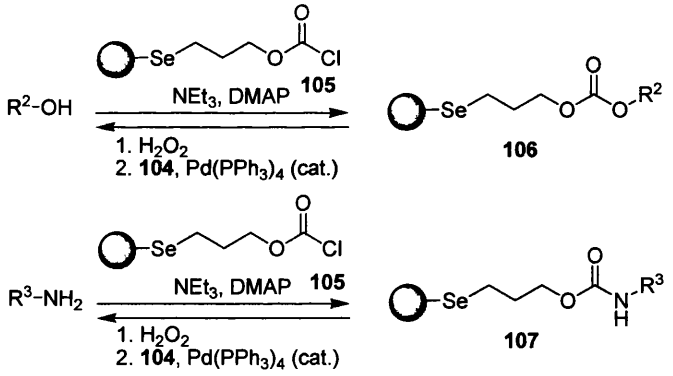
The facile oxidation/elimination of the linking selenide group reveals an allylic functionality, thus serving as a pro-allyl safety catch linker. Thus compounds with acidic functionality **100** could be loaded onto a selenyl alkyl iodide resin **101** to give the pro-alloc derivative **102 (scheme 1.31)**. Oxidation with hydrogen peroxide promoted

1,2-syn elimination to give the terminal alkene **103** and exposure to catalytic amounts of $Pd(PPh_3)_4$ and a tin hydride reagent returned the starting acid **100**. Residual tin was detrimental to purification and biological assays so a polymer-bound tin hydride **104** was used in the deprotection step.




**Scheme 1.31**

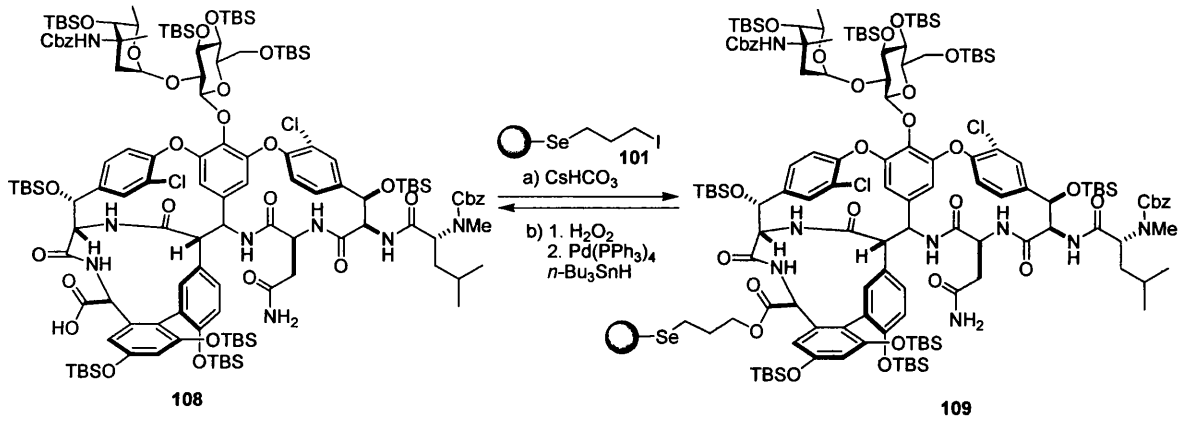
Polymer bound chloroformate resin **105** was synthesised from a selenyl bromide resin and was used to immobilise alcohols and amines to give carbonates **106** and carbamates **107**, respectively **(scheme 1.32)**. Oxidation of the linking selenium atom and elimination, followed by palladium catalysed deprotection of the allyl group regenerated the alcohol or amine starting material.




**Scheme 1.32**

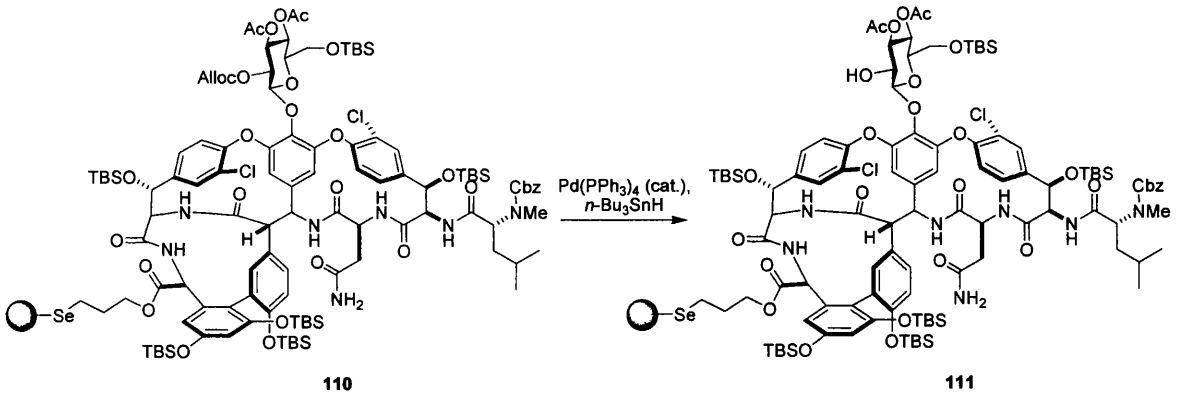
In Nicolaou's solid-phase semisynthesis of Vancomycin, the selenium linker strategy was used to demonstrate an efficient sequence of deglycosidation and reglycosidation reactions leading to Vancomycin **(scheme 1.33)**. Protected Vancomycin derivative **108** was loaded onto a selenyl resin **101** *via* the free carboxylic acid group in the presence

of $CsHCO_3$. Cleavage of the polymer bound derivative **109** with hydrogen peroxide followed by tributyltin hydride and $Pd(PPh_3)_4$ regenerated the carboxylic acid functionality to give **108**.




**Scheme 1.33**

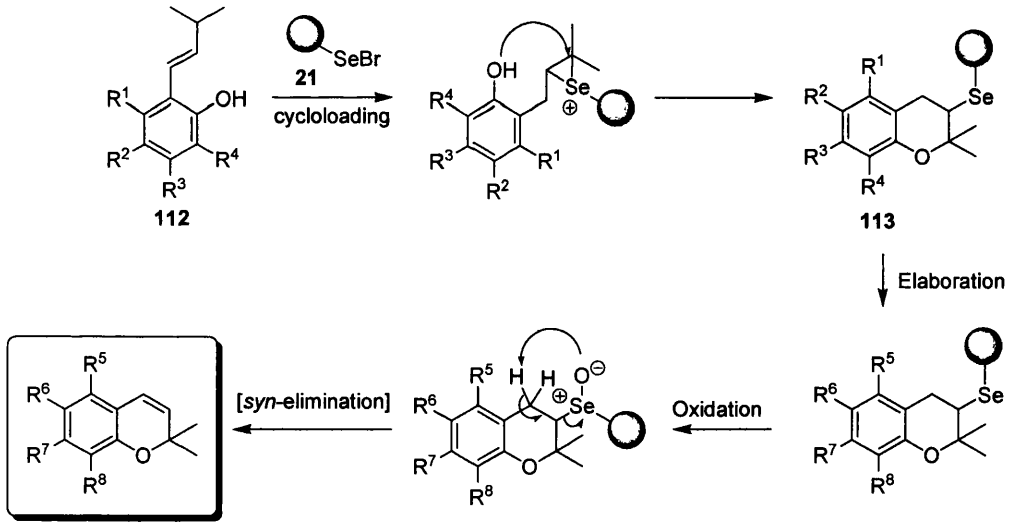
Once Nicolaou had established an efficient loading and cleavage strategy, the selenide linker was used in a solid-phase semisynthesis of Vancomycin. As shown in **scheme 1.33**, the vancomycin derivative **108** was loaded onto the resin **101** to give the supported derivative **109**. This was then subjected to a number of transformations on the solid-support. The disaccharide moiety of **109** was removed under acidic conditions and then a glycosidation reaction was carried out to install an alloc protected sugar moiety, thus giving **110 (scheme 1.34)**. The compatibility of the link with palladium-catalysed transformations was then demonstrated by removal of the C-2 alloc group of **110** using tributyltin hydride and catalytic $Pd(PPh_3)_4$. The free hydroxyl of **111** was then subjected to glycosidation, followed by cleavage from the support by oxidation of the selenide linkage with $H_2O_2$ and *syn* elimination. The solution-phase derivative was then transformed into Vancomycin in 3 steps.




110 111

**Scheme 1.34**

Nicolaou and co-workers have also illustrated the compatibility of their selenide linker with a number of palladium-mediated transformations in the solid-phase synthesis of a range of benzopyrans **(scheme 1.35)**.[30] *o*-Prenylated phenols **112** were immobilised through a cycloloading strategy employing the polystyrene-based selenyl bromide resin **21** to give benzopyran scaffolds **113** which could be elaborated and subsequently cleaved *via* oxidation of the linking selenium atom and spontaneous *syn*-elimination.

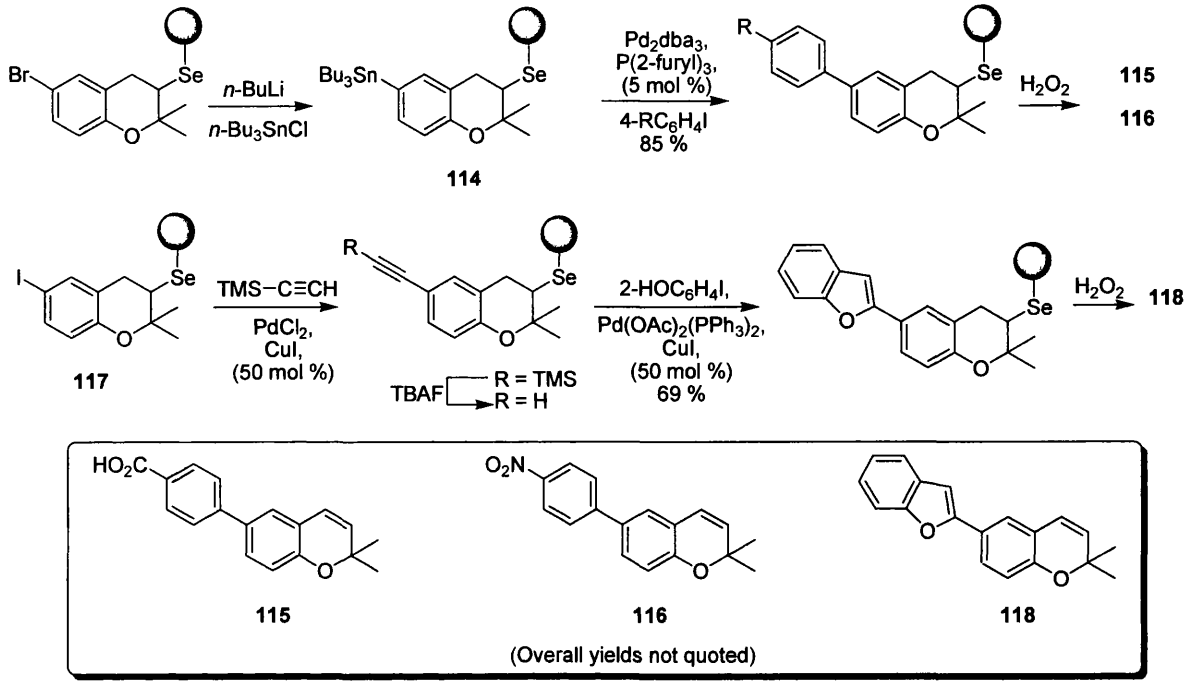



112 113

**Scheme 1.35**

Elaboration was carried out in a number of ways including palladium-catalysed Stille coupling of stannane **114** to give the aryl substituted benzopyrans **115** and **116** **(scheme 1.36)**. Construction of benzofuran **118** was acheived through a Sonogashira/Castro-stevens bis coupling strategy. Aryl iodide **117** was coupled with TMS-acetylene in the presence of $PdCl_2$ at 50 °C. The resulting alkyne was then

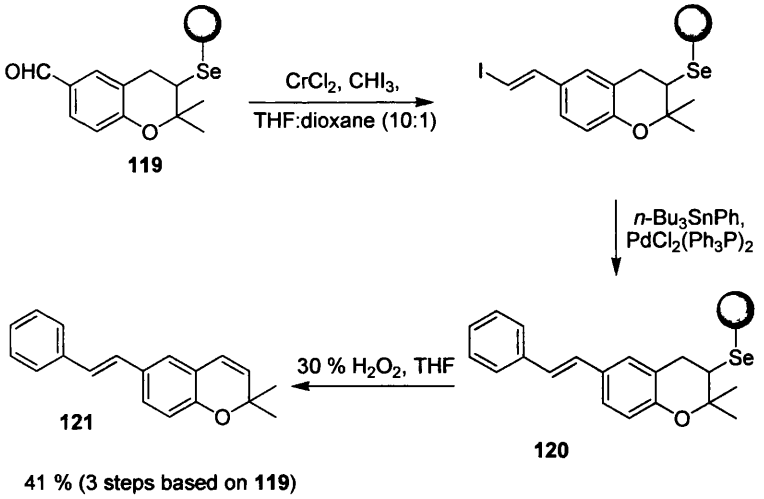
deprotected with TBAF and subsequently coupled to 2-iodophenol using $Pd(OAc)_2(PPh_3)_2$ catalysis.




**Scheme 1.36**

The Stille coupling of **114** was achieved with a low loading of palladium (0.05 equivalent) and only 5 equivalents of the aryl iodide. The bis-Sonogashira coupling sequence was less efficient and required 0.5 equivalents of palladium and copper iodide.

Nicolaou *et al.* have also illustrated the compatibility of their selenide linker with palladium-catalysed Stille cross-coupling in a solid-phase synthesis of an unsymmetrical stilbene.[31] The route uses the benzopyran scaffolds described in **scheme 1.36** and uses the Takai iodo olefination of supported aldehyde **119** to install a vinyl iodide group. Subsequent Stille coupling with *n*-$Bu_3SnPh$ and catalytic $PdCl_2(PPh_3)_2$ gave the resin bound stilbene **120** which was then cleaved from the resin by treatment with hydrogen peroxide to give a good overall yield of the unsymmetrical stilbene **121 (scheme 1.37)**.




**Scheme 1.37**

Horiwake and co workers have employed a selenide linker in the solid-phase synthesis of AM-toxin II using a palladium-catalysed deprotection strategy.[32] AM-toxins are a group of dehydroamino acids **(Fig. 1.7)** and may show biological activity through a Michael acceptor pathway.

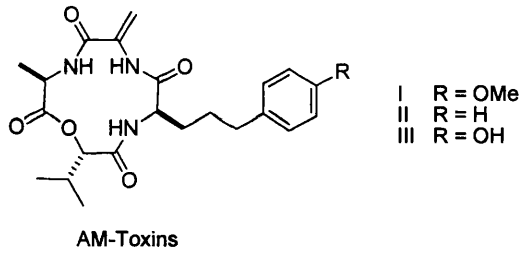
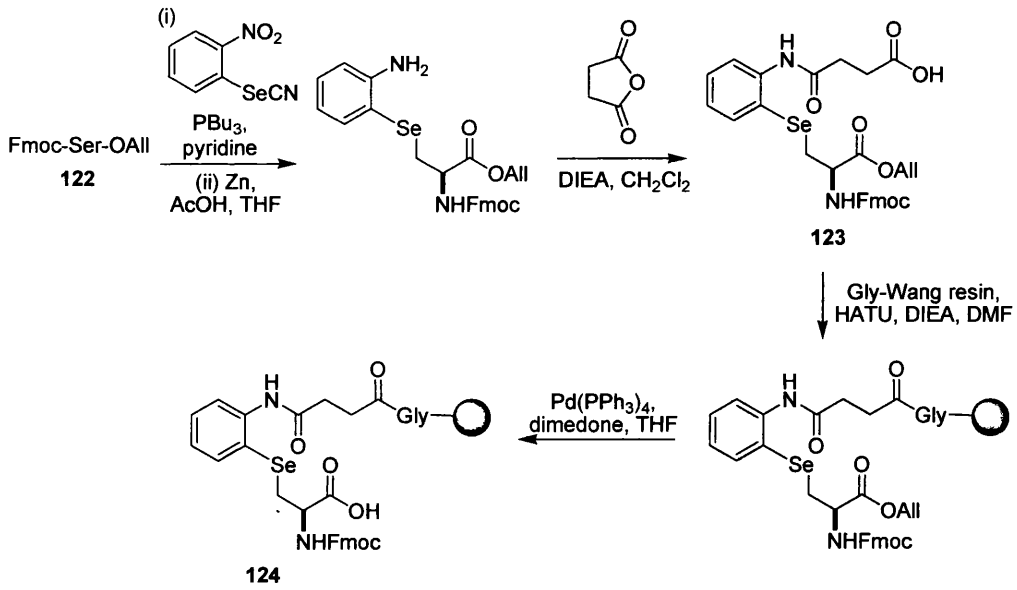


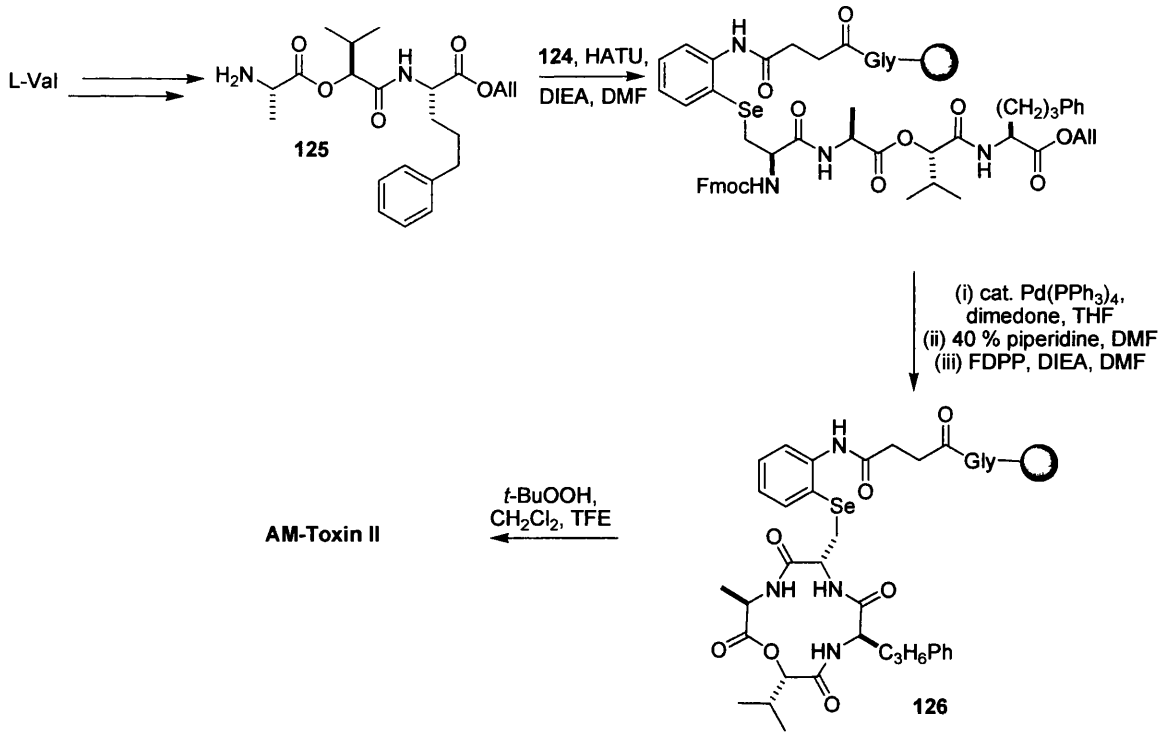

**Fig. 1.7**

Allyl-protected carboxylic acid **123** was prepared in solution by reaction of a protected serine derivative **122** with *o*-nitro phenyl selenocyanate followed by reduction of the nitro group **(scheme 1.38)**. Coupling with succinic anhydride gave the protected carboxylic acid **123** which was immobilised by coupling onto commercially available glycine-Wang resin with HATU and DIEA. Palladium-catalysed deprotection allowed access to the free acid **124** ready for coupling with another solution phase fragment, amine **125 (scheme 1.38)**.




**Scheme 1.38**

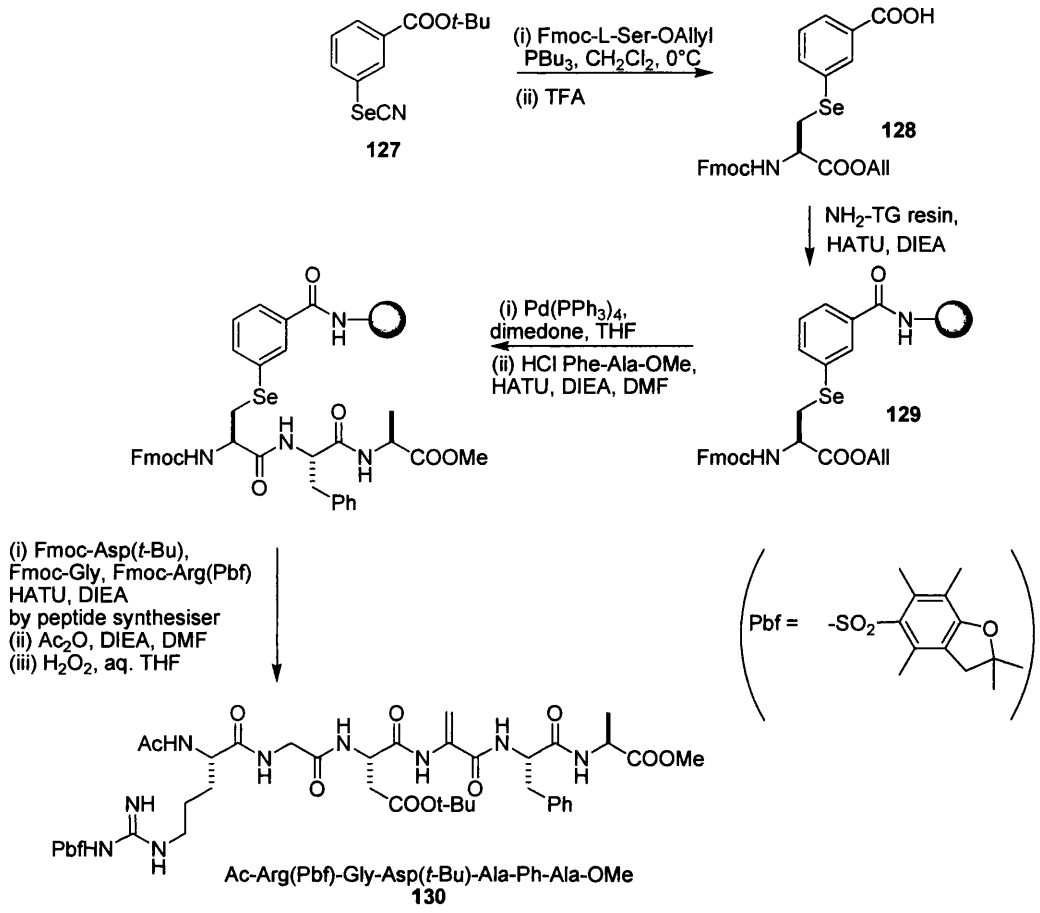
Amine **125** was prepared in solution from L-valine in a number of solution-phase steps and coupled with the supported acid **124 (scheme 1.39)**. Deprotection of the C-terminus acid with $Pd(PPh_3)_4$ and dimedone was followed by removal of the Fmoc protecting group and cyclisation using pentafluorophenyl diphenylphosphinate (FDPP). This gave the supported AM-Toxin precursor **126**. Cleavage of the selenide linker with concomitant double bond formation was achieved under mild oxidative conditions with *tert*-butylhydrogen peroxide.




**Scheme 1.39**

This synthesis shows the compatibility of the selenide linker developed by the group of Nakamura with palladium-catalysed deprotection processes. However the efficiency of the solid-phase route cannot be assessed as no yield for the product was reported. In addition, apart from the key cyclisation step, many of the steps are carried out in solution with only a few relatively simple couplings and deprotections used on the support.

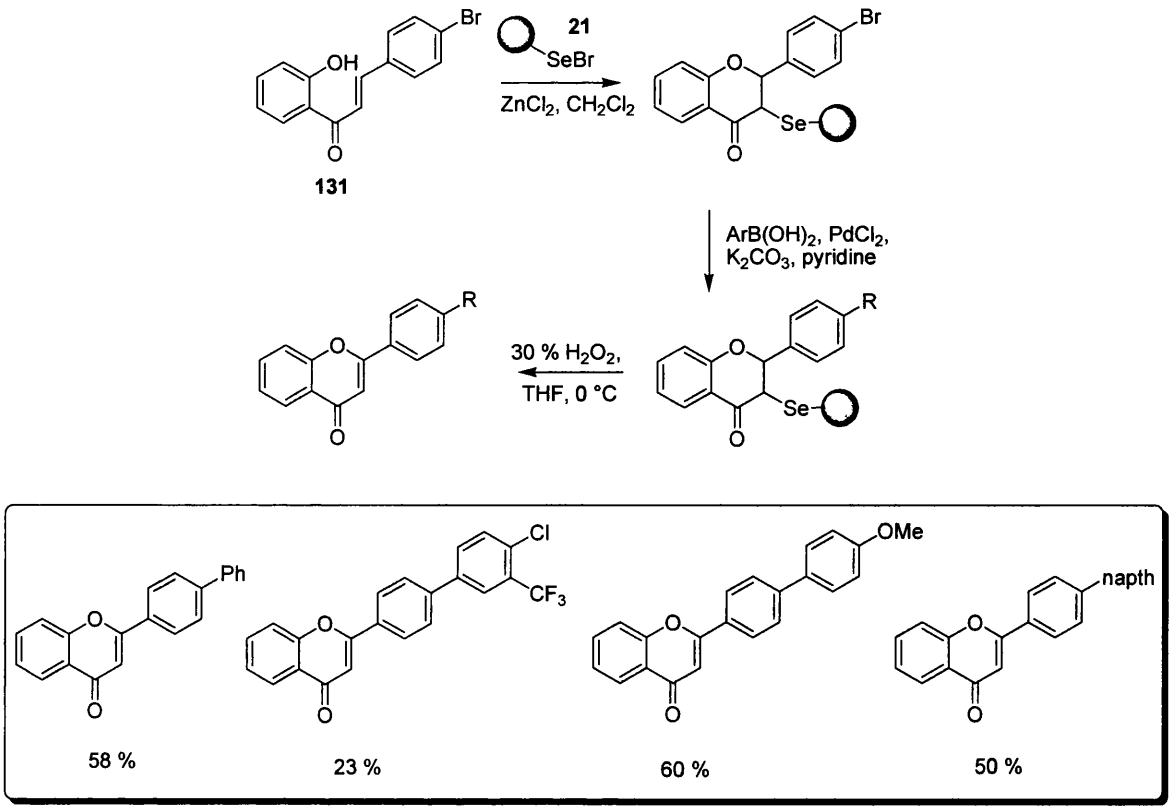
Further optimisation of the route to dihydropeptides using the selenide linker was discussed in a later report by Nakamura *et al.*[33] In this report, some attempts were made to address the problems associated with the synthesis of AM-Toxin II.




**Scheme 1.40**

In this case the selenide linker was constructed from selenocyanate **127 (scheme 1.40)**. The synthetic utility of the linker was demonstrated by the synthesis of a RGD-conjugated dehydropeptide **130**. The RGD sequence is the common recognition motif for the integrin family of receptors, which are involved in cell-cell and cell-matrix adhesion. The C-terminal acid in **129** was deprotected by palladium-catalysed deallylation and subsequent peptide couplings and protections followed by oxidative cleavage gave the RGD-conjugated dehydropeptide **130** in a 77 % yield based on the loading of Fmoc protected resin **128**.

Finally, Huang and co-workers have illustrated the compatibility of a selenide linker with palladium chemistry in the solid-phase synthesis of flavonoids.[34] A series of 2-hydroxychalcones such as **131** were immobilised and cyclised using selenyl bromide resin **21** under Lewis acid conditions. Further derivatisation by palladium-catalysed Suzuki couplings with a range of aryl boronic acids was then carried out. Good overall yields of product were obtained for the three step sequence **(scheme 1.41)**.




**Scheme 1.41**

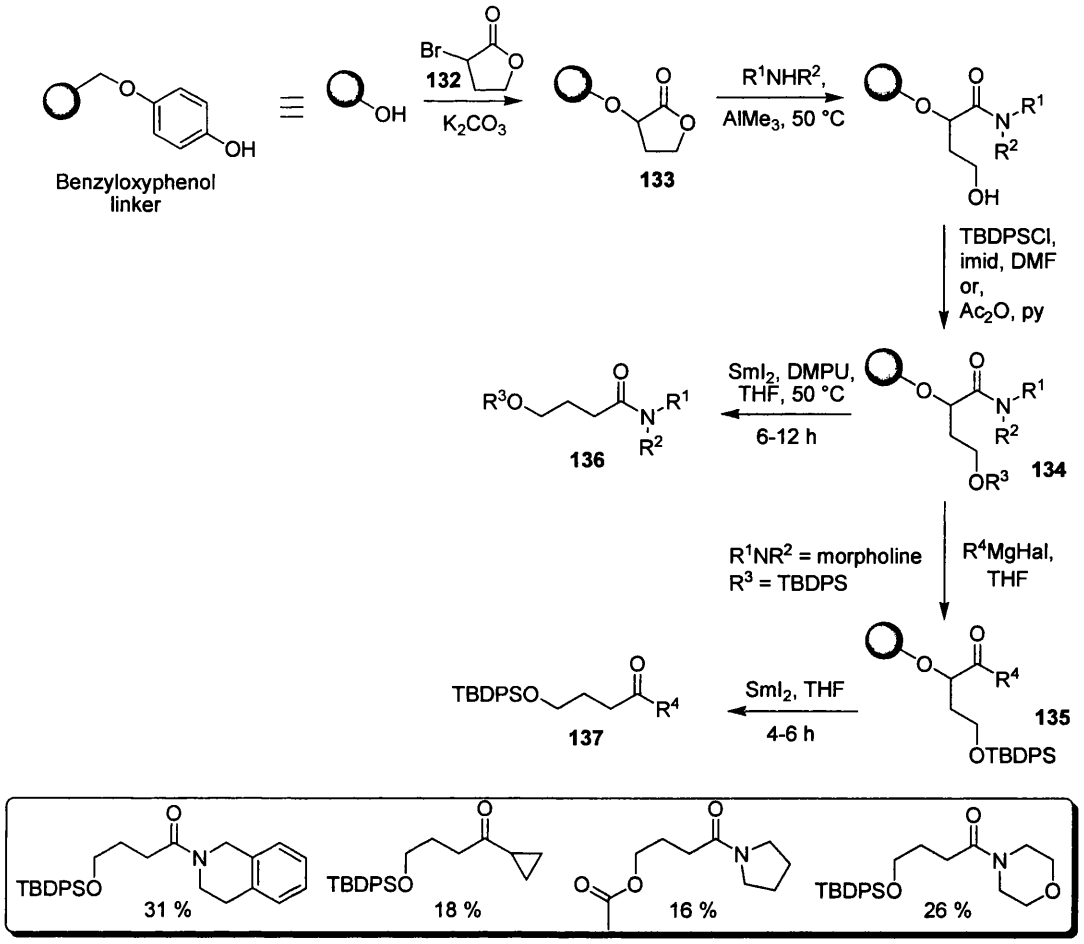
## 1.3.7 SUMMARY

The reports in this review clearly illustrate the compatibility of sulfur and selenium linkers with palladium-mediated transformations. A number of reactions are commonly used on solid-phase including a range of cross-coupling reactions such as Stille, Suzuki and Sonogashira reactions. Palladium-catalysed deprotection of acids and alcohols has been shown to be an efficient reaction on solid-phase and has been used in the solid-phase synthesis of natural products. Some problems with catalyst loading and turnover have been highlighted in these reports and this mainly applies to sulfur linkers. More equivalents of palladium were required in some cross-couplings and in some cases, stoichiometric quantities were used. The presence of free thiol sites on the polymer support is though to lead to "poisoning" of palladium catalysts. In addition in some cases, it has been suggested that the sulfide or selenide linkages coordinate to palladium thus impeding turnover of the catalysts.

# CHAPTER 2: PALLADIUM CATALYSED α-ARYLATIONS OF ESTERS AND AMIDES ON SOLID-PHASE

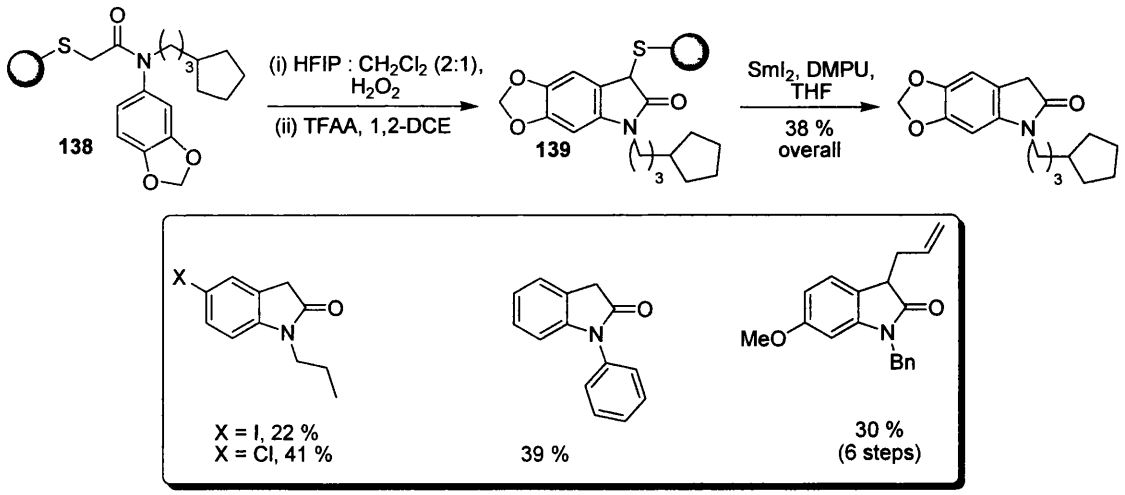
## 2.1 INTRODUCTION

Solid–phase synthesis remains an important tool for the synthesis of collections of small organic molecules.[35, 36] The development of versatile linker designs is important for continued advancements in the area. Previous work in our group led to the development of a new traceless linker strategy for solid-phase organic synthesis where the link to resin is cleaved using samarium(II) iodide ($SmI_2$).[37-46] We refer to this family of linkers as HASC (α-**H**etero-**A**tom-**S**ubstituted **C**arbonyl) linkers. The group originally focused on an oxygen-based HASC linker [47, 48] which was used in the synthesis of a library of carbonyl compounds **(scheme 2.1)**. A diverse range of amides and ketones was synthesised in moderate yields after 4 or 6 steps. γ-Butyrolactone **132** was immobilised through an oxygen HASC linkage to a polystyrene support. Lewis acid catalysed ring-opening of **133** with a variety of secondary amines, followed by acetylation or silylation of the resultant alcohols gave protected alcohols **134**. *Tert*-butyldiphenylsilyl protected morpholine amides were converted to ketones **135** by reaction with Grignard reagents. Cleavage of protected amides **134** and ketones **135** with $SmI_2$ gave the expected amides **136** and ketones **137** in moderate yields.




**Scheme 2.1**

The group have recently begun to explore the considerable potential of sulfur-based HASC linkers.[49] For example, α-sulfanyl N-aryl acetamides such as **138**, attached to resin *via* a sulfur atom, undergo efficient Pummerer cyclisation upon activation of the sulfur link by oxidation to the sulfoxide and treatment with TFAA to give supported oxindoles **139 (scheme 2.2)**. The group has shown that neutral, electron-rich and electron deficient aromatic systems can be cyclised in this way. The addition of $BF_3{\cdot}Et_2O$ is necessary for the cyclisation of neutral and electron deficient systems **(scheme 2.2)**.




**Scheme 2.2**

Modification of the immobilised heterocycles can be carried out and the oxindole products can then be tracelessly cleaved from the polymer support using $SmI_2$ and DMPU.[49] This provides an efficient solid-phase route to libraries of oxindoles. In this approach, the linking sulfur atom operates in a multifunctional sense; mediating C-C bond formation, in addition to its fundamental role as a link to the support.[49]

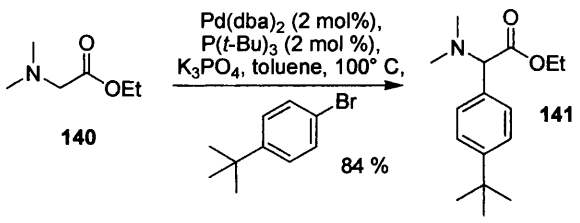
The aim of my project was to further explore the potential of the HASC linker approach by assessing the compatibility of the system with common reagent systems and in particular palladium catalysis. We were also interested in illustrating the ability of the system to access other important heterocyclic systems.

In recent years, the palladium-catalysed α-arylation of a wide range of carbonyl compounds has been reported.[50-60] The solution-phase methodology has only recently reached its full potential with a greater understanding of the full scope, ligand requirements and mechanism of the process. One of the aims of the project was to adapt palladium-catalysed α-arylation methodology to solid phase synthesis using our linker technology.

### 2.1.1 The intermolecular α-arylation of esters

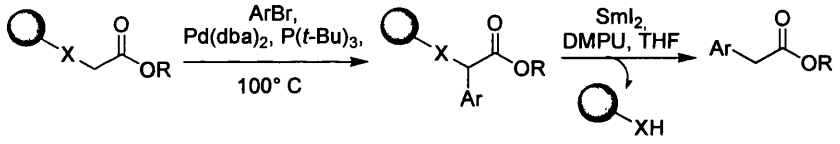
Hartwig has recently shown that esters and protected amino acids can be effectively α-arylated using palladium catalysis.[56] The α-arylation of amino acid derivatives specifically shows that substrates bearing α-heteroatom substituents are well tolerated.

**Scheme 2.3** shows the α-arylation of N,N-dimethylglycine ethyl ester **140** with 4-*tert*-butylbromobenzene using the bulky trialkyl phosphine P(*t*-Bu)$_3$.




**Scheme 2.3**

Our proposed solid-phase route to α-aryl esters is outlined in **scheme 2.4**. A wide range of α-haloesters are commercially available and these would be immobilised using our standard conditions. The option of alkylation at the point of attachment will allow further diversity to be introduced if desired. Subsequent palladium-catalysed α-arylation would then allow a wide range of α-aryl carboxylic acid derivatives to be prepared




**Scheme 2.4**

α-Aryl carboxylic acids are important structural motifs in several important pharmaceuticals (e.g. members of the profen group, ibuprofen, naproxen, **fig 2.1**). We expected that our solid phase approach would allow convenient access to libraries of these compounds.

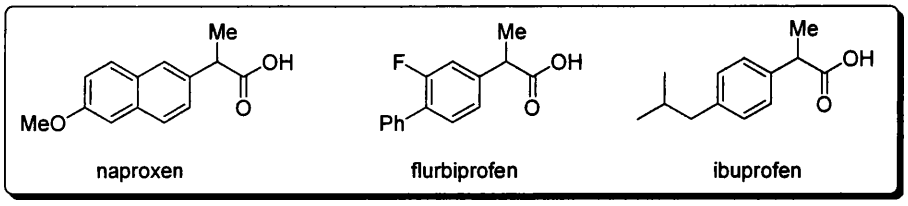
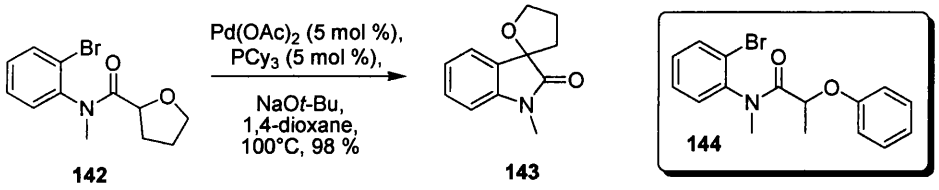



**Fig. 2.1**

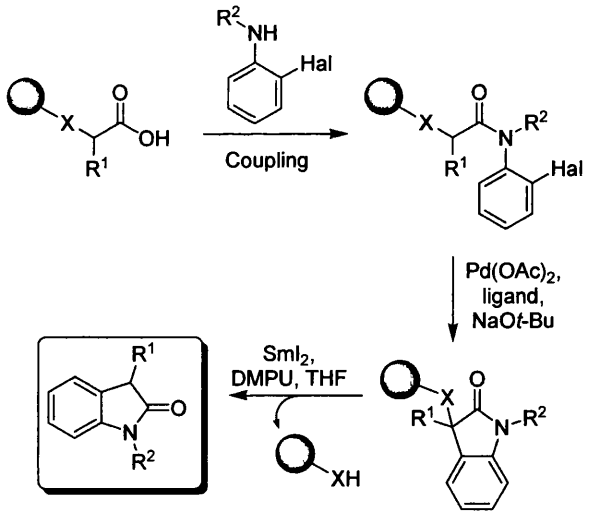
## 2.1.2 The intramolecular α-arylation of amides

Hartwig has recently described the palladium-catalysed synthesis of oxindoles by intramolecular amide α-arylation.[57] In these studies it has again been shown that the reaction conditions are tolerant of α-alkoxy substituents. For example, tetrahydrofuranyl amide **142** underwent cyclisation to give spirocyclic oxindole **143** using $Pd(OAc)_2$ and $PCy_3$ in an excellent yield **(scheme 2.5)**.



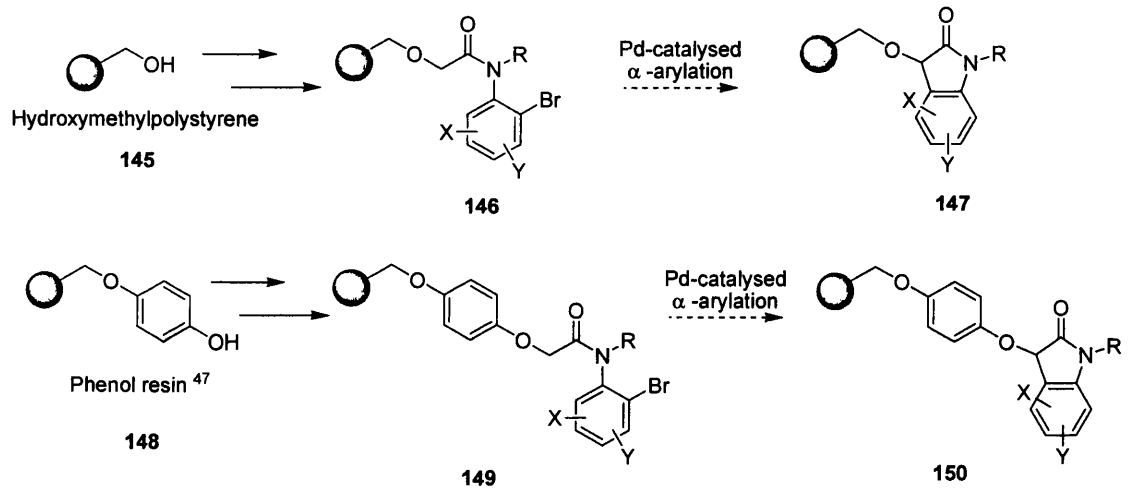

**Scheme 2.5**

Interestingly, Hartwig found that a α-phenoxy substrate **144** failed to undergo cyclisation under similar conditions. We envisaged that adaptation of Hartwig's intramolecular palladium-catalysed amide α-arylation to solid phase using our linker technology would allow oxindole libraries to be prepared conveniently. **Scheme 2.6** shows our proposed solid-phase route to oxindoles using the palladium-catalysed α-arylation process.




**Scheme 2.6**

Initial experimental work concentrated on the solution phase synthesis of model substrates for intramolecular palladium-catalysed α-arylations. Two possible solid phase hydroxy resin systems were identified **(scheme 2.7)**. Phenol resin **148** has an oxygen based phenol linker which was designed within the group and previously used in a solid-phase synthesis of ketones and amides.[47] A suitable solution-phase model for this resin is benzyloxyphenol while benzyl alcohol is a solution-phase model for commercially available hydroxymethyl polystyrene resin **145**. Preparation of solid-supported amides such as **146** and **149** followed by palladium-catalysed α-arylation should give access to solid-supported oxindoles **147** and **150** and in principal the technology could be used to synthesise a library of such compounds.

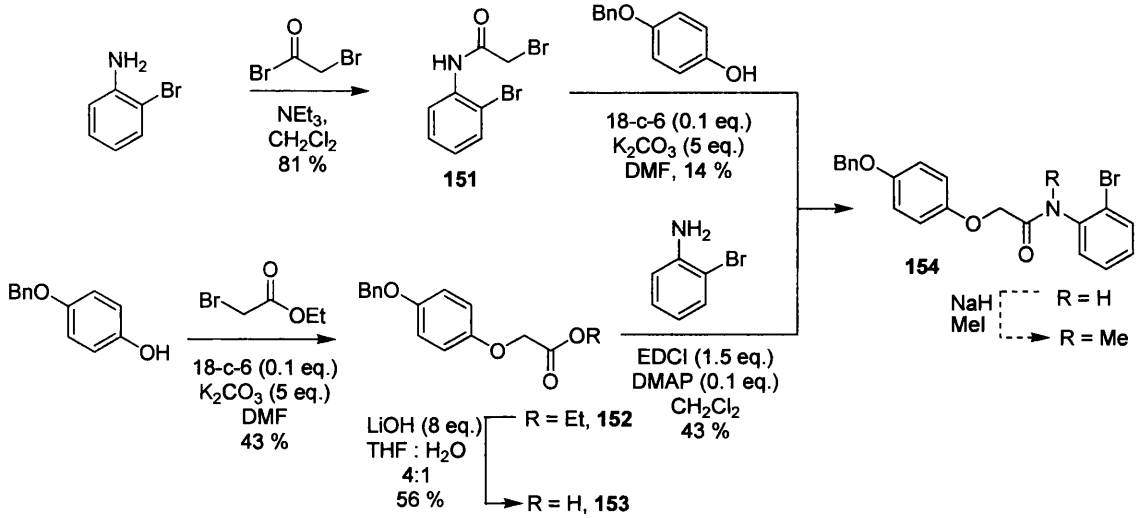



**Scheme 2.7**

2.2.1 Solution phase studies using benzyloxyphenol and benzyl alcohol model systems

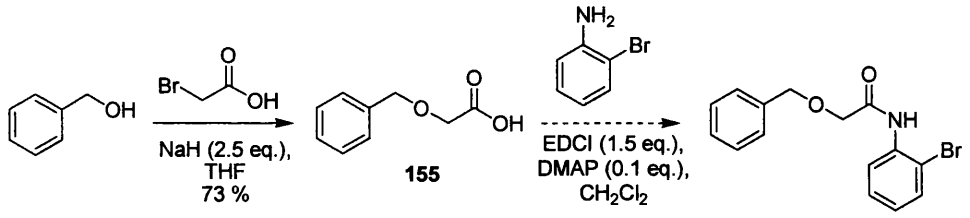
Using benzyloxyphenol as a model for phenol resin **148**, reactions were carried out in solution to assess the viability of our solid-phase route to oxindoles **(scheme 2.8)**. Two routes were investigated. The first involved coupling of benzyloxyphenol with ethylbromoacetate to give ester **152** which was then hydrolysed with LiOH in DMF:$H_2O$ to give acid **153** before coupling with 2-bromoaniline to give amide **154**. All steps occurred in moderate yield. The second route relied on the efficient acylation of 2-bromo aniline with bromoacetyl bromide and coupling of the resultant α-bromo amide **151** with benzyloxyphenol to give the common intermediate amide **154**. N-methylation

of amide **154** was then attempted, but proved difficult. The use of 1.1 equivalents of NaH resulted in no N-methylation whilst using 3 equivalents of NaH and 5 equivalents of MeI saw methylation α- to the amide carbonyl in addition to the desired alkylation on nitrogen.




**Scheme 2.8**

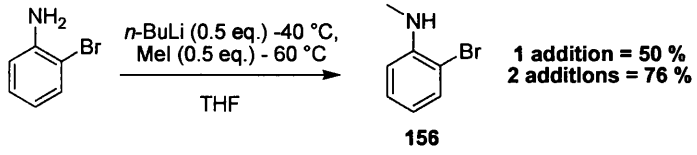
We also began to look at the synthesis of a solution phase model for a substrate linked through an aliphatic oxygen linker. Reaction of benzyl alcohol with bromoacetic acid proceeded in good yield to give acid **155** which was subjected to an EDCI mediated amide coupling with 2-bromo aniline **(scheme 2.9)**. Unfortunately this reaction returned only starting material.




**Scheme 2.9**

The problems described above regarding selective N-methylation in the synthesis of the solution-phase substrates led us to look at the use of 2-bromo-N-methyl aniline **156** in the coupling reactions. N-Methylation of 2-bromoaniline was carried out as described by Barluenga *et al* [61] **(scheme 2.10)**. This resulted in 50% yield of N-

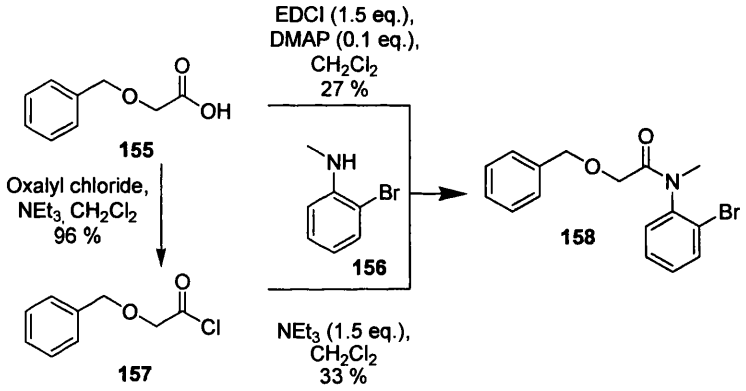
methylated product **156** and 40% recovery of starting material. Modification of Barluengas' procedure by addition of a second 0.5 equivalent portion of *n*-BuLi/MeI after the initial overnight reaction resulted in a yield of 76 % with 10 % recovery of starting material.




**156**

**Scheme 2.10**

Attempts were then made to couple acid **155** directly with 2-bromo-N-methylaniline **156** **(scheme 2.11)**. This reaction proved to be difficult and a range of conditions were tried including various coupling reagents **(Fig 2.2)**.[62, 63]




**Scheme 2.11**

Our attempts to prepare amide **158** are summarised in **table 2.1**. The most effective coupling reagent was found to be BOP-Cl **(Fig. 2.2)** which is known to be useful in coupling sterically hindered amino acids, which are difficult or unreactive with carbodiimide-based systems.[64] These conditions gave amide **158** in a yield of 72 % after 4 days **(table 2.1)**. Conversion to the acid chloride **157** was also investigated however coupling with the secondary amine again gave disappointing results **(scheme 2.11)**. Amide **158** showed AB quartets in the $^1$H NMR spectrum. The source of additional chirality from which these signals arise is discussed in section 3.2.4.

| Acid eq. | Amine eq. | Coupling reagent (eq.) | Base/Additive (eq.) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 1.5 | EDCI (1.5) | DMAP (0.1) HOBt (cat.) | 72 | 0 |
| 1 | 1.5 | EDCI (1.5) | DMAP (0.1) | 36 | 27 |
| 1 | 1.5 | EDCI (1.5) | - | 24 | 25 |
| 1 | 2.4 | BOP-Cl [64] (2) | $NEt_3$ (6) | 96 | 72 |
| 1 | 1 | BOP-Cl (1) | DIEA (2) | 48 | 12 |
| 1 | 1 | BOP-Cl (1) | $NEt_3$ (2) | 48 | 38 |
| 1.2 | 1 | BOP-Cl (1.2) | DIEA (2) | 40 | 32 |
| 1 | 1.3 | PyBOP [65] (2) | $NEt_3$ (1.5) | 24 | 7 |
| 1 | 1.1 | HATU [66] (1) | NMM (2.2) | 24 | 0 |
| 1 | 1 | HATU (1) | DIEA (3) | 48 | 18 |

**Table 2.1**

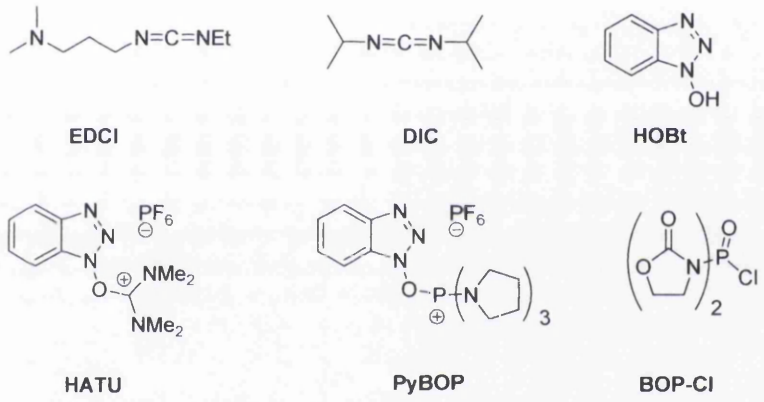
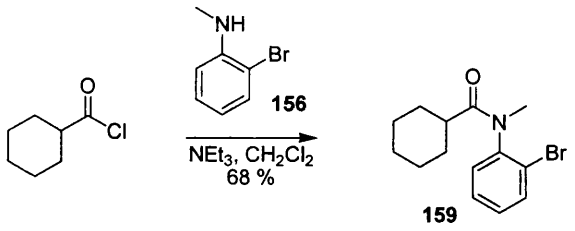



**Fig. 2.2**

With a relatively effective route to solution-phase model substrate **158** now established we moved on to examine the cyclisation reaction.

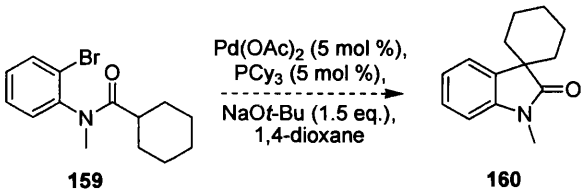
### 2.2.3 Preliminary attempts at palladium-catalysed intramolecular α-arylation

My initial work focused on the reproduction of results reported by Hartwig to gain experience carrying out palladium-catalysed α-arylations.[54] Coupling of cyclohexylcarbonyl chloride with 2-bromo-N-methyl aniline **156** gave test amide **159** in good yield **(scheme 2.12)**.




**Scheme 2.12**

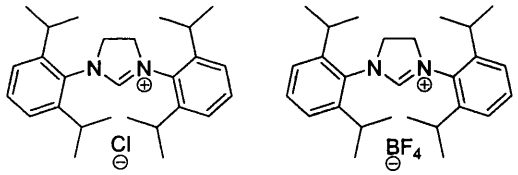
Preliminary attempts at cyclising substrate **159** by palladium-catalysed α-arylation using $Pd(OAc)_2$ and $PCy_3$ as described by Hartwig [54] were unsuccessful **(scheme 2.13)**.




**Scheme 2.13**

Hartwig found $PCy_3$ to be the most general ligand for the cyclisations to give oxindoles. In particular, he reported that the cyclisation of bromoanilide **159** under these conditions gave a 93 % yield of oxindole **160** after 3 h at 50 °C. $PCy_3$ was obtained from Aldrich and made up into a standard solution in fresh, degassed 1,4-dioxane under an inert atmosphere. After two unsuccessful cyclisation attempts the ligand solution was subjected to $^{31}P$ NMR analysis which showed a significant amount of tricyclohexylphosphine oxide was present. Assuming the preparation of the solution allowed no air into the vessel it was concluded that the commercial $PCy_3$ obtained was impure. Procedures to reduce the oxide back to the required phosphine generally use harsh conditions, and it was felt that tricyclohexylphosphine may not be stable enough to allow us the flexibility to optimise reaction conditions when transferring to solid phase.

Imidazolinium salts SIPr-Cl **161** and SIPr-$BF_4$ **162 (Fig. 2.3)** are precursors of carbene ligands and have been identified by Hartwig as excellent ligands for the synthesis of oxindoles using the palladium-catalysed intramolecular α-arylation process. Reaction times using these ligands are comparable to those using $PCy_3$ as a ligand and reactions can be carried out at 50 °C.[54]



SIPr-Cl
**161**

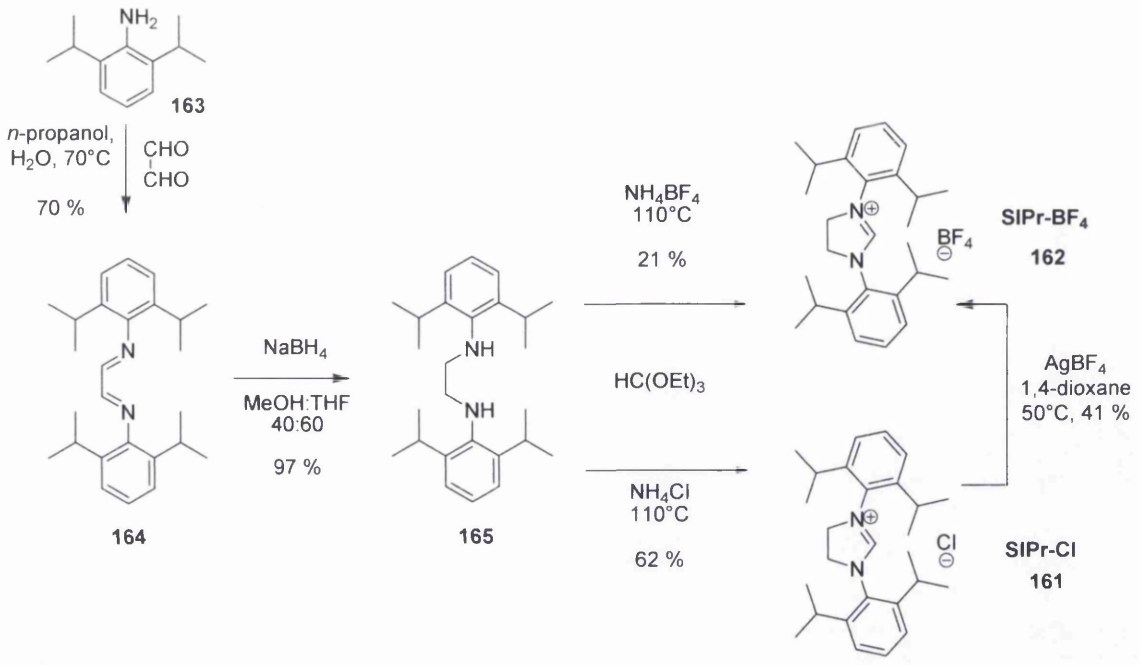
SIPr-$BF_4$
**162**

**Fig. 2.3**

Carbene ligands derived from the imidazolinium salts **161** and **162** have significant advantages over $PCy_3$. They are stable to air and therefore can be made in bulk and stored for later use, allowing convenient use in library synthesis. They also have improved thermal stability allowing elevated temperatures to be used if required.[67] Nucleophilic carbene ligands derived from the salts SIPr-Cl **161** and SIPr-$BF_4$ **162 (Fig. 2.3)** have also been shown to have a stabilising effect resulting in the metal complex having increased resistance to ligand dissociation. We believed these advantages would allow us greater flexibility when optimising reaction conditions to run on solid phase.

### 2.2.4 Synthesis of carbene ligand precursors SIPr-$BF_4$ and SIPr-Cl

The carbene precursors SIPr-Cl **161** and SIPr-$BF_4$ **162** were prepared from 2,6-diisopropyl aniline using the procedure described by Arduengo.[68] 2,6-Diisopropyl aniline **163** was reacted with glyoxal to form the bis imine **164** in good yield **(scheme 2.14)**. This was followed by reduction to the diamine **165** and reaction with triethylorthoformate using the appropriate ammonium salt to form the imidazolinium salts SIPr-$BF_4$ **162** and SIPr-Cl **161**. SIPr-Cl **161** was synthesised in 42 % overall yield and SIPr-$BF_4$ **162** in 14 % overall yield. The disappointing yield obtained for SIPr-$BF_4$ is probably due to the quality of the $NH_4BF_4$ used in the salt forming step. Since the formation of chloride salt was more efficient a counter ion exchange experiment was carried out using $AgBF_4$ and this proceeded to give SIPr-$BF_4$ **162** in moderate yield. The SIPr-$BF_4$ salt was recrystallised and a crystal structure obtained to unambiguously confirm the structure **(Fig. 2.4)**.




**Scheme 2.14**

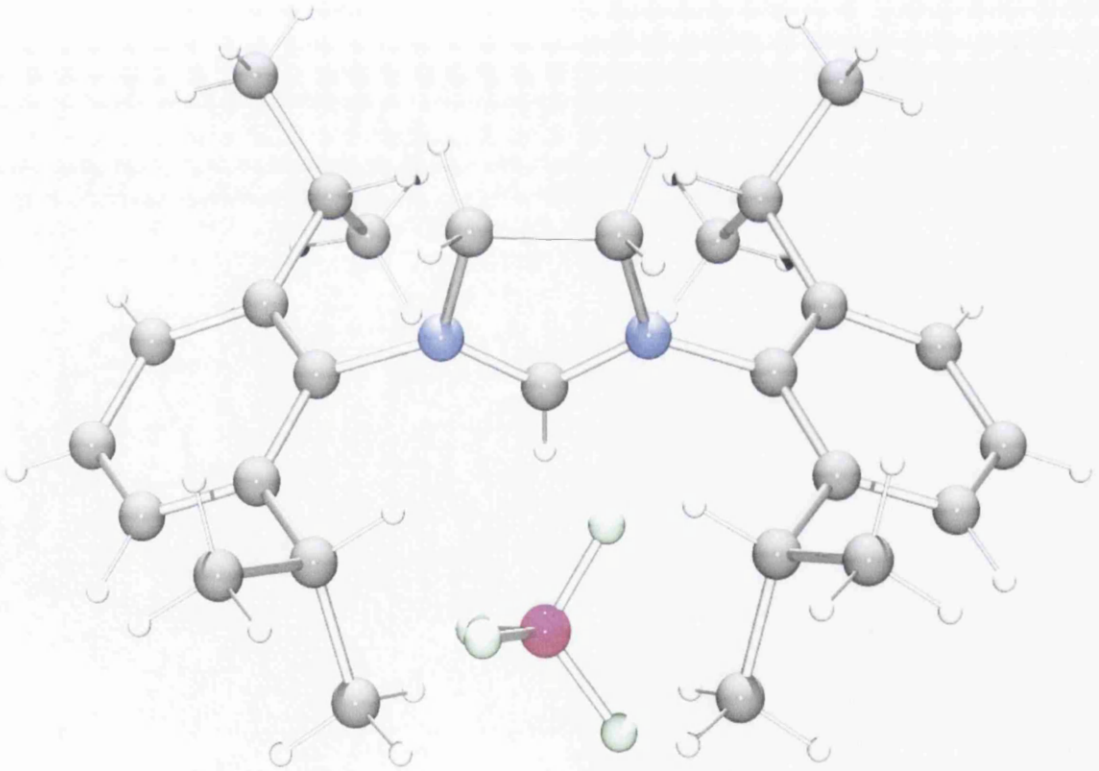
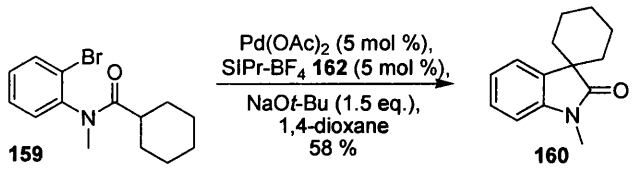


**Fig. 2.4:** X-ray structure of **162**

2.2.5 Palladium-catalysed α- arylation of test substrate using carbene ligands

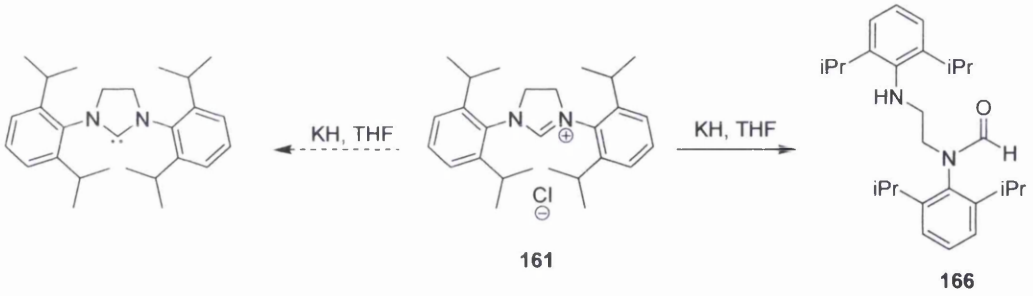
Immediately after preparation of the carbene precursors SIPr-Cl **161** and SIPr-$BF_4$ **162** the palladium-catalysed α-arylation of the test substrate **159** was carried out **(scheme 2.15)**. This gave the expected product **160** in 58 % yield with some recovery of starting material.




**Scheme 2.15**

Subsequent attempts to replicate this result using the same conditions were however unsuccessful, giving only quantitative recovery of starting material. The reaction conditions were screened in order to discover the reason behind this frustrating observation. Several different batches of NaO*t*-Bu and $Pd(OAc)_2$ were used in the reaction. Fresh NaO*t*-Bu was prepared from sodium and *t*-BuOH and dried prior to each use. The dioxane still was refreshed and $Pd(dba)_2$ was tried as an alternative palladium source. Surprisingly, none of these changes led to successful α-arylation to give **160**.

Quantitative recovery of starting material with absolutely no product formation suggested that the ligand and $Pd(OAc)_2$ were not combining to form the active complex. It was decided to attempt to isolate the active carbene species prior to reaction instead of *in situ* formation with NaO*t*-Bu. This would eliminate one possible reason for the failure of the reaction. Following a documented procedure [68] the SIPr-Cl salt **161** was treated with KH in THF in order to generate the active carbene species **(scheme 2.16)**.




161 166

**Scheme 2.16**

This gave an unexpected result. The product obtained was formamide **166**, presumably resulting from hydrolysis of the salt. The identity of **166** was confirmed by X-ray crystallographic analysis **(Fig. 2.5)**. The procedure was repeated with the SIPr-$BF_4$ salt and the same product was obtained.

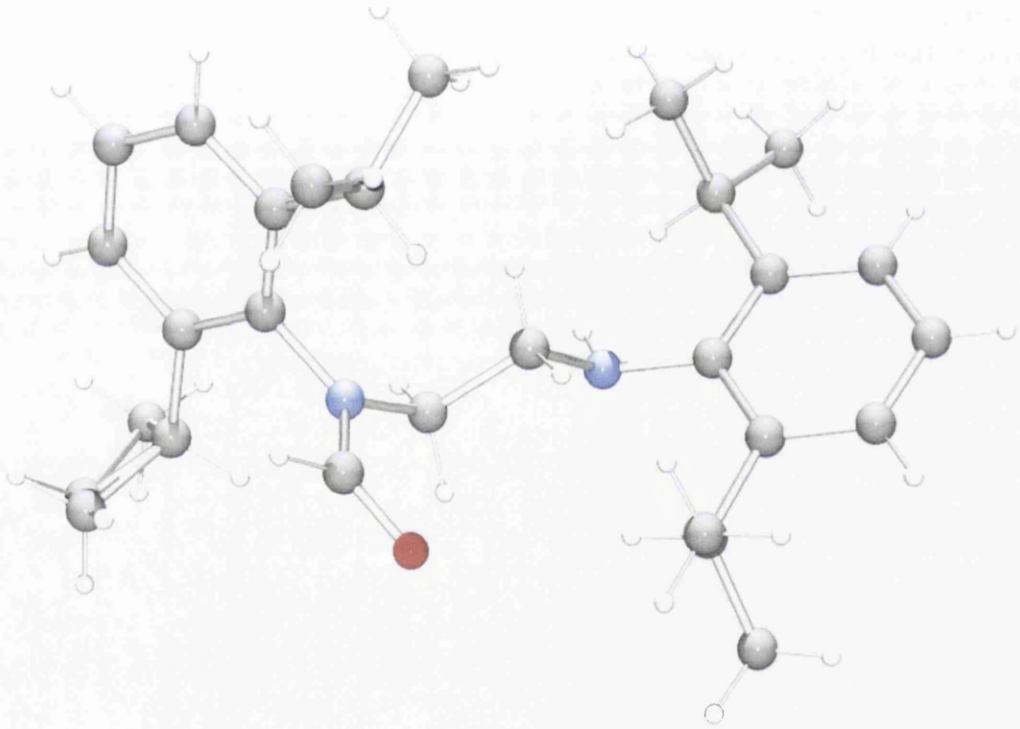
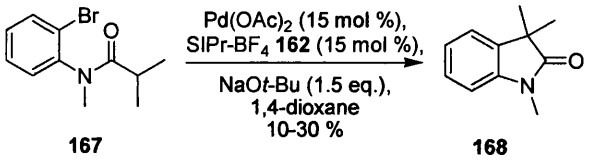


**Fig. 2.5:** X-ray structure of **166**.

It was therefore concluded that both imidazolinium salts SIPr-Cl **161** and SIPr-$BF_4$ **162** are hygroscopic. Water present in the salt appeared to be causing hydrolysis to the formamide **166** upon treatment with NaO*t*-Bu, preventing formation of the active complex. Various strategies for drying the salt were attempted. The carbene precursor

SIPr-$BF_4$ was initially dried under high vacuum at 100 °C for 24 h and stored over silica gel in a dessicator and the reaction repeated. Product was obtained in 10 % yield together with starting material. The salt was then dissolved in dioxane prior to reaction and stirred with powdered molecular sieves but salt "dried" in this way resulted in no product formation in the reaction and quantitative recovery of starting material.

Another test substrate **167** was prepared and this substrate was subjected to the α-arylation conditions. Hartwig obtained 92 % yield of **168** after 3 h using 5 mol % $Pd(OAc)_2$ and $PCy_3$ **(scheme 2.17)**.

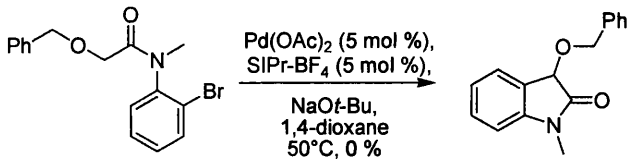



**167** **168**

**Scheme 2.17**

A suspension of NaO*t*-Bu was prepared by the reaction of Na and *t*-BuOH in dioxane. Initial attempts using SIPr-$BF_4$ salt **162** dried under high vacuum at 100°C for 2 h and NaO*t*-Bu suspension gave 10 % yield of the oxindole **168** together with starting material. Different methods for drying the SiPr-$BF_4$ salt were screened in combination with the other parameters of the reaction. Drying of the desired quantity of ligand in a Kugelrohr oven at 150°C and 0.01-0.5 mmHg overnight prior to the reaction proved to be the most effective method and this, combined with the use of freshly prepared NaO*t*-Bu resulted in 30 % conversion to oxindole **168** by $^1H$ NMR. The combination of dry ligand and commercial NaO*t*-Bu resulted in no reaction indicating that the purity of the base is also important.

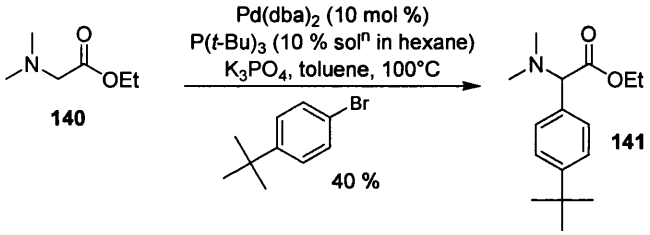
In light of our difficulties cyclising model substrates from Hartwig's studies we were not surprised to find that attempts to cyclise solution-phase model substrate **158**, required for our solid-phase approach, were unsuccessful **(scheme 2.18)**.




**158**

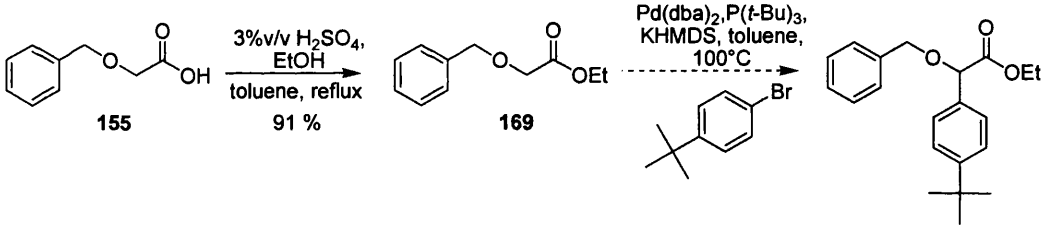
**Scheme 2.18**

Concerned at our inability to reproduce Hartwig's results, we chose next to investigate the palladium-catalysed intermolecular α-arylation of esters. Initial work concentrated on the reproduction of the results reported by Hartwig to demonstrate that the catalytic process would work in our hands. Hartwig reported the α-arylation of N,N-dimethylglycine ethyl ester using $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ in 84 % yield (see **scheme 2.3**). Our initial attempt gave a promising result, and we obtained **141** in 40 % isolated yield **(scheme 2.19)**.




**Scheme 2.19**

With some confidence in the catalyst system, O-linked model substrate ester **169** was prepared by acid catalysed esterification of the corresponding acid **155 (Scheme 2.20)**.

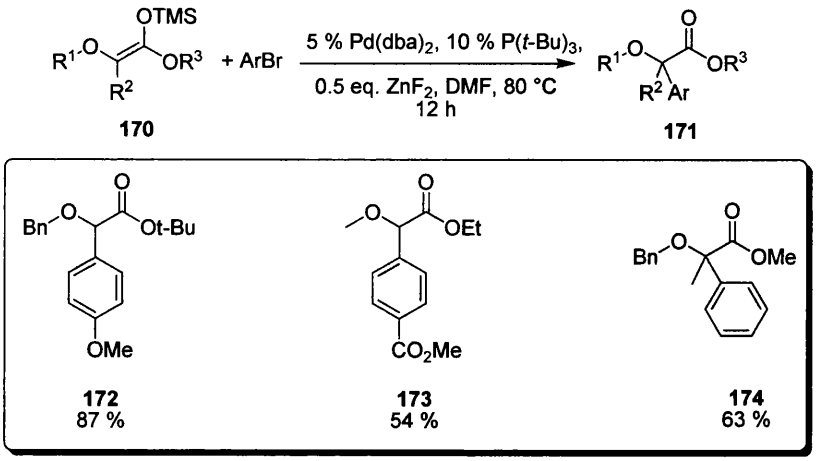



**Scheme 2.20**

Unfortunately, all attempts to carry out the intermolecular α-arylation of **169** were unsuccessful. $K_3PO_4$ and KHMDS were tried as bases and the amount of palladium was increased to 20 mol %. However, in all cases no conversion to the desired product was observed.

Whilst we were working on the project Hartwig described the α-arylation of TMS ketene acetals **170** as a milder method for accessing α-aryl esters **171** .[69] Excellent yields

were reported on a variety of substrates including substrates bearing α-heteroatom substituents **(scheme 2.21)**.




**Scheme 2.21**

TMS ketene acetals **170** were treated with an aryl bromide, catalytic $Pd(dba)_2$ and P(*t*-Bu)$_3$ together with $ZnF_2$ in DMF. Good yields of products were obtained and the reaction tolerates a wide range of esters (*t*-Bu **172**, Et **173**, Me **174**) as well as electron rich and electron deficient aryl bromides. The reaction also tolerates the presence of the benzyloxy group in the α-position which could provide a useful link in a solid-phase route. Unfortunately, we had insufficient time to study this approach in detail. In principle however, the α-arylation of TMS ketene acetals should be compatible with our linker system and thus provide a solid-phase route to α-aryl esters.

## 2.4 SUMMARY

We have prepared amide **158** as a model for cyclisation substrates immobilised using a hydroxyl methyl polystyrene support. Unfortunately attempts to cyclise these compounds using conditions described by Hartwig were unsuccessful. Our attempts to reproduce the intramolecular palladium-catalysed α-arylation from Hartwig's publication have met with limited success, using both phosphine and N-heterocyclic carbene ligand systems. The analogous intermolecular processes were also investigated using model substrate **169** but again no coupling was observed. This has led us to conclude that the palladium-catalysed α-arylation of supported enolates is unlikely to be a viable process on solid-phase using our linker system. The use of immobilised TMS ketene acetals [69] may provide a solution to this problem.

## 3.1 INTRODUCTION

We recognised that systems such as **176** that had proved ineffective in our intramolecular palladium-catalysed α-arylation studies might allow access to other heterocycle frameworks **(Fig. 3.1)**. We also remained interested in assessing the compatibility of HASC linkers with palladium catalysis.

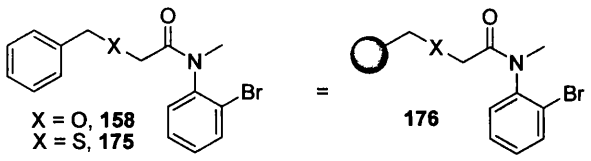



**Fig. 3.1**

We chose to develop an approach to tetrahydroquinolones using a sulfur HASC linker, and a palladium-catalysed Heck reaction of the aryl bromide group in **176**.

The tetrahydroquinolone framework **177** can be found in a number of natural and non-natural biologically active compounds and is therefore an attractive scaffold for synthesis **(Fig. 3.2)**. The group of compounds with the general structure **178** have been investigated as they are known to be antagonists of the 5-$HT_3$ receptor. Evidence has been presented for the therapeutic roles of 5-$HT_3$ antagonists in migraine, schizophrenia, anxiety and chemotherapy-induced emesis.[70] Pinolinone **179** is a natural product isolated from the shrub *Boronia pinnata*.[71] Compound **180** has been evaluated as a HIV-1 reverse transcriptase inhibitor.[72] N-Methyl-D-aspartate (NMDA) receptor antagonists such as **181** may have potential as treatments for stroke, epilepsy and Alzheimers disease.[73] A number of related compounds were synthesised by a group at Merck in a small solution-phase library synthesis. The approach was however not combinatorial and each derivative required different conditions for synthesis. To the best of our knowledge there are no reports in the literature of a solid-phase approach to the tetrahydroquinolone structural motif.

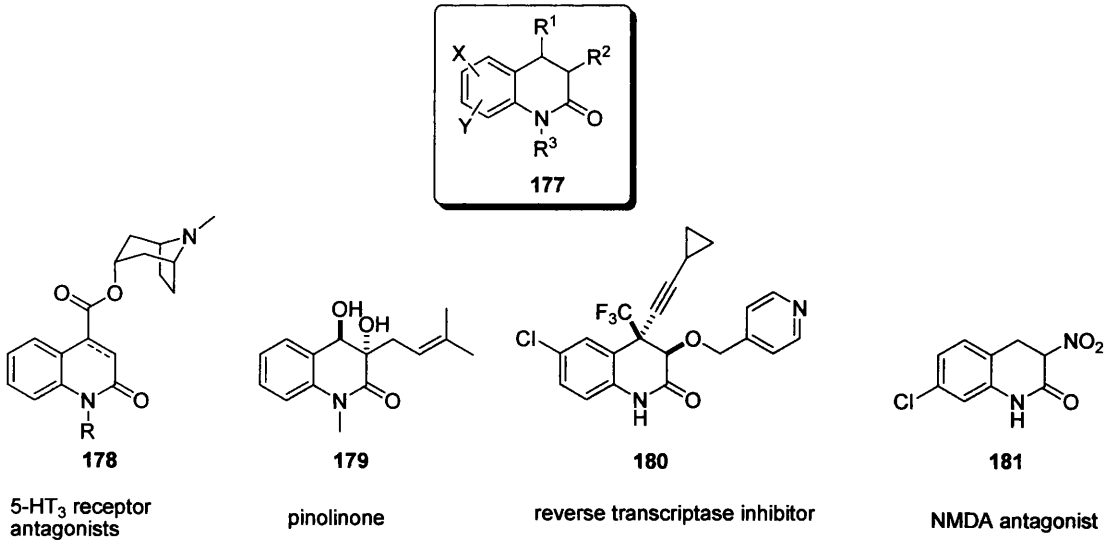
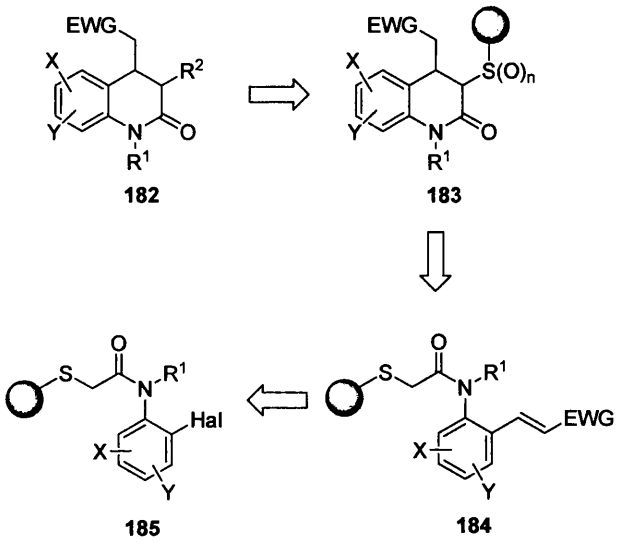



**Fig. 3.2**

Our proposed, solid-phase approach to tetrahydroquinolones **182** is outlined in **scheme 3.1**. Heck reactions of immobilised aryl halides **185** should allow access to alkene intermediates **184**. Base-induced Michael cyclisation should then furnish the tetrahydroquinolone core **183** which can be modified on the solid-support and then cleaved to give a library of heterocycles with the general structure **182**. The nature of the linker will allow the cyclisation to be carried out using a variety of conditions according to the oxidation state of sulfur. This should give us greater flexibility when searching for reaction conditions compatible with the functionality present in the substrates.




**Scheme 3.1**

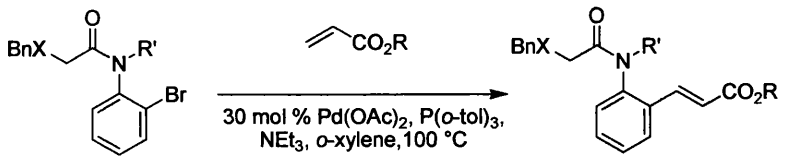
## 3.2 SOLUTION-PHASE STUDIES

Solution-phase studies were carried out to evaluate the reactions in the planned route. Benzyl alcohol and benzyl thiol were used as suitable models for the resin. As illustrated in chapter 2, we initially concentrated on ether HASC linkages and then switched to more versatile sulfur linkages which allowed us to tune the reactivity by adjusting the oxidation state of the sulfur atom.

### 3.2.1 Preparation of solution-phase model substrates

Our route to tetrahydroquinolones began from bromoaryl acetamide substrates **158** and **175**. The palladium-catalysed Heck reactions of a range of S and O-linked model substrates with methyl and *tert*-butyl acrylate was investigated[74] and the reaction conditions were optimised **(Table 3.1)**.

An increase in conversion and yield was obtained by carrying out the reactions in a one-piece condensor flask to minimise loss of methyl acrylate. Using a greater excess of methyl acrylate also increased the conversion. The use of microwave heating was also investigated (entry 6, **Table 3.1**). Using conventional heating S-substrates were less efficient than the O-analogues, reaction times were doubled to 48 h. Microwave heating allowed the reaction time to be reduced from 48 h to 7 h and increased the conversion. Microwave heating has recently received a great deal of attention[75-79], particularly with reference to organo-palladium reactions. Although there is some disagreement over the reason for the greatly reduced heating times and increased catalyst turnover experienced with microwave heating[76, 77], there is a great deal of evidence showing that it is a useful process for improving sluggish palladium-catalysed cross couplings.



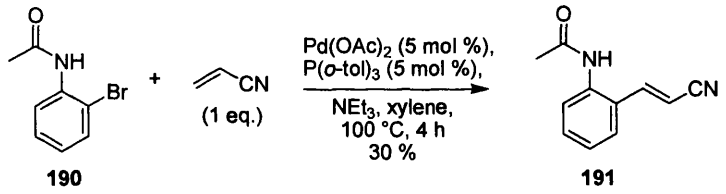

X = O, R' = Me **158**
X = S, R' = Me **175**

| Entry | Product | X | R | R' | Rxn time h | Acrylate Eq. | Conv. % | Yield. % |
|---|---|---|---|---|---|---|---|---|
| 1 | **186** | O | Me | Me | 24 | 1.1 | 64 | 83 |
| 2 | **187** | O | Me | H | 24 | 1.1 | 55 | 82 |
| 3 | **188** | S | Me | Me | 48 | 1.1 | 46 | 34 |
| 4 | **188** | S[a] | Me | Me | 48 | 2 | 56 | 86 |
| 5 | **188** | S[a] | Me | Me | 48 | 5 | 80 | 96 |
| 6 | **189** | S[b] | *t*-Bu | Me | 7 | 6 | 88 | 100 |

Yields based upon conversion, [a] thermal heating with a fitted condenser flask, [b] microwave heating in sealed vial.

**Table 3.1**

Few examples of the Heck reactions of N-2-halophenylamides and carbamates have been reported. Our conditions were adapted from those reported by de Mayo.[74] He treated bromoanilide **190** with acrylonitrile using $Pd(OAc)_2$ and $P(o\text{-tol})_3$ and isolated the product **191** in a moderate yield **(scheme 3.2)**. De Mayo's work clearly illustrates the sluggish nature of Heck reactions on these substrates using conventional heating.

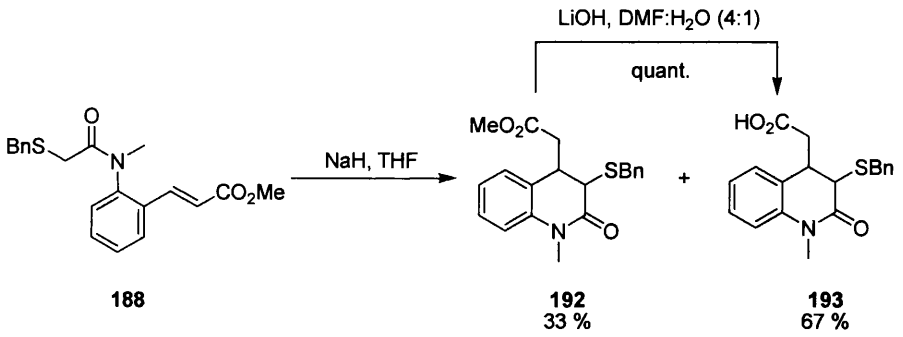



**190** **191**

**Scheme 3.2**

3.2.2 A solution-phase route to tetrahydroquinolones with cyclisation at the sulfide oxidation state

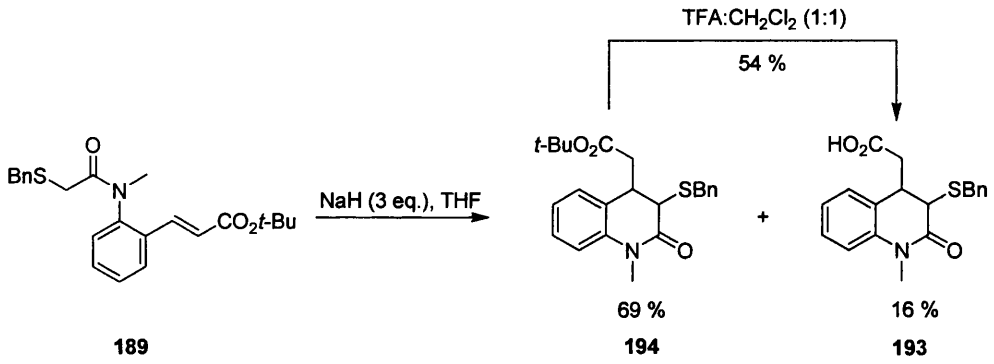
Continuing our proposed route, treatment of sulfide **188** with NaH gave the desired tetrahydroquinolone product **192** in moderate yield **(scheme 3.3)**. However, acid **193** was also isolated as a major-product in 67 % yield after acidification and extraction of the aqueous phase.




**Scheme 3.3**

This suggests almost 100 % conversion to the tetrahydroquinolone ester **192** but highlights problems with the stability of the methyl ester. Several strategies to minimise the hydrolysis of ester **192** were explored. Quenching with anhydrous methanol decreased the amount of acid but did not suppress hydrolysis completely and conversely quenching with water did not lead to complete hydrolysis. Hydrolysis of ester **192** to acid **193** could be achieved quantitatively by treatment with LiOH **(scheme 3.3)**.

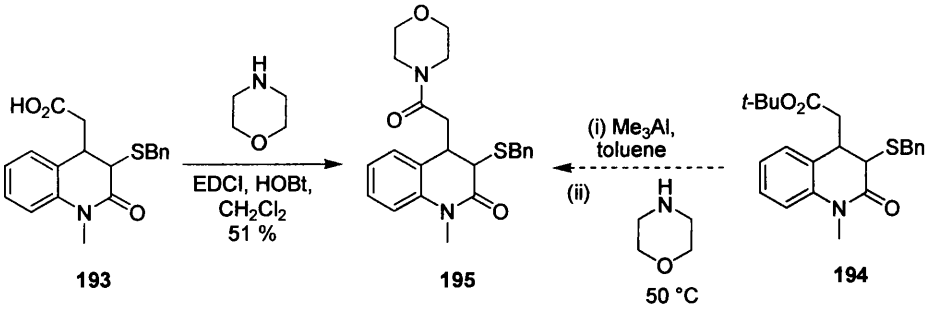
The prevention of hydrolysis by the use of a hindered ester was explored using the *tert*-butyl ester **189**. Cyclisation was attempted using NaH and this gave cyclised ester **194** (69 %) and acid **193** (16 %). Again quenching with *t*-BuOH or with water did not lead to complete formation of either the ester **194** or acid **193**. Hydrolysis of the ester was possible by treatment of **194** with a 1:1 (v/v) mixture of TFA and $CH_2Cl_2$ and this proceeded in moderate yield **(scheme 3.4)**.




**Scheme 3.4**

To investigate the synthetic utility of acid **193** as a means of introducing diversity, we investigated the coupling of acid **193** with amines such as morpholine. EDCI/HOBt

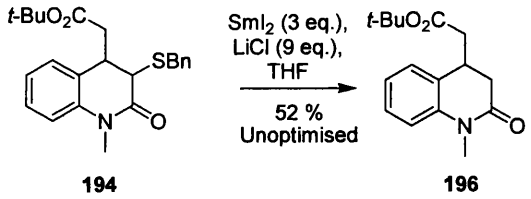
coupling gave the expected morpholine amide **195** in moderate, unoptimised yield **(scheme 3.5)**. Direct access to amide **195** from ester **194** by reaction with $Me_3Al$ and morpholine was investigated however this reaction was unsuccessful. The preparation of amide **195** illustrates the possibility of the introduction of a further point of diversity on the heterocyclic framework.




**Scheme 3.5**

It was hoped that the use of a bulkier base such as LDA in the cyclisation might limit the amount of hydrolysis but similar results were obtained even when the reaction was cooled. Cyclisation of **189** with LDA gave yields of ester **194** ranging from 60 % (0 °C) to 69 % (-20 °C).

The model cleavage of the sulfide linkage of the tetrahydroquinolone was then attempted for the first time. We were pleased to find that treatment of **194** with an excess of $SmI_2$ and an additive LiCl, gave tetrahydroquinolone **196** in a moderate, unoptimised yield **(scheme 3.6)**.

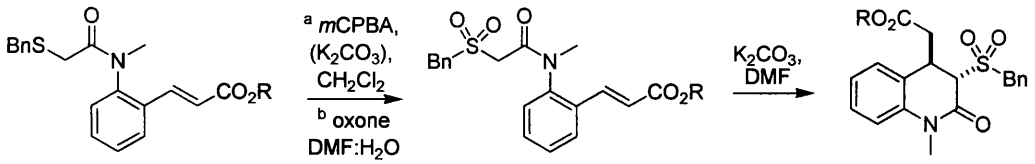



**Scheme 3.6**

The effect of LiCl on the reactivity of $SmI_2$ in THF has been investigated by Flowers and co-workers.[80] The oxidation potential of $SmI_2$ is -1.33 V whereas the oxidation potential of $SmI_2$ containing 12 or more equivalents of LiCl is -2.11 V. Thus, the $SmI_2$/LiCl reagent system is a more powerful reducing agent.

3.2.3 A solution-phase route to tetrahydroquinolones with cyclisation at the sulfone oxidation state

Cyclisation of sulfone substrates was expected to proceed under milder conditions and we felt this might limit hydrolysis of the ester group.




**188** R = Me
**189** R= *t*-Bu

**197** R = Me ([a] 54 %, [b] 55 %)
**198** R= *t*-Bu ([a] 71 %, [b] 90 %)

**199** R = Me (46 %)
**200** R= *t*-Bu (99 %)

**Scheme 3.7**

Oxidation of conjugated esters **188** and **189** proceeded smoothly with both *m*CPBA and Oxone **(scheme 3.7)**. Yields were higher for the *tert*-butyl ester but longer reaction times and the use of more equivalents of *m*CPBA led to some epoxidation of the electron deficient alkene. This was minimised by using only 2 equivalents of *m*CPBA together with $K_2CO_3$ and a reaction time of only 30 min.

Base induced cyclisation to give the dihydroquinolones **199** and **200** proceeded smoothly and again better yields were obtained in the *tert*-butyl series. Acidification of the aqueous phases showed no acid present which supported our view that the milder conditions would suppress the hydrolysis. X-ray analysis of the *tert*-butyl dihydroquinolone **200** allowed the *anti*-relative stereochemistry around the ring to be confirmed **(Fig. 3.3)**.

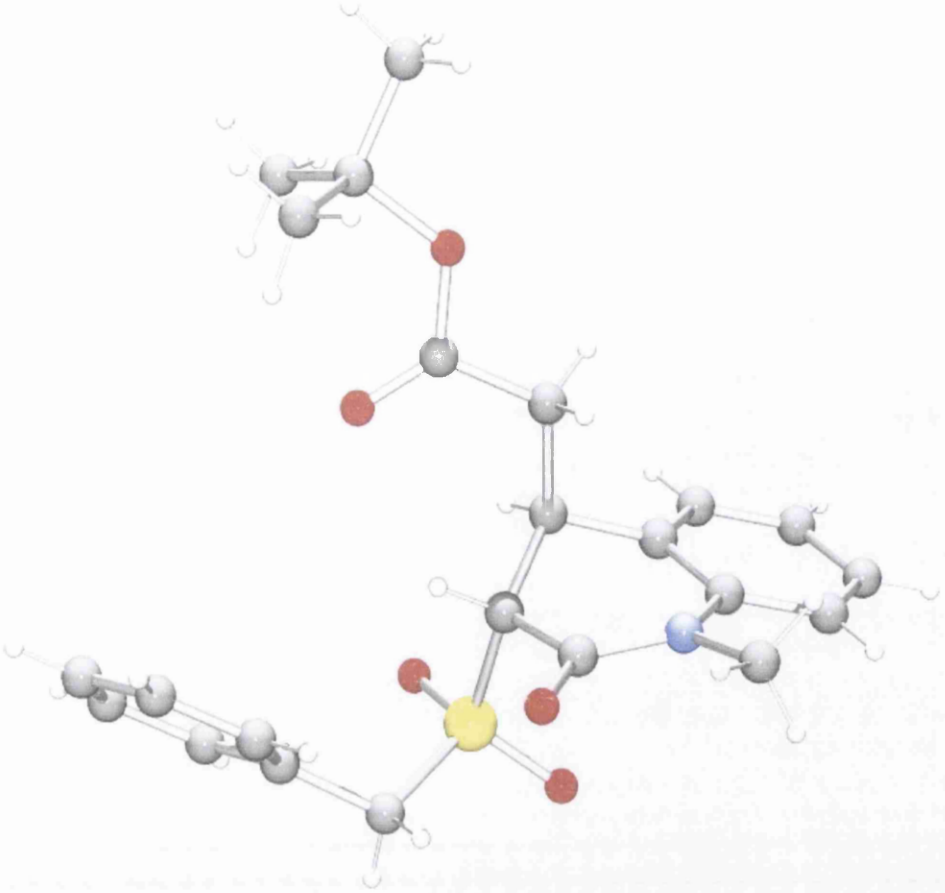
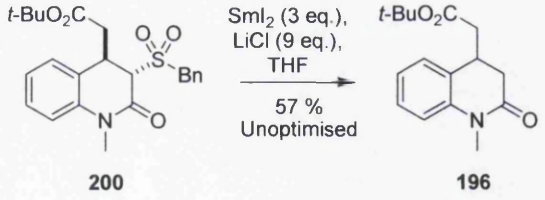


**Figure 3.3:** X-ray structure of **200**.

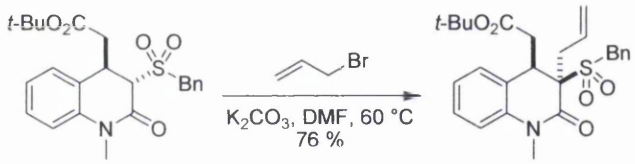
The conditions previously described for the model cleavage of the corresponding sulfide compound **194** were also found to successfully cleave the sulfone **200** to give **196** in moderate yield **(scheme 3.8)**.




**200** **196**

**Scheme 3.8**

We next examined the alkylation with allyl bromide as another possible method for the introduction of diversity to the heterocyclic framework **(scheme 3.9)**. The alkylation of **200** proceeded in high yield under mild conditions to give **201** as a single diastereomer.




200 201

**Scheme 3.9**

X-ray analysis showed that the alkylation of the enolate had occurred from the opposite face to the *tert*-butyl ester "sidechain" **(Fig. 3.4)**.

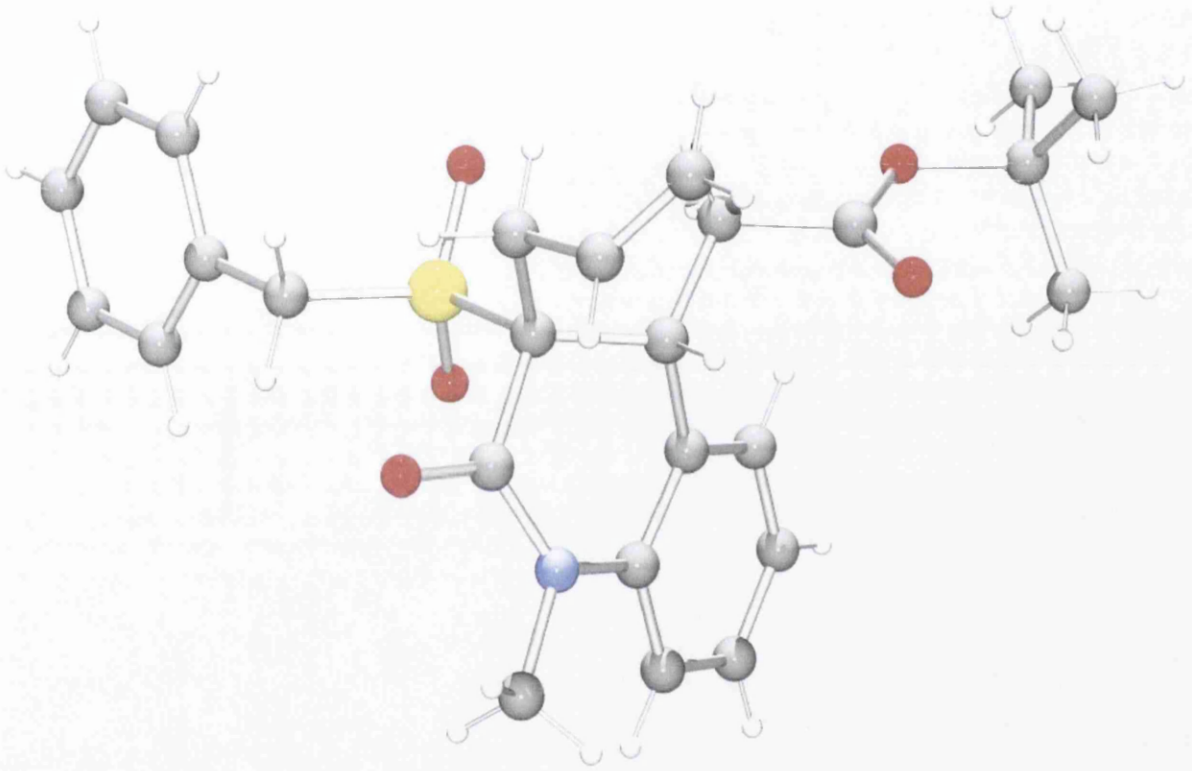
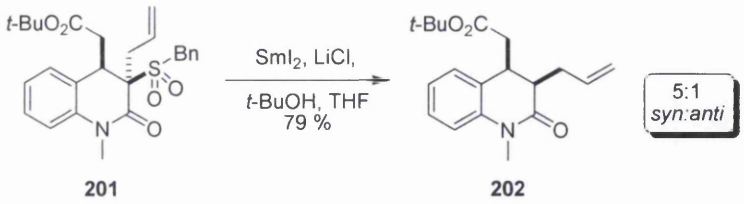


**Fig. 3.4:** X-ray structure of **201**.

As the basic conditions for the alkylation were the same as those used in the previous cyclisation step, we attempted a one-pot cyclisation, alkylation sequence. α,β-Unsaturated ester **198** was treated with excess $K_2CO_3$ in DMF for 2 h before addition of allyl bromide. Unfortunately, only unalkylated heterocycle **200** was obtained. No further attempts to carry out such a sequence were made.

$SmI_2$ cleavage of the alkylated heterocycle **201** was attempted using *t*-BuOH as a bulky proton source. It was hoped that the bulky proton source would give rise to some selectivity in the delivery of the proton to the intermediate samarium (III) enolate.

Pleasingly, cleavage proceeded in good yield and a 5:1 ratio of *syn*:*anti* products was obtained **(scheme 3.10)**.




201 202

**Scheme 3.10**

The major diastereomer **202** could be separated from the mixture and analysis by X-ray crystallography showed this to be the expected *syn* diastereomer resulting from protonation of the intermediate Sm(III) enolate from the opposite face to the bulky ester substituent **(Fig. 3.5)**. Cleavage in the presence of MeOH gave a 1:1 mixture of diastereomers supporting our hypothesis that the bulk of the proton source influences the diastereoselectivity of the cleavage step.

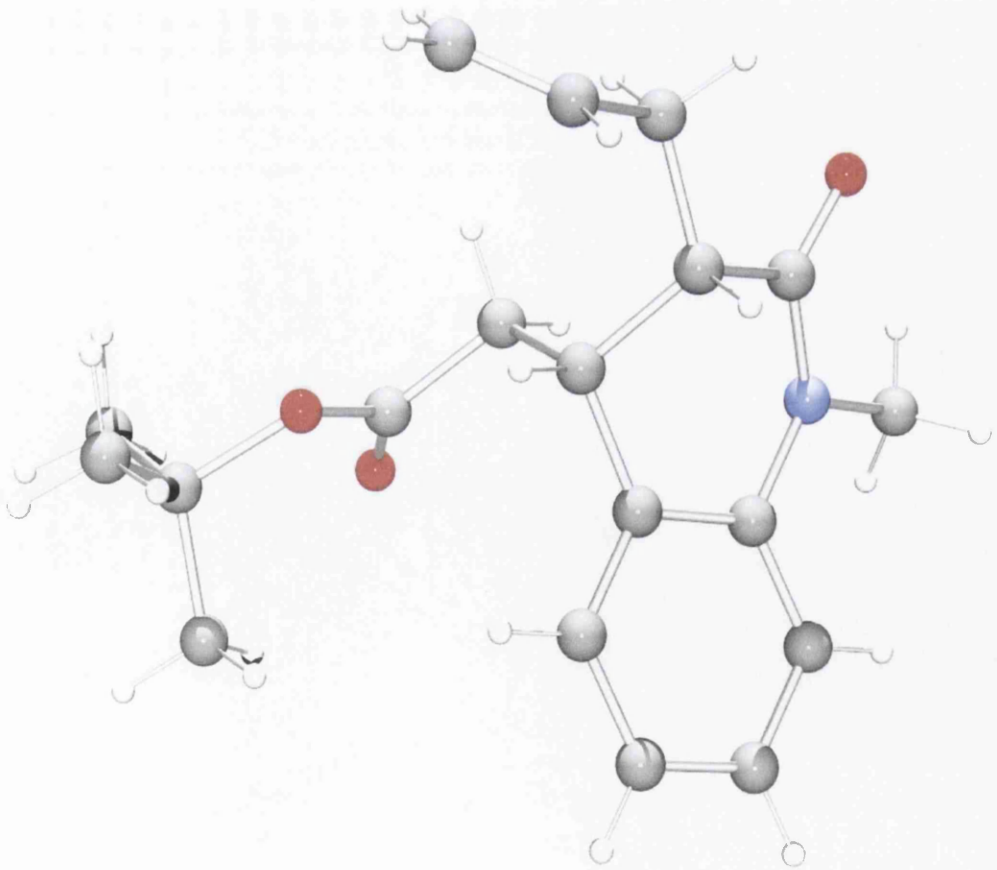
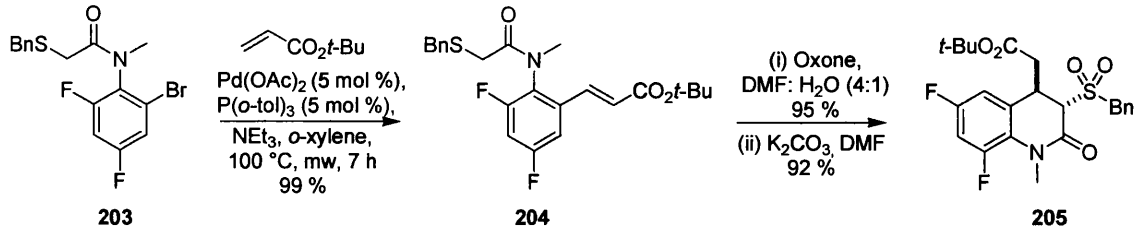


**Fig. 3.5:** X-ray structure of **202**.

The introduction of diversity *via* the parent aniline was next investigated. A number of substituted anilines are commercially available and the route was investigated using 4,6-difluoro aniline. Yields were consistent with those in the unsubstituted series, clearly indicating that the route tolerates functionality on the aromatic ring. Interestingly, the Heck reaction of **203** proceeded in a better yield than in the unsubstituted series, assisted by the electron withdrawing nature of the substituents **(scheme 3.11)**.




**Scheme 3.11**

Oxidation and cyclisation proceeded with similar yields to those obtained in the unsubstituted series and the *anti*-tetrahydroquinolone **205** was again isolated and the relative stereochemistry of the product confirmed by X-ray crystallography **(Fig. 3.6)**.

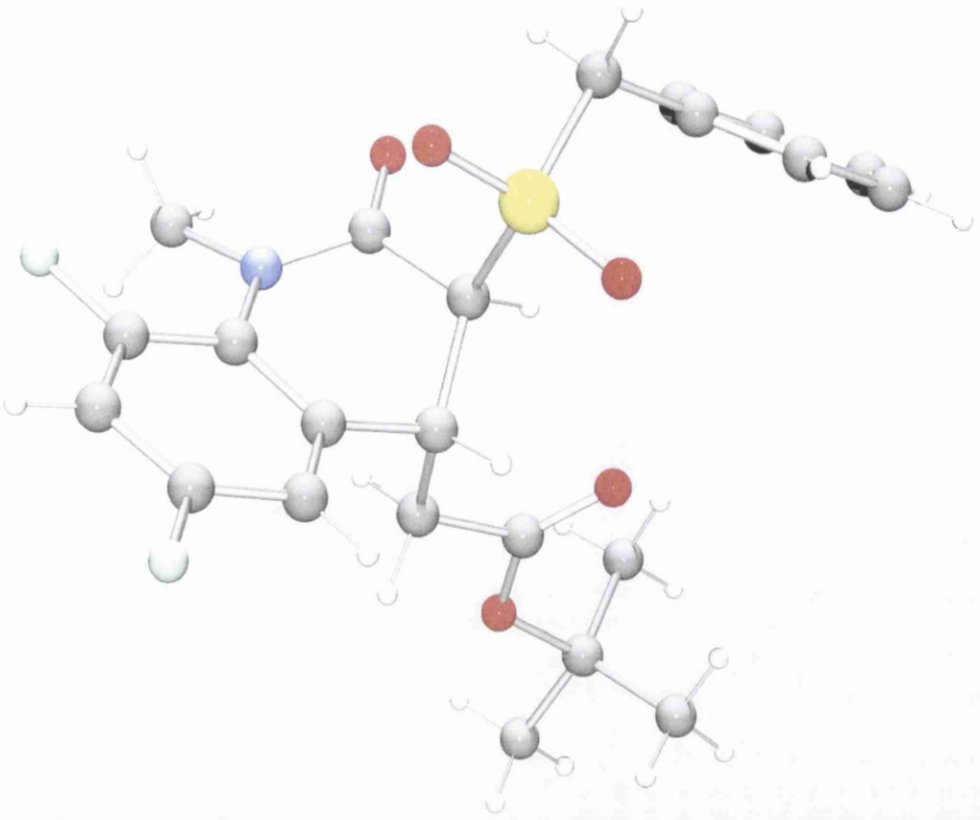
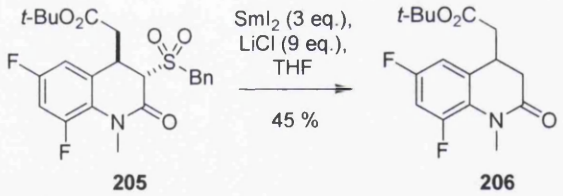


**Fig. 3.6:** X-ray structure of **205**.

Cleavage of the benzyl sulfonyl group using $SmI_2$/LiCl gave the expected product **206** although the yield of this model reaction was not optimised **(scheme 3.12)**.




**Scheme 3.12**

### 3.2.4 Axial chirality in substituted anilides

The $^1$H NMR spectrum of **158** showed interesting characteristics **(fig. 3.7)**. On face-value the spectrum should be simple since each methylene is isolated and the methylene protons are enantiotopic.

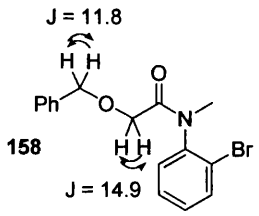



**Fig. 3.7**

However, the spectrum of **158** showed characteristic AB system quartets integrating to two protons for both the benzylic $CH_2$ and the $CH_2$ α to the carbonyl. This indicates that there must be another source of chirality in the molecule which is responsible for the complexity of the methylene signals. A search of the literature reveals that substituted anilides are known to exhibit slow rotation leading to the the existence of atropisomers. In 1969 Siddall and Stewart calculated barrier heights for rotation around the nitrogen-benzene bond for a number of substituted anilides of the type **207**.[81]

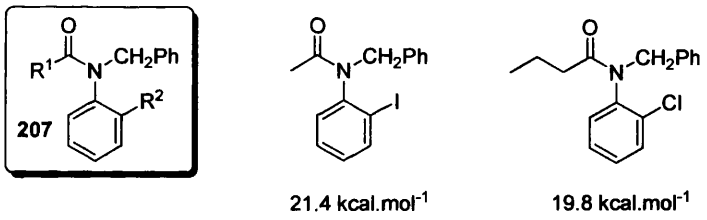
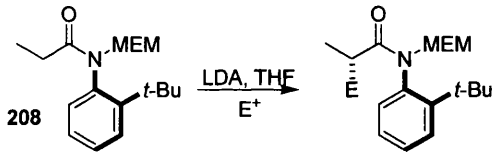



**Fig. 3.8**

The barrier heights for rotation were calculated by matching the experimental AB patterns with calculated patterns; the experimental patterns arose from the non-equivalent methylene protons of the benzyl group. The calculations show that *o*-halo substituted anilides show barriers to rotation around the C-N bond in the order of 20 $kcal.mol^{-1}$.

In a later paper by Simpkins the utility of atropisomeric amides **208** for stereoselective synthesis was explored.[82] The chiral C-N axis was exploited as a stereocontrolling element in enolate alkylations.




**Scheme 3.13**

Returning to the compounds synthesised in this thesis, C-N axial chirality is found in a number of closely related compounds. It is present in all the N-Me substituted α-bromo amides and is greatest when there are two ortho substituents as shown in **212 (fig. 3.9)**. α-Bromo amide **210** is also closely related to the substrates analysed by Siddall and Stewart. No rotational barrier is observed in the secondary anilide **151**.

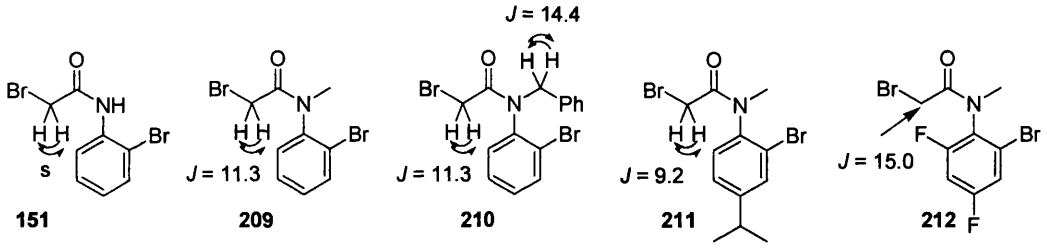



**Fig. 3.9**

When Br is substituted by BnS or BnO the chiral C-N axis also affects the benzylic methylene signals.

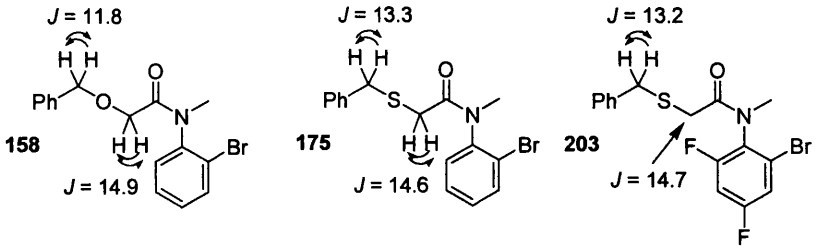



**Fig. 3.10**

A similar effect is seen in the 1H NMR of α, β-unsaturated esters **186** and **188** but not in NH compound **187 (fig. 3.11)**.

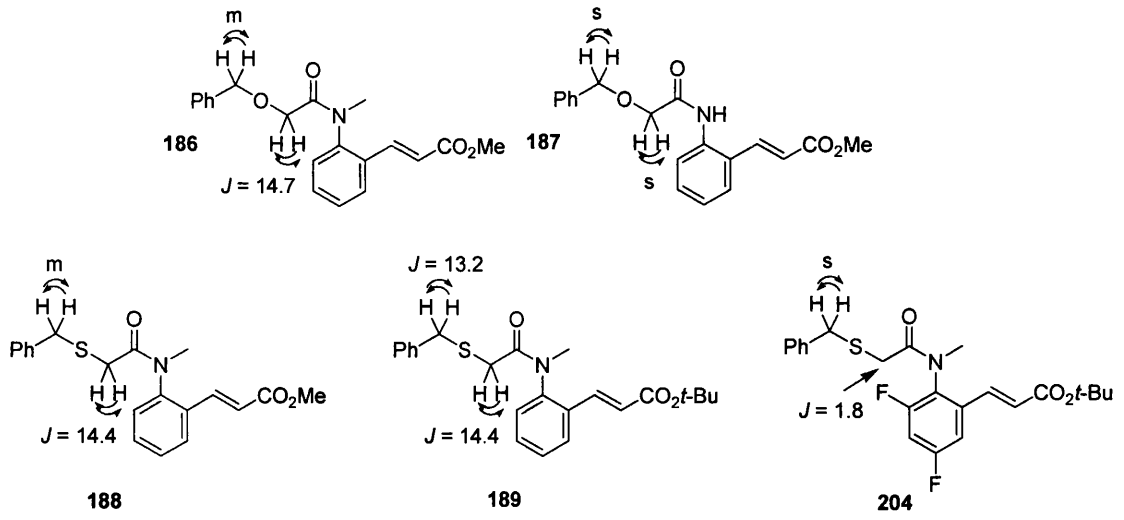



**Fig. 3.11**

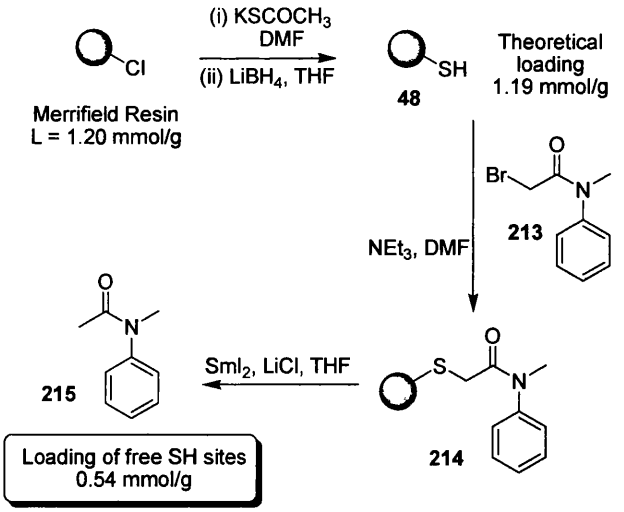
## 3.3 SOLID-PHASE SYNTHESIS

Satisfied that the solid-phase approach to tetrahydroquinolones using our sulfur linker was feasible, we moved from solution-phase model studies to work on polymer support.

### 3.3.1 Developing a solid-phase synthesis of tetrahydroquinolones

Thiol resin **48** was prepared from commercially available Merrifield resin by first preparing the thioacetate and then reducing with $LiBH_4$.[39]

In order to determine accurate yields of products cleaved from the solid support the loading of free SH sites on the resin was first determined. A simple α-bromo amide **213** was immobilised using the thiol resin **48** and then cleaved using $SmI_2$ **(scheme 3.14)**. The mass of acetamide **215** obtained allowed the loading to be determined as 0.54 mmol/g (an average across 3 runs).




**Scheme 3.14**

This is comparable to loadings determined previously in the group where the loading of free SH sites was determined to be 0.55 mmol/g compared to a theoretical loading of 1.10 mmol/g.[49] The discrepancy between the free SH sites and the theoretical loading is probably due to sulfur cross-linking reducing the number of sites available for immobilisation of substrates **(Fig. 3.12)**.

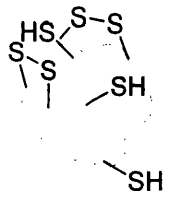
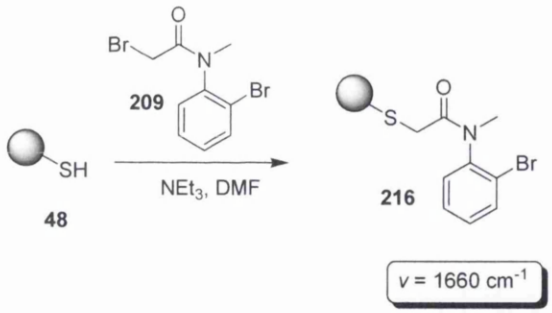



**Fig. 3.12**

Successful immobilisation of α-bromoamide **209 (scheme 3.15)** was indicated by the presence of a strong amide carbonyl stretch in the IR spectrum at 1660 $cm^{-1}$ and also by diagnostic signals in the Magic Angle Spinning NMR spectrum **(Fig. 3.13)**. MAS NMR is a solid-phase NMR technique which can be used to analyse molecules immobilised on solid-phase resins. Spinning the swollen sample at the "magic angle" minimises the response from nuclei on the resin backbone allowing a clean spectrum of the immobilised molecule to be obtained.




**Scheme 3.15**

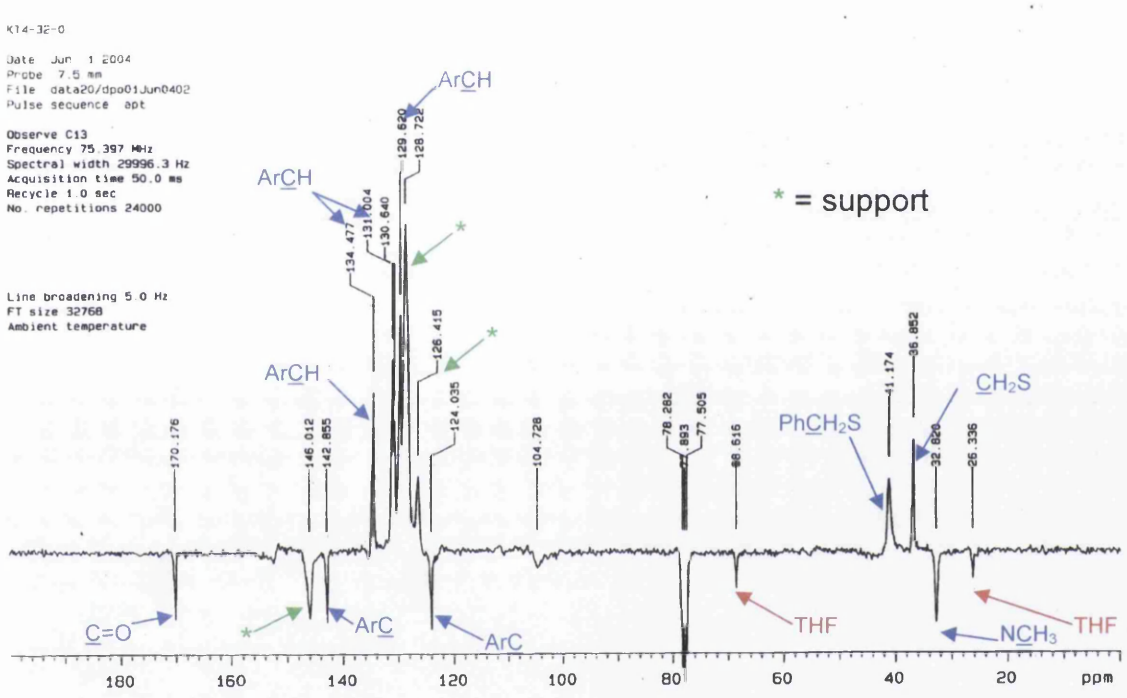
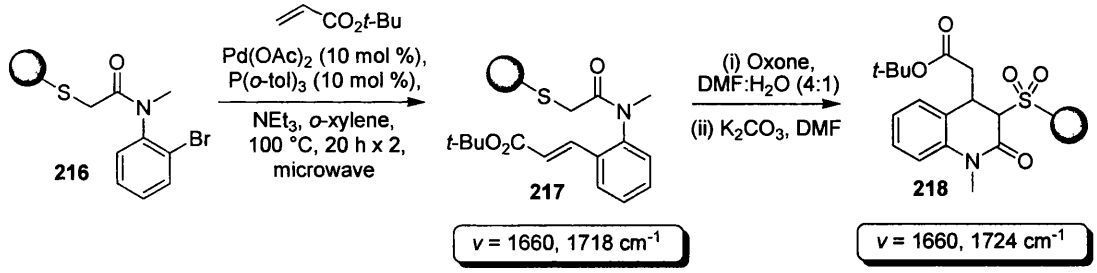


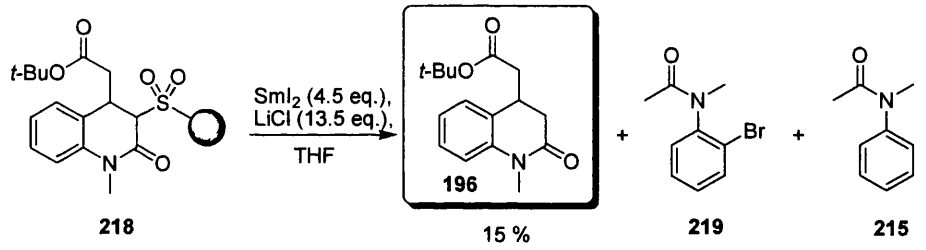

**Fig. 3.13:** APT spectrum of **216**. Plotted with $CH/CH_2$ positive and $_qC/CH_3$ negative

The Heck reaction of **216** with *tert*-butyl acrylate was carried out using the conditions optimised in solution. The reaction time was gradually increased to maximise the intensity of the ester stretch observed in the IR spectrum of the product resin **217 (scheme 3.16)**.




**Scheme 3.16**

IR analysis of the product resin **217** after 10 h looked promising with the absorption at 1718 $cm^{-1}$ indicating the presence of an α,β-unsaturated ester group. The ester stretch was only slightly less intense than the amide stretch. Unfortunately, after completion of the reaction sequence (oxidation/cyclisation), cleavage of this batch of resin using $SmI_2$-LiCl, gave only 15 % of product **196** (5 steps from **48**) **(scheme 3.17)**.

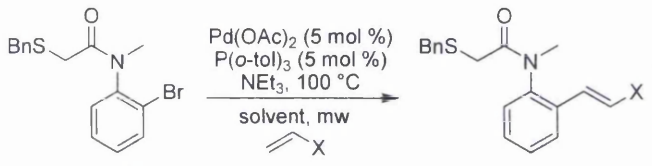



**Scheme 3.17**

The isolation of amide byproducts **215** and **219** indicated that the Heck reaction was not proceeding to completion on solid-phase. Acetamide **215** most probably arises from the reduction of the C-Br bond from either **216** during the palladium-catalysed coupling or of **219** with $SmI_2$ after cleavage from the resin. It was clear that we had to improve the efficiency of the Heck reaction.

We first turned our attention to the solvent used in the reaction. The swelling volume of the resin is an important factor in the efficiency of reactions on solid-phase. Whilst *o*-xylene is the traditional solvent of choice [83-86] for the Heck reaction it produces only minimal swelling of Merrifield resin. *o*-Xylene is also inefficient as a solvent in microwave reactions since it is non-polar and virtually "transparent" to microwaves.[79] Our attention therefore turned to maximising the resin swelling and perhaps maximising the microwave activity of our system. A survey of the literature showed that non-polar solvents such as toluene and benzene were commonly used in the Heck reaction and

indeed in many palladium catalysed cross couplings. These solvents also tend to have minimal resin swelling volumes so may be incompatible with solid-phase synthesis. Some examples of Heck reactions utilising DMF as a solvent have been reported.[87] DMF has excellent resin swelling properties and is also a good solvent for microwave reactions. Initially DMF gave poor results and we concentrated on 'doping' *o*-xylene with DMF **(table 3.2)**.




**175**

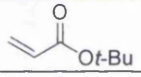
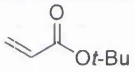
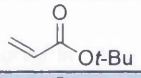
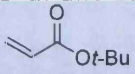
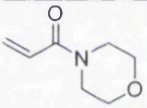
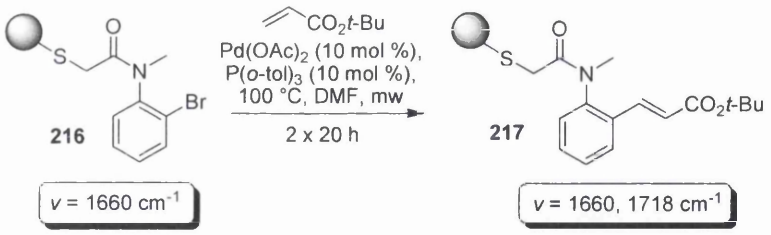
| Entry | Product | Acrylate | Conditions | Time (h) | isolated yield |
|---|---|---|---|---|---|
| 1 | **190** |  | o-xylene, thermal | 48 | 39 % |
| 2 | **190** |  | o-xylene, microwave | 7 | 88 % |
| 3 | **190** |  | DMF-o-xylene (3:7) microwave | 10 x 2 | 75 % |
| 4 | **190** |  | DMF, microwave | 10 x 2 | 90 % |
| 5 | **220** |  | DMF, microwave | 10 x 2 | 76 % |

**Table 3.2**

**Table 3.2** shows the results obtained from screening a number of solvents and reaction conditions. Our studies showed that the use of microwave heating significantly reduces the reaction time and increases conversion although reaction times are still quite long. A 3:7 mixture of DMF and *o*-xylene (entry 3) gave good results however much longer reaction times were required as well as a retreatment after the first 10 h of the reaction. The reaction was repeated with a fresh batch of anhydrous DMF (entry 4) and an excellent conversion was obtained. The conditions were applied to the Heck reaction of substrate **175** with acryloyl morpholine (entry 5) and this also gave good results. Heck reactions with other alkene partners allow another point of diversity to be introduced to the heterocyclic framework.




**Scheme 3.18**

The optimised conditions were then transferred onto solid-phase **(scheme 3.18)** and the formation of solid-supported ester **217** was indicated by the presence of an IR stretch at 1718 $cm^{-1}$ and by characteristic signals in the MAS NMR **(Fig. 3.14)**. Although this was less helpful than in the case of acetamide **216** it clearly showed the presence of the *tert*-butyl group and two carbonyl groups.

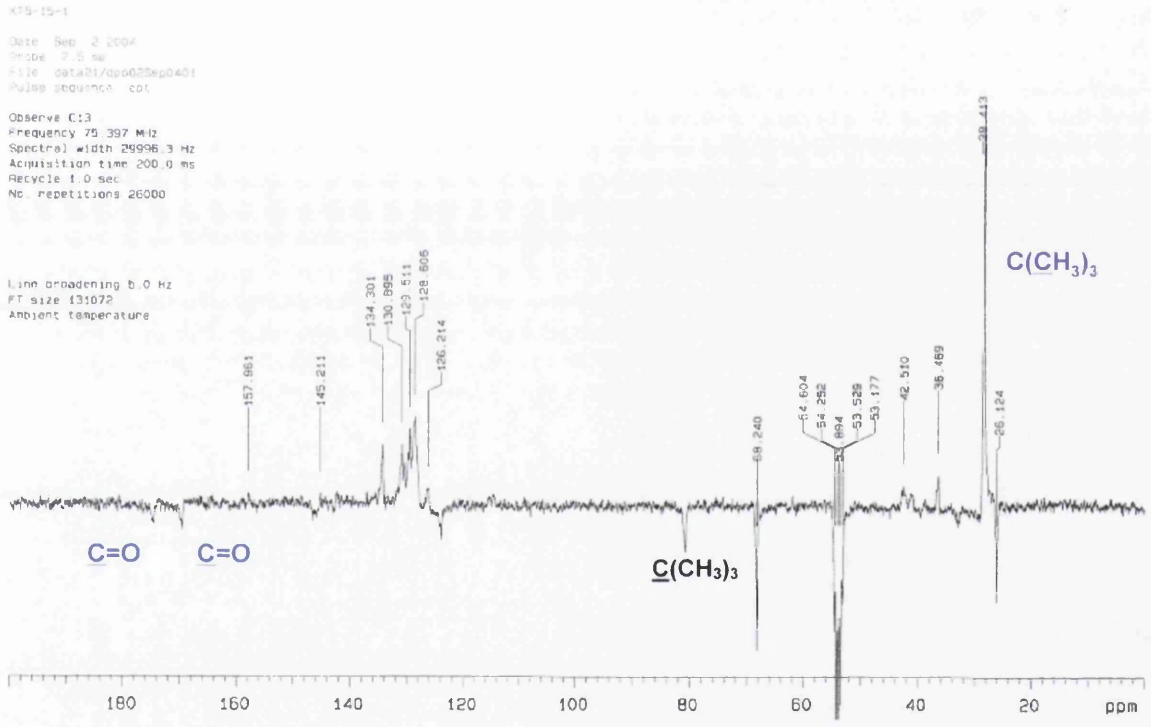



**Fig. 3.14:** APT spectrum of **217**. Plotted with $CH/CH_3$ positive and $_qC/CH_2$ negative.

The use of a different polymer support was also investigated as a way of increasing the efficiency of the Heck reaction. JandaJels are insoluble supports that contain a flexible THF derived cross linker **(Fig. 3.15)**.[88]

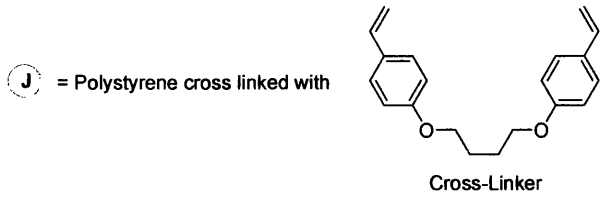
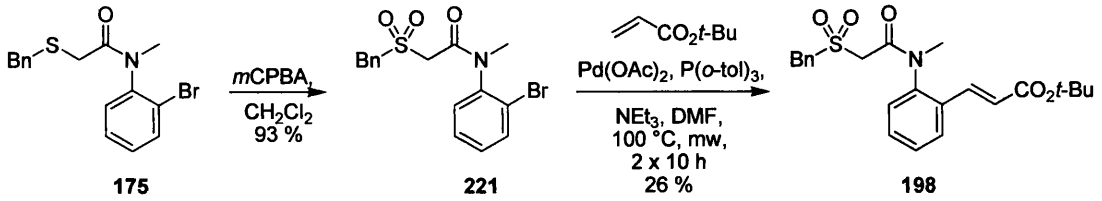



**Fig. 3.15**

JandaJels have been utilised in the synthesis of a number of combinatorial chemistry libraries [89-91] and their properties have been extensively studied. A recent study showed that diffusion values for solvents and small molecules are 20-30% higher in JandaJel compared to Merrifield resin. The results showed that the microenvironments of JandaJels are more solution-like than that of Merrifield resins.[92] The swelling volume of the support is also increased due to the flexibility of the cross-links. It was hoped that this would enable a more efficient Heck reaction and increase the accessibility of the reacting sites. Our synthetic sequence to tetrahydroquinolones was carried out using JandaJel-Cl resin and looked to be proceeding smoothly by IR spectroscopy. Upon cleavage however, only a low yield of product **196** was obtained. Throughout the sequence the resin proved difficult to dry which may also have adversely affected the efficiency of the Heck reaction.

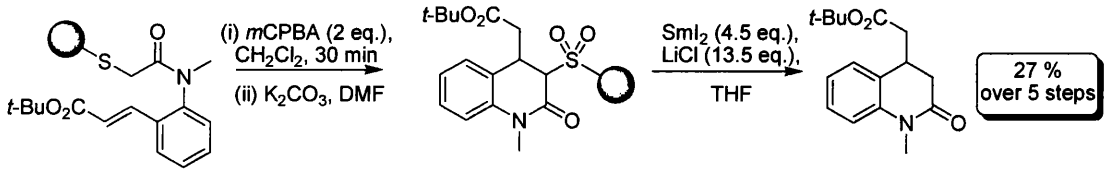
Finally, the Heck reaction of sulfone **221** was also investigated **(scheme 3.19)**. It was hoped that switching the order of the Heck reaction and oxidation might give rise to a more efficient Heck reaction and therefore greater yields for the overall sequence. Disappointingly, Heck reaction of **221** gave **198** in a low yield, possibly due to chelation of the palladium by the sulfone oxygens hindering catalyst turnover.




**Scheme 3.19**

Having arrived at reasonable conditions for the Heck reaction, we turned our attention to the oxidation step. The oxidation of sulfide **217** with oxone also proved to be a problem on solid-phase. The inorganic nature of the reagent together with the requirement for a water co-solvent appeared to reduce the efficiency of the reaction

when transferred to solid-phase. Water is required to dissolve the oxone and a 4:1 mixture of DMF-water is commonly employed. As is typical in many solid-phase reactions, excess reagent is used to drive the reaction to completion. We believe that insufficient oxone was soluble in the solvent mixture to afford reaction. Addition of more water would increase the amount of oxone in solution however it would also cause the resin to contract. *m*CPBA proved to be a suitable alternative however, as previously described, the reaction had to be carefully controlled to avoid epoxidation of the double bond **(scheme 3.20)**.



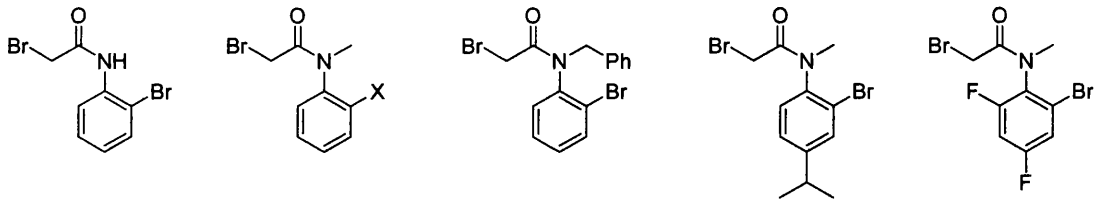

**217** **218** **196**

**Scheme 3.20**

When these improved conditions were applied in our sequence, an improved yield of 27 % (5 steps) of product **196** was obtained. Our attention now turned to the solid-phase synthesis of a library of tetrahydroquinolones using our sulfur linker system.

### 3.3.2 A solid-phase synthesis of a library of tetrahydroquinolones

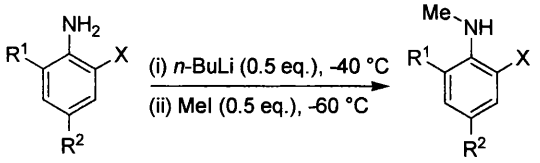
We have utilised the optimised approach described above to synthesise a collection of tetrahydroquinolones using α-bromo amide starting materials **151**, **209-212** and **222** **(Fig. 3.16)**.



**151** **222** X = I **209** X = Br **210** **211** **212**

**Fig. 3.16**

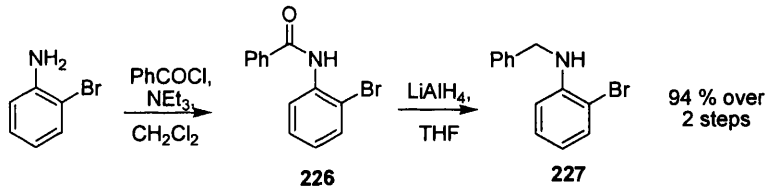
The synthesis of these α-bromo amides utilised a range of substituted anilines. The secondary anilines **156** and **223-225** were prepared by direct N-alkylation **(scheme 3.21)**.




| Compound | X | $R^1$ | $R^2$ | Yield % |
|---|---|---|---|---|
| **156** | Br | H | H | 76 |
| **223** | Br | F | F | 79 |
| **224** | Br | H | $^i$Pr | 66 |
| **225** | I | H | H | 58 |

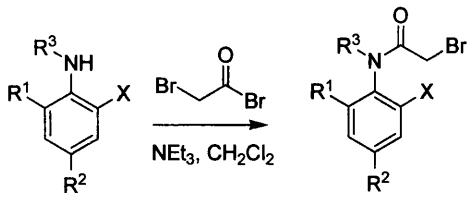
**Scheme 3.21**

The N-benzyl substituted aniline **227** was prepared by reaction of 2-bromoaniline with benzoyl chloride to give the amide **226** followed by reduction with $LiAlH_4$ **(scheme 3.22)**.




**Scheme 3.22**

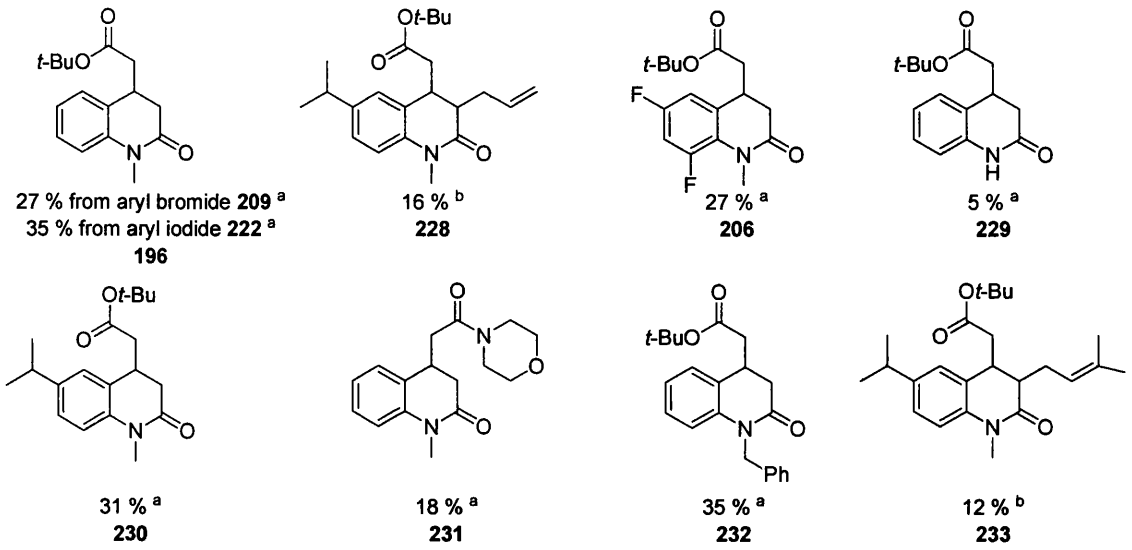
The secondary anilines were then reacted with bromoacetyl bromide to give the corresponding α-bromoamides **151**, **210** and **217-220 (scheme 3.23)**.




| Compound | X | $R^1$ | $R^2$ | $R^3$ | Yield % |
|---|---|---|---|---|---|
| **151** | Br | H | H | H | 81 |
| **209** | Br | H | H | Me | 79 |
| **210** | Br | H | H | Bn | 70 |
| **211** | Br | $^i$Pr | H | Me | 75 |
| **212** | Br | F | F | Me | 90 |
| **222** | I | H | H | Me | 76 |

**Scheme 3.23**

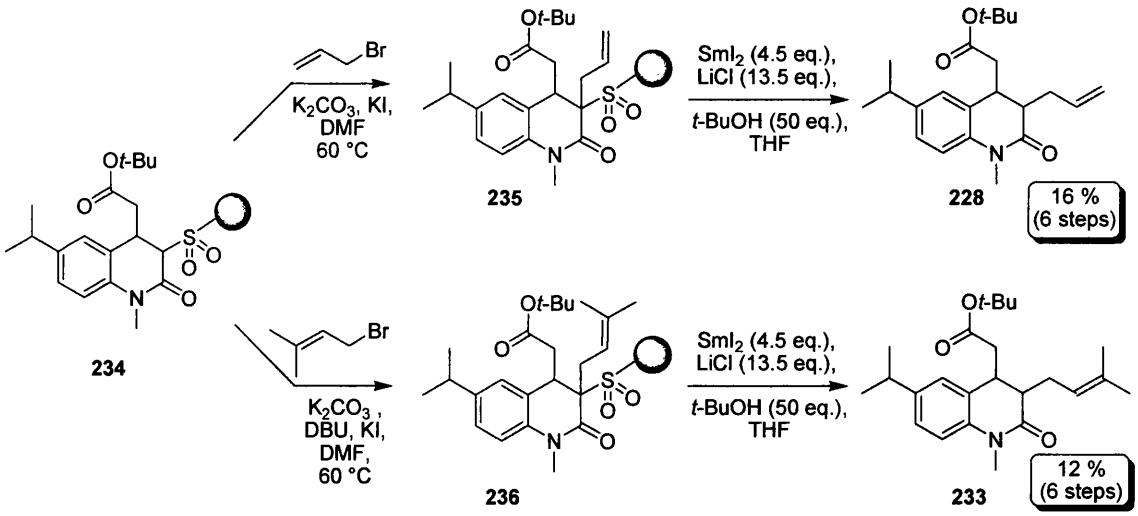
Additional diversity was introduced by Heck reaction with a different olefin and by alkylation of an intermediate sulfone prior to cleavage.




a 5 steps, b 6 steps.

**Fig. 3.16:** Library of tetrahydroquinolones.

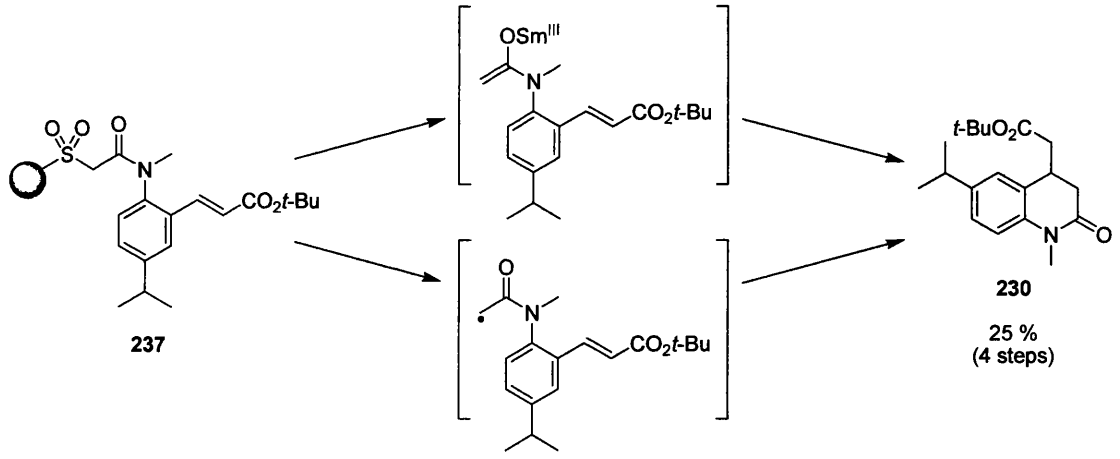
The expected products were mostly obtained in acceptable yields for 5 and 6 steps on solid-phase **(Fig. 3.16)**. The use of an aryl iodide gave improved yields of **196** due to more efficient Heck reactions. The nature of the substituent on the nitrogen had little effect on the yield of the product obtained and similar yields of product were obtained for N-methyl and N-benzyl substituted compounds **196** and **232**. Alkylations of intermediate sulfones proved to be more difficult than solution models had predicted and more forcing conditions were required **(scheme 3.24)**. Alkylation with allyl bromide to produce product **228** required the use of KI and heat (60 °C). Alkylation with prenyl bromide was carried out with DBU as an additive.[93] Products **228** and **233** were obtained with little diastereoselectivity possibly due to residual moisture present in the resin acting as an alternative proton source to the added *t*-BuOH.




**Scheme 3.24**

Access to free NH compounds was possible using the route however the yield was poor at approximately 5 % for 5 steps. It may be possible to synthesise NH compounds from α-bromo amides bearing a protecting group on nitrogen however we had insufficient time to examine this.

Finally, we have also investigated the feasibility of a cyclative cleavage strategy using the HASC linker. Treatment of sulfone **237** with $SmI_2$ resulted in cleavage of the sulfur linkage and cyclisation to give **230** in a moderate overall yield. This could occur by either an anionic or radical mechanism **(scheme 3.25)**.




**Scheme 3.25**

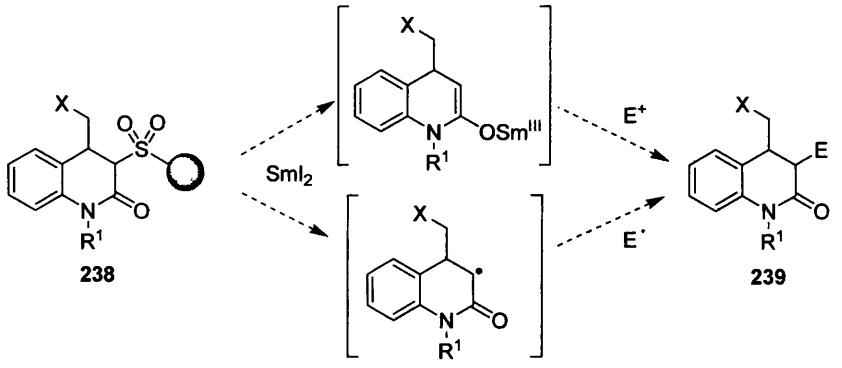
This cyclative-cleavage approach could have exciting possibilities for the construction of polycyclic systems on solid-phase.

## 3.4 SUMMARY

We have developed an efficient solid-phase synthesis of tetrahydroquinolones. The sequence involves a microwave assisted palladium-catalysed Heck reaction which allows access to α,ß-unsaturated ester intermediates. The oxidation state of the sulfur linkage is manipulated to facilitate the Michael cyclisation of α,ß-unsaturated ester and amide intermediates under mild, basic conditions. Diversity is introduced into the library by enolate alkylations, Heck reaction with different acrylates and acrylamides, and from the choice of substitution on the starting aniline. Using our approach, we have prepared 8 tetrahydroquinolones in acceptable yield and purity. In addition, we have illustrated the feasibility of a cyclative-cleavage strategy using $SmI_2$, where cleavage of the link is followed by cyclisation to give the heterocyclic product directly. Our studies have illustrated the compatibility of sulfur HASC linkers with palladium-catalysed transformations and also provided a further illustration of the multi-functional roles possible with sulfur linkers.

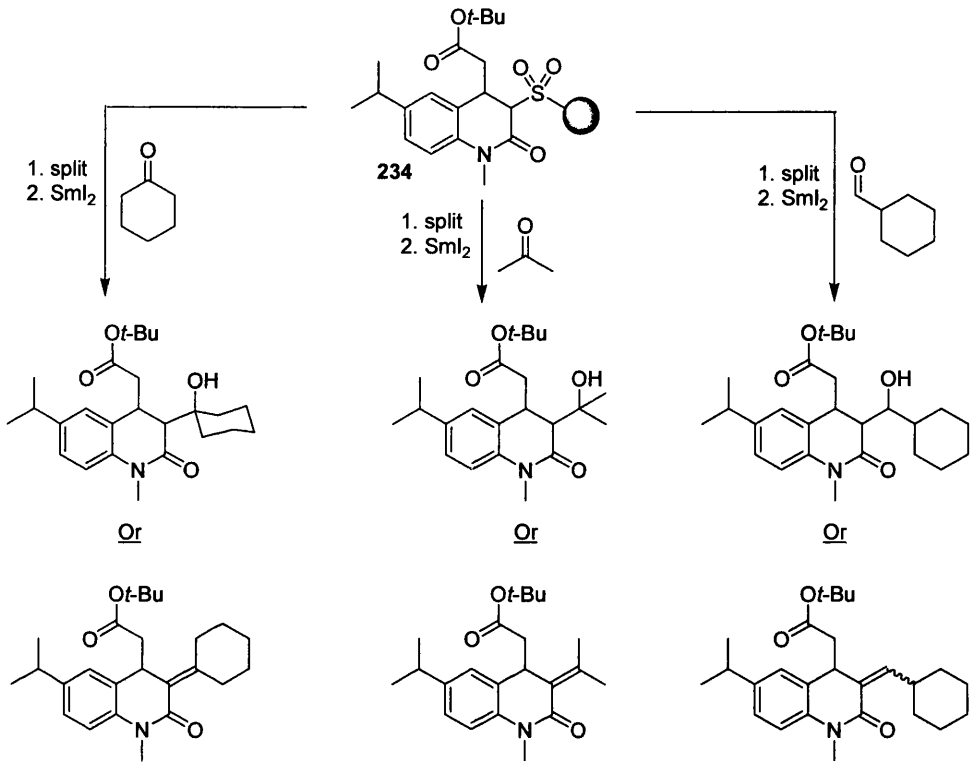
## 3.5 FUTURE WORK

The cyclative-cleavage approach discovered in the course of this project could provide exciting possibilities for future work. We have shown that samarium enolates or radicals can be captured by electron deficient alkenes in an intramolecular fashion **(scheme 3.25)**. It may also be possible to extend this chemistry towards an intermolecular cleavage-trapping strategy. A general outline is shown in **scheme 3.26**. Treatment of intermediate **238** with $SmI_2$ in the presence of an external electrophile should allow the installation of groups α-to the carbonyl.



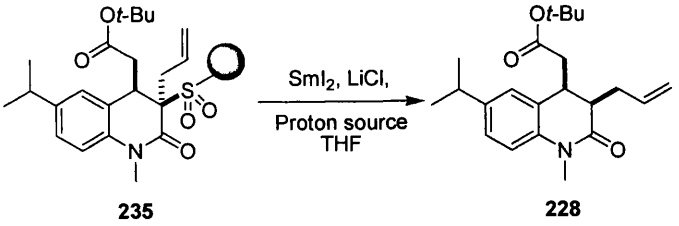

**Scheme 3.26**

**Scheme 3.27** shows some of the possible substituents that could be installed if intermediate **234** was cleaved by $SmI_2$ in the presence of ketone and aldehyde electrophiles and illustrates the considerable diversity that could be provided by this method.




**Scheme 3.27**

During the solution-phase studies we were able to achieve some selectivity in the cleavage of the alkylated intermediate **201**. The use of *t*-BuOH as a bulky proton source gave moderate selectivity for the *syn* diastereomer of **202**. This however did not transfer well onto solid-phase. The possibility of accessing single diastereomers would greatly increase the potential use of this route in discovery chemistry. Other proton sources such as bulkier alcohols or organice acids could be investigated in this reaction however the issue of drying the resin must also be overcome **(scheme 3.28)**. The lack of selectivity in the solid-phase cleavage of **201** was attributed to water in the resin providing an alternative proton source. The drying of the resin could perhaps be carried out by placing the resin in a drying chamber under vacuum for an extended period of time, prior to the cleavage reaction with $SmI_2$.




235 228

**Scheme 3.28**

## 4.1 GENERAL METHODS.

All experiments were carried out under an atmosphere of nitrogen or argon using anhydrous solvents unless otherwise stated. Reactions were carried out using oven-dried glassware. THF was distilled from sodium and benzophenone. $CH_2Cl_2$ was distilled from $CaH_2$. $NEt_3$ was distilled from $CaH_2$ and stored over KOH and under $Ar/N_2$. Anhydrous *o*-xylene and DMF was purchased and stored under $Ar/N_2$. Reagents were purchased and used without purification unless stated.

Samarium (II) iodide was prepared by the method of Imamoto [94] with the modification that the samarium-iodine solution was heated at 60 °C rather than at reflux. Anhydrous LiCl was obtained in ampules and stored under nitrogen. LiCl was dried under vacuum prior to use.

Column chromatography was carried out using Fischer Matrix silica gel 60. Aluminium backed plates, precoated with silica gel 60 ($UV_{254}$) were used for thin layer chromatography and were visualized by UV or staining with alkali $KMnO_4$.
$^1H$ and $^{13}C$ NMR spectra were recorded on a Fourier transform spectrometer with chemical shift values being reported in ppm relative to residual chloroform ($\delta_H$. = 7.27 or $\delta_C$ = 77.2) as an internal standard unless otherwise stated. NMR signals were assigned using DEPT 45, 90 and 135, HMQC and COSY spectra. All coupling constants are reported in Hertz (Hz). Mass Spectra were recorded at the University of Glasgow and the University of Manchester. ATR IR spectra were recorded on a Bio-Rad Merlin Excaliber spectrometer.

Microwave reactions were carried out in a Biotage Initiator, in microwave reactor vials sealed with a crimp cap. Variable power was used to ensure the temperature remained constant. Vials were equipped with stirrer bars and reactions were stirred throughout the heating.

### 4.1.1 General methods for solid phase reactions

Solid phase reactions were carried out in round bottom flasks and were performed with gentle stirring. In some cases reactions were performed in polypropylene bond elute cartridges which were placed in a carousel and rotated, such reactions are indicated

within the experimental. Commercially available Merrifiled resin with a loading of 1.1 mmol/g [copoly(styrene-1 % DVB), 200-400 mesh] was used. Solvents and soluble reagents were removed by high pressure water suction after transferral of the reaction suspension into polypropylene bond elute cartridges (25 ml or 50 ml fitted with a polyethylene porous disc), using 50 ml solvent/g resin for each wash.
THF used for washing resin was distilled prior to use.

Calculation of the theoretical loading of resins was carried out according to the equation:

$$S_{(th)} = \frac{S_{(s)}}{1 + \frac{S_{(s)} \text{x} Wt_{(addn)}}{1000}}$$

$S_{(th)}$ -Theoretical substitution

$S_{(s)}$ - Starting substitution mmol/g

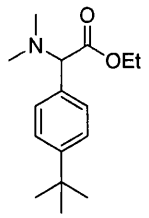
$Wt_{(add)}$ - g/mol added to resin

Magic Angle Spinning NMR spectra were recorded by the EPSRC solid-state NMR facility at the University of Durham.

**General washing and drying procedure**

The resin was washed with THF (30 ml), THF:$H_2O$ (3:1) (3 x 30 ml), THF:$H_2O$ (1:1) (3 x 30 ml), THF:$H_2O$ (1:3) (3 x 30 ml), THF (2 x 30 ml), then alternate washings with $CH_2Cl_2$ (3 x 30 ml) and MeOH (3 x 30 ml), finishing with THF ( 2 x 30 ml). The resin was then left to dry for 10 min under water pump pressure before being dried for at least 6 h under high vacuum.

**2-(4-*tert*-Butylphenyl)-2-dimethylamino acetic acid ethyl ester 141** [56]

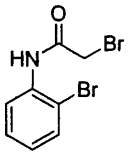


$C_{16}H_{25}NO_2$
Mol. Wt: 263.38

To a round bottomed flask containing N,N-dimethylglycine ethyl ester (0.16 ml, 1.10 mmol), and 1-bromo-4-*tert*-butylbenzene (0.17 ml, 1.00 mmol) was added P(*t*-Bu)$_3$ (0.08 ml, 10 % solution in hexanes, 0.04 mmol), Pd(dba)$_2$ (11.5 mg, 0.02 mmol) and $K_3PO_4$ (637 mg, 3.00 mmol) followed by toluene (3 ml). The flask was placed in an oil bath and stirred at 100 °C overnight. The reaction mixture was filtered through a plug of celite and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 1 % $NEt_3$/pet ether gave **141** as a yellow oil (105 mg, 0.40 mmol, 40 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.14 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.23 (9H, s, $C(C\underline{H}_3)_3$), 2.28 (6H, s, $N(C\underline{H}_3)_2$), 3.76 (1H, s, CH), 4.03-4.17 (2H, m, $OC\underline{H}_2CH_3$), 7.28 (4H, s, Ar$\underline{H}$).
**$\delta_C$ (100 MHz, $CDCl_3$)** 14.5 ($\underline{C}H_3$), 31.7 ($C(\underline{C}H_3)_3$), 34.9 ($\underline{C}(CH_3)_3$), 43.9 ($N(\underline{C}H_3)_2$), 61.2 ($\underline{C}H_2$), 75.5 ($\underline{C}H$), 125.8 (2 x Ar$\underline{C}$H), 128.7 (2 x Ar$\underline{C}$H), 133.8 (Ar$\underline{C}$), 151.6 (Ar$\underline{C}$), 172.3 ($\underline{C}$=O).
**MS (CI mode)** 264.3 ($M^{+\cdot}$ + H, 99 %), 221.3 (6), 190.2 (14), 97.2 (12), 71.1 (22). **HRMS** $C_{16}H_{26}NO_2$ requires 264.1964 found 264.1965.

**2-Bromo-N-(2-bromophenyl)acetamide 151**



$C_8H_7Br_2NO$
Mol Wt: 292.96

To a mixture of 2-bromoaniline (1.00 ml, 9.2 mmol) in $CH_2Cl_2$ (30 ml) was added $NEt_3$ (1.55 ml, 11.0 mmol). The mixture was cooled to 0 °C and bromoacetyl bromide (0.96 ml, 11.0 mmol) was added dropwise with continuous stirring. The mixture was allowed to warm to room temperature and stirred for 1 week. The reaction mixture was diluted with $Et_2O$ (25 ml) and quenched with saturated aqueous $NH_4Cl$ (10 ml). The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to

give 2-bromo-N-(2-bromophenyl)acetamide **151** as a dark brown solid (2.16 g, 7.42 mmol, 81% yield).

**$\delta_H$ (400 MHz, $CDCl_3$)** 4.01 (2H, s, $C\underline{H}_2$), 6.94 (1H, apparent t, *J* 8.2, Ar$\underline{H}$), 7.19 (1H, apparent t, *J* 8.2, Ar$\underline{H}$), 7.42 (1H, d, *J* 8.2, Ar$\underline{H}$), 8.25 (1H, d, *J* 8.2, Ar$\underline{H}$), 8.73 (1H, bs, N$\underline{H}$).

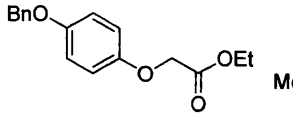
**$\delta_C$ (100 MHz, $CDCl_3$)**, 30.3 ($\underline{C}H_2$),114.3 (Ar$\underline{C}$), 121.9 (Ar$\underline{C}$H), 126.4 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 132.8 (Ar$\underline{C}$H), 135.4 (Ar$\underline{C}$-Br), 163.9 ($\underline{C}$=O).

**MS (EI mode)** 295 ($M^{+\cdot}$, $^{81}Br$ x 2, 4 %), 293 ($M^+$, $^{81}Br$, $^{79}Br$, 6 %), 291 ($M^{+\cdot}$, $^{79}Br$ x 2, 4%), 214 ($^{81}Br$, 24,), 212 ($^{79}Br$, 24), 173 ($^{81}Br$, 19), 171 ($^{79}Br$, 20), 85 ($^{81}Br$, 64), 83 ($^{79}Br$, 98)

**HRMS** $C_8H_8NO^{79}Br_2$ requires 291.8967 found 291.8973.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3225, 3030, 1654 (C=O), 1512, 1420, 1285, 1157, 748, 653, 531.

**4-Benzyloxyphenoxyethylacetate 152** [95]




$C_{17}H_{18}O_4$
Mol. Wt: 286.32

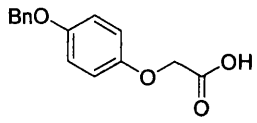
To a solution of 4-benzyloxyphenol (2.00 g, 10.0 mmol), in DMF (50 ml) was added 18-crown-6 (260 mg, 1.00 mmol), ethylbromoacetate (4.43 ml, 40.0 mmol), and $K_2CO_3$ (6.91 g, 50 mmol) and the mixture stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (6 ml), washed with water (15 ml) and extracted with 20 % EtOAc:Pet ether (2 x 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a chalky white solid. The crude product was purified by column chromatography on silica gel using 20 % ethyl acetate: pet ether as eluent to give (4-benzyloxyphenoxy)ethylacetate **152** as a white solid (1.42 g, 4.97 mmol, 43%).

**$\delta_H$ (400 MHz, $CDCl_3$)**, 1.20 (3H, t, *J* 7.1, $C\underline{H}_3$), 4.14 (2H, q, *J* 7.1, $C\underline{H}_2CH_3$), 4.60 (2H, s, $OC\underline{H}_2C$=O), 4.94 (2H, s, $PhC\underline{H}_2O$), 6.77-6.85 (4H, m, Ar$\underline{H}$), 7.23-7.36 (5H, m, ArH).

**$\delta_C$ (100 MHz, $CDCl_3$)** 14.6 ($\underline{C}H_3$), 61.7 ($O\underline{C}H_2CH_3$), 66.7 ($Ph\underline{C}H_2O$), 71.0 ($O\underline{C}H_2C$=O), 116.2 (4 x Ar$\underline{C}$H), 116.3 (Ar$\underline{C}$H), 127.9 (2 x Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 137.5 (Ar$\underline{C}$), 152.6 (Ar$\underline{C}$), 154.1 (Ar$\underline{C}$), 169.6 ($\underline{C}$=O).

**MS (EI mode)** 286.2 ($M^+$,25 %), 213.1 (4), 189.1 (10), 91.1 (98), 83.0 (37), 69.1 (7), 47.0 (6). **HRMS** $C_{17}H_{18}O_4$ requires 286.1205 found 286.1203.

**(4-Benzyloxyphenoxy)acetic acid 153** [95]

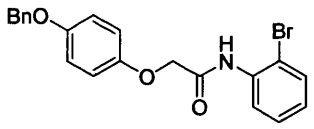



$C_{15}H_{14}O_4$
Mol. Wt: 258.27

LiOH (0.94 g, 22.4 mmol) was added to a solution of (4-benzyloxyphenoxy)ethyl acetate **152** (0.80 g, 2.79 mmol) in THF: $H_2O$ (20 ml: 5 ml) and heated at 40 °C until TLC showed complete hydrolysis. Water (15 ml) was added and the reaction mixture extracted with ethyl acetate (2 x 15 ml). The aqueous layer was separated and acidified with 2M HCl and extracted with ethyl acetate (3 x 15 ml). The organic extracts were combined, washed, dried ($MgSO_4$), filtered and evaporated to give (4-benzyloxyphenoxy)acetic acid **153** as a white solid (0.40 g, 1.55 mmol, 56 %) which was used without further purification.

**$\delta_H$ (400 MHz, $CDCl_3$)** 4.55 (2H, s, $OC\underline{H}_2C{=}O$), 4.95 (2H, s, $PhC\underline{H}_2O$), 6.79-6.86 (4H, m, Ar<u>H</u>), 7.19-7.35 (5H, m, Ar<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 66.2 ($PhC\underline{H}_2O$), 71.0 ($OC\underline{H}_2C{=}O$), 116.3 (Ar<u>C</u>H), 116.4 (2 x Ar<u>C</u>H), 127.8 (2 x Ar<u>C</u>H), 128.4 (2 x Ar<u>C</u>H), 129.9 (2 x Ar<u>C</u>H), 137.4 (Ar<u>C</u>), 152.9 (Ar<u>C</u>), 154.0 (Ar<u>C</u>), 169.7 (<u>C</u>=O).
**MS (EI mode)** 258.2 ($M^+$, 26 %), 91.1 (98), 83.0 (13). **HRMS** $C_{15}H_{14}O_4$ requires 258.0892 found 258.0893.

**2-(4-Benzyloxyphenoxy)-N-(2-bromophenyl)acetamide 154**




$C_{21}H_{18}BrNO_3$
Mol. Wt: 412.28

From 4-benzyloxyphenoxyacetic acid **153** and 2-bromoaniline:-

To a solution of (4-benzyloxy)phenoxyacetic acid **153** (200 mg, 0.76 mmol), 2-bromoaniline (200 mg, 1.14 mmol) and DMAP (10 mg, 0.08 mmol) in $CH_2Cl_2$ (2 ml) at 0 °C was added EDCI (219 mg, 1.14 mmol) in $CH_2Cl_2$ (4 ml). The reaction was stirred at 0 °C for 15 min then stirred at room temperature for 48 h. The reaction mixture was then washed with 1M HCl (2 x 20 ml), brine (2 x 20 ml) and saturated aqueous $NaHCO_3$ (2 x 20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated

*in vacuo* to give the crude product which was recrystallised from pet ether and $CH_2Cl_2$ to give 2-(4-benzyloxyphenoxy)-N-(2-bromophenyl)acetamide **154** as gold coloured crystals (138 mg, 0.34 mmol, 43 %).

From of 4-benzyloxyphenol and 2-bromo-N-(2-bromophenyl)acetamide **151**:-

To a solution of 4-benzyloxyphenol (172 mg, 0.86 mmol) in DMF (30 ml) was added 18-crown-6 (228 mg, 0.09 mmol), 2-bromo-N-(2-bromophenyl)acetamide **151** (1.00 g, 3.44 mmol) and $K_2CO_3$ (594 mg, 4.3 mmol). The reaction mixture was stirred for 24 h and quenched with saturated aqueous $NH_4Cl$ (5 ml) and washed with water (15 ml). The aqueous mixture was extracted with 20 % EtOAc/pet ether (2 x 30 ml) and the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. The crude solid was recrystallised from pet ether and $CH_2Cl_2$ to give 2-(4-benzyloxyphenoxy)-N-(2-bromophenyl)acetamide **154** as gold coloured crystals (49 mg, 0.12 mmol, 14 %).

**M.p.** 138.5-139.5 °C

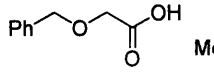
**$\delta_H$ (400 MHz, $CDCl_3$)** 4.52 (2H, s, $OC\underline{H}_2CO$), 4.96 (2H, s, $PhC\underline{H}_2O$), 6.92-6.95 (4H, m, Ar$\underline{H}$), 7.18 (5H, m, Ar$\underline{H}$), 7.46-7.49 (2H, m, Ar$\underline{H}$), 8.36-8.38 (2H, m, Ar$\underline{H}$), 8.98 (1H, bs, N$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 68.8 ($O\underline{C}H_2CO$), 71.0 ($Ph\underline{C}H_2O$), 114.0 (Ar$\underline{C}$), 116.3 (2 x Ar$\underline{C}$H), 116.5 (2 x Ar$\underline{C}$H), 121.9 (Ar$\underline{C}$H), 125.9 (Ar$\underline{C}$H), 127.9 (Ar$\underline{C}$H), 128.4 (2 x Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 129.0 (2 x Ar$\underline{C}$H), 132.8 (Ar$\underline{C}$H), 135.4 (Ar$\underline{C}$), 137.4 (Ar$\underline{C}$), 151.7 (Ar$\underline{C}$), 154.5 (Ar$\underline{C}$), 167.0 ($\underline{C}$=O).

**MS (EI mode)** 413.2 ($M^{+\cdot}$, $^{81}Br$, 25 %), 411.2 ($M^{+\cdot}$, $^{79}Br$, 24 %), 322.1 ($^{81}Br$, 3), 320.1 ($^{79}Br$, 3), 214.0 ($^{81}Br$, 4), 212.0 ($^{79}Br$, 4), 186.0 ($^{81}Br$, 6), 184.0 ($^{79}Br$, 5), 91.1 (99).

**HRMS** $C_{21}H_{18}NO_3{}^{79}Br$ requires 411.0470 found 411.0470.

**Benzyloxy acetic acid 155** [96]




$C_9H_{10}O_3$
Mol. Wt: 166.17

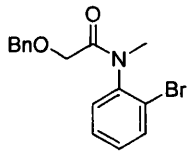
Benzyl alcohol (2.90 ml, 27.7 mmol) was added to a stirred suspension of NaH (1.68 g, 69.4 mmol) in THF at 0 °C (100 ml). After stirring at 0 °C for 30 min, bromoacetic acid (3.85 g, 27.7 mmol) was added and the mixture stirred at 0 °C for a further 15 min, refluxed for 6 h, and stirred overnight with no further heating. The reaction mixture was quenched with methanol (20 ml), concentrated *in vacuo* and partitioned between $Et_2O$

(50 ml) and water (50 ml). The ether layer was washed with water (2 x 50 ml) and the combined aqueous extracts acidified to pH 4 with 2M HCl. The acidified aqueous extracts were extracted with $CH_2Cl_2$, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product benzyloxy acetic acid **155** as an orange oil (3.35 g, 20.2 mmol, 73 %) which was used without further purification.

**$\delta_H$ (400 MHz, $CDCl_3$)** 4.08 (2H, s, $OC\underline{H}_2C=O$), 4.62 (2H, s, $PhC\underline{H}_2$), 7.23-7.32 (5H, m, Ar<u>H</u>), 10.59 (1H, bs, O<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 67.0 ($Ph\underline{C}H_2$), 73.9 ($C\underline{H}_2C=O$), 128.5 (2 x Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 129.0 (2 x Ar<u>C</u>H), 136.9 (Ar<u>C</u>),175.1 (<u>C</u>=O).
**MS (EI mode)** 166.1 ($M^{+\cdot}$ 31 %), 107.1 (97), 91.1 (100), 79.1 (53), 65.1 (36), 60.1 (29), 51.0 (14).

**2-Bromo-N-methyl aniline 156** see general procedure B [61]

**2-Benzyloxy-N-(2-bromophenyl)-N-methylacetamide 158**




$C_{16}H_{16}BrNO_2$
Mol. Wt: 334.21

From reaction of benzyloxyacetic acid **155** and 2-bromo-N-methylaniline **156** *via* the acid chloride **157**.

Oxalyl chloride (0.32 ml, 3.60 mmol) was added to a solution of benzyloxyacetic acid **155** (230 mg, 1.20 mmol) in $CH_2Cl_2$ (5 ml). The reaction mixture was stirred at room temperature for 3 h. Concentration of the reaction mixture *in vacuo* gave benzyloxyethanoylchloride **157** as a brown oil (246 mg, 1.33 mmol, 96 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 4.40 (2H, s, $PhCH_2$), 4.60 (2H, s, $C\underline{H}_2C=O$), 7.24-7.33 (5H, m, Ar<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 74.0 ($Ph\underline{C}H_2$) 75.2 ($\underline{C}H_2C=O$), 128.5 (2 x Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 129.1 (2 x Ar<u>C</u>H), 136.4 (Ar<u>C</u>), 172.3 (<u>C</u>=O).

To a solution of 2-bromo-N-methyl aniline **156** (195 mg, 1.05 mmol) and $NEt_3$ (0.22 ml, 1.57 mmol) in $CH_2Cl_2$ (3 ml) at 0 °C was added benzyloxyethanoyl chloride **157** (232 mg, 1.26 mmol) in $CH_2Cl_2$ (3 ml). The reaction was allowed to warm to room

temperature and stirred overnight. The reaction mixture was diluted with $Et_2O$ (15 ml) and quenched by addition of saturated aqueous $NH_4Cl$ (7 ml). The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 75 % $CH_2Cl_2$: pet ether gave 2-benzyloxy-N-(2-bromophenyl)-N-methylacetamide **158** as a yellow oil (116 mg, 0.35 mmol, 33 %).

From benzyloxyacetic acid **155** and 2-bromo-N-methyl aniline **156** with EDCI

To a solution of benzyloxyacetic acid **155** (100 mg, 0.60 mmol), 2-bromo-N-methylaniline **156** (112 mg, 0.60 mmol) and DMAP (7.4 mg, 0.06 mmol) in $CH_2Cl_2$ (2 ml) at 0 °C was added EDCI (173 mg, 0.90 mmol) in $CH_2Cl_2$ (4.5 ml). The reaction was stirred at 0 °C for 15 min then stirred at room temperature for 48 h. TLC after this time indicated very little reaction and a further portion of 2-bromo-N-methyl aniline **156** (66.0 mg, 0.30 mmol) was added. TLC after 60 h showed little product formation and a further portion of EDCI (173 mg, 0.90 mmol) was added. The reaction was stirred for 2 weeks. The reaction mixture was washed with 1M HCl (3 x 10 ml), brine (20 ml) and saturated aqueous $NaHCO_3$ (3 x 10 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2-benzyloxy-N-(2-bromophenyl)-N-methylacetamide **158** as a yellow oil (67 mg, 0.20 mmol, 27 %) which was used without further purification.

From benzyloxyacetic acid **155** and 2-bromo-N-methyl aniline **156** with BOP-Cl

BOP-Cl (140 mg, 0.55 mmol) was added to a stirred solution of benzyloxyacetic acid **155** (45.6 mg, 0.27 mmol), 2-bromo-N-methyl aniline **156** (168 mg, 0.90 mmol) and $NEt_3$ (0.23 ml, 1.65 mmol) in $CH_2Cl_2$ (5 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature for 4 days. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (2 x 5 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash chromatography on silica gel eluting with 5 % EtOAc/ pet ether gave 2-Benzyloxy-N-(2-bromophenyl)-N-methylacetamide **158** (67 mg, 0.20 mmol, 72 %) as a pale yellow oil.

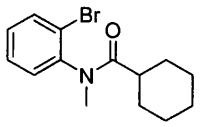
**$\delta_H$ (400 MHz, $CDCl_3$)** 3.16 (3H, s, $NC\underline{H}_3$), 3.69 (1H, d, AB system, *J* 14.9, 1H of $OC\underline{H}_2CO$), 3.77 (1H, d, AB system, *J* 14.9, 1H of $OC\underline{H}_2CO$), 4.44 (1H, d, AB system, *J* 11.8, 1H of $PhC\underline{H}_2O$), 4.52 (1H, d, AB system, *J* 11.8, 1H of $PhC\underline{H}_2O$), 7.15-7.30 (8H, m, Ar$\underline{H}$), 7.59-8.00 (1H, m, Ar$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 36.3 (N<u>C</u>$H_3$), 68.5 (O<u>C</u>$H_2$CO), 73.6 (Ph<u>C</u>$H_2$O), 123.6 (Ar<u>C</u>), 128.1 (Ar<u>C</u>H), 128.4 (2 x Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 130.2 (Ar<u>C</u>H), 130.5 (Ar<u>C</u>H), 134.1 (Ar<u>C</u>H), 134.4 (Ar<u>C</u>H), 137.9 (Ar<u>C</u>), 141.5 (Ar<u>C</u>), 169.5 (<u>C</u>=O).

**MS (CI mode)** 336.2 ($M^{+\cdot}$ + H, $^{81}Br$, 100 %), 334.2 ($M^{+\cdot}$ + H, $^{79}Br$, 99 %), 292.1 ($^{81}Br$, 4), 290.1 ($^{79}Br$, 4), 148.1 (7), 911 (8), 57.1 (99). **HRMS** $C_{16}H_{17}NO_2{}^{79}Br$ requires 334.0443 found 334.0438.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2873, 1676 (C=O), 1583, 1475, 1390, 1331, 1292, 1113, 1053, 1026, 949, 766.

**Cyclohexanecarboxylic acid (2-bromophenyl)methylamide 159** [57]




$C_{14}H_{18}BrNO$
Mol. Wt: 296.2

Cyclohexane carbonyl chloride (0.70 ml, 5.20 mmol) was added dropwise to a stirred solution of 2-bromo-N-methylaniline **156** (0.803 g, 4.30 mmol) and $NEt_3$ (0.91 ml, 6.40 mmol) in $CH_2Cl_2$ (25 ml) and stirred overnight at room temperature. The reaction mixture was diluted with $Et_2O$ and quenched with saturated aqueous $NH_4Cl$ (20 ml). The organic layer was washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. The crude solid was recrystallised from pet ether: $CH_2Cl_2$ to give cyclohexanecarboxylic acid (2-bromophenyl)methylamide **159** as white crystals (0.871 g, 2.94 mmol, 68 %).

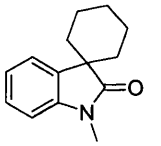
**M.p.** 96-98 °C.

**$\delta_H$ (400 MHz, $CDCl_3$)** 0.85-0.98 (2H, m, $CH_2$), 1.06-1.15 (2H, m, C<u>H</u>$_2$), 1.36-1.71 (6H, m, 3 x C<u>H</u>$_2$), 1.82-1.88 (1H, m, C<u>H</u>C=O), 3.10 (3H, s, C<u>H</u>$_3$), 7.15-7.20 (2H, m, Ar<u>H</u>), 7.31 (1H, m, Ar<u>H</u>), 7.62 (1H, d, *J* 8.4, Ar<u>H</u>).

**$\delta_C$ (100 MHz, $CDCl_3$)** 25.8 (<u>C</u>$H_2$), 25.9 (<u>C</u>$H_2$), 26.0 (<u>C</u>$H_2$), 29.4 (<u>C</u>$H_2$), 30.2 (<u>C</u>$H_2$), 36.2 (<u>C</u>$H_3$), 42.4 (<u>C</u>HC=O), 124.0 (Ar<u>C</u>-N), 129.2 (Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 130.9 (Ar<u>C</u>H), 134.3 (Ar<u>C</u>H), 143.4 (Ar<u>C</u>-Br), 176.7 (<u>C</u>=O).

**MS (CI mode)** 298.2 ($M^{+\cdot}$ + H, $^{81}Br$, 28 %), 296.2 ($M^{+\cdot}$ + H, $^{79}Br$, 30 %), 216.2 (11), 57.1 (99). **HRMS** $C_{14}H_{19}NO^{79}Br$ requires 296.0650 found 296.0648.

**1-Methyl-3-spirocyclohexyloxindole 160** [57]

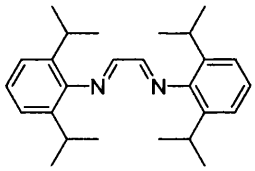


$C_{14}H_{17}NO$
Mol. Wt: 215.29

$Pd(OAc)_2$ (1.9 mg, 0.01 mmol), SIPr-$BF_4$ **162** (4.1 mg, 0.01 mmol) and NaO*t*-Bu (24.9 mg, 0.26 mmol) were combined together in a round-bottomed flask. 1,4-Dioxane (3.1 ml) was added and the resulting mixture allowed to stir for 1 min before addition of cyclohexanecarboxylic acid (2-bromophenyl)methylamide **159** (50.3 mg, 0.17 mmol). The flask was heated in an oil bath at 50 °C and stirred for 3.5 h. The reaction mixture was poured into saturated aqueous $NH_4Cl$ (10 ml) and extracted in turn with $Et_2O$ (3 x 10 ml), $CH_2Cl_2$ (15 ml) and EtOAc (10 ml). The organic extracts were dried, filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 15 % EtOAc: pet ether, gave 1-methyl-3-spirocyclohexyloxindole **160** as a pale yellow oil (21 mg, 0.10 mmol, 58 %) and recovered starting material **159** (18 mg, 0.06 mmol).

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.46 (10H, m, 5 x $C\underline{H}_2$), 3.13 (3H, s, $NC\underline{H}_3$), 6.77 (1H, d, *J* 7.7, Ar<u>H</u>), 6.98 (1H, app t, *J* 7.7, Ar<u>H</u>), 7.21 (1H, app t, *J* 7.7, Ar<u>H</u>), 7.38 (1H, d, *J* 7.7, Ar<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 21.6 (2 x $\underline{C}H_2$), 25.6 ($\underline{C}H_2$), 26.5 ($N\underline{C}H_3$), 33.4 (2 x $\underline{C}H_2$), 47.9 (<u>C</u>), 108.2 (Ar<u>C</u>H), 122.3 (Ar<u>C</u>H), 124.2 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 135.8 (Ar<u>C</u>), 143.2 (Ar<u>C</u>), 181.1 (<u>C</u>=O).
**MS (EI mode)** 215.3 ($M^{+\cdot}$, 55 %), 160.2 (99), 159.2 (19), 147.2 (14), 85.0 (52), 83.0(87), 47.0 (16). **HRMS** $C_{14}H_{17}NO$ requires 215.1310 found 215.1311.

**Glyoxal-bis-(2,6-diisopropylphenyl)imine 164** [68]



$C_{26}H_{36}N_2$
Mol. Wt: 376.58

To a solution of 2,6-di*iso*propylaniline **163** (15.8 ml, 84 mmol) in *n*-propanol (60 ml) were added glyoxal (4.80 ml of a 40 % w/w aqueous solution, 42 mmol), *n*-propanol (6 ml) and distilled water (15 ml) and the reaction mixture stirred at 70 °C for 2 h. The reaction mixture was cooled to room temperature and the resulting solid filtered and

washed with a small amount of methanol to give glyoxal-bis-(2,6-di*iso*propylphenyl)imine **164** as bright yellow needles (11.0 g, 29.2 mmol, 70 %).

**M.p.** 92.5 - 94.5 °C

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.12 (24H, d, *J* 6.9, 8 x $C\underline{H}_3$), 2.87 (4H, sept, *J* 6.9, 4 x C<u>H</u>), 7.09 (6H, m, 6 x Ar<u>H</u>), 8.03 (2H, s, 2 x N=C<u>H</u>).

**$\delta_C$ (100 MHz, $CDCl_3$)** 23.8 (8 x $\underline{C}H_3$), 28.4 (2 x <u>C</u>H), 123.6 (2 x Ar<u>C</u>H), 125.5 (4 x Ar<u>C</u>H), 137.1 (2 x Ar<u>C</u>), 138.5 (2 x Ar<u>C</u>), 148.4 (2 x Ar<u>C</u>), 163.5 (2 x N=<u>C</u>H).

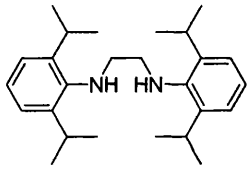
**MS (FAB mode)** 377.3 ($M^{+\cdot}$ + H, 35 %), 333.2 (98), 188.1 (26), 146.0 (24), 73.7 (28).

**HRMS** $C_{26}H_{37}N_2$ requires 377.2957 found 377.2953.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3062, 2960, 2864, 2359, 1623 (C=N), 1589, 1464, 1435, 1383, 1362, 1329, 1290, 1254, 1175.

**Anal.** calculated $C_{26}H_{36}N_2$: C 82.93; H, 9.64; N, 7.44 %. Found: C, 82.93; H, 9.68; N, 7.41 %.

**N,N-Bis (2,6-di*iso*propyl-phenyl)-ethane-1,2-diamine 165** [68]




$C_{26}H_{40}N_2$
Mol. Wt: 380.61

Glyoxal-bis-(2,6-di*iso*propylphenyl)imine **164** (11.0 g, 29.2 mmol) was added to a stirred suspension of $NaBH_4$ (10.9 g, 29.2 mmol) in MeOH:THF (72 ml:108 ml) at 0 °C and the reaction mixture stirred at room temperature until the suspension turned white, indicating complete reduction. The reaction was quenched with saturated aqueous $NH_4Cl$ (90 ml) and extracted with ether (3 x 100 ml). The combined organic extracts were washed with water (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give N,N-bis (2,6-di*iso*propyl-phenyl)-ethane-1,2-diamine **165** as a white, crystalline solid (10.8 g, 28.5 mmol, 97 % yield).

**M.p** 94–96 °C.

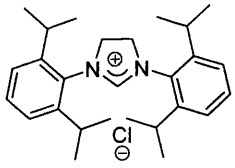
**$\delta_H$ (400 MHz, $CDCl_3$)** 1.18 (24H, d, *J* 6.9, 8 x $C\underline{H}_3$), 3.09 (4H, s, 2 x $C\underline{H}_2N$), 3.28 (4H, sept, *J* 6.9, 4 x C<u>H</u>), 7.02 (6H, m, 6 x ArC<u>H</u>).

**$\delta_C$ (100 MHz, $CDCl_3$)** 24.6 (4 x $\underline{C}H_3$), 28.1 (4 x $\underline{C}H_3$), 52.7 (2 x $\underline{C}H_2N$), 124.0 (4 x Ar<u>C</u>H), 124.2 (2 x Ar<u>C</u>H), 142.9 (2 x Ar<u>C</u>), 143.7 (4 x Ar<u>C</u>).

**MS (EI mode)** 380.4 ($M^+$, 15 %), 190.2 (97), 160.2 (23). **HRMS** $C_{26}H_{40}N_2$ requires 380.3191 found 380.3191.

**Anal.** calculated $C_{26}H_{40}N_2$: C 82.05; H, 10.59; N, 7.36 %. Found: C, 81.87; H, 10.70; N, 7.47 %.

**1,3-Bis(2,6-di*iso*propylphenyl)imidazolinium chloride (SIPr-Cl) 161** [68]



$C_{27}H_{39}ClN_2$
Mol. Wt: 427.06

A mixture of N,N-bis (2,6-di*iso*propyl-phenyl)-ethane-1,2-diamine **165** (1.50 g, 5.07 mmol), $NH_4Cl$ (0.30 g, 5.59 mmol) and triethylorthoformate (210 ml, 12.7 mmol) were stirred together at 110 °C until the reaction mixture solidified. The reaction mixture was then cooled to room temperature before isolation of the crude product by filtration. The solid was dissolved in a minimum amount of $CH_2Cl_2$ and re-precipitated with $Et_2O$ to give 1,3-bis(2,6-di*iso*propylphenyl)imidazolinium chloride **161** as a white, crystalline solid (1.06 g, 2.48 mmol, 62 %).

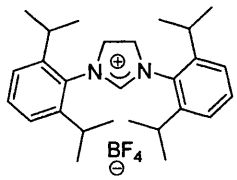
**M.p.** 214-215 °C

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.19 (12H, d, *J* 6.8, 4 x C$\underline{H}_3$), 1.33 (12H, d, *J* 6.8, 4 x C$\underline{H}_3$), 2.96 (4H, sept, *J* 6.8, 4 x C$\underline{H}$), 4.82 (4H, s, 2 x C$\underline{H}_2$), 7.21 (4H, d, *J* 7.8, 4 x Ar$\underline{H}$), 7.41 (2H, t, *J* 7.8, 2 x Ar$\underline{H}$), 8.28 (1H, s, NC$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 24.1 (4 x $\underline{C}H_3$), 25.8 (4 x $\underline{C}H_3$), 29.6 ($\underline{C}$H), 55.9 (2 x $\underline{C}H_2$), 125.4 (2 x Ar$\underline{C}$H), 129.6 (2 x Ar$\underline{C}$), 132.0 (2 x Ar$\underline{C}$H), 146.5 (6 x Ar$\underline{C}$), 158.4 (N$\underline{C}$H).

**MS (FAB mode)** 391.3 ($M^+$-Cl, 100 %). **HRMS** $C_{27}H_{39}N_2$ requires 391.3113 found 391.3108.

**1,3-Bis(2,6-di*iso*propylphenyl)imidazolinium tetrafluoroborate (SIPr-$BF_4$) 162** [68]



$C_{27}H_{39}BF_4N_2$
Mol. Wt: 478.42

A mixture of diamine **165** (0.15 g, 0.39 mmol), $NH_4BF_4$ (0.05 g, 0.43 mmol) and triethylorthoformate (0.32 ml, 1.97 mmol) were stirred together at 110 °C until the reaction mixture solidified. The mixture was then cooled to room temperature before isolation of the crude product by filtration. The solid was dissolved in a minimum

amount of $CH_2Cl_2$ and re-precipitated with $Et_2O$ to give the product 1,3-bis(2,6-di*iso*propylphenyl)imidazolinium tetrafluoroborate **162** as a white, crystalline solid (0.039 g, 0.01 mmol, 21 % yield).

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

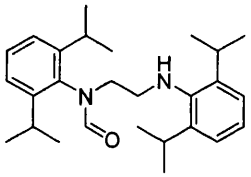
**M.p.** >285 °C

**$\delta_H$ (400 MHz, DMSO)** 1.19 (12H, d, *J* 6.8, 4 x C$\underline{H}_3$), 1.35 (12H, d, *J* 6.8, 4 x C$\underline{H}_3$), 3.09 (4H, sept, *J* 6.8, 4 x C$\underline{H}$), 4.53 (4H, s, C$\underline{H}_2$), 7.42 (4H, d, *J* 7.8, 4 x ArC$\underline{H}$), 7.54 (2H, app t, *J* 7.8, 2 x ArC$\underline{H}$), 9.53 (1H, s, NC$\underline{H}$).

**$\delta_C$ (100 MHz)** 23.7 (4 x $\underline{C}H_3$), 25.3 (4 x $\underline{C}H_3$), 28.6 (2 x $\underline{C}$H), 54.0 (2 x $\underline{C}H_2$), 125.2 (3 x Ar$\underline{C}$H), 130.2 (3 x Ar$\underline{C}$), 131.4 (3 x Ar$\underline{C}$H), 146.5 (3 x Ar$\underline{C}$), 161.1 (N$\underline{C}$H).

**MS (FAB mode)** 391.3 ($M^{+\cdot}$-$BF_4$, 100 %). **HRMS** $C_{27}H_{39}N_2$ requires 391.3113 found 391.3108.

**N-(2,6-Di*iso*propylphenyl)-N-[2-(2,6-di*iso*propylphenylamino)-ethyl]formamide 164**




$C_{27}H_{40}N_2O$
Mol. Wt: 408.62

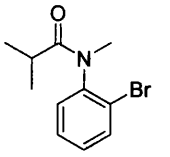
To a suspension of potassium hydride (0.29 g, 7.23 mmol) in THF (10 ml) at room temperature were added a suspension of 1,4-bis(2,6-di*iso*propylphenyl)imidazolinium chloride **161** (782 mg, 1.77 mmol) and a single crystal of 18-crown-6 in THF (21 ml) and the reaction stirred at room temperature for 5 h. The inorganic salts were filtered from the mixture and the filtrate evaporated to give the crude product, which was recrystallised from THF: hexane (1:1) to give N-(2,6-di*iso*propylphenyl)-N-[2-(2,6-di*iso*propylphenylamino)-ethyl]formamide **164** as a white, crystalline solid (197 mg, 0.48 mmol, 27 %).

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

**$\delta_H$ (400 MHz, benzene-$d_6$)** 0.94 (6H, d, *J* 6.9, 2 x C$\underline{H}_3$), 1.08 (6H, d, *J* 6.9, 2 x C$\underline{H}_3$), 1.22 (12H, d, *J* 6.9, 4 x C$\underline{H}_3$), 3.05 (2H, sept, *J* 6.9, 2 x C$\underline{H}$), 3.17 (2H, t, *J* 6.9, C$\underline{H}_2$), 3.37 (2H, sept, *J* 6.9, 2 x C$\underline{H}$), 3.85 (2H, t, *J* 6.9, C$\underline{H}_2$), 6.94 (2H, d, *J* 7.7, 2 x ArC$\underline{H}$), 7.04-7.11 (4H, m, 4 x ArC$\underline{H}$), 8.23 (1H, s, $\underline{H}$C=O).

**$\delta_C$ (100 MHz, benzene-$d_6$)** 23.9 (<u>C</u>$H_3$), 24.6 (2 x <u>C</u>H), 25.8 (<u>C</u>$H_3$), 28.1 (<u>C</u>$H_3$), 28.7 (<u>C</u>$H_3$), 49.1 (<u>C</u>$H_2$), 49.2 (<u>C</u>$H_2$), 123.9 (2 x Ar<u>C</u>H), 124.0 (Ar<u>C</u>H), 124.1 (2 x Ar<u>C</u>H), 124.9 (Ar<u>C</u>H), 142.6 (2 x Ar<u>C</u>), 142.9 (2 x Ar<u>C</u>), 148.0 (2 x Ar<u>C</u>), 164.3 (<u>C</u>=O).
**MS (EI mode)** 408.6 ($M^{+\cdot}$, 25 %), 190.3 (98), 188.3 (34), 160.2 (25), 132.2 (14). **HRMS** $C_{27}H_{40}NO_2$ requires 408.3141 found 408.3141.

**Isobutylcarboxylic acid (2-bromophenyl)methylamide 165** [57]

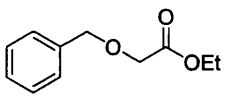



$C_{11}H_{14}BrNO$
Mol. Wt: 256.14

2-Bromo-N-methyl aniline **156** (2.73 g, 14.7 mmol) in $CH_2Cl_2$ (20 ml) was added dropwise to a solution of isobutyryl chloride (1.85 ml, 17.6 mmol) and $NEt_3$ (3.1 ml, 22.0 mmol) in $CH_2Cl_2$ (25 ml) at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with $Et_2O$ (50 ml) and the reaction quenched by addition of saturated aqueous $NH_4Cl$. The organic phase was dried ($MgSO_4$), filtered and concentrated to give the crude product. Recrystallisation from hot pet ether gave isobutylcarboxylic acid (2-bromophenyl)methylamide **165** as colourless needles (2.94 g, 11.5 mmol, 78 %).

**M.p.** 79.5-80.5 °C
**$\delta_H$ (400 MHz, $CDCl_3$)** 0.84 (3H, d, *J* 6.9, C<u>H</u>$_3$), 0.91 (3H, d, *J* 6.9, C<u>H</u>$_3$), 2.19 (1H, sept, *J* 6.9, C<u>H</u>), 3.12 (3H, s, NC<u>H</u>$_3$), 7.15-7.22 (2H, m, Ar<u>H</u>), 7.32 (1H, app t, *J* 7.6, Ar<u>H</u>), 7.62 (1H, d, *J* 8.0, Ar<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 19.8 (<u>C</u>$H_3$), 20.3 (<u>C</u>$H_3$), 32.0 (<u>C</u>H), 36.3 (N<u>C</u>$H_3$), 124.0 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>H), 134.3 (Ar<u>C</u>H), 143.0 (Ar<u>C</u>), 178.2 (<u>C</u>=O).
**MS (CI mode)** 258.07 ($M^{+\cdot}$ + H, $^{81}$Br, 97 %), 256.07 ($M^{+\cdot}$ + H, $^{79}$Br, 99 %), 176.14 (41).
**HRMS** $C_{11}H_{15}NO^{79}Br$ requires 256.0337 found 256.0331.
**Anal.** calculated $C_{11}H_{14}NOBr$: C 51.59; H, 5.47, N, 5.47, Br 32.65 %. Found: C, 51.33; H, 5.42; N, 5.41, Br 32.52 %.

**Benzyloxyethyl acetate 168**

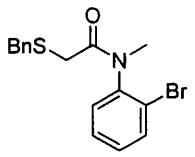



$C_{11}H_{14}O_3$
Mol. Wt: 194.23

Using a Dean-Stark apparatus, benzyloxy acetic acid **155** (4.75 g, 38.6 mmol) was dissolved in toluene (45 ml) and EtOH (20 ml) and concentrated aqueous $H_2SO_4$ (0.15 g, 3 % w/w) added. The reaction mixture was heated under reflux for 48 h and then washed with $H_2O$ (2 x 50 ml). $Et_2O$ was added and the organic phase separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give benzyloxyethyl acetate **168** as a pale yellow liquid (5.06 g, 26.1 mmol, 91 % yield) which was used without further purification.

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.31 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 4.11 (2H, s, $C\underline{H}_2$), 4.26 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 4.66 (2H, s, $PhC\underline{H}_2$), 7.28-7.41 (5H, m, Ar<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 14.6 ($\underline{C}H_3$), 61.3 ($O\underline{C}H_2Me$), 67.6 ($\underline{C}H_2$), 73.7 ($Ph\underline{C}H_2$), 128.4 (Ar<u>C</u>H), 128.5 (2 x Ar<u>C</u>H), 128.9 (2 x Ar<u>C</u>H), 137.5 (Ar<u>C</u>), 170.8 (<u>C</u>=O).
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2073, 2031, 1959, 1751 (C=O), 1201, 1130.

**2-(Benzylsulfanyl)-N-(2-bromophenyl)-N-methylacetamide 175**




$C_{16}H_{16}BrNOS$
Mol. Wt: 350.27

Benzyl thiol (0.24 ml, 2.02 mmol) was added to a solution of 2-bromo-N-(2-bromophenyl)-N-methylacetamide **210** (620 mg, 2.02 mmol) and $NEt_3$ (0.71 ml, 5.05 mmol) in DMF (20 ml) and the reaction stirred at room temperature overnight. The reaction mixture was diluted with 40 % EtOAc/ pet ether (20 ml) and washed with $H_2O$ (3 x 50 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product 2-(benzylsulfanyl)-N-(2-bromophenyl)-N-methylacetamide **175** as a pale yellow oil which solidified on standing (571 mg, 1.63 mmol, 81 %) and was used without further purification. A portion of the solid was recrystallised from $CH_2Cl_2$/Pet ether to give pale yellow crystals.

**M.p.** 42-43.5 °C
**$\delta_H$ (400 MHz, $CDCl_3$)** 2.70 (1H, d, AB system, *J* 14.6, 1H of $SCH_2CO$), 2.82 (1H, d, AB system, *J* 14.6, 1H of $SCH_2CO$), 3.15 (3H, s, $NC\underline{H}_3$), 3.77 (1H, d, AB system, *J* 13.3, 1H of $PhC\underline{H}_2S$), 3.81 (1H, d, AB system, *J* 13.3, 1H of $PhC\underline{H}_2S$), 7.12-7.30 (8H, m, Ar<u>H</u>), 7.56 (1H, d, *J* 9.3, Ar<u>H</u>).

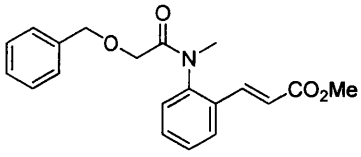
**$\delta_C$ (100 MHz, $CDCl_3$)** 32.3 (Ph$\underline{C}H_2$S), 36.6 (S$\underline{C}H_2$CO) 36.7 (N$\underline{C}H_3$), 123.7 (Ar$\underline{C}$), 127.4 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 129.1 (2 x Ar$\underline{C}$H), 129.6 (2 x Ar$\underline{C}$H), 130.3 (Ar$\underline{C}$H), 130.6 (Ar$\underline{C}$H), 134.2 (Ar$\underline{C}$H), 138.0 (Ar$\underline{C}$), 142.5 (Ar$\underline{C}$), 169.8 ($\underline{C}$=O).

**MS (EI mode)** 351.1 (M+, 3 %), 270.2 (15), 227.0 (18), 148.1 (73), 83.0 (99), **HRMS** $BrC_{16}H_{16}NOS$ requires 351.0116 found 351.0117.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2360, 1660 (C=O), 1583, 1527, 1477, 1369, 1307, 1264.

**Anal.** calculated $^{79}BrC_{16}H_{16}NOS$: C 54.86; H, 4.60; Br, 22.81; N, 4.00; S, 9.15%. Found: C, 55.05; H, 4.56; Br, 22.67; N, 4.05; S, 9.37.

***(E)*-Methyl-3-(2-(2-benzyloxy)-N-methylacetamido)phenyl acrylate 186**




$C_{20}H_{21}NO_4$
Mol. Wt: 339.39

2-Benzyloxy-N-(2-bromophenyl)-N-methylacetamide **157** (86.5 mg, 0.259 mmol) was weighed into a round-bottomed flask and dried under high vacuum. The flask was then flushed with argon and P(*o*-tol)$_3$ (24 mg, 0.08 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), $NEt_3$ (40 μl, 0.285 mmol), methyl acrylate (26 μl, 0.285 mmol) and anhydrous *o*-xylene (1 ml) were added and the flask sealed with a rubber septum. The flask was placed in an oil bath at 100 °C and stirred overnight. A further portion of $Pd(OAc)_2$ (18 mg, 0.08 mmol) and P(*o*-tol)$_3$ (24 mg, 0.08 mmol) was added and the reaction stirred at 100 °C for a further 2 hours. The reaction mixture was then cooled and quenched by dropwise addition of $H_2O$. The mixture was extracted with $Et_2O$ (3 x 15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel gave recovered starting material **157** (31.4 mg, 0.09 mmol, 36 % recovery) and *(E)*-methyl-3-(2-(2-benzyloxy)-N-methylacetamido)phenyl acrylate **186** as an orange oil (46.5 mg, 0.14 mmol, 83 % based upon 64 % conversion).

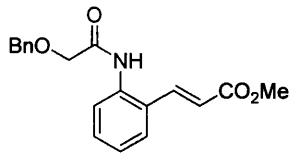
**$\delta_H$ (400 MHz, $CDCl_3$)** 3.18 (3H, s, N$\underline{C}H_3$), 3.60 (1H, d, *J* 14.7, 1H of O$\underline{C}H_2$CO), 3.73 (1H, d, *J* 14.7, 1H of O$\underline{C}H_2$CO), 3.74 (3H, s, $\underline{C}H_3$), 4.42 - 4.47 (2H, m, Ph$\underline{C}H_2$O), 6.34 (1H, d *J* 16.0, =C$\underline{H}$), 7.01-7.36 (9H, m, Ar$\underline{H}$), 7.55 (1H, d, *J* 16.0, =C$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 37.6 (N$\underline{C}H_3$), 52.3 ($\underline{C}H_3$), 68.5 (Ph$\underline{C}H_2$S), 73.6 (O$\underline{C}H_2$CO), 121.7 (=$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$), 129.1 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 129.6 (Ar$\underline{C}$H), 130.2 (Ar$\underline{C}$H), 130.5 (Ar$\underline{C}$H), 132.0 (Ar$\underline{C}$H), 132.4 (Ar$\underline{C}$H), 133.3 (Ar$\underline{C}$H), 137.7 (Ar$\underline{C}$), 138.7 (=$\underline{C}$H), 141.8 (Ar$\underline{C}$), 166.9 ($\underline{C}$=O), 169.7 ($\underline{C}$=O).

**MS (CI mode)** 340.2 ($M^{+\cdot}$ +H, 99 %), 107.1 (72), 85.1 (22), 71.1 (32). **HRMS** $C_{20}H_{22}NO_4$ requires 340.1549 found 340.1550.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2947, 1714 (C=O, ester), 1672 (C=O, amide), 1597, 1487, 1433, 1390, 1319, 1272, 1196, 1173, 1117, 1088, 1028, 982, 862.

### *(E)*-Methyl-3-(2-(2-benzyloxy)acetamido)phenyl acrylate 187




$C_{19}H_{19}NO_4$
Mol. Wt: 325.36

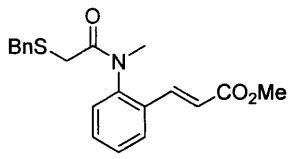
2-Benzyloxy-N-(2-bromophenyl)-N-acetamide (85.1 mg, 0.266 mmol) was weighed into a round-bottomed flask and dried under high vacuum. The flask was then flushed with argon and P(*o*-tol)$_3$ (24.3 mg, 0.08 mmol), Pd(OAc)$_2$ (17.9 mg, 0.08 mmol), $NEt_3$ (0.04 ml, 0.292 mmol), methyl acrylate (0.03 ml, 0.292 mmol) and anhydrous *o*-xylene (1.5 ml) were added and the flask sealed with a rubber septum. The reaction was heated in an oil bath at 100 °C and stirred overnight. The reaction mixture was then cooled and quenched by dropwise addition of $H_2O$. The mixture was extracted with $Et_2O$ (3 x 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel gave recovered starting material (38.0 mg, 0.12 mmol, 45 % recovery) and pure product *(E)*-methyl-3-(2-(2-benzyloxy)acetamido)phenyl acrylate **187** (38.8 mg, 0.12 mmol, 82 % based upon 55 % conversion).

**$\delta_H$ (400 MHz, $CDCl_3$)** 3.72 (3H, s, $CO_2\underline{C}H_3$), 4.08 (2H, s, $O\underline{C}H_2CO$), 4.56 (2H, s, $Ph\underline{C}H_2O$), 5.99 (1H, d *J* 15.9, $=\underline{C}HCO_2Me$), 7.07-7.15 (1H, m, Ar$\underline{H}$), 7.25-7.34 (6H, m, Ar$\underline{H}$), 7.47 (1H, app d, *J* 7.8, Ar$\underline{H}$), 7.75 (1H, d, *J* 15.9, PhC$\underline{H}$=), 7.83 (1H, app d, *J* 8.2, Ar$\underline{H}$), 8.42 (1H, bs, N$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 52.2 ($\underline{C}H_3$), 70.0 ($O\underline{C}H_2CO$), 74.1 ($Ph\underline{C}H_2O$), 121.2 ($=\underline{C}HCO_2Me$), 124.4 (Ar$\underline{C}$H), 126.1 (Ar$\underline{C}$H), 126.1 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$), 128.0 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 131.3 (Ar$\underline{C}$H), 135.5 (Ar$\underline{C}$), 136.9 (Ar$\underline{C}$), 139.7 (Ph$\underline{C}$H=), 167.2 ($\underline{C}$=O), 168.3 ($\underline{C}$=O).

**MS (EI mode)** 325.2 ($M^{+\cdot}$, 6 %), 219.1 (13), 160.1 (27), 91.1 (64), 85.0 (65), 83.0 (99), 63.0 (14), 47.0 (20). **HRMS** $C_{19}H_{19}NO_4$ requires 325.1314 found 325.1313.

**(*E*)-Methyl-3-(2-(2-benzylsulfanyl)-N-methylacetamido)phenyl acrylate 188**

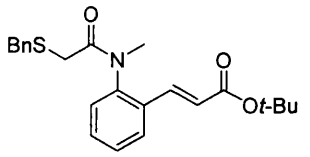



$C_{20}H_{21}NO_3S$
Mol. Wt.: 355.45

2-(Benzylsulfanyl)-N-(2-bromophenyl)-N-methylacetamide **175** (460 mg, 1.31 mmol) was weighed into a one-piece condenser flask and the flask flushed with argon. $Pd(OAc)_2$ (89 mg, 0.39 mmol), P(*o*-tol)$_3$ (120 mg, 0.394 mmol), $NEt_3$ (0.20 ml, 1.45 mmol) and methyl acrylate (0.60 ml, 6.57 mmol) were added to the flask followed by degassed *o*-xylene (5 ml) and the flask placed in an oil bath at 100 °C and stirred for 45 h. The reaction was quenched by addition of water (5 ml) and extracted with $Et_2O$ (3 x 10 ml). The combined ethereal extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Purification by flash chromatography on silica gel eluting with 30 % ethyl acetate/ petroleum ether gave starting material **175** (92 mg, 0.26 mmol, 20 %) and *(E)*-Methyl-3-(2-(2-benzylsulfanyl)-N-methylacetamido)phenyl acrylate **188** (356 mg, 1.00 mmol, 96 % based on 80 % conversion).

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.70 (1H, d, *J* 14.4, 1H of C$\underline{H}_2$), 2.75 (1H, d, *J* 14.4, 1H of C$\underline{H}_2$), 3.22 (3H, s, NC$\underline{H}_3$), 3.75 (3H, s, C$\underline{H}_3$), 3.70-3.82 (2H, m, PhC$\underline{H}_2$), 6.35 (1H, d, *J* 16.0, =C$\underline{H}$CO), 7.09-7.23 (5H, m, Ar$\underline{H}$), 7.25-7.37 (4H, m, Ar$\underline{H}$), 7.68 (1H, d, *J* 16.0, PhC$\underline{H}$=).
**$\delta_C$ (100 MHz, $CDCl_3$)** 32.3 (C$\underline{H}_2$), 36.7 (PhC$\underline{H}_2$), 37.8 (NC$\underline{H}_3$), 52.3 (C$\underline{H}_3$), 121.6 (=C$\underline{H}$CO), 127.4 (ArC$\underline{H}$), 127.7 (ArC$\underline{H}$), 128.2 (ArC$\underline{H}$), 128.8 (2 x ArC$\underline{H}$), 129.4 (ArC$\underline{H}$), 129.5 (ArC$\underline{H}$), 129.6 (ArC$\underline{H}$), 129.9 (ArC$\underline{H}$), 131.9 (ArC$\underline{H}$), 132.7 (Ar$\underline{C}$),139.1 (C$\underline{H}$=), 142.8 (Ar$\underline{C}$), 167.0 ($\underline{C}$=O), 170.0 ($\underline{C}$=O).
**MS (EI mode)** 355.1 (M+, 10 %), 233.1 (97), 201.1 (26), 174.1 (82), 147.1 (73), 91.1 (99), 82.9 (57), 44.0 (94). **HRMS** $C_{20}H_{21}NO_3S$ requires 355.1242 found 355.1246.
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 1714 (C=O, ester), 1653 (C=O, amide), 1486, 1452, 1171.

**(*E*)-*tert*-Butyl 3-(2-(2-(benzylsulfanyl)-N-methylacetamido)phenyl)acrylate 189**




$C_{23}H_{27}NO_3S$
Mol. Wt.: 397.53

2-(Benzylsulfanyl)-*N*-(2-bromophenyl)-*N*-methylacetamide **175** (1.05 g, 3.00 mmol) was weighed into a microwave reactor vial. $Pd(OAc)_2$ (34 mg, 0.15 mmol), P(*o*-tol)$_3$ (46 mg, 0.15 mmol) and distilled *tert*-butyl acrylate (2.63 ml, 18.0 mmol) were added to the vessel and it was sealed with a crimp cap septum. The vessel was flushed with argon and dry *o*-xylene (1.5 ml) and $NEt_3$ (0.85 ml, 6.00 mmol) were added. The vessel was placed in the microwave cavity and heated to 100 °C for 7 h. The reaction mixture was diluted with $Et_2O$ (20 ml) and quenched with $H_2O$ (5 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Purification by flash chromatography on silica gel eluting with 3 % EtOAc/Pet Ether gave recovered **175** (142 mg, 0.40 mmol, 13 %) and *(E)-tert*-butyl 3-(2-(2-benzylsulfanyl-N-methylacetamido)phenyl)acrylate **189** as an orange oil (1.07 g, 2.69 mmol, 87 %).

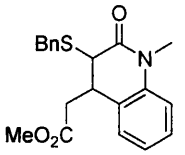
**$\delta_H$ (400 MHz, $CDCl_3$)** 1.45 (9H, s, C($CH_3$)$_3$), 2.70 (1H, d, AB system, *J* 14.4, 1H of $SCH_2CO$), 2.75 (1H, d, AB system, *J* 14.4, 1H of $SCH_2CO$) 3.16 (3H, s, $NCH_3$), 3.72 (1H, d, AB system, *J* 13.2, 1H of $PhCH_2S$), 3.76 (1H, d, AB system, *J* 13.2, 1H of $PhCH_2S$), 6.28 (1H, d, *J* 16.0, =CHCO), 7.10-7.33 (8H, m, ArH), 7.50 (1H, d, *J* 16.0, CH=), 7.56 (1H, d, *J* 7.3, ArH).

**$\delta_C$ (100 MHz, $CDCl_3$)** 27.1 (C($CH_3$)$_3$), 31.0 ($SCH_2CO$), 35.2 ($PhCH_2S$), 36.4 ($NCH_3$), 79.9 (C($CH_3$)$_3$), 122.4 (ArCH), 126.0 (ArCH), 126.7 (ArCH), 127.4 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.5 (ArCH), 128.8 (ArCH), 130.0 (=CHCO), 131.5 (2 x ArC), 136.5 (CH=), 141.3 (ArC), 164.54 (C=O), 168.5 (C=O).

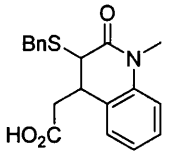
**MS (EI mode)** 397.2 (5 %, $M^{+\cdot}$), 341.2 (13), 275.2 (9), 219.1 (99), 201.1 (12), 174.1 (41), 160.1 (61), 147.1 (62), 91.1 (67), 57.1 (27) **HRMS** $C_{23}H_{27}NO_3S$ requires 397.1712 found 397.1713.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2977, 1707 (C=O, conjugated ester), 1656 (C=O, amide), 1598, 1487, 1454, 1421, 1367, 1321, 1203, 1149, 1089.

**3-(Benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetate 192** and **3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetic acid 193** by cyclisation of sulfide **190** with NaH.




$C_{20}H_{21}NO_3S$
Mol. Wt.: 355.45




$C_{19}H_{19}NO_3S$
Mol. Wt.: 341.42

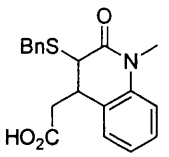
NaH (3.0 mg, 0.122 mmol) was added to a solution of *(E)-tert*-butyl 3-(2-(2-(benzylsulfanyl)-*N*-methylacetamido)phenyl)acrylate **189** (28.8 mg, 0.081 mmol) in THF (3 ml) and the reaction stirred at room temperature for 1 h. The reaction was quenched by dropwise addition of MeOH (until effervescence ceased) and concentrated *in vacuo*. The reaction mixture was then partitioned between $Et_2O$ (5 ml) and $H_2O$ (5 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography on silica gel using 40 % ethyl acetate: petroleum ether as eluent to give 3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetate **193** (10.7 mg, 0.030 mmol, 36 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.32-2.48 (2H, m, $C\underline{H}_2CO$), 3.03-3.34 (4H, m, $NC\underline{H}_3$ + C$\underline{H}$), 3.42 (1H, s, C$\underline{H}$), 3.50 (3H, s, $CO_2C\underline{H}_3$), 3.77 (1H, d, AB system, *J* 13.4, 1H of $PhC\underline{H}_2$), 3.86 (1H, d, AB system, *J* 13.4, 1H of $PhC\underline{H}_2$), 6.93-7.04 (2H, m, Ar$\underline{H}$), 7.09 (1H, d, *J* 7.4, Ar$\underline{H}$), 7.14-7.37 (6H, m, Ar$\underline{H}$).
**$\delta_C$ (100 MHz, $CDCl_3$)** 30.0 ($N\underline{C}H_3$), 36.1 ($Ph\underline{C}H_2$), 39.3 ($\underline{C}H$), 39.4 ($\underline{C}H_2CO$), 47.8 ($\underline{C}H$), 52.3 ($CO_2\underline{C}H_3$), 115.2 (2 x Ar$\underline{C}$H), 123.8 (Ar$\underline{C}$H), 125.5 (Ar$\underline{C}$), 127.6 (Ar$\underline{C}$H), 128.9 (2 x Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 129.7 (2 x Ar$\underline{C}$H), 137.8 (Ar$\underline{C}$), 138.9 (Ar$\underline{C}$), 167.7 ($\underline{C}$=O), 171.3 ($\underline{C}$=O).

The hydrolysis product **193** was obtained by acidification of the aqueous extract with 5 M HCl and extraction with EtOAc (2 x 10 ml). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetic acid **193** (17.8 mg, 0.052 mmol, 64 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.41-2.53 (2H, m, $C\underline{H}_2CO$), 3.02-3032 (4H, s, $NC\underline{H}_3$ + C$\underline{H}$), 3.55 (1H, s, C$\underline{H}$), 3.77 (1H, d, AB system, *J* 13.4, 1H of $PhC\underline{H}_2$), 3.89 (1H, d, AB system, *J* 13.4, 1H of $PhC\underline{H}_2$), 6.96-7.37 (9H, m, Ar$\underline{H}$).

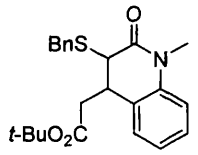
**2-(3-(Benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetic acid 193** by hydrolysis of methyl ester **192** with LiOH.




$C_{19}H_{19}NO_3S$
Mol. Wt.: 341.42

LiOH (21 mg, 0.494 mmol) was added to a solution of 3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetate **192** (21 mg, 0.062 mmol) in THF (2 ml) and $H_2O$ (0.5 ml) and the flask placed in an oil bath and stirred at 40 °C for 24 h. The reaction was quenched by addition of $H_2O$ (10 ml) and extracted with EtOAc (2 x 15 ml). The aqueous phase was acidified with aqueous 1M HCl and re-extracted with EtOAc (2 x 15 ml). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2-(3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetic acid **193** as a yellow oil (21.1 mg, 0.62 mmol, 100 %) which was used without further purification.

***tert*-Butyl 2-(3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 194**




$C_{23}H_{27}NO_3S$
Mol. Wt.: 397.53

LDA (0.17 ml of a 2.0 M solution in THF, 0.334 mmol) was added dropwise to a solution of *(E)-tert*-butyl 3-(2-(2-(benzylsulfanyl)-*N*-methylacetamido)phenyl)acrylate **189** (111 mg, 0.29 mmol) in THF (2.5 ml) at -10°C. The reaction was quenched, when TLC showed no starting material remained (approx 15 min) by addition of saturated aqueous $NH_4Cl$ (2 ml) and extracted with EtOAc (2 x 15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *tert*-butyl 2-(3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **194** (74.9 mg, 0.188 mmol, 69 %) and 2-(3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetic acid **193** (15.0 mg, 0.04 mmol, 16 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.26 (9H, s, $C(C\underline{H}_3)_3$), 2.26 (1H, dd, AB system, *J* 15.5, 7.8, 1H of $C\underline{H}_2CO_2t$-Bu), 2.34 (1H, dd, AB system, *J* 15.5, 7.8, 1H of $C\underline{H}_2CO_2t$-Bu), 3.28 (1H, dt, *J*

2.0, 7.8, C<u>H</u>($CH_2CO_2t$-Bu), 3.36 (3H, s, NC<u>H</u>$_3$), 3.40 (1H, d, *J* 2.0, SC<u>H</u>CO), 3.66 (1H, d, AB system, *J* 13.5, 1H of PhC<u>H</u>$_2$S), 3.85 (1H, d, AB system, *J* 13.5, 1H of PhC<u>H</u>$_2$S), 6.94 (1H, t, *J* 7.4, Ar<u>H</u>), 7.08-7.32 (8H, m, Ar<u>H</u>).

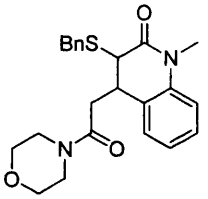
**$\delta_C$ (100 MHz, $CDCl_3$)** 28.4 (C(<u>C</u>H$_3$)$_3$), 30.0 (NCH$_3$), 35.6 (<u>C</u>H$_2$CO$_2$*t*-Bu), 39.5 (<u>C</u>H($CH_2CO_2t$-Bu)), 40.71 (Ph<u>C</u>H$_2$S) 46.7 (S<u>C</u>H(CO)), 81.6 (<u>C</u>(CH$_3$)$_3$), 115.1 (Ar<u>C</u>H), 123.6 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>), 127.5 (Ar<u>C</u>), 127.5 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 138.9 (Ar<u>C</u>), 138.0 (Ar<u>C</u>), 167.7 (<u>C</u>=O), 170.1 (<u>C</u>=O).

**MS (EI mode)** 397.2 (2 %, $M^{+\cdot}$), 282.1 (11), 250.1 (9), 218.1 (18), 160.1 (99), 91.1 (28)

**HRMS** $C_{23}H_{27}O_3NS$ requires 397.1712 found 397.1711.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2983, 2359, 1726 (C=O, ester), 1666 (C=O, amide), 1603, 1473, 1367, 1254, 115.

**3-(Benzylsulfanyl)-1-methyl-4-(2-morpholino-2-oxoethyl)-3,4-dihydroquinolin-2(1H)-one 195**




$C_{23}H_{26}N_2O_3S$
Mol. Wt.: 410.53

EDCI (15.8 mg, 0.08 mmol) was added to a solution of acid **193** (18.7 mg, 0.05 mmol), morpholine (7.2 µl, 0.0824 mmol) and HOBt (1.5 mg, 0.011 mmol) in $CH_2Cl_2$ (2 ml). The reaction was stirred at room temperature for 60 h. The reaction mixtured was diluted with $CH_2Cl_2$ (8 ml) and washed with aqueous 1 M HCl (10 ml), $NaHCO_3$ (10 ml) and brine (10 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 50 % EtOAc/Pet ether to give 3-(benzylsulfanyl)-1-methyl-4-(2-morpholino-2-oxoethyl)-3,4-dihydroquinolin-2(1H)-one **195** as a yellow oil (11.4 mg, 0.03 mmol, 51 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.34-2.46 (2H, m, C<u>H</u>$_2$CO), 2.92-2.98 (1H, m, 1H of C<u>H</u>$_2$), 3.11-3.20 (1H, m, 1H of C<u>H</u>$_2$), 3.34 (3H, s, NC<u>H</u>$_3$), 3.37-3.88 (8H, m, 3 x C<u>H</u>$_2$, C<u>H</u>CO + C<u>H</u>CH$_2$CO), 3.81 (1h, d, *J* 13.3, 1H of PhC<u>H</u>$_2$S), 3.86 (1H, d, *J* 13.3, 1H of PhC<u>H</u>$_2$S), 6.93-7.03 (2H, m, 2 x Ar<u>H</u>), 7.14-7.30 (7H, m, 7 x Ar<u>H</u>).

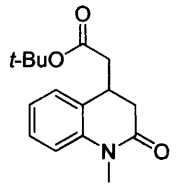
**$\delta_C$ (100 MHz, $CDCl_3$)** 30.0 (N<u>C</u>H$_3$), 36.2 (Ph<u>C</u>H$_2$S), 37.1 (<u>C</u>H$_2$CO), 39.6 (<u>C</u>HCH$_2$CO), 42.4 (<u>C</u>H$_2$N), 46.3 (<u>C</u>H$_2$N), 47.3 (S<u>C</u>HCO), 66.6 (<u>C</u>H$_2$O), 67.0 (<u>C</u>H$_2$O), 115.0 (Ar<u>C</u>H),

123.8 (ArCH), 126.0 (ArC), 127.5 (2 x ArCH), 128.8 (ArCH), 129.6 (2 x ArCH), 129.7 (2 x ArCH), 137.7 (ArC), 139.0 (ArC), 168.1 (C=O), 168.7 (C=O)

**MS (CI mode)** 411.2 ($M^{+\cdot}$+H, 100 %), 289.2 (48), 287.2 (46), 160.0 (23) **HRMS** $C_{23}H_{27}O_3N_2S$ requires 411.1742 found 411.1743.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2856, 2357, 1653 (C=O, amide), 1600, 1496, 1459, 1368, 1271, 1241, 1114, 1070, 1030.

***tert*-Butyl 2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 196**




$C_{16}H_{21}NO_3$
Mol. Wt: 275.34

Cleavage from solution-phase model, *tert*-butyl 2-(3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **194**

LiCl (20.7 mg, 0.489 mmol) was placed in a dry 25 ml round-bottomed flask and dried under vacuum for 5 min, the flask was then flushed with nitrogen. THF (1 ml) was added followed by a solution of *tert*-butyl 2-(3-(benzylsulfanyl)-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **194** (32.4 mg, 0.082 mmol) in THF (1.5 ml). $SmI_2$ (2.46 ml of a 0.1 M solution in THF, 0.45 mmol) was added and the reaction stirred for 18 h. The reaction mixture was diluted with $CH_2Cl_2$ (10 ml) and quenched with saturated aqueous $NaHCO_3$ (8 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel using 30 % EtOAc/Pet ether as eluent gave *tert*-butyl 2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **196** (11.3 mg, 0.0418 mmol, 52 %, unoptimised) as a pale yellow oil.

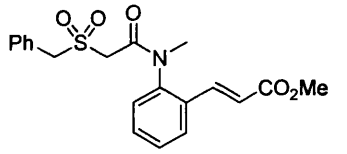
Cleavage from solution phase model, *tert*-butyl 2-(3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **200**

LiCl (205 mg, 4.82 mmol) was placed in a dry 25 ml round-bottomed flask and dried under vacuum for 5 min, the flask was then flushed with nitrogen. THF (5 ml) was added followed by a solution of *tert*-butyl 2-(3-(benzylsulfonyl)-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **200** (230 mg, 0.54 mmol) in THF (5 ml). $SmI_2$ (21.4 ml, of a 0.1 M solution in THF, 2.14 mmol) was added and the reaction stirred for 18 h.

The reaction mixture was diluted with $CH_2Cl_2$ (15 ml) and quenched with saturated aqueous $NaHCO_3$ (15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel using 30 % EtOAc/Pet ether as eluent gave *tert*-butyl 2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **196** (84.8 mg, 0.34 mmol, 57 %, unoptimised) as a pale yellow oil.

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.36 (9H, s, $C(C\underline{H}_3)_3$), 2.34-2.45 (2H, m, $C\underline{H}_2CO_2t$-Bu), 2.55 (1H, dd, *J* 16.1, 5.4, 1H of $C\underline{H}_2CON$), 2.70 (1H, dd, *J* 16.1, 5.4, 1H of $C\underline{H}_2CON$), 3.30 (3H, s, $NC\underline{H}_3$), 3.37 (1H, app quintet, *J* 5.4, C<u>H</u>), 6.96-6.98 (2H, m, 2 x Ar<u>H</u>), 7.14 (1H, d, *J* 7.5, Ar<u>H</u>), 7.18-7.22 (1H, m, Ar<u>H</u>).
**$\delta_C$ (100 MHz, $CDCl_3$)** 28.1 ($C(\underline{C}H_3)_3$), 29.4 ($N\underline{C}H_3$), 32.7 (<u>C</u>H), 36.9 ($\underline{C}H_2CON$), 39.6 ($\underline{C}H_2CO_2t$-Bu), 81.1 ($\underline{C}(CH_3)_3$), 115.0 (Ar<u>C</u>H), 123.0 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>), 139.8 (Ar<u>C</u>), 169.1 (<u>C</u>=O), 170.7 (<u>C</u>=O).
**MS (EI mode)** 275.2 (4 % $M^{+\cdot}$), 219.1 (9), 218.1(8), 160.1 (26), 85.0 (65), 83.0 (100), 47.0 (17) **HRMS** $C_{16}H_{21}NO_3$ requires 275.1521 found 275.1518.
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2979, 2359, 2010, 1726 (C=O, ester), 1681 (C=O, amide), 1603, 1474, 1367, 1269, 1140, 784.

**Preparation of *(E)*-Methyl-3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl) acrylate 197**




$C_{20}H_{21}NO_5S$
Mol. Wt: 387.45

Oxidation with Oxone.

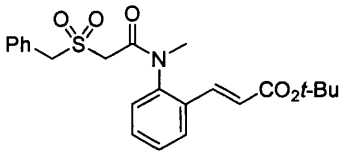
Oxone (2.62 g, 4.26 mmol) was added to a solution of *(E)*-methyl 3-(2-(2-benzylsulfanyl-N-methylacetamido)phenyl)acrylate **188** (252 mg, 0.71 mmol) in DMF (20 ml) and $H_2O$ (5 ml) and the reaction stirred overnight. The reaction was quenched by addition of $H_2O$ (20 ml) and the mixture extracted with $CH_2Cl_2$ (2 x 30 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *(E)*-methyl-3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl)acrylate **197** as a pale yellow oil which solidified on standing (151 mg, 0.46 mmol, 55 %).

Oxidation with *m*CPBA.

*m*CPBA (163 mg, max 72 % *m*CPBA, 0.68 mmol) was added to a solution of *(E)*-methyl-3-(2-(2-benzylsulfanyl-N-methylacetamido)phenyl)acrylate **188** (30.0 mg, 0.08 mmol) in $CH_2Cl_2$ (5 ml) at 0 °C. The reaction was stirred at 0 °C for 10 min and warmed to room temperature and stirred for 6 h. The reaction was quenched by addition of $H_2O$ (10 ml) and then diluted with $CH_2Cl_2$ (15 ml) before washing with saturated aqueous $NaHCO_3$ (10 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *(E)*-methyl-3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl)acrylate **197** as a pale yellow oil (17.6 mg, 0.05 mmol, 54 %).

**$\delta_H$ (300 MHz, $CDCl_3$)** 3.15 (3H, s, $C\underline{H}_3$), 3.33 (1H, d, *J* 13.6, 1H of $SO_2C\underline{H}_2CO$), 3.37 (1H, d, *J* 13.6, 1H of $SO_2C\underline{H}_2CO$), 3.75 (3H, m, $NC\underline{H}_3$), 4.43 (1H, d, *J* 13.5, 1H of $PhC\underline{H}_2SO_2$), 4.72 (1H, d, *J* 13.5, 1H of $PhC\underline{H}_2SO_2$), 6.36 (1H, d, *J* 16.0, CH=C<u>H</u>CO), 7.01-7.54 (10 H, m, 9 x Ar<u>H</u> + C<u>H</u>=).
**$\delta_C$ (100 MHz, $CDCl_3$)** 38.0 ($\underline{C}H_3$), 52.4 ($SO_2\underline{C}H_2CO$), 53.1 ($N\underline{C}H_3$), 59.8 ($Ph\underline{C}H_2SO_2$), 122.3 (=<u>C</u>HCO), 128.4 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>), 129.4 (2 x Ar<u>C</u>H), 129.9 (2 x Ar<u>C</u>H), 130.1 (Ar<u>C</u>H), 131.6 (Ar<u>C</u>H), 132.5 (Ar<u>C</u>H), 132.6 (Ar<u>C</u>H), 138.3 (<u>C</u>H=), 138.5 (Ar<u>C</u>), 141.6 (Ar<u>C</u>), 163.1 (<u>C</u>=O), 166.9 (<u>C</u>=O).
**MS (EI mode)** 387.2 ($M^{+\cdot}$, 29 %), 231.1 (58), 200.1 (5), 160.1 (12), 144.1 (23), 130.1 (9), 91.1 (99), 83.0 (13). **HRMS** $C_{20}H_{21}NO_5S$ requires 387.1140 found 387.1139.

***(E)-tert*-Butyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl) acrylate 198**




$C_{23}H_{27}NO_5S$
Mol. Wt: 429.53

Oxidation with Oxone.

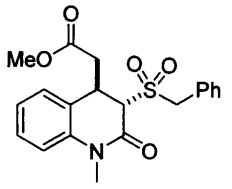
Oxone (914 mg, 1.49 mmol) was added to a solution of *(E)-tert*-butyl 3-(2-(2-benzylsulfanyl-N-methylacetamido)phenyl)acrylate **189** (148 mg, 0.37 mmol) in DMF (8 ml) and $H_2O$ (2 ml) and the reaction stirred overnight. The reaction was quenched by addition of $H_2O$ (10 ml) and the mixture extracted with $CH_2Cl_2$ (2 x 15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *(E)-tert*-butyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl)acrylate **198** as a pale yellow oil which solidified on standing (147 mg, 0.37 mmol, 100 %).

Oxidation with *m*CPBA.

*m*CPBA (266 mg, max 77 % *m*CPBA, 1.19 mmol) was added to a solution of *(E)-tert*-butyl 3-(2-(2-benzylsulfanyl-N-methylacetamido)phenyl)acrylate **189** (236 mg, 0.59 mmol) and $K_2CO_3$ (164 mg, 1.19 mmol) in $CH_2Cl_2$ (5 ml) at 0 °C. The reaction was stirred at 0 °C for 10 min and warmed to room temperature and stirred for 20 min. The reaction was quenched by addition of $H_2O$ (10 ml) and then diluted with $CH_2Cl_2$ (15 ml) before washing with saturated aqueous $NaHCO_3$ (10 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *(E)-tert*-butyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl)acrylate **198** as a yellow oil (179 mg, 4.17 mmol, 71 %).

**$\delta_H$ (300 MHz, $CDCl_3$)** 1.57 (9H, s, $C(C\underline{H}_3)_3$), 3.36 (3H, s, $NC\underline{H}_3$), 3.51 (1H, d, AB system, *J* 15.0, 1H of $SO_2C\underline{H}_2CO$), 3.54 (1H, d, AB system, *J* 15.0, 1H of $SO_2C\underline{H}_2CO$), 4.52 (1H, d, AB system, *J* 15.0, 1H of $PhC\underline{H}_2SO_2$), 4.86 (1H, d, AB system, *J* 15.0, 1H of $PhC\underline{H}_2SO_2$), 6.41 (1H, d, *J* 18.0, CH=C<u>H</u>CO), 7.35-7.71 (10H, m, 9 x Ar<u>H</u> + C<u>H</u>=).
**$\delta_C$ (100 MHz, $CDCl_3$)** 28.4 (3 x $C(\underline{C}H_3)_3$), 37.9 ($N\underline{C}H_3$), 52.9 ($SO_2\underline{C}H_2CO$), 59.7 ($Ph\underline{C}H_2SO_2$), 81.4 ($\underline{C}(CH_3)_3$), 124.4 (Ar<u>C</u>), 128.1 (Ar<u>C</u>H), 128.5 (=<u>C</u>HCO), 129.2 (Ar<u>C</u>H x 2), 129.8 (Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 131.4 (Ar<u>C</u>H), 132.1 (Ar<u>C</u>H), 132.7 (Ar<u>C</u>H x 2), 136.9 (Ar<u>C</u> x 2), 141.4 (<u>C</u>H=), 162.9 (<u>C</u>=O), 165.6 (<u>C</u>=O).
**MS (EI mode)** 447 ($M^{+\cdot}$ + $NH_4$, 36 %), 391(98), 237 (43), 188 (40), 174 (51), 160 (100), 108 (49). **HRMS** $C_{23}H_{31}NO_5S$ requires 447.1948, found 447.1949.
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3036, 2975, 1706 (C=O, ester), 1657 (C=O, amide), 1601, 1485, 1450, 1367, 1313, 1257, 1146, 1122.

***rac*-Methyl 2-(*3S,4R*-3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate 199**



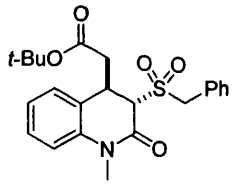

$C_{20}H_{21}NO_5S$
Mol. Wt: 387.45

$K_2CO_3$ (39.2 mg, 0.28 mmol) was added to a solution of *(E)*-methyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl)acrylate **197** (22.0 mg, 0.06 mmol) in DMF (5 ml) at room temperature. The reaction was stirred overnight. The reaction was

quenched by addition of $H_2O$ (10 ml) and the mixture extracted into $CH_2Cl_2$ (2 x 10 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 50 % EtOAc/Pet ether gave *rac*-methyl 2-(3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **199** (10.2 mg, 0.03 mmol, 46 %).

**$\delta_H$ (300 MHz, $CDCl_3$)** 2.36-2.50 (2H, m, C$\underline{H}_2$CO$_2$Me), 3.43 ($CH_3$), 3.44 ($NCH_3$), 3.97 (1H, apparent t, J 7.6, C$\underline{H}$CH$_2$CO$_2$Me), 4.10 (1H, s, C$\underline{H}$), 4.21 (1H, d, *J* 14.0, 1H of PhC$\underline{H}_2$SO$_2$), 4.58 (1H, d, *J* 14.0, PhC$\underline{H}_2$SO$_2$), 6.99-7.05 (2H, m, 2 x Ar$\underline{H}$), 7.08-7.33 (5H, m, 5 x Ar$\underline{H}$), 7.49-7.51 (2H, m, 2 x Ar$\underline{H}$).
**$\delta_C$ (100 MHz, $CDCl_3$)** 30.0 ($CH_3$), 32.3 ($\underline{C}$HCH$_2$CO$_2$Me), 39.7 ($\underline{C}$H$_2$CO$_2$Me), 52.3 (N$\underline{C}$H$_3$), 59.8 (Ph$\underline{C}$H$_2$SO$_2$), 63.7 ($\underline{C}$H), 115.6 (Ar$\underline{C}$H), 124.4 (Ar$\underline{C}$), 124.7 (Ar$\underline{C}$H), 127.8 (Ar$\underline{C}$), 128.8 (Ar$\underline{C}$H), 129.3 (2 x Ar$\underline{C}$H), 129.5 (2 x Ar$\underline{C}$H), 131.9 (2 x Ar$\underline{C}$H), 138.5 (Ar$\underline{C}$), 162.4 ($\underline{C}$=O), 170.6 ($\underline{C}$=O).
**MS (EI mode)** 447 ($M^{+\cdot}$ + $NH_4$, 36 %), 391(98), 237 (43), 188 (40), 174 (51), 160 (100), 108 (49). **HRMS** $C_{23}H_{31}NO_5S$ requires 447.1948, found 447.1949.
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2360, 2341, 1736 (C=O, ester), 1660 (C=O, amide), 1602, 1475.

***rac-tert*-Butyl 2-(*3S,4R*-3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate 200**



$C_{23}H_{27}NO_5S$
Mol. Wt: 429.53

$K_2CO_3$ (415 mg, 3.00 mmol) was added to a solution of *(E)-tert*-butyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)phenyl)acrylate **198** (322 mg, 0.75 mmol) in DMF (6 ml) at room temperature. The reaction was stirred until complete by TLC (approx 5 h). The reaction was quenched by addition of $H_2O$ (15 ml) and the mixture extracted into $CH_2Cl_2$ (2 x 20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product rac-*tert*-butyl 2-(3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **200** as a brown solid (320 mg, 0.75 mmol, 99 %) which was used without further purification. A portion of the product was recrystallised from hot methanol to provide colourless, rhombic crystals suitable for x-ray analysis.

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

**M.p.** 174-175 °C

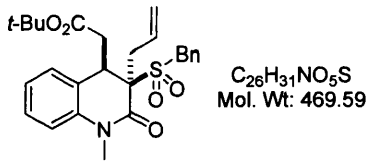
**$\delta_H$ (400 MHz, $CDCl_3$)** 1.33 (9H, s, $C(C\underline{H}_3)_3$), 2.41-2.47 (2H, m, $C\underline{H}_2CO_2t$-Bu), 3.54 (3H, s, $NC\underline{H}_3$), 4.06 (1H, t, *J* 7.5, $C\underline{H}CH_2CO_2t$-Bu), 4.18 (1H, s, $BnSO_2C\underline{H}CO$), 4.29 (1H, d, AB system, *J* 14.1, 1H of $PhC\underline{H}_2$), 4.69 (1H, d, AB system, *J* 14.1, 1H of $PhC\underline{H}_2$), 7.12 (2H, apparent q, *J* 6.6, Ar<u>H</u>), 7.14-7.34 (2H, m, Ar<u>H</u>), 7.42-7.44 (3H, m, Ar<u>H</u>), 7.61-7.63 (2H, m, Ar<u>H</u>).

**$\delta_C$ (100 MHz, $CDCl_3$)** 28.3 (3 x $C(\underline{C}H_3)_3$), 30.7 ($\underline{C}HCH_2CO_2t$-Bu), 32.4 ($N\underline{C}H_3$), 41.1 ($\underline{C}H_2CO_2t$-Bu), 59.7 ($Ph\underline{C}H_2$), 63.8 ($BnSO_2\underline{C}HCO$), 82.1 ($\underline{C}(CH_3)_3$), 115.5 (Ar<u>C</u>H), 124.6 (Ar<u>C</u>H), 124.8 (Ar<u>C</u>), 127.9 (Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 129.3 (2 x Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 131.9 (Ar<u>C</u>H), 138.5 (Ar<u>C</u>), 162.5 (<u>C</u>=O), 169.3 (<u>C</u>=O).

**MS (CI mode)** 430 ($M^{+\cdot}$ + H, 32 %), 391 (13), 374 (15), 274 (35), 160 (100). **HRMS** $C_{23}H_{27}NO_5S$ requires 429.1604 found 429.1593.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3050, 2932, 1723 (C=O, ester), 1654 (C=O, amide), 1604, 1470, 1371, 1310, 1132, 1137, 926.

***rac-tert*-Butyl 2-(*3R,4R*-3-allyl-3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 201**




$K_2CO_3$ (51 mg, 0.370 mmol) was added to a solution of *tert*-butyl 2-(3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **200** (53 mg, 0.123 mmol) in DMF (1.5 ml) and stirred at room temperature for 20 min. Allyl bromide (0.03 ml, 0.370 mmol) was added and the reaction stirred at room temperature for 2 h. The reaction was then heated to 50 °C and stirred overnight. The reaction was cooled to room temperature and quenched by addition of $H_2O$ (10 ml). The mixture was extracted with EtOAc (2 x 10 ml) and the organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel gave *rac-tert*-butyl 2-(*3R,4R*-3-allyl-3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **201** as a white solid (44 mg, 0.093 mmol, 76 %) A portion of the solid was recrystallised from $CH_2Cl_2$/Pet ether and analysed by X-ray crystallography.

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

**M.p.** 201-202 °C

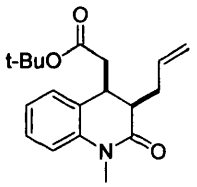
**$\delta_H$ (300 MHz, $CDCl_3$)** 1.40 (9H, s, $C(C\underline{H}_3)_3$), 2.81-2.92 (2H, m, 1H of $C\underline{H}_2CH=$ + 1H of $C\underline{H}_2CO_2t$-Bu), 2.95-3.10 (1H, m, 1H of $C\underline{H}_2CH=$), 3.29 (1H, dd, *J* 16.8, 2.4, 1H of $C\underline{H}_2CO_2t$-Bu), 3.52 (3H, s, $NC\underline{H}_3$), 4.05 (1H, dd, *J* 11.7, 2.4, C<u>H</u>), 4.43 (1H, d, AB system, *J* 12.6, $PhC\underline{H}_2SO_2$), 4.63 (1H, d, AB system, *J* 12.6, $PhC\underline{H}_2SO_2$), 5.13 (1H, d, *J* 16.8, 1H of $=C\underline{H}_2$), 5.27 (1H, d, *J* 10.5, 1H of $=C\underline{H}_2$), 5.81-5.93 (1H, m, C<u>H</u>=), 7.05-7.15 (4H, m, Ar<u>H</u>), 7.27-7.39 (5H, m, Ar<u>H</u>).

**$\delta_C$ (100 MHz, $CDCl_3$)** 28.3 ($C(\underline{C}H_3)_3$), 31.0 ($N\underline{C}H_3$), 35.6 ($C\underline{H}_2CH=$), 36.0 ($\underline{C}H_2CO_2t$-Bu), 37.8 (<u>C</u>H), 59.2 ($Ph\underline{C}H_2SO_2$), 73.0 ($SO_2\underline{C}CO$), 81.2 ($\underline{C}(CH_3)_3$), 114.9 (<u>C</u>H=), 121.2 ($=\underline{C}H_2$), 124.3 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>), 126.1 (Ar<u>C</u>), 127.8 (2 x Ar<u>C</u>H), 128.6 (2 x Ar<u>C</u>H), 129.2 (2 x Ar<u>C</u>H), 130.5 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 138.4 (Ar<u>C</u>), 165.8 (<u>C</u>=O), 170.7 (<u>C</u>=O).

**MS (ES+ mode)** 961 (69%, $2M^{+\cdot}$ + Na), 673 (30), 492 (92 %, $M^{+\cdot}$ + Na), 214 (100). HRMS $C_{26}H_{31}O_5NNaS$ requires 492.1815 found 492.1815.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3072, 2974, 1716 (C=O, ester), 1655 (C=O, amide), 1604, 1467, 1368, 1298, 1128.

***rac-tert*-Butyl 2-(*3R,4S*-3-allyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 202**




$C_{19}H_{25}NO_3$
Mol. Wt: 315.41

*rac-tert*-Butyl 2-(*3R,4R*-3-allyl-3-benzylsulfonyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **201** (64.1 mg, 0.14 mmol) and dry LiCl (56 mg, 1.23 mmol) were added to THF (1 ml) and the mixture was thoroughly flushed with nitrogen. Distilled *tert*-butanol (0.33 ml, 3.43 mmol) was added to the mixture followed by $SmI_2$ (4.1 ml, 0.1 M solution in THF, 0.41 mmol). The reaction was stirred until the $SmI_2$ decolourised (approx 16 h) and the reaction mixture was diluted with $CH_2Cl_2$ (10 ml) and washed with water (8 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica gel using 30 % EtOAc/Pet ether as eluent gave *rac-tert*-butyl 2-(*3R,4S*-3-allyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **202** (34.1 mg, 0.11 mmol, 79 %) as a 5:1 mixture of *syn* and *anti* diastereomers. The *syn* diastereomer could be separated by further careful, chromatography. Recrystallisation

from $CH_2Cl_2$/Pet ether gave colourless crystals suitable for analysis by X-ray crystallography.

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

**M.p.** 96.5-98 °C

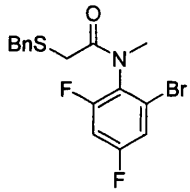
$\delta_H$ **(300 MHz, $CDCl_3$)** 1.39 (9H, s, $C(C\underline{H}_3)_3$), 2.17-2.32 (2H, m, 1H of $C\underline{H}_2CH=CH_2$, 1H of $C\underline{H}_2CO_2t$-Bu), 2.51 (1H, dd, *J* 15.0, 4.5, 1H of $C\underline{H}_2CO_2t$-Bu), 2.76-2.91 (2H, m, 1H of $C\underline{H}_2CH=$ + $C\underline{H}CO$), 3.41 (3H, s, $NC\underline{H}_3$), 3.43-3.46 (1H, m, CH), 5.12 (1H, apparent d, *J* 8.4, 1H of $=CH_2$), 5.17 (1H, apparent d, *J* 17.1, 1H of $=C\underline{H}_2$), 5.82-5.98 (1H, m, $C\underline{H}=CH_2$), 7.00-7.05 (2H, m, Ar$\underline{H}$), 7.25-7.33 (2H, m, Ar$\underline{H}$).

$\delta_C$ **(100 MHz, $CDCl_3$)** 28.3 (3 x $C(\underline{C}H_3)_3$), 30.1 ($N\underline{C}H_3$), 31.2 ($\underline{C}H_2CO_2$t-Bu), 35.2 ($\underline{C}H_2CH=CH_2$), 36.0 ($CO\underline{C}H$), 44.3 ($C\underline{H}$-$CH_2CO_2$t-Bu), 81.1 ($\underline{C}(CH_3)_3$), 115.2 (Ar$\underline{C}$H), 117.3 ($=\underline{C}H_2$), 123.2 (Ar$\underline{C}$H), 128.2 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 136.1 ($\underline{C}H=CH_2$), 139.8 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$), 171.1 ($\underline{C}$=O), 171.3 ($\underline{C}$=O).

**MS (CI mode)** 316 (100 %, $M^{+\cdot}$), 260 (24). **HRMS** $C_{19}H_{26}NO_3$ requires 316.1907 found 316.1910.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 2970, 2353, 1727 (C=O, ester), 1676 (C=O, amide), 1470, 1373, 1267.

**2-(Benzylsulfanyl)-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide 203**




$C_{16}H_{14}BrF_2NOS$
Mol. Wt: 386.25

Benzyl thiol (2.49 ml, 21.2 mmol) was added to a solution of 2-bromo-N-(2-bromophenyl)-N-methylacetamide **220** (7.00 g, 21.2 mmol) and $NEt_3$ (7.43 ml, 52.9 mmol) in DMF (150 ml) and the reaction stirred at room temperature overnight. The reaction mixture was diluted with 40 % EtOAc/ pet ether (100 ml) and washed with $H_2O$ (3 x 100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product 2-(benzylsulfanyl)-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide **203** as a clear oil which solidified on standing to give a white solid (7.21 g, 19.3 mmol, 91 %).

**M.p.** 50-51 °C.

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.86 (1H, d, AB system *J* 14.7, 1H of $C\underline{H}_2$), 2.93 (1H, d, AB system, *J* 14.7, 1H of $C\underline{H}_2$), 3.21 (3H, s, $NC\underline{H}_3$), 3.79 (1H, d, AB system, *J* 13.2, 1H of $PhC\underline{H}_2S$), 3.84 (1H, d, AB system, *J* 13.2, 1H of $PhC\underline{H}_2S$), 6.90-6.95 (1H, m, Ar<u>H</u>), 7.21-7.37 (6H, m, Ar<u>H</u>).

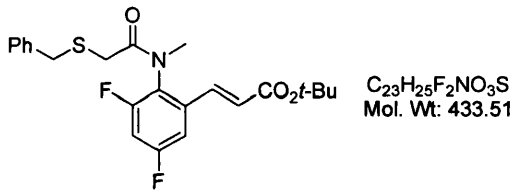
**$\delta_C$ (100 MHz, $CDCl_3$)** 32.7 ($\underline{C}H_2$), 36.0 ($N\underline{C}H_3$), 36.6 ($Ph\underline{C}H_2S$), 105.3 (t, *J* 25.0, Ar<u>C</u>H), 117.2 (d, *J* 25.0, Ar<u>C</u>H), 125.6 (d, *J* 11.7, Ar<u>C</u>N), 125.8 (Ar<u>C</u>H), 127.6 (m, Ar<u>C</u>Br), 128.8 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 137.8 ($Ar\underline{C}CH_2$), 159.7 (dd, *J* 13.0, 258.4, Ar<u>C</u>F), 162.2 (dd, *J* 12.7, 253.9, Ar<u>C</u>F), 169.7 (<u>C</u>=O).

**MS (EI mode)** 387.04 (9 %, $M^{+\cdot}$, ($^{81}Br$)), 385.04 (9 %, $M^{+\cdot}$, ($^{79}Br$)), 265.01 (28($^{81}Br$)), 263.01 (28 ($^{79}Br$)), 184.1 (99), 91.1 (59). **HRMS** $C_{16}H_{14}ONBrF_2S$ requires 386.9928 found 386.9925.

**$\upsilon_{max}$ (ATR,$cm^{-1}$)** 2360, 1667 (C=O), 1586, 1485, 1427, 1363, 1317, 1260, 1126.

**Anal.** calculated $C_{16}H_{14}ONBrF_2S$: C 49.75; H, 3.65; N, 3.63; S, 8.36%. Found: C, 49.74; H, 3.51; N, 3.67; S, 8.34.

### *(E)-tert*-Butyl-3-(2-(2-benzylsulfanyl)-N-methylacetamido)-3,5-difluorophenyl)acrylate 204




$C_{23}H_{25}F_2NO_3S$
Mol. Wt: 433.51

2-(Benzylsulfanyl)-*N*-(2-bromo-4,6-difluorophenyl)-N-methylacetamide **203** (1.00 g, 2.67 mmol) was weighed into a microwave reactor vial. $Pd(OAc)_2$ (30.0 mg, 0.13 mmol), P(*o*-tol)$_3$ (40.6 mg, 0.13 mmol) and distilled *tert*-butyl acrylate (2.35 ml, 16.0 mmol) and the vial was sealed with a crimp cap septum. The vial was flushed with argon and dry *o*-xylene (2 ml) and $NEt_3$ (0.14 ml, 2.94 mmol) were added. The vessel was placed in the microwave cavity and heated to 100 °C for 7 h. The reaction mixture was diluted with $Et_2O$ (20 ml) and quenched with $H_2O$ (5 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Purification by flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *(E)-tert*-butyl-3-(2-(2-benzylsulfanyl-N-methylacetamido)-3,5-difluorophenyl)acrylate **204** as an orange oil (1.17 g, 2.67 mmol, 100 %).

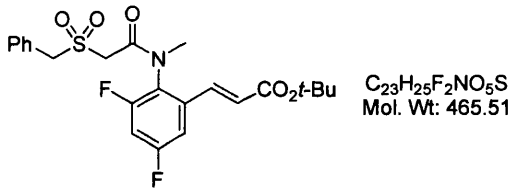
**$\delta_H$ (400 MHz, $CDCl_3$)** 1.54 (9H, s, $C(C\underline{H}_3)_3$), 2.83 (2H, apparent d, *J* 1.8, $SC\underline{H}_2CO$), 3.24 (3H, s, $NC\underline{H}_3$), 3.82 (2H, s, $PhC\underline{H}_2S$), 6.37 (1H, d, *J* 16.0, $=C\underline{H}$-$CO_2t$-Bu), 6.90-6.95 (1H, m, Ar$\underline{H}$), 7.14-7.30 (6H, m, Ar$\underline{H}$), 7.54 (1H, d, *J* 16.0, $C\underline{H}$=$CHCO_2t$-Bu).

**$\delta_C$ (100 MHz, $CDCl_3$)** 28.5 (3 x $C(\underline{C}H_3)_3$), 32.5 ($S\underline{C}H_2CO$), 36.5 ($Ph\underline{C}H_2S$), 37.0 ($NCH_3$), 81.8 ($\underline{C}(CH_3)_3$), 106.5 (t, *J* 24.6, Ar$\underline{C}$H), 110.1 (d, *J* 23.0, Ar$\underline{C}$H), 126.8-126.9 (m, Ar$\underline{C}$), 127.4 (2 x Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$), 128.8 (2 x Ar$\underline{C}$H), 129.8 (=$\underline{C}HCO_2t$-Bu), 136.0 (Ar$\underline{C}$H), 136.4-136.6 (m, Ar$\underline{C}$N), 159.4 (dd, *J* 12.7, 250.0, Ar$\underline{C}$F), 162.3 (dd, *J* 12.5, 244, Ar$\underline{C}$F), 165.6 ($\underline{C}$=O), 171.5 ($\underline{C}$=O).

**MS (EI mode)** 433.2 ($M^{+\cdot}$, 6 %), 377.1 (36), 255.1 (99), 210.1 (60), 196.0 (61), 183.1 (65), 166.1 (16), 91.1 (74), 57.1 (28). **HRMS** $C_{23}H_{25}NO_3SF_2$ requires 433.1523 found 433.1523.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2982, 2359, 1713 (C=O, ester), 1668 (C=O, amide), 1484, 1367, 1314, 1153.

***(E)-tert-Butyl* 3-(2-(2-benzylsulfonyl-N-methylacetamido)-3,5-difluorophenyl)acrylate**




$C_{23}H_{25}F_2NO_5S$
Mol. Wt: 465.51

Oxone (3.52 g, 5.73 mmol) was added to solution of *(E)-tert*-butyl 3-(2-(2-benzylsulfanyl-N-methylacetamido)-3,5-difluorophenyl)acrylate **204** (621 mg, 1.43 mmol) in DMF (12 ml) and $H_2O$ (3 ml) and the reaction stirred overnight. The reaction was quenched by addition of $H_2O$ (20 ml) and the mixture extracted in $CH_2Cl_2$ (2 x 30 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *(E)-tert*-butyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)-3,5-difluorophenyl)acrylate as a pale orange oil (634 mg, 1.36 mmol, 95 %) which was used without further purification.

**$\delta_H$ (300 MHz, $CDCl_3$)** 1.55 (9H, s, $C(C\underline{H}_3)_3$), 3.28 (3H, s, $NC\underline{H}_3$), 3.45 (1H, d, AB system, *J* 15.3, 1H of $SO_2C\underline{H}_2CO$), 3.53 (1H, d, AB system, *J* 15.3, 1H of $SO_2C\underline{H}_2CO$), 4.57 (1H, d, AB system, *J* 14.0, 1H of $PhC\underline{H}_2SO_2$), 4.70 (1H, d, AB system, *J* 14.0, 1H of $PhC\underline{H}_2SO_2$), 6.40 (1H, d, J 15.9, =$C\underline{H}CO_2t$-Bu), 6.93-7.00 (1H, m, Ar$\underline{H}$), 7.18-7.22 (1H, m, Ar$\underline{H}$), 7.39-7.44 (3H, m, Ar$\underline{H}$), 7.53-7.58 (3H, m, 2 x ArH + PhCH=).

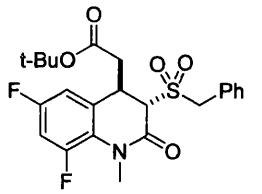
**$\delta_C$ (100 MHz, $CDCl_3$)** 28.3 (3 x C($\underline{C}H_3)_3$), 37.1 (N$\underline{C}H_3$), 52.8 ($SO_2\underline{C}H_2CO$), 59.6 (Ph$\underline{C}H_2SO_2$), 81.8 ($\underline{C}(CH_3)_3$), 106.5 (m, Ar$\underline{C}$F), 110.2 (m, Ar$\underline{C}$F), 126.8 (Ar$\underline{C}$H), 126.9 (=$\underline{C}$HCO), 128.4 (2 x Ar$\underline{C}$), 129.2 (2 x Ar$\underline{C}$H), 129.3 (2 x Ar$\underline{C}$H), 131.4 (2 x Ar$\underline{C}$H), 135.1 (Ar$\underline{C}$), 135.2 (Ph$\underline{C}$H=), 163.5 ($\underline{C}$=O), 164.8 ($\underline{C}$=O). C-F couplings were not seen due to signal to noise ratio.

**MS (EI mode)** 483 ($M^{+\cdot}$ + $NH_4$, 37 %), 427 (40), 273 (30), 213 (36), 108 (100), 91 (24).

**HRMS** $C_{23}H_{29}NO_5SF_2$ requires 483.1760, found 483.1759.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2935, 1708 (C=O, ester), 1664 (C=O, amide), 1448, 1367, 1306, 1249, 1147, 1129, 1037.

***rac-tert*-Butyl 2-(*3S,4R*-3-benzylsulfonyl-6,8-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetate 205**




$C_{23}H_{25}F_2NO_5S$
Mol. Wt: 465.51

$K_2CO_3$ (606 mg, 4.38 mmol) was added to a solution of *(E)-tert*-butyl 3-(2-(2-benzylsulfonyl-N-methylacetamido)-3,5-difluorophenyl)acrylate (510 mg, 1.10 mmol) in DMF (5 ml) at room temperature. The reaction was stirred until complete by TLC (approx 3 h). The reaction was quenched by addition of $H_2O$ (15 ml) and the mixture extracted into $CH_2Cl_2$ (2 x 20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product *tert*-butyl 2-(3-benzylsulfonyl)-6,8-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetate **205** as a brown solid (462 mg, 1.00 mmol, 92 %) which was used without further purification. A portion of the product was recrystallised from hot methanol to provide colourless, rhombic crystals suitable for X-ray analysis.

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

**M.p.** 142-143 °C

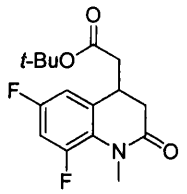
**$\delta_H$ (300 MHz, $CDCl_3$)** 1.36 (9H, s, C($\underline{C}H_3)_3$), 2.45 (2H, app sept, *J* 7.9, $\underline{C}H_2CO_2t$-Bu), 3.59 (3H, d, *J* 6.9, N$\underline{C}H_3$), 3.97 (1H, app t, *J* 7.8, $\underline{C}HCH_2CO_2t$-Bu), 4.12 (1H, s, $BnSO_2\underline{C}HCO$), 4.28 (1H, d, AB system, *J* 14.1, 1H of Ph$\underline{C}H_2$), 4.65 (1H, d, AB system, *J* 14.1, 1H of Ph$\underline{C}H_2$), 6.82-6.90 (2H, m, Ar$\underline{H}$), 7.42-7.45 (3H, m, Ar$\underline{H}$), 7.59-7.62 (2H, m, Ar$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 28.2 (3 x C($\underline{C}H_3)_3$), 33.0 ($C\underline{H}CH_2CO_2$t-Bu), 34.5 (t, *J* 16.0, $NC\underline{H}_3$), 39.8 ($C\underline{H}_2CO_2$t-Bu), 59.7 ($PhC\underline{H}_2SO_2$), 63.5 ($BnSO_2C\underline{H}CO$), 82.4 ($\underline{C}(CH_3)_3$), 105.5 (t, *J* 34.7, Ar$\underline{H}$), 111.7 (m, Ar$\underline{H}$), 127.4 (Ar$\underline{C}$), 129.3 (4 x Ar$\underline{C}$H), 129.5 (2 x Ar$\underline{C}$), 131.7 (Ar$\underline{C}$H), 162.6 ($\underline{C}$=O), 168.6 ($\underline{C}$=O). ArC-F signals were not seen due to signal to noise ratio.

**MS (CI mode)** 483 ($M^{+\cdot}$ + $NH_4$, 45 %), 466 ($M^{+\cdot}$ + H, 12 %), 465 ($M^{+\cdot}$, 5 %), 310 (52), 196 (100). **HRMS** $C_{23}H_{25}NO_5SF_2$ requires 465.1416 found 465.1422.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3079, 2967, 2939, 1726 (C=O, ester), 1664 (C=O, amide), 1491, 1314, 1361, 1134, 1072.

***tert*-Butyl 2-(6,8-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 206**




$C_{16}H_{19}F_2NO_3$
Mol. Wt: 311.32

Cleavage from solution-phase model, *tert*-Butyl 2-(3-benzylsulfonyl)-6,8-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl) acetate **205**.

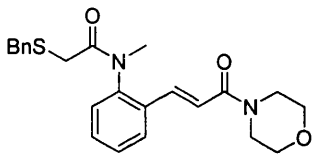
LiCl (32.8 mg, 0.75 mmol) was placed in a dry 25 ml round-bottomed flask and dried under vacuum for 5 min, the flask was then flushed with nitrogen. THF (1 ml) was added followed by a solution of *tert*-butyl 2-(3-(benzylsulfonyl)-6,8-difluoro-1-methyl-2-oxo-1,2,3,4,-tetrahydroquinolin-4-yl)acetate **205** (40.1 mg, 0.086 mmol) in THF (1.5 ml). $SmI_2$ (25 ml, 0.1 M solution in THF) was added and the reaction stirred for 18 h. The reaction mixture was diluted with $CH_2Cl_2$ (10 ml) and quenched with saturated aqueous $NaHCO_3$ (8 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel using 30 % EtOAc/Pet ether as eluent gave *tert*-butyl 2-(6,8-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **206** (12.0 mg, 0.039 mmol, 45 %, unoptimised) as a pale yellow oil.

**$\delta_H$ (300 MHz, $CDCl_3$)** 1.48 (9H, s, $C(CH_3)_3$), 2.48 (2H, app d, *J* 7.5, $C\underline{H}_2CO_2$*t*-Bu), 2.61 (1H, dd, *J* 5.4, 5.1, 1H of $C\underline{H}_2$), 2.74 (1H, dd, *J* 5.4, 5.1, 1H of $C\underline{H}_2$), 3.40-3.47 (1H, m, C$\underline{H}$), 3.45 (3H, d, *J* 6.3, $NC\underline{H}_3$), 6.79-6.86 (2H, m, Ar$\underline{H}$).

**$\delta_C$ (100 MHz, $CDCl_3$)** 28.3 (C($\underline{C}H_3)_3$), 33.4 ($\underline{C}H$), 33.6 (N$\underline{C}H_3$), 37.2 ($\underline{C}H_2$), 38.8 ($\underline{C}H_2CO_2$t-Bu), 81.8 ($\underline{C}(CH_3)_3$), 104.3 (Ar$\underline{C}H$), 110.4 (d, *J* 30.5, Ar$\underline{C}H$), 134.5 (2 x Ar$\underline{C}$), 169.5 ($\underline{C}$=O), 170.4 ($\underline{C}$=O). ArC-F signals were not seen due to signal to noise ratio.
**MS (CI mode)** 329 ($M^{+\cdot}$ + $NH_4$, 91 %), 312 ($M^{+\cdot}$ + H, 100), 273 (18), 256 (49), 196 (15), 160 (18). **HRMS** $C_{16}H_{20}NO_3F_2$ requires 312.1406 found 312.1404.
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2977, 2929, 1726 (C=O, ester), 1683, (C=O, amide), 1605, 1493, 1362, 1310, 1259, 1145.

**2-Bromo-N-(2-bromophenyl)-N-methylacetamide 209** see general procedure A

**2-Benzylsulfanyl-N-[2-(1-(morpholin-4-yl)-1-oxo-prop-2-en-3-yl)phenyl]-N-methylacetamide 220**




$C_{23}H_{26}N_2O_3S$
Mol. Wt: 410.53

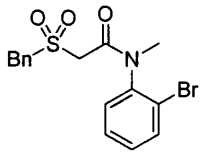
2-Benzylsulfanyl-*N*-(2-bromophenyl)-*N*-methylacetamide **175** (135 mg, 0.39 mmol) was added to a microwave reactor vial. $Pd(OAc)_2$ (13.0 mg, 0.06 mmol), P(*o*-tol)$_3$ (46 mg, 0.15 mmol) and distilled acryloyl morpholine (0.15 ml, 116 mmol) were added to the vessel and it was sealed with a crimp cap septum. The vessel was flushed with argon and dry DMF (0.18 ml) and $NEt_3$ (0.11 ml, 0.77 mmol) were added. The vessel was placed in the microwave cavity and heated to 100 °C for 10 h. The reaction mixture was diluted with $Et_2O$ (10 ml) and quenched with $H_2O$ (5 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then retreated under the same reaction conditions. Purification by flash chromatography on silica gel eluting with 50 % EtOAc/Pet Ether gave 2-benzylsulfanyl-N-[2-(1-(morpholin-4-yl)-1-oxo-prop-2-en-3-yl)phenyl]-N-methylacetamide **220** and as an orange oil (121 mg, 0.29 mmol, 76 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.83 (2H, app d, *J* 14.4, SC$\underline{H}_2$CO), 3.27 (3H, s, NC$\underline{H}_3$), 3.60-3.74 (8H, m, C$\underline{H}_2$ x 4), 3.86 (2H, s, PhC$\underline{H}_2$S), 6.83 (1H, d, *J* 15.6, CH=C$\underline{H}$CO), 7.25-7.41 (8H, m, Ar$\underline{H}$), 7.65 (1H, d, *J* 15.6, C$\underline{H}$=CH), 7.63-7.68 (1Hm, Ar$\underline{H}$).
**$\delta_C$ (100 MHz, $CDCl_3$)** 32.0 (S$\underline{C}H_2$CO), 37.4 (Ph$\underline{C}H_2$S), 37.4 (N$\underline{C}H_3$), 67.1 (4 x $\underline{C}H_2$), 120.5 (CH=$\underline{C}$HCO), 127.3 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.6 (Ar$\underline{C}$H x 2), 128.7 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$), 129.5 (2 x Ar$\underline{C}$H), 129.6 (Ar$\underline{C}$H), 131.1 (Ar$\underline{C}$H), 133.2 (Ar$\underline{C}$), 137.6 (Ph$\underline{C}$H=CH), 137.9 ($\underline{C}$H=), 142.4 (Ar$\underline{C}$), 165.2 ($\underline{C}$=O), 170.0 ($\underline{C}$=O).

**MS (CI mode)** 428 ($M^{+\cdot}$ + $NH_4$, 16 %), 411 (16), 306 (18), 287 (28), 170 (23), 160 (23), 160 (44), 88 (100). **HRMS** $C_{23}H_{30}N_3O_3S$ requires 428.2002 found 428.2000.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2960, 2920, 2854, 1645 (C=O, amide), 1600, 1488, 1451, 1428, 1301, 1228, 1195, 1041, 977.

**2-(Benzylsulfonyl)-N-(2-bromophenyl)-N-methylacetamide 221**




$C_{16}H_{16}BrNO_3S$
Mol. Wt: 382.27

*m*CPBA (1.70 g, max 55 % *m*CPBA, 6.66 mol) was added to a solution of 2-(benzylsulfanyl)-N-(2-bromophenyl)-N-methylacetamide **175** (389 mg, 1.11 mmol) in $CH_2Cl_2$ (5 ml) at 0 °C. The reaction was allowed to warm to room temperature and stirred for until TLC showed the reaction to be complete (3 h). The reaction was quenched by addition of saturated, aqueous $NaHCO_3$ (10 ml) and diluted with $CH_2Cl_2$ (15 ml). The organic phase was washed with water (10 ml), and saturated aqueous $NaHCO_3$ (3 x 20 ml) dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give 2-(benzylsulfonyl)-N-(2-bromophenyl)-N-methylacetamide **221** as a white solid (394 mg, 1.03 mmol, 93 %).

$\delta_H$ **(400 MHz, $CDCl_3$)** 3.23 (3H, s, $NC\underline{H}_3$), 3.34 (1H, d, *J* 17.0, 1H of $SO_2C\underline{H}_2CO$), 3.56 (1H, d, *J* 17.0, 1H of $SO_2C\underline{H}_2CO$), 4.36 (1H, d, *J* 14.0, 1H of $PhC\underline{H}_2SO_2$), 4.80 (1H, d, *J* 14.0, 1H of $PhC\underline{H}_2SO_2$), 7.31-7.57 (7H, m 7 x Ar$\underline{H}$), 7.81-7.99 (2H, m, 2 x Ar$\underline{H}$).

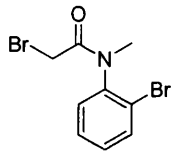
$\delta_C$ **(100 MHz, $CDCl_3$)** 36.7 ($N\underline{C}H_3$), 53.2 ($SO_2\underline{C}H_2CO$), 128.6 ($Ph\underline{C}H_2SO_2$), 128.6 (Ar$\underline{C}$), 129.3 (Ar$\underline{C}$H x 2), 129.9 (Ar$\underline{C}$H), 130.1 (Ar$\underline{C}$H), 130.5 (Ar$\underline{C}$H), 130.9 (Ar$\underline{C}$H), 131.0 (Ar$\underline{C}$H), 131.5 (2 x Ar$\underline{C}$H), 134.2 (2 x Ar$\underline{C}$), 160.3 ($\underline{C}$=O).

**MS (EI mode)** 401 ($M^{+\cdot}$ + $NH_4$ $^{81}$Br, 55 %), 399 ($M^{+\cdot}$ + $NH_4$ $^{79}$Br, 51 %), 220 (32), 188 (28), 173 (25), 165 (61), 148 (39), 108 (99), 93 (38). **HRMS** $BrC_{16}H_{20}N_2O_3S$ requires 399.0373 found 399.0373.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3066, 2990, 2932, 1721, 1662 (C=O), 1578, 1532, 1478, 1431, 1384, 1320, 1219, 1121.

## 4.1.2 GENERAL PROCEDURE A: PREPARATION OF α-BROMO AMIDES FROM SECONDARY ANILINES

### 2-Bromo-N-(2-bromophenyl)-N-methylacetamide 209



$C_9H_9Br_2NO$
Mol. Wt: 306.98

To a solution of 2-bromo-N-methyl aniline **156** (485 mg, 2.60 mmol) in $CH_2Cl_2$ (10 ml) at 0 °C was added $NEt_3$ (0.44 ml, 3.13 mmol) followed by bromoacetyl bromide (0.40 ml, 3.13 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction mixture was diluted with $Et_2O$ (25 ml) and quenched with saturated aqueous $NH_4Cl$ (15 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel using 30 % EtOAc/Pet ether as eluent gave 2-bromo-N-(2-bromophenyl)-N-methylacetamide **209** as a pale orange solid (632 mg, 2.06 mmol, 79 %) which was used without further purification.

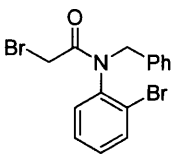
$\delta_H$ **(400 MHz, $CDCl_3$)** 3.25 (3H, s, $NC\underline{H}_3$), 3.53 (1H, d, *J* 11.3, 1H of $C\underline{H}_2$), 3.69 (1H, d, *J* 11.3, 1H of $C\underline{H}_2$), 7.28-7.35 (1H, m, ArC<u>H</u>), 7.39-7.47 (2H, m, Ar<u>H</u>), 7.70-7.73 (1H, d, *J* 7.5, Ar<u>H</u>).

$\delta_C$ **(100 MHz, $CDCl_3$)** 27.2 ($N\underline{C}H_3$), 37.2 ($\underline{C}H_2$), 123.5 (Ar<u>C</u>), 129.6 (Ar<u>C</u>H), 130.3 (Ar<u>C</u>H), 130.9 (Ar<u>C</u>H), 134.4 (Ar<u>C</u>H), 141.9 (Ar<u>C</u>), 167.0 (<u>C</u>=O).

**MS (CI isobutane mode)** 308.0 (100 %, $M^{+\cdot}$, ($^{81}Br$)), 306.0 (54, $M^{+\cdot}$, $^{79}Br$)), 264.0 (18, ($^{81}Br$)), 262.0 (11, ($^{79}Br$)), 228.1 (41, ($^{81}Br$)), 226.1 (28, ($^{79}Br$)), 148.1 (63). **HRMS** $C_9H_{10}NOBr_2$ requires 307.9109 found 307.9106.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 3055, 3005, 2940, 1664 (C=O), 1465, 1363, 1303.

### N-Benzyl-2-bromo-N-(2-bromophenyl)acetamide 210



$C_{15}H_{13}Br_2NO$
Mol. Wt: 383.08

According to general procedure A: 2-Bromo-N-benzyl aniline **227** (1.46 g, 5.61 mmol) was treated with bromoacetyl bromide (0.59 ml, 4.60 mmol) and $NEt_3$ (0.64 ml, 4.60 mmol) in $CH_2Cl_2$ (20 ml) to give N-benzyl-2-bromo-N-(2-bromophenyl)acetamide **210** as a white crystalline solid (1.22 g, 4.60 mmol, 70 %) following purification by flash chromatography eluting with 10 % EtOAc/Pet ether.

**M.p.** 74.5-76.5 °C

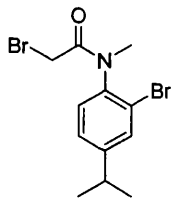
$\delta_H$ **(300 MHz, $CDCl_3$)** 3.56 (1H, d, AB system, *J* 11.4, 1H of $C\underline{H}_2Br$), 3.74 (1H, d, AB system, *J* 11.4, 1H of $C\underline{H}_2Br$), 4.14 (1H, d, AB system, *J* 14.4, 1H of $C\underline{H}_2Ph$), 5.62 (1H, d, AB system, *J* 14.4, 1H of $C\underline{H}_2Ph$), 6.92-6.96 (1H, m, Ar<u>H</u>), 7.23-7.32 (7H, m, Ar<u>H</u>), 7.70-7.75 (1H, m, Ar<u>H</u>).

$\delta_C$ **(100 MHz, $CDCl_3$)** 28.0 ($\underline{C}H_2Br$), 52.5 ($\underline{C}H_2Ph$), 123.8 (Ar<u>C</u>), 128.1 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.9 (2 x Ar<u>C</u>H), 129.6 (2 x Ar<u>C</u>H), 130.8 (Ar<u>C</u>H), 131.6 (Ar<u>C</u>), 134.2 (Ar<u>C</u>), 136.4 (Ar<u>C</u>H), 139.8 (Ar<u>C</u>H), 166.5 (<u>C</u>=O).

**MS (CI mode)** 403 ($M^{+\cdot}$ + $NH_4$, $^{81}Br$ x 2, 49 %), 401 ($M^{+\cdot}$ + $NH_4$, $^{79}Br$, $^{81}Br$, 100 %), 399 ($M^{+\cdot}$ + $NH_4$, $^{79}Br$ x 2, 60 %), 386 ($^{81}Br$ x 2, 23), 384 ($^{79}Br$, $^{81}Br$, 56), 382 ($^{79}Br$ x 2, 28), 264, 106. **HRMS** $C_{15}H_{17}NO_2{}^{79}Br$ requires 398.9702 found 398.9699.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 3030, 2338, 1659 (C=O), 1430, 1388, 1292, 1195, 1023, 880.

**2-Bromo-N-(2-bromo-4-*iso*propylphenyl)-N-methylacetamide 211**




$C_{12}H_{15}Br_2NO$
Mol. Wt: 349.06

According to general procedure A: 2-Bromo-4-*iso*propyl-N-methyl aniline **224** (5.04 g, 22.0 mmol) was treated with bromoacetyl bromide (3.37 ml, 22.0 mmol) and $NEt_3$ (3.70 ml, 26.4 mmol) in $CH_2Cl_2$ (80 ml) to give 2-bromo-N-(2-bromo-4-*iso*propylphenyl)-N-methylacetamide **211** as an orange oil (5.79 g, 16.6 mmol, 75%) following purification by flash chromatography eluting with 30 % EtOAc/Pet ether.

$\delta_H$ **(400 MHz, $CDCl_3$)** 1.29 (6H, d, *J* 7.8, $CH(C\underline{H}_3)_2$), 2.96 (1H, sept, J 7.8, $C\underline{H}(CH_3)_2$), 3.56 (1H, d, AB system, *J* 9.2, 1H of $C\underline{H}_2Br$), 3.69 (1H, d, AB system, *J* 9.2, 1H of $C\underline{H}_2Br$), 7.22-7.34 (2H, m, Ar<u>H</u>), 7.76 (1H, s, Ar<u>H</u>).

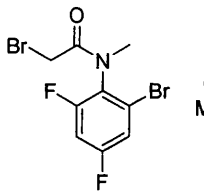
$\delta_C$ **(100 MHz, $CDCl_3$)** 24.0 (2 x $CH(\underline{C}H_3)_2$), 27.5 ($CH_2$), 34.0 ($\underline{C}H(CH_3)_2$), 37.0 ($N\underline{C}H_3$), 123.0 (Ar$\underline{C}$), 127.6 (Ar$\underline{C}$H), 129.7 (Ar$\underline{C}$H), 132.1 (Ar$\underline{C}$H), 139.4 (Ar$\underline{C}$), 152.1 (Ar$\underline{C}$), 166.8 ($\underline{C}$=O).

**MS (CI mode)** 352 ($M^{+\cdot}$, $^{81}Br$ x 2, 16 %), 350 ($M^{+\cdot}$, $^{81}Br$, $^{79}Br$, 38 %), 348 ($M^{+\cdot}$, $^{79}Br$ x 2, 24 %), 272 ($^{81}Br$ x 2, 21)270 ($^{81}Br$, $^{79}Br$, 32), 268 ($^{79}Br$ x 2, 18), 207 (28), 190 (100).

**HRMS** $C_{12}H_{16}NO^{79}Br_2$ requires 347.9593 found 347.9599.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 2960, 2929, 2871, 1667 (C=O, amide), 1490, 1429, 1370, 1305, 1216, 1119, 1052, 1027, 881.

**2-Bromo-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide 212**




$C_9H_7Br_2F_2NO$
Mol. Wt: 342.96

According to general procedure A: 2-Bromo-4,6-difluoro-*N*-methyl aniline **223** (1.16 g, 5.22 mmol) was treated with bromoacetyl bromide (0.55 ml, 6.27 mmol) and $NEt_3$ (0.88 ml, 6.27 mmol) in $CH_2Cl_2$ (10 ml) to give 2-bromo-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide **212** as an orange oil (1.62 g, 4.72 mmol, 90%) following purification by flash chromatography eluting with 30 % EtOAc/Pet ether.

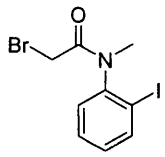
$\delta_H$ **(400 MHz, $CDCl_3$)** 3.23 (3H, s, $NC\underline{H}_3$), 3.61 (1H, d, AB system, *J* 15.0, 1H of $C\underline{H}_2$), 3.68 (1H, d, AB system, *J* 15.0, 1H of $C\underline{H}_2$), 7.00-7.04 (1H, m, Ar$\underline{H}$), 7.29-7.33 (1H, m, Ar$\underline{H}$).

$\delta_C$ **(100 MHz, $CDCl_3$)** 26.5 ($N\underline{C}H_3$), 36.2 ($CH_2$), 105.5 (t, *J* 26.0, Ar$\underline{C}$H), 117.2 (d, *J* 25.0, Ar$\underline{C}$H), 166.9 ($\underline{C}$=O), ArC-F signals not seen due to signal to noise ratio.

**MS (CI mode)** 363 ($M^{+\cdot}$ $^{81}Br$, $^{81}Br$, 45 %), 361 ($M^{+\cdot}$ $^{79}Br$, $^{81}Br$, 90 %) 359 ($M^{+\cdot}$ $^{79}Br$, $^{79}Br$, 49 %), 283 (29), 264 (78), 201 (54), 184 (99).

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 3087, 2949, 1674 (C=O), 1587, 1484, 1427, 1371, 1315, 1169, 1126, 995.

**2-Bromo-N-(2-iodophenyl)-N-methylacetamide 222**



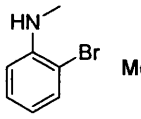
$C_9H_9BrINO$
Mol. Wt: 353.98

According to general procedure A: 2-Iodo-N-methyl aniline **225** (442 mg, 1.90 mmol) was treated with bromoacetyl bromide (0.20 ml, 2.28 mmol) and $NEt_3$ (0.32 ml, 2.28 mmol) in $CH_2Cl_2$ (10 ml) to give 2-bromo-N-(2-iodophenyl)-N-methylacetamide **222** as an orange oil (491 mg, 1.45 mmol, 76 %) following flash chromatography eluting with 40 % EtOAc/Pet ether.

$\delta_H$ **(500 MHz, $CDCl_3$)** 3.03 (3H, s, $NC\underline{H}_3$), 3.29 (1H, d, AB system, *J* 11.5, 1H of $C\underline{H}_2$), 3.46 (1H, d, AB system, *J* 11.5, 1H of $C\underline{H}_2$), 6.93-7.08 (1H, m, Ar$\underline{H}$), 7.08-7.30 (2H, m, Ar$\underline{H}$), 7.76 (1H, m, Ar$\underline{H}$).
$\delta_C$ **(100 MHz, $CDCl_3$)** 27.7 ($N\underline{C}H_3$), 37.3 ($\underline{C}H_2$), 129.6 (2 x Ar$\underline{C}$H), 130.5 (Ar$\underline{C}$H), 130.9 (Ar$\underline{C}$H), 140.7 (Ar$\underline{C}$), 145.4 (Ar$\underline{C}$), 166.6 ($\underline{C}$=O).
**MS (CI mode)** 373 ($M^{+\cdot}$ + $NH_4$, $^{81}Br$, 82 %), 371 ($M^{+\cdot}$ + $NH_4$, $^{79}Br$, 99 %), 293 (11), 165 (76), 148 (38). **HRMS** $C_9H_{13}N_2OBrI$ requires 370.9250 found 370.9253.
$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 3052, 2931, 2348, 1660 (C=O), 1576, 1459, 1434, 1370, 1220, 1020.

4.1.3 GENERAL PROCEDURE B: N-METHYLATION OF PRIMARY ANILINES

**2-Bromo-N-methyl aniline 156** [61]



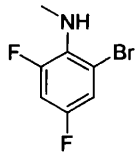
$C_7H_8BrN$
Mol. Wt: 186.05

*n*-BuLi (9.50 ml of a 2.5 M sol$^n$ in hexanes, 23.0 mmol) was added to a solution of 2-bromoaniline (8.00 g, 46.0 mmol) in THF (60 ml) at -40 °C, stirred for 15 min, allowed to warm to room temperature and stirred for a further 45 min. MeI (1.43 ml, 23.0 mmol) was added at -60 °C, stirred for 15 min, warmed to room temperature and stirred overnight. The procedure was repeated with a further 0.5 eq portion of *n*-BuLi/MeI and again stirred overnight. The reaction was quenched with water (40 ml) and extracted with ethyl acetate (3 x 40 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The

crude product was purified by column chromatography on silica gel using 3 % ethyl acetate: pet ether as eluent and gave the product **156** as an orange oil (6.52 g, 35.0 mmol, 76 % yield), and recovered 2-bromoaniline (0.85 g, 4.91 mmol, 10 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.74 (3H, s, $C\underline{H}_3$), 4.22 (1H, bs, N$\underline{H}$), 6.43-6.50 (2H, m, Ar$\underline{H}$), 7.08 (1 H, t, *J* 8.4 Ar$\underline{H}$), 7.30 (1H, d, *J* 6.4, Ar$\underline{H}$).
**$\delta_C$ (100 MHz)** 31.0 ($\underline{C}H_3$), 110.0 (Ar$\underline{C}$), 111.2 (Ar$\underline{C}$H), 118.0 (Ar$\underline{C}$H), 129.0 (Ar$\underline{C}$H), 134.4 (Ar$\underline{C}$H), 146.4 (Ar$\underline{C}$).
**MS (EI mode)** 187.0 ($M^{+\cdot}$, $^{81}Br$, 95 %), 186.0 (90), 185.0 ($M^{+\cdot}$, $^{79}Br$, 99 %), 184.0 (87), 105.1 (25), 83.0 (74), 77.1 (34), 47.0 (13). **HRMS** $C_7H_7NBr$ requires 183.9762 found 183.9758.

**2-Bromo-4,6-difluoro-N-methyl aniline 223** [61]

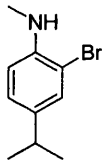



$C_7H_6BrF_2N$
Mol. Wt: 222.03

According to general procedure B: 2-bromo-4,6-fluoroaniline (10.00 g, 48.1 mmol) was treated with *n*-BuLi (11.3 ml of a 2.13 M sol$^n$ in hexanes, 24.0 mmol) and MeI (1.50 ml, 24.0 mmol) in THF (60 ml) to give 2-bromo-4,6-difluoro-N-methyl aniline **223** as an orange oil (8.43 g, 38.0 mmol, 79 % yield) following purification by flash chromatography eluting with 5 % EtOAc/ Pet ether.

**$\delta_H$ (400 MHz, $CDCl_3$)** 2.91 (3H, s, $NC\underline{H}_3$), 6.67-6.74 (1H, m, Ar$\underline{H}$), 6.92-6.97 (1H, m, Ar$\underline{H}$).

**2-Bromo-4-*iso*propyl-N-methylaniline 224**



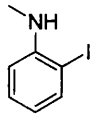

$C_{10}H_{14}BrN$
Mol. Wt: 228.13

According to general procedure B: 2-bromo-4-*iso*propyl aniline (7.17 g, 33.5 mmol) was treated with *n*-BuLi (7.9 ml of a 2.13 M sol$^n$ in hexanes, 16.7 mmol) and MeI (1.04 ml, 16.7 mmol) in THF (50 ml) to give 2-bromo-4-*iso*propyl-N-methyl aniline **224** as an

orange oil (8.04 g, 22.1 mmol, 66 % yield) following purification by flash chromatography eluting with 10 % EtOAc/ Pet ether.

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.23 (6H, d, *J* 7.0, 2 x $CH_3$), 2.83 (1H, sept, *J* 7.0, C<u>H</u>), 2.90 (3H, s, NC<u>H</u>$_3$), 6.60 (1H, d, *J* 8.3, Ar<u>H</u>), 7.10 (1H, d, *J* 8.3, Ar<u>H</u>), 7.32 (1H, s, Ar<u>H</u>).
**$\delta_C$ (100 MHz)** 24.5 (2 x <u>C</u>$H_3$), 31.2 (N<u>C</u>$H_3$), 33.4 (<u>C</u>H), 110.0 (Ar<u>C</u>), 111.2 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 130.6 (Ar<u>C</u>H), 138.9 (Ar<u>C</u>), 144.4 (Ar<u>C</u>).
**MS (EI mode)** 229.1 ($M^{+\cdot}$, $^{81}Br$, 26 %), 227.06 ($M^{+\cdot}$, $^{79}Br$, 27 %), 214.0 ($^{81}Br$, 64), 212.0 ($^{79}Br$, 70), 133.1 (43), 83.0 (99).

**2-Iodo-N-methylaniline 225** [97]

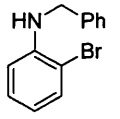



$C_7H_8IN$
Mol. Wt: 233.05

According to general procedure B: 2-iodoaniline (4.00 g, 18.3 mmol) was treated with *n*-BuLi (3.65 ml of a 2.5 M sol$^n$ in hexanes, 9.13 mmol) and MeI (0.57 ml, 9.13 mmol) in THF (45 ml) to give 2-iodo-N-methyl aniline **225** as an orange oil (2.46 g, 10.6 mmol, 58 % yield) following purification by flash chromatography eluting with 10 % EtOAc/ Pet ether.

**$\delta_H$ (400 MHz, $CDCl_3$)** 3.09 (3H, s, NC<u>H</u>$_3$), 6.44-6.49 (2H, m, 2 x ArC<u>H</u>), 7.15-7.18 (1H, m, Ar<u>H</u>), 7.56-7.59 (1H, m, Ar<u>H</u>).

**2-Bromo-N-benzylaniline 227**




$C_{13}H_{12}BrN$
Mol. Wt: 262.15

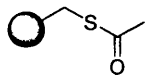
To a solution of 2-bromoaniline (4.00 g, 23.3 mmol) and $NEt_3$ (3.89 ml, 28.0 mmol) in $CH_2Cl_2$ (120 ml) at 0 °C was added benzoyl chloride (2.98 ml, 25.1 mmol). The reaction was stirred at room temperature overnight and quenched by addition of $H_2O$ (100 ml). The organic phase was washed with $H_2O$ (80 ml), saturated aqueous $NaHCO_3$ (4 x 80 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude benzoyl amide as a pale orange solid (5.43 g, 19.9 mmol). The crude amide was dissolved in THF (100 ml) and cooled to 0 °C and $LiAlH_4$ (1.66 g, 43.8 mmol) added.

The reaction was stirred at room temperature overnight and quenched with $H_2O$ (100 ml). The organic phase was washed with $H_2O$ (3 x 50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2-bromo-N-benzylaniline **227** as a pale yellow oil (5.74 g, 21.9 mmol, 94 % overall).

**$\delta_H$ (500 MHz, $CDCl_3$)** 4.87 (2H, s, C$\underline{H}_2$), 4.87 (1H, bs, N$\underline{H}$), 6.66-6.70 (2H, m, 2 x Ar$\underline{H}$), 7.20-7.55 (7H, m, 7 x Ar$\underline{H}$).
**$\delta_C$ (100 MHz)** 48.3 ($\underline{C}H_2$), 110.0 (Ar$\underline{C}$), 112.0 (Ar$\underline{C}$H), 118.3 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$H), 127.7 (2 x Ar$\underline{C}$H), 128.8 (2 x Ar$\underline{C}$H), 129.1 (Ar$\underline{C}$H), 132.7 (Ar$\underline{C}$H), 139.0 (Ar$\underline{C}$), 145.1 (Ar$\underline{C}$).
**MS (CI mode)** 264 ($M^{+\cdot}$, $^{81}Br$, 92 %), 262 ($M^{+\cdot}$, $^{79}Br$, 99 %). **HRMS** $C_{13}H_{12}NBr$ requires 261.0148 found 261.0146.

## 4.2 SOLID-PHASE SYNTHESIS

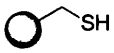
**Merrifield thioacetate resin** [39]




Merrifield resin (5.00 g, 6.00 mmol) was swollen in DMF (50 ml) for 15 min. Potassium thioacetate (1.88 g, 16.5 mmol) in DMF (10 ml) was added and the reaction mixture stirred slowly at room temperature for 24 h before washing according to the standard procedure.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2917, 2023, 1687 (C=O), 1493, 1450, 1130.

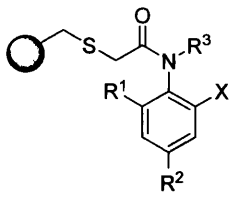
**Thiol resin 48** [39]




Thioacetate resin (5.15 g, 6.13 mmol) was swollen in THF for 15 min. $LiBH_4$ (0.66 g, 30.6 mmol) was added and the reaction mixture stirred slowly at room temperature for 48 h. The reaction was then quenched by dropwise addition of MeOH and washed according to the standard procedure.

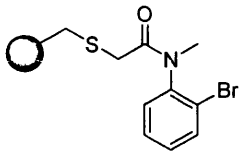
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3024, 2918, 1601, 1493, 1450, 1065.

## 4.2.1 GENERAL PROCEDURE C: IMMOBILISATION OF α-BROMO AMIDES USING THIOL RESIN **48**



| $R^1$ | $R^2$ | $R^3$ | X | No. |
|---|---|---|---|---|
| H | H | H | Br | **151a** |
| H | H | Bn | Br | **210a** |
| H | $^i$Pr | Me | Br | **211a** |
| F | F | Me | Br | **212a** |
| H | H | Me | Br | **216** |
| H | H | Me | I | **222a** |

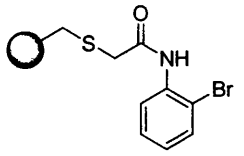
**S-Merrifield supported 2-sulfanyl-N-(2-bromophenyl)-N-methylacetamide 216**



Thiol resin **48** (1.00 g, 1.20 mmol) was swollen in DMF (10 ml) for 15 min. $NEt_3$ (0.85 ml, 6.00 mmol) was added followed by a solution of 2-bromo-N-(2-bromophenyl)-N-methylacetamide **209** (0.737 g, 2.40 mmol) in DMF (5 ml) and the reaction mixture stirred slowly for 24 h before washing according to the standard procedure.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2918, 1660 (C=O), 1493, 1450, 1365, 1061, 1028.
$\delta_c$ **(MAS, 75 MHz, $CH_2Cl_2$)** 23.8 ($\underline{C}H_2S$), 36.9 ($NC\underline{H}_3$), 124.0 (Ar$\underline{C}$Br), 129.6 (Ar$\underline{C}$H), 130.6 (Ar$\underline{C}$H), 131.0 (Ar$\underline{C}$H), 134.5 (Ar$\underline{C}$H), 142.9 (Ar$\underline{C}$N), 170.2 ($\underline{C}$=O).

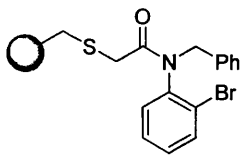
**S-Merrifield supported-2-sulfanyl-N-(2-bromophenyl)acetamide 151a**



According to general procedure C: Thiol resin **48** (1.20 g, 1.49 mmol) was treated with 2-bromo-N-(2-bromophenyl) acetamide **151** (872 mg, 2.78 mmol) in $NEt_3$ and DMF.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3024, 2919, 1691 (C=O, amide), 1589, 1504, 1435, 1297, 1018.

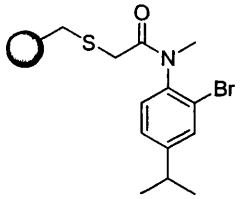
**S-Merrifield supported 2-sulfanyl-N-(2-bromophenyi)-N-benzylacetamide 210a**




According to general procedure C: Thiol resin **48** (1.33 g, 1.59 mmol) was treated with 2-bromo-N-(2-bromo)-N-benzylacetamide **210** (1.22 g, 3.18 mmol) in $NEt_3$ and DMF.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2914, 1658 (C=O), 1428, 1366, 1294.

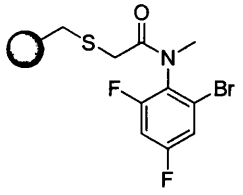
**S-Merrifield supported 2-sulfanyl-N-(2-bromo-4-*iso*propylphenyl)-N-methylacetamide 211a**




According to general procedure C: Thiol resin **48** (2.00 g, 2.40 mmol) was treated with 2-bromo-N-(2-bromo-4-*iso*propylphenyl)-N-methylacetamide **211** (2.51 g, 7.20 mmol) in $NEt_3$ and DMF.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3024, 2920, 1661(C=O), 1601, 1491, 1449, 1365, 1308, 1122, 1058, 1026.

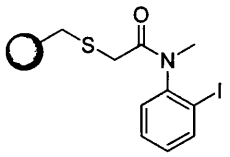
**S-Merrifield supported 2-sulfanyl-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide 212a**



According to general procedure C: Thiol resin **48** (3.94 g, 4.73 mmol) was treated with 2-bromo-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide **212** (3.24 g, 9.46 mmol) in $NEt_3$ and DMF.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3024, 2919, 1671 (C=O), 1590, 1481, 1428, 1363, 1313, 1111, 1057, 995.

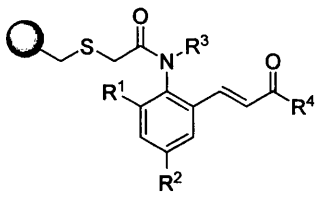
**S-Merrifield supported 2-sulfanyl-N-(2-iodophenyl)-N-methylacetamide 222a**



According to general procedure C: Thiol resin **48** (650 mg, 0.78 mmol) was treated with 2-bromo-N-(2-iodophenyl)-N-methylacetamide **222** (550 mg, 1.56 mmol) in $NEt_3$ and DMF.

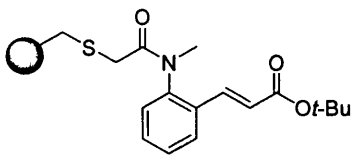
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3024, 2917, 1659 (C=O), 1597, 1442, 1364, 1060, 904.

4.2.2 GENERAL PROCEDURE D: PALLADIUM-CATALYSED HECK REACTIONS ON SOLID-PHASE



| $R^1$ | $R^2$ | $R^3$ | $R^4$ | No. |
|---|---|---|---|---|
| H | H | H | O*t*-Bu | **151b** |
| H | H | Me | Morph | **209b** |
| H | H | Bn | O*t*-Bu | **210b** |
| H | $^iPr$ | Me | O*t*-Bu | **211b** |
| F | F | Me | O*t*-Bu | **212b** |
| H | H | Me | O*t*-Bu | **217** |

**S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl]-N-methyl acetamide 217**

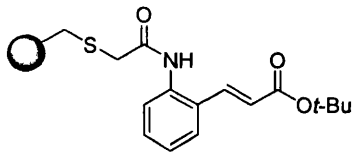


S-Merrifield supported 2-sulfanyl-N-(2-bromophenyl)-N-methylacetamide **216** (970 mg, 0.95 mmol) was added to a microwave vial equipped with magnetic stirrer bar and swollen in DMF (0.33 ml) for 15 min. $Pd(OAc)_2$ (21.3 mg, 0.95 mmol) and P(*o*-tol)$_3$ (28.9 mg, 0.95 mmol) were added followed by $NEt_3$ (0.53 ml, 3.80 mmol) and *o*-xylene (0.81 mmol). The vial was stirred and flushed with nitrogen before sealing with a crimp cap. The vial was placed in the microwave cavity and heated to 100 °C for 20 h. The resin was then washed using the standard procedure and dried under vacuum before retreatment as above.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3023, 2923, 2861, 1723 (C=O, ester), 1661 (C=O, amide), 1449, 1366, 1148, 1063.

$\delta_c$ **(MAS, 75 MHz, $CD_2Cl_2$)** 28.5 (C($\underline{C}H_3)_3$), 33.1 (S$\underline{C}H_2$CO), 80.8 ($\underline{C}(CH_3)_3$), 123.8-138.1 (ArCH signals + support), 165.9 (C=O, ester), 169.5 (C=O, amide).

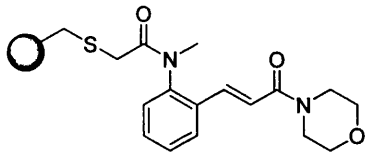
**S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl] acetamide 151b**




According to general procedure D: S-Merrifield supported 2-sulfanyl-N-(2-bromophenyl) acetamide **151a** (1.39 g, 1.35 mmol) was treated with *tert*-butyl acrylate (2.37 ml, 16.2 mmol), $Pd(OAc)_2$ (30.2 mg, 0.14 mmol), P(*o*-tol)$_3$ (41.0 mg, 0.14 mmol) and $NEt_3$ (0.38 ml, 2.70 mmol) in DMF (1.5 ml).

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2919, 1716 (C=O, ester), 1696 (C=O, amide), 1515, 1448, 1296, 1147.

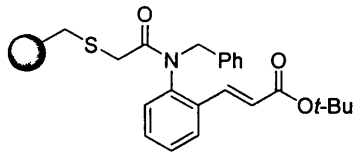
**S-Merrifield supported-2-sulfanyl-N-[2-(1-(morpholin-4-yl)-1-oxo-prop-2-en-3-yl)phenyl]-N-methylacetamide 209b**



According to general procedure D: S-Merrifield supported 2-sulfanyl-N-(2-bromophenyl)-N-methylacetamide **216** (642 mg, 0.58 mmol) was treated with acryloyl morpholine (0.44 ml, 3.51 mmol), $Pd(OAc)_2$ (19.7 mg, 0.09 mmol), P(*o*-tol)$_3$ (26.7 mg, 0.09 mmol), and $NEt_3$ (0.16 ml, 1.17 mmol) in DMF.

**$\upsilon_{max}$ (ATR, cm$^{-1}$)** 3017, 2918, 1651(C=O, amide x 2), 1435, 1365, 1303, 1228, 1114.

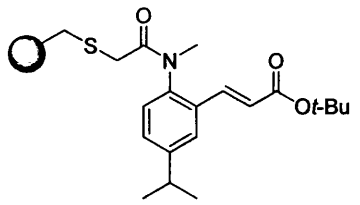
**S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl) phenyl]-N-benzyl acetamide 210b**




According to general procedure D: S-Merrifield supported 2-sulfanyl-N-(2-bromo)-N-benzylacetamide **210a** (600 mg, 0.88 mmol) was treated with *tert*-butyl acrylate (0.93 ml, 6.33 mmol), $Pd(OAc)_2$ (11.9 mg, 0.05 mmol), P(*o*-tol)$_3$ (16.1 mg, 0.05 mmol), and $NEt_3$ (0.15 ml, 1.06 mmol) in DMF and *o*-xylene.

**$\upsilon_{max}$ (ATR, cm$^{-1}$)** 3026, 2920, 1713 (C=O, ester), 1659 (C=O, amide), 1600, 1493, 1474, 1452, 1390, 1367, 1319, 1147, 756.

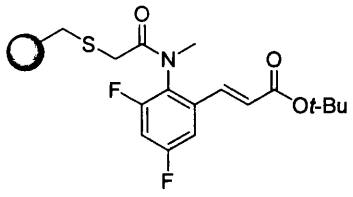
**S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4-*iso*propylphenyl]-N-methyl acetamide 211b**




According to general procedure D: S-Merrifield supported 2-sulfanyl-N-(2-bromo-4-*iso*propylphenyl)-N-methylacetamide **211a** (1.50 mg, 1.37 mmol) was treated with *tert*-butyl acrylate (2.10 ml, 16.4 mmol), $Pd(OAc)_2$ (30.6 mg, 0.14 mmol), P(*o*-tol)$_3$ (41.5 mg, 0.14 mmol), and $NEt_3$ (0.38 ml, 2.73 mmol) in DMF and *o*-xylene.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3017, 2916, 1721(C=O, ester), 1662 (C=O, amide), 1481, 1443, 1366, 1147.

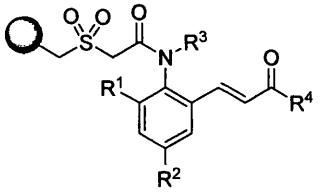
**S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4,6-difluorophenyl]-N-methyl acetamide 212b**




According to general procedure D: S-Merrifield supported 2-sulfanyl-N-(2-bromo-4,6-difluorophenyl)-N-methylacetamide **212a** (2.50 g, 2.28 mmol) was treated with *tert*-butyl acrylate (3.50 ml, 27.3 mmol), $Pd(OAc)_2$ (51.0 mg, 0.23 mmol), P(*o*-tol)$_3$ (69.0 mg, 0.23 mmol), and $NEt_3$ (0.64 ml, 4.55 mmol) in DMF.

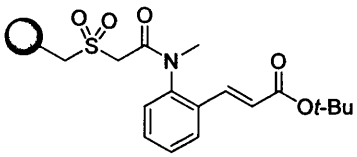
$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3016, 2916, 1723 (C=O, ester), 1671 (C=O, amide), 1599, 1449, 1358, 1251, 1142.

4.2.3 GENERAL PROCEDURE E: OXIDATION OF SULFIDES TO SULFONES




| $R^1$ | $R^2$ | $R^3$ | $R^4$ | No. |
|---|---|---|---|---|
| H | H | H | O*t*-Bu | **151c** |
| H | H | Me | Morph | **209c** |
| H | H | Bn | O*t*-Bu | **210c** |
| H | $^i$Pr | Me | O*t*-Bu | **237** |
| F | F | Me | O*t*-Bu | **212c** |
| H | H | Me | O*t*-Bu | **217c** |

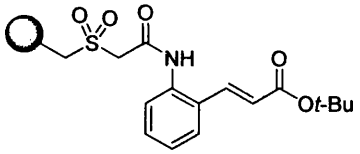
**S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl]-N-methyl acetamide 217c**



S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl]-N-methyl acetamide **217** (1.05 g, 0.99 mmol) was swollen in $CH_2Cl_2$ (8 ml) for 15 min and cooled to 0 °C. $K_2CO_3$ (273 mg, 1.97 mmol) was added followed by *m*CPBA (443 mg, max. *m*CPBA 77 %, 1.97 mmol) and the reaction allowed to warm to room temperature. The reaction was stopped after 30 min by filtration of the resin, washing and drying.

**$\upsilon_{max}$ (ATR, cm$^{-1}$)** 3024, 2969, 2922, 2860, 1724 (C=O, ester), 1660 (C=O, amide), 1602, 1490, 1450, 1367, 1147, 1061.

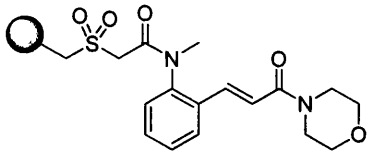
**S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl] acetamide 151c**




According to general procedure E: S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl] acetamide **151b** (1.80 g, 1.67 mmol) was treated with *m*CPBA (750 mg, 3.35 mmol) and $K_2CO_3$ (463 mg, 3.35 mmol) in $CH_2Cl_2$ (5 ml).

**$\upsilon_{max}$ (ATR, cm$^{-1}$)** 3062, 3024, 2973, 2920, 2852, 1724 (C=O, ester), 1698 (C=O, amide), 1598, 1493, 1386, 1322, 1250.

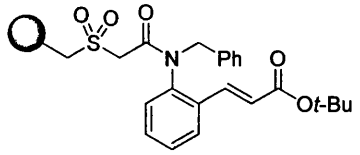
**S-Merrifield supported-2-sulfonyl-N-[2-(1-(morpholin-4-yl)-1-oxo-prop-2-en-3-yl)phenyl]-N-methylacetamide 209c**




According to general procedure E: S-Merrifield supported-2-sulfonyl-N-[2-(1-(morpholin-4-yl)-1-oxo-prop-2-en-3-yl)phenyl]-N-methylacetamide **209b** (705 mg, 0.61 mmol) was treated with *m*CPBA (272 mg, 1.21 mmol) and $K_2CO_3$ (168 mg, 1.21 mmol) in $CH_2Cl_2$ (5 ml).

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3058, 3024, 2918, 2853, 1644 (C=O, amide x 2), 1607, 1488, 1448, 1369, 1319, 1113, 1028, 1060, 882.

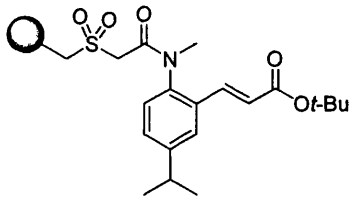
**S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl) phenyl]-N-benzyl acetamide 210c**




According to general procedure E: S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl) phenyl]-N-benzyl acetamide **210b** (610 mg, 0.51 mmol) was treated with *m*CPBA (230 mg, 1.02 mmol) and $K_2CO_3$ (142 mg, 1.02 mmol) in $CH_2Cl_2$ (4 ml).

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3060, 3026, 2978, 2923, 1724 (C=O, ester), 1655 (C=O, amide), 1600, 1492, 1451, 1391, 1366, 1324, 1255, 1147, 1060, 1030, 755.

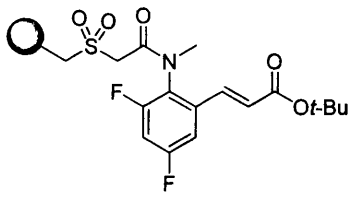
**S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4-*iso*propylphenyl]-N-methyl acetamide 237**




According to general procedure E: S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4-*iso*propylphenyl]-N-methyl acetamide **211b** (1.60 g, 1.41 mmol) was treated with *m*CPBA (631 mg, 2.42 mmol) and $K_2CO_3$ (389 mg, 2.82 mmol) in $CH_2Cl_2$ (10 ml).

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3017, 2921, 1723 (C=O, ester), 1660 (C=O, amide), 1493, 1450, 1367, 1142, 1057.

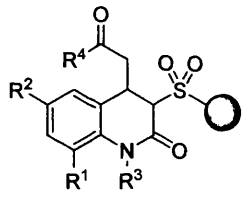
**S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4,6-difluorophenyl]-N-methyl acetamide 212c**



According to general procedure E: S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4,6-difluorophenyl]-N-methyl acetamide **212b** (2.81 g, 2.44 mmol) was treated with *m*CPBA (1.10 g, 4.89 mmol) and $K_2CO_3$ (679 mg, 4.89 mmol) in $CH_2Cl_2$ (10 ml).

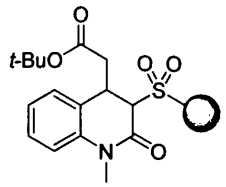
**$\upsilon_{max}$ (ATR, cm$^{-1}$)** 2922, 1724 (C=O, ester), 1668 (C=O, amide), 1597, 1450, 1367, 1319, 1252, 1057.

4.2.4 GENERAL PROCEDURE F: CYCLISATION OF SOLID-SUPPORTED SULFONE SUBSTRATES



| $R^1$ | $R^2$ | $R^3$ | $R^4$ | No. |
|---|---|---|---|---|
| H | H | H | O*t*-Bu | **151d** |
| H | H | Me | Morph | **209d** |
| H | H | Bn | O*t*-Bu | **210d** |
| H | $^i$Pr | Me | O*t*-Bu | **234** |
| F | F | Me | O*t*-Bu | **212d** |
| H | H | Me | O*t*-Bu | **218** |

**S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate 218**

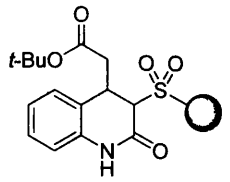


S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl]-N-methyl acetamide **217c** (1.05 g, 0.96 mmol) was swollen in DMF (7 ml) for 15 min.

$K_2CO_3$ (1.06 g, 7.64 mmol) was added and the reaction mixture stirred slowly overnight before washing using the standard procedure.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3023, 2973, 2921, 2855, 1725 (C=O, ester), 1661 (C=O, amide), 1488, 1449, 1367, 1148, 1060.

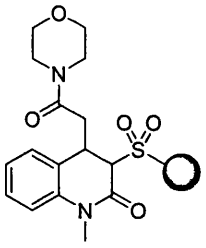
**S-Merrifield supported *tert*-butyl-2-(2-oxo-3-sulfonyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate 151d**




According to general procedure F: S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)phenyl] acetamide **151c** (2.64 g, 2.38 mmol) was treated with $K_2CO_3$ (1.97 g, 14.3 mmol) in DMF (15 ml).

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3058, 3024, 2977, 2920, 2850, 1723 (C=O, ester), 1698 (C=O, amide), 1599, 1517, 1492, 1449, 1365, 1251, 1026.

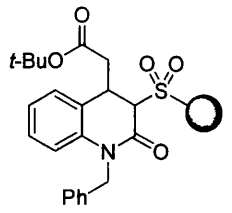
**S-Merrifield supported-1-methyl-2-oxo-4-[2-(morpholin-4-yl)-2-oxo-ethyl]-3-sulfonyl-1,2,3,4-tetrahydroquinoline 209d**




According to general procedure F: S-Merrifield supported-2-sulfonyl-N-[2-(1-(morpholin-4-yl)-1-oxo-prop-2-en-3-yl)phenyl]-N-methylacetamide **209c** (700 mg, 0.59 mmol) was treated with $K_2CO_3$ (488 mg, 3.53 mmol) in DMF (6 ml).

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3017, 2918, 1644 (C=O, amide x 2), 1443, 1369, 1308, 1229, 1028.

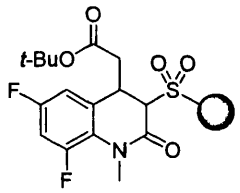
**S-Merrifield supported *tert*-butyl-2-(1-benzyl-2-oxo-3-sulfonyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate 210d**




According to general procedure F: S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl) phenyl]-N-benzyl acetamide **210c** (605 mg, 0.51 mmol) was treated with $K_2CO_3$ (421 mg, 3.05 mmol) in DMF (6 ml).

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3058, 3026, 2977, 2920, 1724 (C=O, ester), 1660 (C=O, amide), 1600, 1493, 1451, 1390, 1367, 1323, 1255, 1147, 1060, 1029, 752.

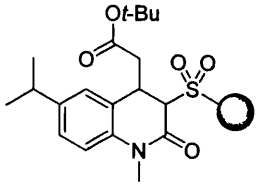
**S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-7,9-difluoro-1,2,3,4-tetrahydroquinolin-4-yl) acetate 212d**




According to general procedure F: S-Merrifield supported-2-sulfanyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4,6-difluorophenyl]-N-methyl acetamide **220c** (2.94 g, 2.47 mmol) was treated with $K_2CO_3$ (1.37 g, 9.88 mmol) in DMF (15 ml).

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2921, 1724 (C=O, ester), 1669 (C=O, amide), 1597, 1481, 1443, 1366, 1252, 1142.

**S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate 234**

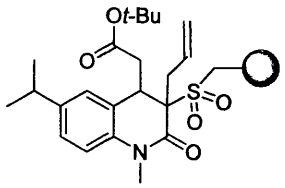


According to general procedure F: S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4-*iso*propylphenyl]-N-methyl acetamide **237** (1.60 g, 1.30 mmol) was treated with $K_2CO_3$ (1.52 g, 11.0 mmol) in DMF (15 ml).

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 2922, 1721(C=O, ester), 1662 (C=O, amide), 1601, 1443, 1364, 1143.

4.2.5 GENERAL PROCEDURE G: ALKYLATION OF CYCLIC SULFONES

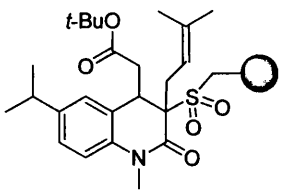
**S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-allyl-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate 235**




S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **234** (195 mg, 0.43 mmol) was swollen in DMF (6 ml) for 15 min. $K_2CO_3$ (353 mg, 2.55 mmol), KI (424 mg, 2.55 mmol) and allyl bromide (0.22 ml, 2.55 mmol) were added and the reaction mixture stirred at 60 °C overnight before filtering and washing using the standard procedure.

**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3017, 2922, 1724 (C=O, ester), 1660 (C=O, amide), 1603, 1443, 1366, 1142, 1056.

**S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-prenyl-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate 236** [93]



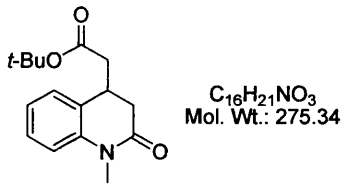

S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **234** (625 mg, 0.54 mmol) was swollen in DMF (3 ml)

for 15 min. $K_2CO_3$ (451 mg, 3.26 mmol), KI (541 mg, 3.26 mmol), DBU (0.49 ml, 3.26 mmol) and prenyl bromide (0.63 ml, 5.44 mmol) were added and the reaction mixture stirred at 60 °C overnight before filtering and washing using the standard procedure.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 3028, 3018, 2924, 1725 (C=O, ester), 1661 (C=O, amide), 1603, 1442, 1366, 1142, 1056.

### 4.2.6 TETRAHYDROQUINOLONE PRODUCTS FROM SOLID-PHASE SYNTHESIS

**_tert_-Butyl 2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 196**

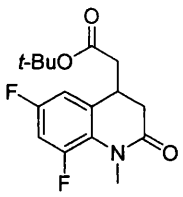



$C_{16}H_{21}NO_3$
Mol. Wt.: 275.34

Dry LiCl (250 mg, 5.88 mmol) was added to a round bottomed followed by THF (2 ml) and S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **218** (479 mg, 0.44 mmol). The flask was thoroughly flushed with nitrogen and $SmI_2$ (19.6 ml of a 0.1 M solution in THF, 1.96 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred (approx. 20 h) and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product as a brown oil. Purification using flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *tert*-butyl 2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **197** (21.3 mg, 0.08 mmol, 35 %) as a colourless oil.

See earlier for data.

***tert*-Butyl 2-(7,9-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 206**

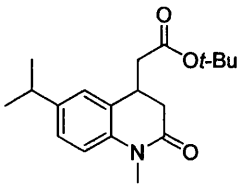



$C_{16}H_{19}F_2NO_3$
Mol. Wt: 311.32

Dry LiCl (257 mg, 6.07 mmol) was added to a round bottomed followed by THF (5 ml) and S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-7,9-difluoro-1,2,3,4-tetrahydroquinolin-4-yl) acetate **212d** (535 mg, 0.45 mmol). The flask was flushed with nitrogen and $SmI_2$ (20.2 ml, 0.1 M solution in THF, 2.02 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred (approx. 23 h) and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *tert*-butyl 2-(7,9-difluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **206** (20.6 mg, 0.07 mmol, 27 %) as a pale yellow oil.

See earlier for data.

***tert*-Butyl 2-(6-*iso*propyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 230**




$C_{19}H_{27}NO_3$
Mol. Wt: 317.42

Dry LiCl (247 mg, 5.83 mmol) was added to a round bottomed followed by THF (3 ml) and S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **234** (502 mg, 0.43 mmol). The flask was flushed with nitrogen and $SmI_2$ (19.4 ml, 0.1 M solution in THF, 1.94 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard

procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *tert*-butyl 2-(6-*iso*propyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **230** (22.0 mg, 0.07 mmol, 31 %) as a pale yellow oil.

Cyclative cleavage of S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4-*iso*propylphenyl]-N-methyl acetamide **237**

S-Merrifield supported-2-sulfonyl-N-[2-(1-*tert*-butoxy-1-oxo-prop-2-en-3-yl)-4-*iso*propylphenyl]-N-methyl acetamide **237** (540 mg, 0.47 mmol) was swollen in THF (5 ml) for 15 min. Dry LiCl (269 mg, 6.34 mmol) was added and the flask was thoroughly flushed with nitrogen before addition of $SmI_2$ (21 ml, 0.1 M solution in THF, 2.11 mmol). The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave **230** (19.0 mg, 0.06 mmol, 25 %) as a pale yellow oil and N-(2-bromo-4-*iso*propylphenyl)-N-methylacetamide (13.0 mg, 0.05 mmol, 19 %) as a pale yellow oil.

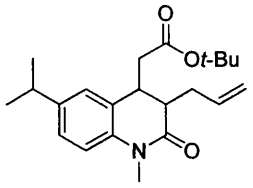
$\delta_H$ **(400 MHz, $CDCl_3$)** 1.26-1.29 (6H, m, $CH(C\underline{H}_3)_2$), 1.47 (9H, s, $C(C\underline{H}_3)_3$), 2.50 (2H, dd, *J* 7.5, 2.1, $C\underline{H}_2CO_2t$-Bu), 2.65 (1H, dd, *J* 16.0, 4.8, 1H of $C\underline{H}_2CO$), 2.80 (1H, dd, *J* 16.0, 5.7, 1H of $C\underline{H}_2CO$), 2.82-2.92 (1H, m, $C\underline{H}(CH_3)_2$), 3.22 (3H, s, $NC\underline{H}_3$), 3.22-3.47 (1H, m, C<u>H</u>), 7.12-7.18 (3H, m, Ar<u>H</u>).

$\delta_C$ **(100 MHz, $CDCl_3$)** 24.2 ($CH(\underline{C}H_3)_2$), 24.3 ($CH(\underline{C}H_3)_2$), 28.4 (3 x $C(\underline{C}H_3)_3$), 29.7 ($N\underline{C}H_3$), 33.0 ($\underline{C}H(CH_3)_2$), 33.7 ($\underline{C}HCH_2CO_2t$-Bu), 37.2 ($\underline{C}H_2CO$), 38.0 ($\underline{C}H_2CO_2t$-Bu), 81.3 ($\underline{C}(CH_3)_3$), 115.1 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>), 137.9 (Ar<u>C</u>), 144.0 (Ar<u>C</u>), 169.3 (<u>C</u>=O), 171.0 (<u>C</u>=O).

**MS (EI mode)** 318 (99 %, $M^{+\cdot}$ + H), 262 (71), 222 (33), 218 (29), 202 (18). **HRMS** $C_{19}H_{28}NO_3$ requires 318.2069 found 318.2068.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 2963, 2929, 2361, 1724 (C=O, ester), 1675 (C=O, amide), 1501, 1459, 1420, 1368, 1254, 1204, 1148.

***tert*-Butyl 2-(3-allyl-7-*iso*propyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 228**




$C_{22}H_{31}NO_3$
Mol. Wt: 357.49

Dry LiCl (219 mg, 5.18 mmol) was added to a round bottomed followed by THF (5 ml) and S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-allyl-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydrquinolin-4-yl) acetate **235** (462 mg, 0.38 mmol). The flask was thoroughly flushed with nitrogen and $SmI_2$ (17.3 ml, 0.1 M solution in THF, 1.73 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 30 % EtOAc/Pet ether gave *tert*-butyl 2-(3-allyl-7-*iso*propyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **228** (13.2 mg, 0.04 mmol, 16 %, 3:1 mixture of diastereoisomers). Further careful chromatography allowed the major diastereomer to be isolated and analysed.

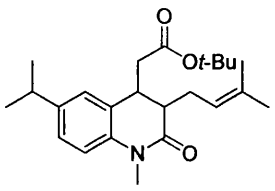
$\delta_H$ **(400 MHz, $CDCl_3$)** 1.17-1.71 (6H, m, $(C\underline{H}_3)_2CH$), 1.36 (9H, s, $(C\underline{H}_3)_3C$), 2.08-2.11 (2H, m, 1H from $C\underline{H}_2CH$= and 1H from $C\underline{H}_2CO_2t$-Bu), 2.47 (1H, dd, *J* 14.9, 4.1 Hz, 1H from $C\underline{H}_2CO_2t$-Bu), 2.75-2.80 (1H, m, CH), 2.80-3.29 (1H, m, 1H from $C\underline{H}_2CH$=), 2.77 (1H, septet, J 6.9 Hz, , $(CH_3)_2C\underline{H}$), 3.35 (3H, s $NC\underline{H}_3$), 3.35-3.40 (1H, m, $C\underline{H}CO$), 5.09 (1H, d, *J* 10.2 Hz, 1H from $C\underline{H}_2$=CH-), 5.13 (1H, d, *J* 15.9 Hz, 1H from $C\underline{H}_2$=CH-), 5.82-5.96 (1H, m, -C<u>H</u>=), 6.91 (1H, d, J 8.3 Hz, ArH), 7.06-7.13 (2H, m, 2 × ArH).

$\delta_C$ **(100 MHz, $CDCl_3$)** 24.2 ($(\underline{C}H_3)_2CH$), 24.3 ($(\underline{C}H_3)_2CH$), 28.3 ($(\underline{C}H_3)_3C$), 30.0 ($N\underline{C}H_3$), 31.2 ($\underline{C}H_2CH$=), 33.7 ($\underline{C}H(CH_3)_2$), 35.2 ($\underline{C}H_2CO_2t$-Bu), 36.1 ($\underline{C}HCO$), 44.3 ($\underline{C}H$), 81.0 ($\underline{C}(CH_3)_3$), 115.2 (Ar<u>C</u>H), 117.2 ($\underline{C}H_2$=), 125.9 (Ar<u>C</u>H × 2), 126.4 (Ar<u>C</u>), 136.2 (-<u>C</u>H=), 137.8 (Ar<u>C</u>), 143.7 (Ar<u>C</u>), 170.1 (<u>C</u>=O), 171.3 (<u>C</u>=O).

**MS (CI mode)** 358 ($M^{+\cdot}$ + H, 100 %), 302 (41), 218 (43), 137 (22). **HRMS** $C_{22}H_{32}NO_3$ requires 358.2377 found 358.2381.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 2959, 2925, 2855, 1727 (C=O, ester), 1674 (C=O, amide), 1459, 1366, 1258, 1144, 1095.

***tert*-Butyl 2-(3-prenyl-7-*iso*propyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 233**




$C_{24}H_{35}NO_3$
Mol. Wt: 385.54

Dry LiCl (580 mg, 6.42 mmol) was added to a round bottomed followed by THF (2 ml) and S-Merrifield supported *tert*-butyl-2-(1-methyl-2-oxo-3-prenyl-3-sulfonyl-7-*iso*propyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **236** (580 mg, 0.48 mmol). The flask was thoroughly flushed with nitrogen and $SmI_2$ (21.4 ml, 0.1 M solution in THF, 2.14 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 15 % EtOAc/Pet ether gave *tert*-butyl 2-(3-prenyl-7-*iso*propyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate **233** (11.0 mg, 0.03 mmol, 12 %, 2:1 mixture of diastereomers) and **230** (18.7 mg, 0.059 mmol, 19%). Further careful chromatography allowed the major diastereoisomer of **233** to be isolated and analysed.

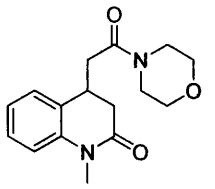
$\delta_H$ **(400 MHz, $CDCl_3$)** 1.22 (3H, d, J 6.9 Hz, $(C\underline{H}_3)_2CH$), 1.23 (3H, d, J 6.9 Hz, $(C\underline{H}_3)_2CH$), 1.37 (9H, s, $(C\underline{H}_3)_3C$), 1.58 (3H, s, $C\underline{H}_3$), 1.73 (3H, s, $C\underline{H}_3$), 2.03-2.11 (2H, m, 1H from $C\underline{H}_2CH$= and 1H from $C\underline{H}_2CO_2t$-Bu), 2.47 (1H, dd, *J* 15.0, 4.0 Hz, 1H from $C\underline{H}_2CO_2t$-Bu), 2.55-2.57 (2H, m, 1H of $C\underline{H}_2CH$= and C<u>H</u>), 2.77 (1H, septet, *J* 6.9 Hz, $(CH_3)_2C\underline{H}$), 3.48 (3H, s, $NC\underline{H}_3$), 3.48-3.50 (1H, m, C<u>H</u>CO), 5.12 (1H, broad s, -C<u>H</u>=), 6.91 (1H, d, J 8.3 Hz, ArH), 7.01-7.05 (2H, m, 2 × ArH).

$\delta_C$ **(100 MHz, $CDCl_3$)** 17.8 ($(\underline{C}H_3)_2C$=), 23.9 ($(\underline{C}H_3)_2CH$), 24.0 ($(\underline{C}H_3)_2CH$), 25.8 ($(\underline{C}H_3)_2C$=), 28.0 ($(\underline{C}H_3)_3C$), 29.7 ($N\underline{C}H_3$), 29.7 ($\underline{C}H_2CH$=), 33.5 ($(CH_3)_2\underline{C}H$), 35.1 ($\underline{C}H_2CO_2t$-Bu), 35.8 (<u>C</u>HCO), 44.6 (<u>C</u>H), 80.6 ($\underline{C}(CH_3)_3$), 114.8 (Ar<u>C</u>H), 121.3 (<u>C</u>H=), 125.5 (Ar<u>C</u>H × 2), 126.1 ($(CH_3)_2\underline{C}$= or Ar<u>C</u>), 133.5 ($(CH_3)_2\underline{C}$= or Ar<u>C</u>), 137.4 ($(CH_3)_2\underline{C}$= or Ar<u>C</u>), 143.3 ($(CH_3)_2\underline{C}$= or Ar<u>C</u>), 171.2 (<u>C</u>=O × 2).

**MS (CI mode)** 386 ($M^{+\cdot}$ + H, 100%), 330 (20), 202 (15). **HRMS** $C_{24}H_{36}NO_3$ requires 386.2690 found 386.2700.

$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2961, 2924, 1724 (C=O, ester), 1675 (C=O, amide), 1501, 1459, 1417, 1367,1328, 1265, 1145.

**1-Methyl-2-oxo-4-[2-(morpholin-4-yl)-2-oxoethyl]-1,2,3,4-tetrahydroquinoline 231**

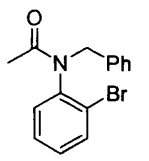


$C_{16}H_{20}N_2O_3$
Mol. Wt: 288.34

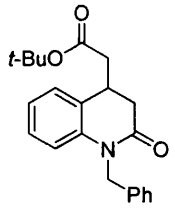
Dry LiCl (315mg, 7.43 mmol) was added to a round bottomed followed by THF (3 ml) and S-Merrifield supported-1-methyl-2-oxo-4-[2-(morpholin-4-yl)-2-oxo-ethyl]-3-sulfonyl-1,2,3,4-tetrahydroquinoline **209d** (655 mg, 0.55 mmol). The flask was flushed with nitrogen and $SmI_2$ (24.8 ml, 0.1 M solution in THF, 2.48 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 60 % EtOAc/Pet ether gave the product **231** (15.9 mg, 0.05 mmol, 18 % overall) as a pale yellow oil and acetamide **215** (22.3 mg, 0.10 mmol, 32 %).

$\delta_H$ **(400 MHz, $CDCl_3$)** 2.40-2.50 (2H, m, C$\underline{H}_2$CO), 2.65 (1H, dd, *J* 16.4, 3.2, 1H of C$\underline{H}_2$CO), 2.75 (1H, dd, *J* 16.4, 6.0, 1H of C$\underline{H}_2$CO), 3.11-3.17 (1H, m, 1H of C$\underline{H}_2$), 3.28-3.36 (2H, m, 1H of C$\underline{H}_2$ and 1H of $CH_2$), 3.38 (3H, s, NC$\underline{H}_3$), 3.47-3.57 (6H, m, 5H of C$\underline{H}_2$ + C$\underline{H}$), 6.93-7.00 (2H, m, Ar$\underline{H}$), 7.18-7.24 (2H, m, Ar$\underline{H}$).
$\delta_C$ **(100 MHz, $CDCl_3$)** 29.4 (N$\underline{C}H_3$), 32.9 ($\underline{C}$H), 36.3 ($\underline{C}H_2$CO), 36.9 ($\underline{C}H_2$CO), 42.0 ($\underline{C}H_2$), 45.9 ($\underline{C}H_2$), 66.3 ($\underline{C}H_2$), 66.7 ($\underline{C}H_2$), 114.8 (Ar$\underline{C}$H), 123.2 (Ar$\underline{C}$H), 128.1 (2 x Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$), 139.7 (Ar$\underline{C}$), 169.1 ($\underline{C}$=O), 169.3 ($\underline{C}$=O).
**MS (CI mode)** 306 ($M^{+\cdot}$ + $NH_4$, 70%), 289 (100), 160 (20). **HRMS** $C_{16}H_{21}N_2O_3$ requires 289.1547 found 289.1543.
$\upsilon_{max}$ **(ATR, cm$^{-1}$)** 2922, 2856, 1645 (C=O), 1465, 1375, 1268, 131, 1115.

***tert*-Butyl 2-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 232**



$C_{15}H_{14}BrNO$
Mol. Wt.: 304.18



$C_{22}H_{25}NO_3$
Mol. Wt.: 351.44

Dry LiCl (264 mg, 6.24 mmol) was added to a round bottomed followed by THF (2.5 ml) and S-Merrifield supported *tert*-butyl-2-(1-benzyl-2-oxo-3-sulfonyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **210d** (550 mg, 0.46 mmol). The flask was thoroughly flushed with nitrogen and $SmI_2$ (21 ml, 0.1 M solution in THF, 2.10 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 10 % EtOAc/Pet ether gave **232** (30.0 mg, 0.09 mmol, 35 %) and N-benzyl-N-(2-bromophenyl)acetamide (19.3 mg, 0.06 mmol, 26 %) as an inseparable mixture.

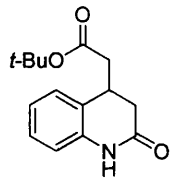
$\delta_H$ **(400 MHz, $CDCl_3$)** 1.34 (9H, s, $C(C\underline{H}_3)_3$), 1.74 (3H, s, $NCOC\underline{H}_3$ {acetamide}), 2.37-2.45 (2H, m, $C\underline{H}_2$), 2.66 (1H, dd, *J* 15.9, 4.6 1H of $C\underline{H}_2$), 2.83 (1H, dd, *J* 15.9, 5.8, 1H of $C\underline{H}_2$), 3.37-3.40 (1H, m, $C\underline{H}$), 3.92 (1H, d, *J* 15.0 1H of $C\underline{H}_2Ph$ {acetamide}), 4.96 (1H, app d, *J* 16.2, 1H of $C\underline{H}_2Ph$), 5.24 (1H, app. d, *J* 16.2, 1H of $C\underline{H}_2Ph$), 5.52 (1H, d, *J* 15.0, 1H of $C\underline{H}_2Ph$ {acetamide}), 6.67-6.69 (1H, m, Ar$\underline{H}$), 6.80 (1H, d, *J* 5.0, Ar$\underline{H}$), 6.88 (1H, t, *J* 5.0, Ar$\underline{H}$), 7.01-7.22 (1H, m, Ar$\underline{H}$), 7.57-7.59 (1H, m, Ar$\underline{H}$).

$\delta_C$ **(100 MHz, $CDCl_3$)** 28.5 ($\underline{C}H_3$ {acetamide}), 33.3 ($C(\underline{C}H_3)_3$), 37.4 ($\underline{C}H$), 40.0 ($\underline{C}H_2CO$), 46.5 ($\underline{C}H_2Ph$), 51.6 ($\underline{C}H_2Ph$ {acetamide}), 81.5 ($\underline{C}(CH_3)_3$), 116.2 (Ar$\underline{C}H$), 116.3 (Ar$\underline{C}H$), 123.5 (Ar$\underline{C}H$), 124.2 (Ar$\underline{C}H$), 126.8 (Ar$\underline{C}H$), 127.0 (Ar$\underline{C}H$), 128.0 (2 x Ar$\underline{C}H$), 128.3 (Ar$\underline{C}H$), 128.4 (Ar$\underline{C}H$), 128.7 (2 x Ar$\underline{C}H$), 128.8 (Ar$\underline{C}$), 129.2 (Ar$\underline{C}H$), 129.6 (Ar$\underline{C}H$), 129.8 (Ar$\underline{C}H$), 131.6 (Ar$\underline{C}H$), 131.7 (Ar$\underline{C}H$), 137.3 (Ar$\underline{C}$ x 2), 137.4 (Ar$\underline{C}$ x 2), 139.4 (Ar$\underline{C}$), 141.5 (Ar$\underline{C}$).

**MS (EI mode)** 169 ($M^{+\cdot}$ + $NH_4$, **229**, 74 %), 352 ($M^{+\cdot}$, **229**, 32 %), 321 (42), 306 ($M^{+\cdot}$, $^{81}Br$, acetamide, 88 %), 304 ($M^{+\cdot}$, $^{79}Br$, acetamide, 100 %), 224 (23), 108 (21). **HRMS** $C_{15}H_{15}NO^{79}Br$ (acetamide) requires 304.0332 found 304.0334, $C_{22}H_{26}NO_3$ (**229**) requires 352.1907 found 352.1907.

$\upsilon_{max}$ **(ATR, $cm^{-1}$)** 3063, 3031, 2975, 2929, 1722 (C=O, ester), 1668 (C=O, amide), 1602, 1495, 1457, 1433, 1379, 1256, 1184.

***tert*-Butyl 2-(2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)acetate 229**




$C_{15}H_{19}NO_3$
Mol. Wt: 261.32

Dry LiCl (327 mg, 7.72 mmol) was added to a round bottomed followed by THF (3 ml) and S-Merrifield supported *tert*-butyl-2-(2-oxo-3-sulfonyl-1,2,3,4-tetrahydroquinolin-4-yl) acetate **151d** (635 mg, 0.57 mmol). The flask was thoroughly flushed with nitrogen and $SmI_2$ (25.7 ml, 0.1 M solution in THF, 2.57 mmol) was added. The reaction was slowly stirred until decolourisation of the $SmI_2$ solution occurred and the resin was filtered from the reaction mixture and washed and dried using the standard procedure. The filtrate was collected and concentrated *in vacuo* before partitioning between $CH_2Cl_2$ (20 ml) and $H_2O$ (20 ml). The organic phase was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification using flash chromatography on silica gel eluting with 5 % EtOAc/Pet ether gave **229** (3.4 mg, 0.01 mmol, 5 %) and *N*-(2-bromophenyl)acetamide (7.0 mg, 0.03 mmol, 11 %).

**$\delta_H$ (400 MHz, $CDCl_3$)** 1.44 (9H, s, C($C\underline{H}_3$)$_3$), 2.54 (1H, dd, *J* 9.2, 4.4, C$\underline{H}$), 2.64-2.68 (2H, m, $C\underline{H}_2CO_2t$-Bu), 2.68-2.91 (2H, m, $C\underline{H}_2$), 7.12-7.26 (2H, m, 2 x Ar$\underline{H}$), 7.30-7.54 (2H, m, 2 x Ar$\underline{H}$), 8.94 (1H, bs, N$\underline{H}$).
**MS (EI mode)** 279 ($M^{+\cdot}$ + $NH_4$, 5 %), 208 (21), 153 (29), 136 (99). **HRMS** $C_{15}H_{19}NO_3$ requires 261.1359 found 261.1352.
**$\upsilon_{max}$ (ATR, $cm^{-1}$)** 3276, 2974, 2926, 2859, 1724 (C=O, ester), 1669 (C=O, amide), 1560, 1543, 1498, 1443, 1316, 1258, 1150.

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# APPENDIX I

## Crystal structure data

X-ray data of imidazolinium salt **162**

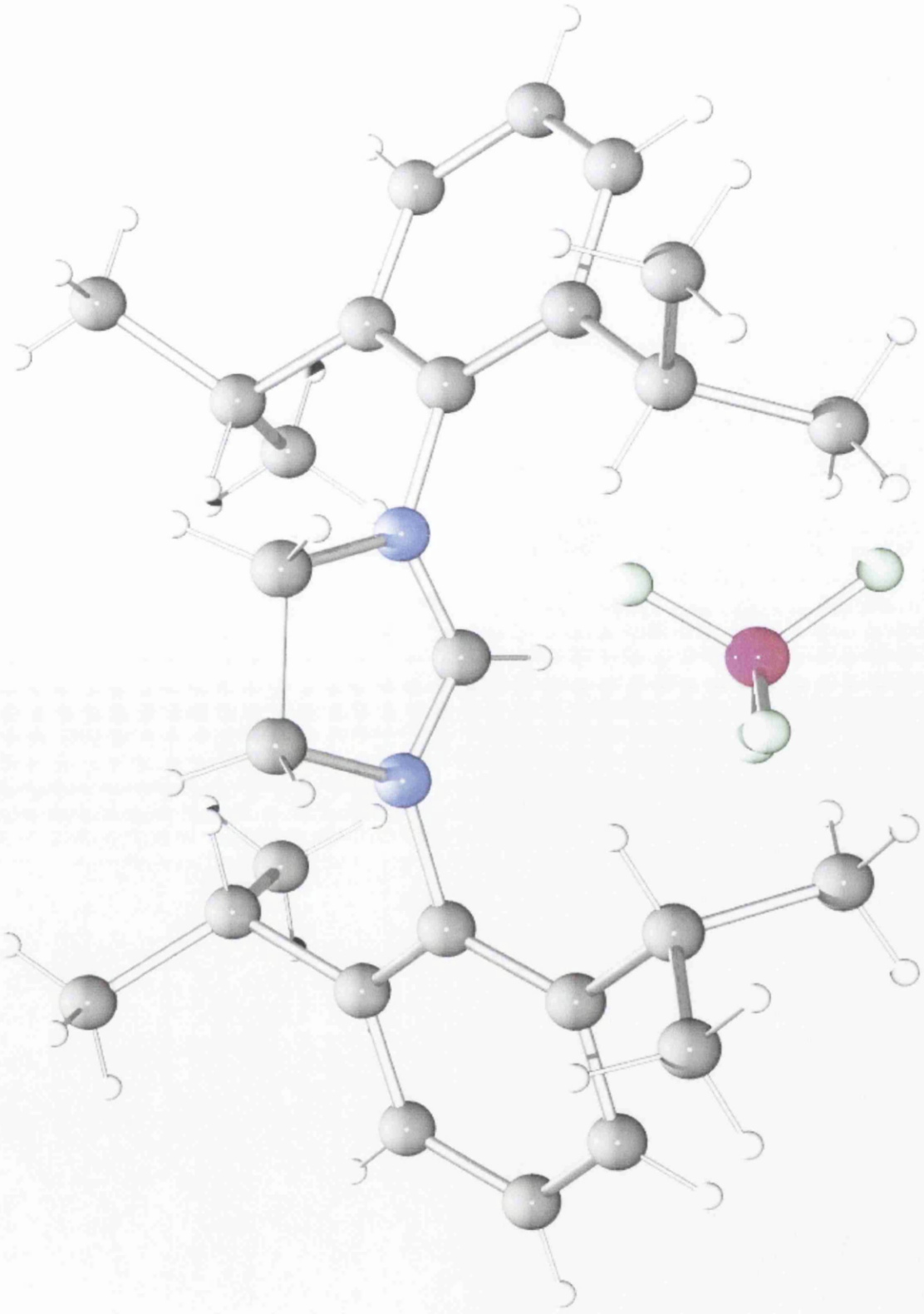

**Table 1.** Crystal data and structure refinement for **162**.

| | | |
|---|---|---|
| Identification code | **162** | |
| Empirical formula | C 27 H 39 B F 4 N 2 | |
| Formula weight | 478.41 | |
| Temperature | 120(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P ccn | |
| Unit cell dimensions | a = 11.1479(3) Å | α= 90°. |
| | b = 12.5768(4) Å | β= 90°. |
| | c = 19.2391(6) Å | γ = 90°. |
| Volume | 2697.42(14) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.178 $Mg/m^3$ | |
| Absorption coefficient | 0.087 $mm^{-1}$ | |
| F(000) | 1024 | |
| Crystal size | 0.45 x 0.25 x 0.17 $mm^3$ | |
| Theta range for data collection | 2.12 to 30.02°. | |
| Index ranges | -15<=h<=15, -17<=k<=17, -26<=l<=26 | |
| Reflections collected | 12288 | |
| Independent reflections | 3928 [R(int) = 0.067] | |
| Completeness to theta = 30.02° | 99.5 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3928 / 0 / 166 | |
| Goodness-of-fit on $F^2$ | 1.039 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0542, wR2 = 0.1248 | |
| R indices (all data) | R1 = 0.0987, wR2 = 0.1429 | |
| Largest diff. peak and hole | 0.39 and -0.25 $e.Å^{-3}$ | |

**Table 2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **162**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 2158(1) | 1684(1) | 4231(1) | 20(1) |
| C(1) | 1727(1) | 687(1) | 3954(1) | 21(1) |
| C(2) | 491(1) | 577(1) | 3844(1) | 24(1) |
| C(3) | 96(1) | -388(1) | 3564(1) | 30(1) |
| C(4) | 902(1) | -1181(1) | 3398(1) | 33(1) |
| C(5) | 2116(2) | -1048(1) | 3519(1) | 32(1) |
| C(6) | 2565(1) | -114(1) | 3813(1) | 25(1) |
| C(7) | -396(1) | 1462(1) | 3997(1) | 29(1) |
| C(8) | -1411(2) | 1091(2) | 4468(1) | 48(1) |
| C(9) | -891(2) | 1935(1) | 3324(1) | 45(1) |
| C(10) | 3898(1) | 3(1) | 3957(1) | 29(1) |
| C(11) | 4379(2) | -925(1) | 4392(1) | 40(1) |
| C(12) | 4615(2) | 112(2) | 3283(1) | 50(1) |

| | | | | |
|---|---|---|---|---|
| C(13) | 2230(1) | 1936(1) | 4984(1) | 23(1) |
| C(14) | 2500 | 2500 | 3858(1) | 19(1) |
| F(1) | 2290(2) | 1612(2) | 1474(1) | 78(1) |
| F(2) | 1518(1) | 2688(1) | 2310(1) | 51(1) |
| F(3) | 1611(13) | 2093(10) | 1460(6) | 75 |
| F(4) | 2042(13) | 3246(10) | 2302(6) | 75 |
| B(1) | 2500 | 2500 | 1885(1) | 40(1) |

**Table 3**. Bond lengths [Å] and angles [°] for **162**.

| | | | |
|---|---|---|---|
| N(1)-C(14) | 1.3102(13) | F(2)-B(1) | 1.3872(17) |
| N(1)-C(1) | 1.4444(16) | F(3)-B(1) | 1.383(12) |
| N(1)-C(13) | 1.4840(15) | F(4)-B(1) | 1.336(12) |
| C(1)-C(6) | 1.4006(19) | F(4)-F(1)#1 | 1.767(13) |
| C(1)-C(2) | 1.4013(19) | B(1)-F(4)#1 | 1.336(12) |
| C(2)-C(3) | 1.3986(18) | B(1)-F(3)#1 | 1.383(12) |
| C(2)-C(7) | 1.5178(19) | B(1)-F(2)#1 | 1.3872(17) |
| C(3)-C(4) | 1.379(2) | B(1)-F(1)#1 | 1.388(2) |
| C(3)-H(3) | 0.9500 | C(14)-N(1)-C(1) | 125.04(10) |
| C(4)-C(5) | 1.384(2) | C(14)-N(1)-C(13) | 110.61(10) |
| C(4)-H(4) | 0.9500 | C(1)-N(1)-C(13) | 124.31(10) |
| C(5)-C(6) | 1.3964(19) | C(6)-C(1)-C(2) | 123.73(12) |
| C(5)-H(5) | 0.9500 | C(6)-C(1)-N(1) | 118.26(12) |
| C(6)-C(10) | 1.518(2) | C(2)-C(1)-N(1) | 118.01(12) |
| C(7)-C(8) | 1.522(2) | C(3)-C(2)-C(1) | 117.00(13) |
| C(7)-C(9) | 1.528(2) | C(3)-C(2)-C(7) | 120.40(13) |
| C(7)-H(7) | 1.0000 | C(1)-C(2)-C(7) | 122.58(12) |
| C(8)-H(8A) | 0.9800 | C(4)-C(3)-C(2) | 120.74(14) |
| C(8)-H(8B) | 0.9800 | C(4)-C(3)-H(3) | 119.6 |
| C(8)-H(8C) | 0.9800 | C(2)-C(3)-H(3) | 119.6 |
| C(9)-H(9A) | 0.9800 | C(3)-C(4)-C(5) | 120.72(13) |
| C(9)-H(9B) | 0.9800 | C(3)-C(4)-H(4) | 119.6 |
| C(9)-H(9C) | 0.9800 | C(5)-C(4)-H(4) | 119.6 |
| C(10)-C(12) | 1.528(2) | C(4)-C(5)-C(6) | 121.38(14) |
| C(10)-C(11) | 1.533(2) | C(4)-C(5)-H(5) | 119.3 |
| C(10)-H(10) | 1.0000 | C(6)-C(5)-H(5) | 119.3 |
| C(11)-H(11A) | 0.9800 | C(5)-C(6)-C(1) | 116.38(14) |
| C(11)-H(11B) | 0.9800 | C(5)-C(6)-C(10) | 120.37(13) |
| C(11)-H(11C) | 0.9800 | C(1)-C(6)-C(10) | 123.25(12) |
| C(12)-H(12A) | 0.9800 | C(2)-C(7)-C(8) | 112.05(12) |
| C(12)-H(12B) | 0.9800 | C(2)-C(7)-C(9) | 110.85(12) |
| C(12)-H(12C) | 0.9800 | C(8)-C(7)-C(9) | 110.84(14) |
| C(13)-C(13)#1 | 1.541(3) | C(2)-C(7)-H(7) | 107.6 |
| C(13)-H(13A) | 0.9900 | C(8)-C(7)-H(7) | 107.6 |
| C(13)-H(13B) | 0.9900 | C(9)-C(7)-H(7) | 107.6 |
| C(14)-N(1)#1 | 1.3102(14) | C(7)-C(8)-H(8A) | 109.5 |
| C(14)-H(14) | 0.9500 | C(7)-C(8)-H(8B) | 109.5 |
| F(1)-F(3) | 0.969(14) | H(8A)-C(8)-H(8B) | 109.5 |
| F(1)-B(1) | 1.388(2) | C(7)-C(8)-H(8C) | 109.5 |
| F(1)-F(4)#1 | 1.767(13) | H(8A)-C(8)-H(8C) | 109.5 |
| F(2)-F(4) | 0.912(13) | H(8B)-C(8)-H(8C) | 109.5 |

| | | | |
|---|---|---|---|
| C(7)-C(9)-H(9A) | 109.5 | B(1)-F(1)-F(4)#1 | 48.3(4) |
| C(7)-C(9)-H(9B) | 109.5 | F(4)-F(2)-B(1) | 67.4(8) |
| H(9A)-C(9)-H(9B) | 109.5 | F(1)-F(3)-B(1) | 69.8(8) |
| C(7)-C(9)-H(9C) | 109.5 | F(2)-F(4)-B(1) | 73.5(8) |
| H(9A)-C(9)-H(9C) | 109.5 | F(2)-F(4)-F(1)#1 | 111.3(10) |
| H(9B)-C(9)-H(9C) | 109.5 | B(1)-F(4)-F(1)#1 | 50.8(4) |
| C(6)-C(10)-C(12) | 111.45(12) | F(4)-B(1)-F(4)#1 | 106.1(10) |
| C(6)-C(10)-C(11) | 111.63(12) | F(4)-B(1)-F(3) | 110.0(7) |
| C(12)-C(10)-C(11) | 110.42(13) | F(4)#1-B(1)-F(3) | 111.7(7) |
| C(6)-C(10)-H(10) | 107.7 | F(4)-B(1)-F(3)#1 | 111.7(7) |
| C(12)-C(10)-H(10) | 107.7 | F(4)#1-B(1)-F(3)#1 | 110.0(7) |
| C(11)-C(10)-H(10) | 107.7 | F(3)-B(1)-F(3)#1 | 107.5(10) |
| C(10)-C(11)-H(11A) | 109.5 | F(4)-B(1)-F(2)#1 | 93.9(5) |
| C(10)-C(11)-H(11B) | 109.5 | F(4)#1-B(1)-F(2)#1 | 39.1(6) |
| H(11A)-C(11)-H(11B) | 109.5 | F(3)-B(1)-F(2)#1 | 148.3(5) |
| C(10)-C(11)-H(11C) | 109.5 | F(3)#1-B(1)-F(2)#1 | 81.2(6) |
| H(11A)-C(11)-H(11C) | 109.5 | F(4)-B(1)-F(2) | 39.1(6) |
| H(11B)-C(11)-H(11C) | 109.5 | F(4)#1-B(1)-F(2) | 93.9(5) |
| C(10)-C(12)-H(12A) | 109.5 | F(3)-B(1)-F(2) | 81.2(6) |
| C(10)-C(12)-H(12B) | 109.5 | F(3)#1-B(1)-F(2) | 148.3(5) |
| H(12A)-C(12)-H(12B) | 109.5 | F(2)#1-B(1)-F(2) | 107.70(18) |
| C(10)-C(12)-H(12C) | 109.5 | F(4)-B(1)-F(1) | 147.4(6) |
| H(12A)-C(12)-H(12C) | 109.5 | F(4)#1-B(1)-F(1) | 80.9(5) |
| H(12B)-C(12)-H(12C) | 109.5 | F(3)-B(1)-F(1) | 40.9(5) |
| N(1)-C(13)-C(13)#1 | 102.60(6) | F(3)#1-B(1)-F(1) | 94.8(5) |
| N(1)-C(13)-H(13A) | 111.2 | F(2)#1-B(1)-F(1) | 109.35(9) |
| C(13)#1-C(13)-H(13A) | 111.2 | F(2)-B(1)-F(1) | 109.86(9) |
| N(1)-C(13)-H(13B) | 111.2 | F(4)-B(1)-F(1)#1 | 80.9(5) |
| C(13)#1-C(13)-H(13B) | 111.2 | F(4)#1-B(1)-F(1)#1 | 147.4(6) |
| H(13A)-C(13)-H(13B) | 109.2 | F(3)-B(1)-F(1)#1 | 94.8(5) |
| N(1)#1-C(14)-N(1) | 113.41(15) | F(3)#1-B(1)-F(1)#1 | 40.9(5) |
| N(1)#1-C(14)-H(14) | 123.3 | F(2)#1-B(1)-F(1)#1 | 109.86(9) |
| N(1)-C(14)-H(14) | 123.3 | F(2)-B(1)-F(1)#1 | 109.35(9) |
| F(3)-F(1)-B(1) | 69.3(7) | F(1)-B(1)-F(1)#1 | 110.7(2) |
| F(3)-F(1)-F(4)#1 | 107.0(8) | | |

Symmetry transformations used to generate equivalent atoms: #1 -x+1/2,-y+1/2,z

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **162**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 27(1) | 17(1) | 17(1) | 0(1) | 0(1) | -2(1) |
| C(1) | 27(1) | 16(1) | 18(1) | 1(1) | -2(1) | -2(1) |
| C(2) | 26(1) | 21(1) | 25(1) | 5(1) | -6(1) | 0(1) |
| C(3) | 28(1) | 26(1) | 36(1) | 4(1) | -12(1) | -4(1) |
| C(4) | 39(1) | 22(1) | 38(1) | -4(1) | -13(1) | -4(1) |
| C(5) | 37(1) | 21(1) | 37(1) | -6(1) | -7(1) | 2(1) |
| C(6) | 27(1) | 21(1) | 25(1) | -1(1) | -2(1) | -1(1) |
| C(7) | 24(1) | 24(1) | 38(1) | 4(1) | -4(1) | 2(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(8) | 48(1) | 43(1) | 51(1) | 15(1) | 18(1) | 12(1) |
| C(9) | 38(1) | 48(1) | 48(1) | 21(1) | 3(1) | 15(1) |
| C(10) | 26(1) | 27(1) | 35(1) | -8(1) | -1(1) | 1(1) |
| C(11) | 32(1) | 42(1) | 45(1) | -3(1) | -10(1) | 4(1) |
| C(12) | 36(1) | 66(1) | 48(1) | 5(1) | 7(1) | 1(1) |
| C(13) | 29(1) | 23(1) | 16(1) | 2(1) | 0(1) | -1(1) |
| C(14) | 20(1) | 17(1) | 18(1) | 0 | 0 | 2(1) |
| F(1) | 70(1) | 125(1) | 37(1) | -36(1) | -2(1) | 6(1) |
| F(2) | 31(1) | 91(1) | 30(1) | 1(1) | 7(1) | 22(1) |
| B(1) | 30(1) | 73(2) | 17(1) | 0 | 0 | 14(1) |

**Table 5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **162**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3) | -737 | -499 | 3487 | 36 |
| H(4) | 620 | -1825 | 3198 | 40 |
| H(5) | 2655 | -1603 | 3400 | 38 |
| H(7) | 47 | 2038 | 4247 | 34 |
| H(8A) | -1926 | 1697 | 4585 | 71 |
| H(8B) | -1074 | 790 | 4896 | 71 |
| H(8C) | -1885 | 547 | 4228 | 71 |
| H(9A) | -224 | 2127 | 3017 | 67 |
| H(9B) | -1363 | 2572 | 3432 | 67 |
| H(9C) | -1404 | 1410 | 3092 | 67 |
| H(10) | 4015 | 670 | 4231 | 35 |
| H(11A) | 3940 | -961 | 4833 | 60 |
| H(11B) | 5234 | -816 | 4485 | 60 |
| H(11C) | 4269 | -1592 | 4136 | 60 |
| H(12A) | 4546 | -545 | 3013 | 75 |
| H(12B) | 5460 | 244 | 3394 | 75 |
| H(12C) | 4298 | 708 | 3011 | 75 |
| H(13A) | 2756 | 1428 | 5231 | 27 |
| H(13B) | 1425 | 1929 | 5202 | 27 |
| H(14) | 2500 | 2500 | 3364 | 22 |

**Table 6.** Torsion angles [°] for **162**.

| | | | |
|---|---|---|---|
| C(14)-N(1)-C(1)-C(6) | 89.26(14) | C(4)-C(5)-C(6)-C(1) | -2.1(2) |
| C(13)-N(1)-C(1)-C(6) | -93.24(15) | C(4)-C(5)-C(6)-C(10) | 178.49(14) |
| C(14)-N(1)-C(1)-C(2) | -90.83(14) | C(2)-C(1)-C(6)-C(5) | 2.62(19) |
| C(13)-N(1)-C(1)-C(2) | 86.67(15) | N(1)-C(1)-C(6)-C(5) | -177.48(11) |
| C(6)-C(1)-C(2)-C(3) | -1.16(19) | C(2)-C(1)-C(6)-C(10) | -177.95(12) |
| N(1)-C(1)-C(2)-C(3) | 178.94(11) | N(1)-C(1)-C(6)-C(10) | 1.94(19) |
| C(6)-C(1)-C(2)-C(7) | -179.55(12) | C(3)-C(2)-C(7)-C(8) | 54.85(18) |
| N(1)-C(1)-C(2)-C(7) | 0.55(17) | C(1)-C(2)-C(7)-C(8) | -126.82(15) |
| C(1)-C(2)-C(3)-C(4) | -0.93(19) | C(3)-C(2)-C(7)-C(9) | -69.56(17) |
| C(7)-C(2)-C(3)-C(4) | 177.49(13) | C(1)-C(2)-C(7)-C(9) | 108.78(15) |
| C(2)-C(3)-C(4)-C(5) | 1.4(2) | C(5)-C(6)-C(10)-C(12) | 70.78(18) |
| C(3)-C(4)-C(5)-C(6) | 0.1(2) | C(1)-C(6)-C(10)-C(12) | -108.62(16) |

| | | | |
|---|---|---|---|
| C(5)-C(6)-C(10)-C(11) | -53.20(17) | F(1)-F(3)-B(1)-F(3)#1 | 76.6(7) |
| C(1)-C(6)-C(10)-C(11) | 127.40(14) | F(1)-F(3)-B(1)-F(2)#1 | -25.2(15) |
| C(14)-N(1)-C(13)-C(13)#1 | -3.57(16) | F(1)-F(3)-B(1)-F(2) | -134.7(6) |
| C(1)-N(1)-C(13)-C(13)#1 | 178.62(13) | F(1)-F(3)-B(1)-F(1)#1 | 116.4(6) |
| C(1)-N(1)-C(14)-N(1)#1 | 179.27(14) | F(4)-F(2)-B(1)-F(4)#1 | 111.0(11) |
| C(13)-N(1)-C(14)-N(1)#1 | 1.48(7) | F(4)-F(2)-B(1)-F(3) | -137.6(10) |
| F(4)#1-F(1)-F(3)-B(1) | 30.7(7) | F(4)-F(2)-B(1)-F(3)#1 | -28.5(13) |
| B(1)-F(2)-F(4)-F(1)#1 | 34.7(5) | F(4)-F(2)-B(1)-F(2)#1 | 73.7(8) |
| F(2)-F(4)-B(1)-F(4)#1 | -75.8(7) | F(4)-F(2)-B(1)-F(1) | -167.3(8) |
| F(1)#1-F(4)-B(1)-F(4)#1 | 147.3(6) | F(4)-F(2)-B(1)-F(1)#1 | -45.7(8) |
| F(2)-F(4)-B(1)-F(3) | 45.1(9) | F(3)-F(1)-B(1)-F(4) | 33.4(13) |
| F(1)#1-F(4)-B(1)-F(3) | -91.8(6) | F(4)#1-F(1)-B(1)-F(4) | -105.7(13) |
| F(2)-F(4)-B(1)-F(3)#1 | 164.4(8) | F(3)-F(1)-B(1)-F(4)#1 | 139.1(10) |
| F(1)#1-F(4)-B(1)-F(3)#1 | 27.5(7) | F(4)#1-F(1)-B(1)-F(3) | -139.1(10) |
| F(2)-F(4)-B(1)-F(2)#1 | -113.6(6) | F(3)-F(1)-B(1)-F(3)#1 | -111.4(12) |
| F(1)#1-F(4)-B(1)-F(2)#1 | 109.52(12) | F(4)#1-F(1)-B(1)-F(3)#1 | 109.5(7) |
| F(1)#1-F(4)-B(1)-F(2) | -136.9(7) | F(3)-F(1)-B(1)-F(2)#1 | 166.3(8) |
| F(2)-F(4)-B(1)-F(1) | 22.6(14) | F(4)#1-F(1)-B(1)-F(2)#1 | 27.2(6) |
| F(1)#1-F(4)-B(1)-F(1) | -114.3(9) | F(3)-F(1)-B(1)-F(2) | 48.3(8) |
| F(2)-F(4)-B(1)-F(1)#1 | 136.9(7) | F(4)#1-F(1)-B(1)-F(2) | -90.8(6) |
| F(1)-F(3)-B(1)-F(4) | -161.6(8) | F(3)-F(1)-B(1)-F(1)#1 | -72.6(8) |
| F(1)-F(3)-B(1)-F(4)#1 | -44.1(10) | F(4)#1-F(1)-B(1)-F(1)#1 | 148.3(6) |

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,-y+1/2,z

Crystal structure data of formamide **166**

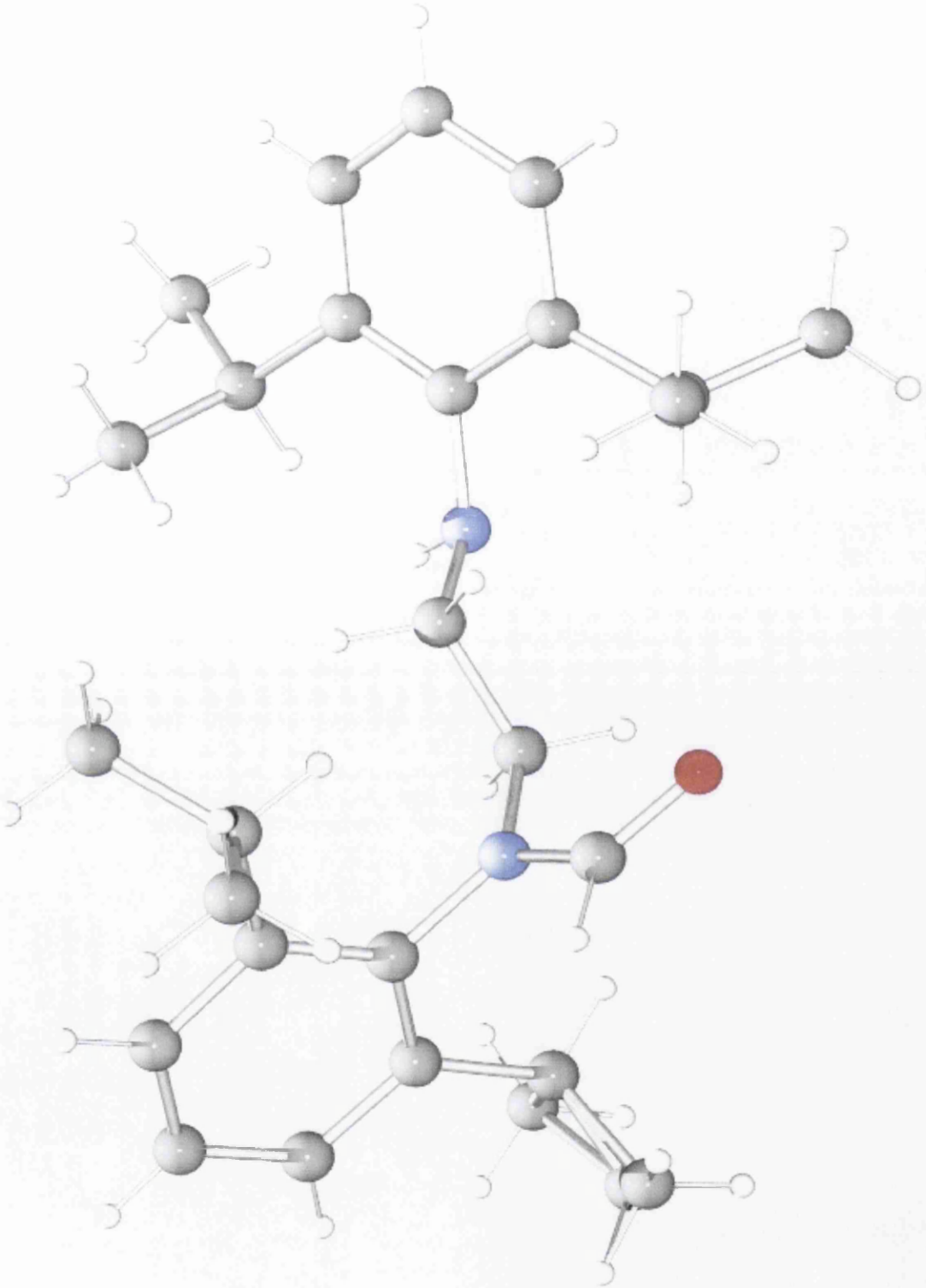

**Table 1.** Crystal data and structure refinement for **166**.

| | | |
|---|---|---|
| Identification code | 166 | |
| Empirical formula | C 27 H 39 N 2 O | |
| Formula weight | 391.60 | |
| Temperature | 120(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pbca | |
| Unit cell dimensions | a = 22.1310(6) Å | α= 90°. |
| | b = 19.0837(5) Å | β= 90°. |
| | c = 11.8970(3) Å | γ = 90°. |
| Volume | 5024.6(2) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.035 $Mg/m^3$ | |
| Absorption coefficient | 0.060 $mm^{-1}$ | |
| F(000) | 1720 | |
| Crystal size | 0.32 x 0.20 x 0.18 $mm^3$ | |
| Theta range for data collection | 2.13 to 30.02°. | |
| Index ranges | -31<=h<=31, -26<=k<=26, -16<=l<=16 | |
| Reflections collected | 12370 | |
| Independent reflections | 7231 [R(int) = 0.0389] | |
| Completeness to theta = 30.02° | 98.5 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9894 and 0.9812 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 7231 / 0 / 292 | |
| Goodness-of-fit on $F^2$ | 1.022 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0640, wR2 = 0.1387 | |
| R indices (all data) | R1 = 0.1095, wR2 = 0.1610 | |
| Largest diff. peak and hole | 0.590 and -0.428 $e.Å^{-3}$ | |

**Table 2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **166**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | -2253(1) | 2419(1) | 882(1) | 24(1) |
| N(2) | -3648(1) | 3022(1) | 2386(1) | 25(1) |
| C(1) | -1694(1) | 2353(1) | 1505(1) | 25(1) |
| C(2) | -1513(1) | 1682(1) | 1848(1) | 30(1) |
| C(3) | -975(1) | 1625(1) | 2450(1) | 36(1) |
| C(4) | -633(1) | 2209(1) | 2702(1) | 37(1) |
| C(5) | -818(1) | 2867(1) | 2360(1) | 34(1) |
| C(6) | -1355(1) | 2954(1) | 1753(1) | 28(1) |
| C(7) | -1864(1) | 1037(1) | 1527(2) | 45(1) |
| C(8) | -1939(2) | 524(2) | 2476(3) | 95(1) |
| C(9) | -1553(2) | 697(2) | 487(3) | 79(1) |

| | | | | |
|---|---|---|---|---|
| C(10) | -1524(1) | 3677(1) | 1325(2) | 33(1) |
| C(11) | -1074(1) | 3905(1) | 417(2) | 44(1) |
| C(12) | -1556(1) | 4223(1) | 2269(2) | 46(1) |
| C(13) | -4056(1) | 3598(1) | 2368(1) | 24(1) |
| C(14) | -4327(1) | 3792(1) | 1337(1) | 28(1) |
| C(15) | -4722(1) | 4363(1) | 1332(1) | 33(1) |
| C(16) | -4859(1) | 4731(1) | 2299(2) | 32(1) |
| C(17) | -4606(1) | 4520(1) | 3314(1) | 29(1) |
| C(18) | -4208(1) | 3956(1) | 3373(1) | 24(1) |
| C(19) | -4215(1) | 3390(1) | 251(1) | 35(1) |
| C(20) | -3884(1) | 3840(1) | -629(2) | 45(1) |
| C(21) | -4805(1) | 3110(1) | -248(2) | 55(1) |
| C(22) | -3919(1) | 3757(1) | 4495(1) | 27(1) |
| C(23) | -3298(1) | 4107(1) | 4601(2) | 33(1) |
| C(24) | -4310(1) | 3925(1) | 5523(1) | 40(1) |
| C(25) | -3064(1) | 3111(1) | 1814(1) | 24(1) |
| C(26) | -2832(1) | 2391(1) | 1483(1) | 24(1) |
| C(27) | -2252(1) | 2502(1) | -245(1) | 29(1) |
| O(1) | -2711(1) | 2566(1) | -815(1) | 37(1) |
| C(89) | -1670(8) | 400(9) | 1171(15) | 40(6) |

**Table 3.** Bond lengths [Å] and angles [°] for **166**.

| | | | |
|---|---|---|---|
| N(1)-C(27) | 1.3505(19) | C(10)-H(10) | 1.0000 |
| N(1)-C(1) | 1.4473(19) | C(11)-H(11A) | 0.9800 |
| N(1)-C(26) | 1.468(2) | C(11)-H(11B) | 0.9800 |
| N(2)-C(13) | 1.422(2) | C(11)-H(11C) | 0.9800 |
| N(2)-C(25) | 1.470(2) | C(12)-H(12A) | 0.9800 |
| N(2)-H(2) | 0.87(2) | C(12)-H(12B) | 0.9800 |
| C(1)-C(6) | 1.401(2) | C(12)-H(12C) | 0.9800 |
| C(1)-C(2) | 1.402(2) | C(13)-C(14) | 1.416(2) |
| C(2)-C(3) | 1.394(2) | C(13)-C(18) | 1.418(2) |
| C(2)-C(7) | 1.506(3) | C(14)-C(15) | 1.395(2) |
| C(3)-C(4) | 1.381(3) | C(14)-C(19) | 1.523(2) |
| C(3)-H(3) | 0.9500 | C(15)-C(16) | 1.381(3) |
| C(4)-C(5) | 1.381(3) | C(15)-H(15) | 0.9500 |
| C(4)-H(4) | 0.9500 | C(16)-C(17) | 1.390(2) |
| C(5)-C(6) | 1.401(2) | C(16)-H(16) | 0.9500 |
| C(5)-H(5) | 0.9500 | C(17)-C(18) | 1.393(2) |
| C(6)-C(10) | 1.518(2) | C(17)-H(17) | 0.9500 |
| C(7)-C(8) | 1.503(3) | C(18)-C(22) | 1.528(2) |
| C(7)-C(9) | 1.556(4) | C(19)-C(21) | 1.529(3) |
| C(7)-H(7) | 1.0000 | C(19)-C(20) | 1.541(3) |
| C(8)-H(8A) | 0.9800 | C(19)-H(19) | 1.0000 |
| C(8)-H(8B) | 0.9800 | C(20)-H(20A) | 0.9800 |
| C(8)-H(8C) | 0.9800 | C(20)-H(20B) | 0.9800 |
| C(9)-H(9A) | 0.9800 | C(20)-H(20C) | 0.9800 |
| C(9)-H(9B) | 0.9800 | C(21)-H(21A) | 0.9800 |
| C(9)-H(9C) | 0.9800 | C(21)-H(21B) | 0.9800 |
| C(10)-C(11) | 1.533(3) | C(21)-H(21C) | 0.9800 |
| C(10)-C(12) | 1.533(3) | C(22)-C(23) | 1.531(2) |

| | | | |
|---|---|---|---|
| C(22)-C(24) | 1.532(2) | C(10)-C(11)-H(11A) | 109.5 |
| C(22)-H(22) | 1.0000 | C(10)-C(11)-H(11B) | 109.5 |
| C(23)-H(23A) | 0.9800 | H(11A)-C(11)-H(11B) | 109.5 |
| C(23)-H(23B) | 0.9800 | C(10)-C(11)-H(11C) | 109.5 |
| C(23)-H(23C) | 0.9800 | H(11A)-C(11)-H(11C) | 109.5 |
| C(24)-H(24A) | 0.9800 | H(11B)-C(11)-H(11C) | 109.5 |
| C(24)-H(24B) | 0.9800 | C(10)-C(12)-H(12A) | 109.5 |
| C(24)-H(24C) | 0.9800 | C(10)-C(12)-H(12B) | 109.5 |
| C(25)-C(26) | 1.519(2) | H(12A)-C(12)-H(12B) | 109.5 |
| C(25)-H(25A) | 0.9900 | C(10)-C(12)-H(12C) | 109.5 |
| C(25)-H(25B) | 0.9900 | H(12A)-C(12)-H(12C) | 109.5 |
| C(26)-H(26A) | 0.9900 | H(12B)-C(12)-H(12C) | 109.5 |
| C(26)-H(26B) | 0.9900 | C(14)-C(13)-C(18) | 120.21(14) |
| C(27)-O(1) | 1.228(2) | C(14)-C(13)-N(2) | 119.01(14) |
| C(27)-H(27) | 1.02(2) | C(18)-C(13)-N(2) | 120.74(13) |
| C(27)-N(1)-C(1) | 121.18(13) | C(15)-C(14)-C(13) | 118.26(15) |
| C(27)-N(1)-C(26) | 119.26(13) | C(15)-C(14)-C(19) | 119.43(14) |
| C(1)-N(1)-C(26) | 119.56(11) | C(13)-C(14)-C(19) | 122.29(14) |
| C(13)-N(2)-C(25) | 117.49(12) | C(16)-C(15)-C(14) | 122.04(15) |
| C(13)-N(2)-H(2) | 112.5(13) | C(16)-C(15)-H(15) | 119.0 |
| C(25)-N(2)-H(2) | 108.4(13) | C(14)-C(15)-H(15) | 119.0 |
| C(6)-C(1)-C(2) | 122.20(14) | C(15)-C(16)-C(17) | 119.27(15) |
| C(6)-C(1)-N(1) | 119.64(14) | C(15)-C(16)-H(16) | 120.4 |
| C(2)-C(1)-N(1) | 118.16(14) | C(17)-C(16)-H(16) | 120.4 |
| C(3)-C(2)-C(1) | 117.77(16) | C(16)-C(17)-C(18) | 121.38(16) |
| C(3)-C(2)-C(7) | 120.40(16) | C(16)-C(17)-H(17) | 119.3 |
| C(1)-C(2)-C(7) | 121.74(15) | C(18)-C(17)-H(17) | 119.3 |
| C(4)-C(3)-C(2) | 121.00(17) | C(17)-C(18)-C(13) | 118.75(14) |
| C(4)-C(3)-H(3) | 119.5 | C(17)-C(18)-C(22) | 120.03(14) |
| C(2)-C(3)-H(3) | 119.5 | C(13)-C(18)-C(22) | 121.14(13) |
| C(3)-C(4)-C(5) | 120.56(16) | C(14)-C(19)-C(21) | 111.50(16) |
| C(3)-C(4)-H(4) | 119.7 | C(14)-C(19)-C(20) | 111.91(15) |
| C(5)-C(4)-H(4) | 119.7 | C(21)-C(19)-C(20) | 109.76(16) |
| C(4)-C(5)-C(6) | 120.72(17) | C(14)-C(19)-H(19) | 107.8 |
| C(4)-C(5)-H(5) | 119.6 | C(21)-C(19)-H(19) | 107.8 |
| C(6)-C(5)-H(5) | 119.6 | C(20)-C(19)-H(19) | 107.8 |
| C(1)-C(6)-C(5) | 117.75(16) | C(19)-C(20)-H(20A) | 109.5 |
| C(1)-C(6)-C(10) | 122.81(14) | C(19)-C(20)-H(20B) | 109.5 |
| C(5)-C(6)-C(10) | 119.31(15) | H(20A)-C(20)-H(20B) | 109.5 |
| C(8)-C(7)-C(2) | 113.49(19) | C(19)-C(20)-H(20C) | 109.5 |
| C(8)-C(7)-C(9) | 112.0(3) | H(20A)-C(20)-H(20C) | 109.5 |
| C(2)-C(7)-C(9) | 108.3(2) | H(20B)-C(20)-H(20C) | 109.5 |
| C(8)-C(7)-H(7) | 107.6 | C(19)-C(21)-H(21A) | 109.5 |
| C(2)-C(7)-H(7) | 107.6 | C(19)-C(21)-H(21B) | 109.5 |
| C(9)-C(7)-H(7) | 107.6 | H(21A)-C(21)-H(21B) | 109.5 |
| C(6)-C(10)-C(11) | 109.54(15) | C(19)-C(21)-H(21C) | 109.5 |
| C(6)-C(10)-C(12) | 112.58(15) | H(21A)-C(21)-H(21C) | 109.5 |
| C(11)-C(10)-C(12) | 110.73(16) | H(21B)-C(21)-H(21C) | 109.5 |
| C(6)-C(10)-H(10) | 107.9 | C(18)-C(22)-C(23) | 109.88(13) |
| C(11)-C(10)-H(10) | 107.9 | C(18)-C(22)-C(24) | 114.11(14) |
| C(12)-C(10)-H(10) | 107.9 | C(23)-C(22)-C(24) | 110.51(14) |

| | | | |
|---|---|---|---|
| C(18)-C(22)-H(22) | 107.3 | N(2)-C(25)-H(25A) | 110.1 |
| C(23)-C(22)-H(22) | 107.3 | C(26)-C(25)-H(25A) | 110.1 |
| C(24)-C(22)-H(22) | 107.3 | N(2)-C(25)-H(25B) | 110.1 |
| C(22)-C(23)-H(23A) | 109.5 | C(26)-C(25)-H(25B) | 110.1 |
| C(22)-C(23)-H(23B) | 109.5 | H(25A)-C(25)-H(25B) | 108.4 |
| H(23A)-C(23)-H(23B) | 109.5 | N(1)-C(26)-C(25) | 112.91(13) |
| C(22)-C(23)-H(23C) | 109.5 | N(1)-C(26)-H(26A) | 109.0 |
| H(23A)-C(23)-H(23C) | 109.5 | C(25)-C(26)-H(26A) | 109.0 |
| H(23B)-C(23)-H(23C) | 109.5 | N(1)-C(26)-H(26B) | 109.0 |
| C(22)-C(24)-H(24A) | 109.5 | C(25)-C(26)-H(26B) | 109.0 |
| C(22)-C(24)-H(24B) | 109.5 | H(26A)-C(26)-H(26B) | 107.8 |
| H(24A)-C(24)-H(24B) | 109.5 | O(1)-C(27)-N(1) | 123.97(16) |
| C(22)-C(24)-H(24C) | 109.5 | O(1)-C(27)-H(27) | 124.9(11) |
| H(24A)-C(24)-H(24C) | 109.5 | N(1)-C(27)-H(27) | 111.2(11) |
| H(24B)-C(24)-H(24C) | 109.5 | | |
| N(2)-C(25)-C(26) | 108.20(12) | | |

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **166**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 23(1) | 30(1) | 20(1) | -1(1) | -3(1) | 4(1) |
| N(2) | 24(1) | 26(1) | 26(1) | 6(1) | 2(1) | 5(1) |
| C(1) | 23(1) | 34(1) | 19(1) | -1(1) | -1(1) | 5(1) |
| C(2) | 31(1) | 33(1) | 27(1) | -1(1) | -4(1) | 7(1) |
| C(3) | 33(1) | 41(1) | 33(1) | 4(1) | -5(1) | 11(1) |
| C(4) | 24(1) | 56(1) | 32(1) | 4(1) | -6(1) | 5(1) |
| C(5) | 24(1) | 45(1) | 33(1) | 0(1) | -2(1) | -4(1) |
| C(6) | 24(1) | 35(1) | 24(1) | -1(1) | 2(1) | 1(1) |
| C(7) | 47(1) | 31(1) | 59(1) | -3(1) | -23(1) | 8(1) |
| C(8) | 97(2) | 75(2) | 113(3) | 52(2) | -54(2) | -52(2) |
| C(9) | 90(2) | 58(2) | 88(2) | -36(2) | -7(2) | 6(2) |
| C(10) | 28(1) | 32(1) | 39(1) | 1(1) | -3(1) | -1(1) |
| C(11) | 41(1) | 45(1) | 45(1) | 9(1) | 1(1) | -7(1) |
| C(12) | 36(1) | 44(1) | 59(1) | -12(1) | 1(1) | -1(1) |
| C(13) | 19(1) | 23(1) | 29(1) | 5(1) | 0(1) | -1(1) |
| C(14) | 26(1) | 29(1) | 29(1) | 6(1) | -2(1) | 0(1) |
| C(15) | 25(1) | 36(1) | 37(1) | 12(1) | -6(1) | 3(1) |
| C(16) | 23(1) | 29(1) | 45(1) | 9(1) | 1(1) | 6(1) |
| C(17) | 22(1) | 29(1) | 36(1) | 3(1) | 3(1) | 2(1) |
| C(18) | 20(1) | 23(1) | 30(1) | 4(1) | 1(1) | -1(1) |
| C(19) | 37(1) | 37(1) | 30(1) | 3(1) | -8(1) | 3(1) |
| C(20) | 56(1) | 48(1) | 31(1) | 7(1) | 2(1) | 10(1) |
| C(21) | 52(1) | 66(2) | 46(1) | -4(1) | -17(1) | -4(1) |
| C(22) | 28(1) | 25(1) | 27(1) | 2(1) | 0(1) | 3(1) |
| C(23) | 32(1) | 32(1) | 37(1) | 1(1) | -7(1) | 0(1) |
| C(24) | 39(1) | 49(1) | 31(1) | 6(1) | 6(1) | 7(1) |
| C(25) | 23(1) | 25(1) | 25(1) | 0(1) | 0(1) | 2(1) |
| C(26) | 24(1) | 24(1) | 24(1) | -1(1) | -2(1) | 1(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(27) | 33(1) | 32(1) | 22(1) | -2(1) | -2(1) | 1(1) |
| O(1) | 39(1) | 46(1) | 25(1) | 1(1) | -9(1) | -1(1) |

**Table 5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for **166**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3) | -841 | 1176 | 2691 | 43 |
| H(4) | -268 | 2159 | 3115 | 45 |
| H(5) | -578 | 3264 | 2539 | 41 |
| H(7) | -2277 | 1191 | 1290 | 55 |
| H(8A) | -1540 | 384 | 2756 | 142 |
| H(8B) | -2156 | 109 | 2206 | 142 |
| H(8C) | -2169 | 744 | 3085 | 142 |
| H(9A) | -1508 | 1049 | -107 | 118 |
| H(9B) | -1802 | 309 | 210 | 118 |
| H(9C) | -1154 | 520 | 704 | 118 |
| H(10) | -1933 | 3645 | 971 | 39 |
| H(11A) | -670 | 3952 | 749 | 65 |
| H(11B) | -1200 | 4356 | 101 | 65 |
| H(11C) | -1062 | 3552 | -181 | 65 |
| H(12A) | -1851 | 4072 | 2833 | 69 |
| H(12B) | -1680 | 4676 | 1955 | 69 |
| H(12C) | -1158 | 4270 | 2621 | 69 |
| H(15) | -4901 | 4502 | 643 | 39 |
| H(16) | -5122 | 5123 | 2270 | 39 |
| H(17) | -4708 | 4767 | 3982 | 35 |
| H(19) | -3952 | 2979 | 432 | 41 |
| H(20A) | -4131 | 4250 | -816 | 68 |
| H(20B) | -3814 | 3562 | -1309 | 68 |
| H(20C) | -3495 | 3995 | -323 | 68 |
| H(21A) | -5018 | 2831 | 319 | 82 |
| H(21B) | -4714 | 2815 | -901 | 82 |
| H(21C) | -5060 | 3503 | -481 | 82 |
| H(22) | -3852 | 3239 | 4486 | 32 |
| H(23A) | -3034 | 3938 | 3998 | 50 |
| H(23B) | -3120 | 3989 | 5331 | 50 |
| H(23C) | -3344 | 4616 | 4541 | 50 |
| H(24A) | -4334 | 4434 | 5621 | 60 |
| H(24B) | -4129 | 3713 | 6194 | 60 |
| H(24C) | -4717 | 3734 | 5411 | 60 |
| H(25A) | -2772 | 3344 | 2322 | 29 |
| H(25B) | -3115 | 3407 | 1137 | 29 |
| H(26A) | -2783 | 2103 | 2169 | 29 |
| H(26B) | -3136 | 2159 | 999 | 29 |
| H(27) | -1824(9) | 2504(10) | -554(16) | 40(5) |
| H(2) | -3580(9) | 2870(11) | 3062(17) | 39(5) |

**Table 6.** Torsion angles [°] for **166**.

| | |
|---|---|
| C(27)-N(1)-C(1)-C(6)78.82(19) | N(2)-C(13)-C(14)-C(15)-179.31(14) |
| C(26)-N(1)-C(1)-C(6)-101.42(17) | C(18)-C(13)-C(14)-C(19)-175.33(15) |
| C(27)-N(1)-C(1)-C(2)-101.65(18) | N(2)-C(13)-C(14)-C(19)2.2(2) |
| C(26)-N(1)-C(1)-C(2)78.12(18) | C(13)-C(14)-C(15)-C(16)-1.0(3) |
| C(6)-C(1)-C(2)-C(3) -0.3(2) | C(19)-C(14)-C(15)-C(16)177.51(16) |
| N(1)-C(1)-C(2)-C(3)-179.84(14) | C(14)-C(15)-C(16)-C(17)-1.3(3) |
| C(6)-C(1)-C(2)-C(7)-176.85(16) | C(15)-C(16)-C(17)-C(18)1.4(3) |
| N(1)-C(1)-C(2)-C(7) 3.6(2) | C(16)-C(17)-C(18)-C(13)0.7(2) |
| C(1)-C(2)-C(3)-C(4) 0.2(3) | C(16)-C(17)-C(18)-C(22)177.45(15) |
| C(7)-C(2)-C(3)-C(4)176.78(18) | C(14)-C(13)-C(18)-C(17)-3.0(2) |
| C(2)-C(3)-C(4)-C(5) -0.1(3) | N(2)-C(13)-C(18)-C(17)179.50(14) |
| C(3)-C(4)-C(5)-C(6) 0.1(3) | C(14)-C(13)-C(18)-C(22)-179.72(14) |
| C(2)-C(1)-C(6)-C(5) 0.3(2) | N(2)-C(13)-C(18)-C(22)2.8(2) |
| N(1)-C(1)-C(6)-C(5)179.83(14) | C(15)-C(14)-C(19)-C(21)-57.0(2) |
| C(2)-C(1)-C(6)-C(10)176.03(15) | C(13)-C(14)-C(19)-C(21)121.49(19) |
| N(1)-C(1)-C(6)-C(10) -4.5(2) | C(15)-C(14)-C(19)-C(20)66.4(2) |
| C(4)-C(5)-C(6)-C(1) -0.2(2) | C(13)-C(14)-C(19)-C(20)-115.14(18) |
| C(4)-C(5)-C(6)-C(10)-176.06(15) | C(17)-C(18)-C(22)-C(23)-94.55(17) |
| C(3)-C(2)-C(7)-C(8) 46.4(3) | C(13)-C(18)-C(22)-C(23)82.12(18) |
| C(1)-C(2)-C(7)-C(8) -137.2(2) | C(17)-C(18)-C(22)-C(24)30.2(2) |
| C(3)-C(2)-C(7)-C(9) -78.6(2) | C(13)-C(18)-C(22)-C(24)-153.13(15) |
| C(1)-C(2)-C(7)-C(9) 97.8(2) | C(13)-N(2)-C(25)-C(26)-155.28(13) |
| C(1)-C(6)-C(10)-C(11)-108.40(18) | C(27)-N(1)-C(26)-C(25)-87.20(17) |
| C(5)-C(6)-C(10)-C(11)67.3(2) | C(1)-N(1)-C(26)-C(25)93.02(16) |
| C(1)-C(6)-C(10)-C(12)127.93(17) | N(2)-C(25)-C(26)-N(1)178.89(12) |
| C(5)-C(6)-C(10)-C(12)-56.4(2) | C(1)-N(1)-C(27)-O(1)-179.41(16) |
| C(25)-N(2)-C(13)-C(14)68.68(19) | C(26)-N(1)-C(27)-O(1)0.8(3) |
| C(25)-N(2)-C(13)-C(18)-113.80(16) | |
| C(18)-C(13)-C(14)-C(15)3.2(2) | |

Symmetry transformations used to generate equivalent atoms:

**Table 7.** Hydrogen bonds for **166** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(2)-H(2)...O(1)#1 | 0.87(2) | 2.48(2) | 3.1835(18) | 138.1(17) |

Symmetry transformations used to generate equivalent atoms: #1 x,-y+1/2,z+1/2

X-ray data of **200**

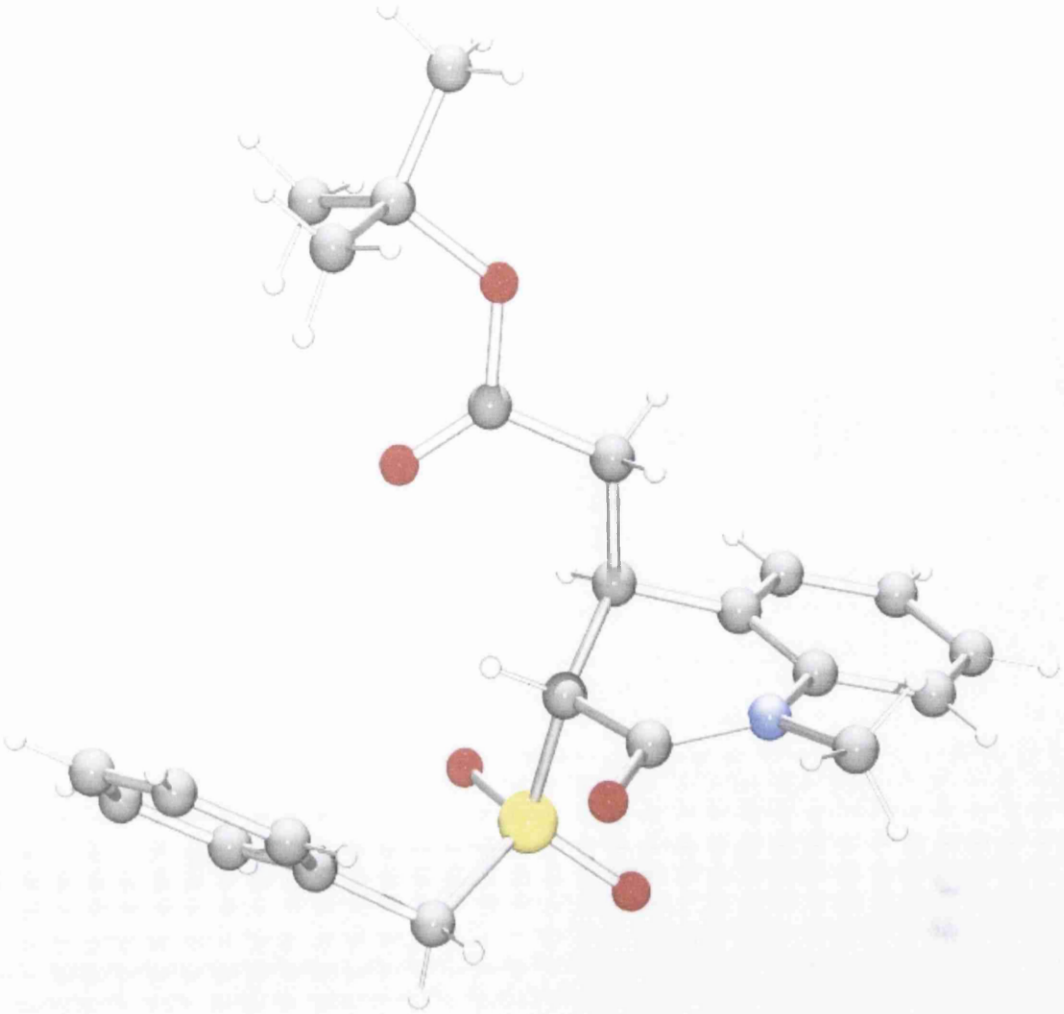

**Table 1**. Crystal data and structure refinement for **200**.

| | | |
|---|---|---|
| Identification code | **200** | |
| Empirical formula | C23 H27 N O5 S | |
| Formula weight | 429.52 | |
| Temperature | 295(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | C2/c | |
| Unit cell dimensions | a = 16.1963(18) Å | α= 90°. |
| | b = 17.0849(19) Å | β= 99.234(2)°. |
| | c = 16.2600(18) Å | γ = 90°. |
| Volume | 4441.0(9) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.285 $Mg/m^3$ | |
| Absorption coefficient | 0.179 $mm^{-1}$ | |
| F(000) | 1824 | |
| Crystal size | 0.30 x 0.30 x 0.20 $mm^3$ | |
| Theta range for data collection | 1.74 to 28.29°. | |
| Index ranges | -20<=h<=21, -22<=k<=21, -21<=l<=20 | |
| Reflections collected | 18799 | |
| Independent reflections | 5234 [R(int) = 0.0297] | |
| Completeness to theta = 28.29° | 94.7 % | |
| Max. and min. transmission | 1.000 and 0.790 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5234 / 0 / 275 | |
| Goodness-of-fit on $F^2$ | 1.052 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0474, wR2 = 0.1220 | |
| R indices (all data) | R1 = 0.0645, wR2 = 0.1315 | |
| Largest diff. peak and hole | 0.410 and -0.234 e.$Å^{-3}$ | |

**Table 2**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)for **200**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | 3551(1) | 3568(1) | 1425(1) | 41(1) |
| O(1) | 2875(1) | 5411(1) | 1261(1) | 59(1) |
| O(2) | 3334(1) | 2756(1) | 1329(1) | 53(1) |
| O(3) | 4376(1) | 3805(1) | 1314(1) | 57(1) |
| O(4) | 994(1) | 3496(1) | 283(1) | 67(1) |
| O(5) | 395(1) | 3864(1) | -1002(1) | 50(1) |
| N(1) | 3396(1) | 5213(1) | 66(1) | 46(1) |
| C(1) | 3028(1) | 4970(1) | 714(1) | 42(1) |
| C(2) | 2782(1) | 4112(1) | 718(1) | 37(1) |
| C(3) | 2645(1) | 3734(1) | -148(1) | 38(1) |
| C(4) | 3367(1) | 3932(1) | -585(1) | 41(1) |
| C(5) | 3705(1) | 4684(1) | -486(1) | 43(1) |
| C(6) | 4342(1) | 4905(1) | -915(1) | 56(1) |
| C(7) | 4642(1) | 4377(2) | -1435(1) | 69(1) |

| | | | | |
|---|---|---|---|---|
| C(8) | 4321(1) | 3629(2) | -1529(1) | 70(1) |
| C(9) | 3684(1) | 3407(1) | -1103(1) | 54(1) |
| C(10) | 1831(1) | 4016(1) | -683(1) | 42(1) |
| C(11) | 1039(1) | 3751(1) | -394(1) | 43(1) |
| C(12) | -476(1) | 3661(1) | -917(1) | 49(1) |
| C(13) | -540(1) | 2810(1) | -696(2) | 81(1) |
| C(14) | -767(2) | 4193(2) | -280(2) | 86(1) |
| C(15) | -947(1) | 3835(2) | -1778(2) | 82(1) |
| C(16) | 3545(2) | 6056(1) | -8(1) | 66(1) |
| C(17) | 3410(1) | 3886(1) | 2437(1) | 51(1) |
| C(18) | 2582(1) | 3678(1) | 2687(1) | 49(1) |
| C(19) | 2002(2) | 4256(1) | 2755(1) | 67(1) |
| C(20) | 1252(2) | 4081(2) | 3009(2) | 89(1) |
| C(21) | 1076(2) | 3325(2) | 3198(2) | 95(1) |
| C(22) | 1644(2) | 2741(2) | 3136(2) | 85(1) |
| C(23) | 2398(2) | 2915(1) | 2878(1) | 65(1) |

**Table 3.** Bond lengths [Å] and angles [°] for **200**.

| | | | |
|---|---|---|---|
| S(1)-O(2) | 1.4332(13) | C(12)-C(15) | 1.512(3) |
| S(1)-O(3) | 1.4347(13) | C(13)-H(13A) | 0.9600 |
| S(1)-C(17) | 1.7830(18) | C(13)-H(13B) | 0.9600 |
| S(1)-C(2) | 1.8106(16) | C(13)-H(13C) | 0.9600 |
| O(1)-C(1) | 1.222(2) | C(14)-H(14A) | 0.9600 |
| O(4)-C(11) | 1.197(2) | C(14)-H(14B) | 0.9600 |
| O(5)-C(11) | 1.330(2) | C(14)-H(14C) | 0.9600 |
| O(5)-C(12) | 1.480(2) | C(15)-H(15A) | 0.9600 |
| N(1)-C(1) | 1.356(2) | C(15)-H(15B) | 0.9600 |
| N(1)-C(5) | 1.420(2) | C(15)-H(15C) | 0.9600 |
| N(1)-C(16) | 1.469(2) | C(16)-H(16A) | 0.9600 |
| C(1)-C(2) | 1.519(2) | C(16)-H(16B) | 0.9600 |
| C(2)-C(3) | 1.532(2) | C(16)-H(16C) | 0.9600 |
| C(2)-H(2A) | 0.9800 | C(17)-C(18) | 1.504(3) |
| C(3)-C(4) | 1.500(2) | C(17)-H(17A) | 0.9700 |
| C(3)-C(10) | 1.536(2) | C(17)-H(17B) | 0.9700 |
| C(3)-H(3A) | 0.9800 | C(18)-C(19) | 1.379(3) |
| C(4)-C(9) | 1.386(3) | C(18)-C(23) | 1.384(3) |
| C(4)-C(5) | 1.395(2) | C(19)-C(20) | 1.377(3) |
| C(5)-C(6) | 1.388(2) | C(19)-H(19A) | 0.9300 |
| C(6)-C(7) | 1.376(3) | C(20)-C(21) | 1.369(4) |
| C(6)-H(6A) | 0.9300 | C(20)-H(20A) | 0.9300 |
| C(7)-C(8) | 1.379(3) | C(21)-C(22) | 1.371(4) |
| C(7)-H(7A) | 0.9300 | C(21)-H(21A) | 0.9300 |
| C(8)-C(9) | 1.385(3) | C(22)-C(23) | 1.385(3) |
| C(8)-H(8A) | 0.9300 | C(22)-H(22A) | 0.9300 |
| C(9)-H(9A) | 0.9300 | C(23)-H(23A) | 0.9300 |
| C(10)-C(11) | 1.505(2) | O(2)-S(1)-O(3) | 118.46(8) |
| C(10)-H(10A) | 0.9700 | O(2)-S(1)-C(17) | 109.26(8) |
| C(10)-H(10B) | 0.9700 | O(3)-S(1)-C(17) | 106.82(9) |
| C(12)-C(13) | 1.505(3) | O(2)-S(1)-C(2) | 107.27(7) |
| C(12)-C(14) | 1.509(3) | O(3)-S(1)-C(2) | 109.58(8) |

| | | | |
|---|---|---|---|
| C(17)-S(1)-C(2) | 104.60(8) | C(13)-C(12)-C(15) | 111.52(19) |
| C(11)-O(5)-C(12) | 122.77(14) | C(14)-C(12)-C(15) | 110.5(2) |
| C(1)-N(1)-C(5) | 122.69(14) | C(12)-C(13)-H(13A) | 109.5 |
| C(1)-N(1)-C(16) | 117.49(16) | C(12)-C(13)-H(13B) | 109.5 |
| C(5)-N(1)-C(16) | 119.56(16) | H(13A)-C(13)-H(13B) | 109.5 |
| O(1)-C(1)-N(1) | 122.97(16) | C(12)-C(13)-H(13C) | 109.5 |
| O(1)-C(1)-C(2) | 120.49(16) | H(13A)-C(13)-H(13C) | 109.5 |
| N(1)-C(1)-C(2) | 116.51(14) | H(13B)-C(13)-H(13C) | 109.5 |
| C(1)-C(2)-C(3) | 113.70(13) | C(12)-C(14)-H(14A) | 109.5 |
| C(1)-C(2)-S(1) | 110.13(11) | C(12)-C(14)-H(14B) | 109.5 |
| C(3)-C(2)-S(1) | 110.44(11) | H(14A)-C(14)-H(14B) | 109.5 |
| C(1)-C(2)-H(2A) | 107.4 | C(12)-C(14)-H(14C) | 109.5 |
| C(3)-C(2)-H(2A) | 107.4 | H(14A)-C(14)-H(14C) | 109.5 |
| S(1)-C(2)-H(2A) | 107.4 | H(14B)-C(14)-H(14C) | 109.5 |
| C(4)-C(3)-C(2) | 109.38(13) | C(12)-C(15)-H(15A) | 109.5 |
| C(4)-C(3)-C(10) | 108.93(13) | C(12)-C(15)-H(15B) | 109.5 |
| C(2)-C(3)-C(10) | 111.87(13) | H(15A)-C(15)-H(15B) | 109.5 |
| C(4)-C(3)-H(3A) | 108.9 | C(12)-C(15)-H(15C) | 109.5 |
| C(2)-C(3)-H(3A) | 108.9 | H(15A)-C(15)-H(15C) | 109.5 |
| C(10)-C(3)-H(3A) | 108.9 | H(15B)-C(15)-H(15C) | 109.5 |
| C(9)-C(4)-C(5) | 119.29(16) | N(1)-C(16)-H(16A) | 109.5 |
| C(9)-C(4)-C(3) | 122.38(16) | N(1)-C(16)-H(16B) | 109.5 |
| C(5)-C(4)-C(3) | 118.29(15) | H(16A)-C(16)-H(16B) | 109.5 |
| C(6)-C(5)-C(4) | 120.18(17) | N(1)-C(16)-H(16C) | 109.5 |
| C(6)-C(5)-N(1) | 120.68(16) | H(16A)-C(16)-H(16C) | 109.5 |
| C(4)-C(5)-N(1) | 119.13(15) | H(16B)-C(16)-H(16C) | 109.5 |
| C(7)-C(6)-C(5) | 119.62(19) | C(18)-C(17)-S(1) | 115.45(12) |
| C(7)-C(6)-H(6A) | 120.2 | C(18)-C(17)-H(17A) | 108.4 |
| C(5)-C(6)-H(6A) | 120.2 | S(1)-C(17)-H(17A) | 108.4 |
| C(6)-C(7)-C(8) | 120.80(19) | C(18)-C(17)-H(17B) | 108.4 |
| C(6)-C(7)-H(7A) | 119.6 | S(1)-C(17)-H(17B) | 108.4 |
| C(8)-C(7)-H(7A) | 119.6 | H(17A)-C(17)-H(17B) | 107.5 |
| C(7)-C(8)-C(9) | 119.8(2) | C(19)-C(18)-C(23) | 118.8(2) |
| C(7)-C(8)-H(8A) | 120.1 | C(19)-C(18)-C(17) | 120.06(18) |
| C(9)-C(8)-H(8A) | 120.1 | C(23)-C(18)-C(17) | 121.12(19) |
| C(8)-C(9)-C(4) | 120.3(2) | C(20)-C(19)-C(18) | 120.9(2) |
| C(8)-C(9)-H(9A) | 119.8 | C(20)-C(19)-H(19A) | 119.5 |
| C(4)-C(9)-H(9A) | 119.8 | C(18)-C(19)-H(19A) | 119.5 |
| C(11)-C(10)-C(3) | 115.29(14) | C(21)-C(20)-C(19) | 119.8(3) |
| C(11)-C(10)-H(10A) | 108.5 | C(21)-C(20)-H(20A) | 120.1 |
| C(3)-C(10)-H(10A) | 108.5 | C(19)-C(20)-H(20A) | 120.1 |
| C(11)-C(10)-H(10B) | 108.5 | C(20)-C(21)-C(22) | 120.2(3) |
| C(3)-C(10)-H(10B) | 108.5 | C(20)-C(21)-H(21A) | 119.9 |
| H(10A)-C(10)-H(10B) | 107.5 | C(22)-C(21)-H(21A) | 119.9 |
| O(4)-C(11)-O(5) | 125.48(16) | C(21)-C(22)-C(23) | 120.1(3) |
| O(4)-C(11)-C(10) | 125.21(16) | C(21)-C(22)-H(22A) | 120.0 |
| O(5)-C(11)-C(10) | 109.29(14) | C(23)-C(22)-H(22A) | 120.0 |
| O(5)-C(12)-C(13) | 110.66(16) | C(18)-C(23)-C(22) | 120.2(2) |
| O(5)-C(12)-C(14) | 109.31(15) | C(18)-C(23)-H(23A) | 119.9 |
| C(13)-C(12)-C(14) | 112.1(2) | C(22)-C(23)-H(23A) | 119.9 |
| O(5)-C(12)-C(15) | 102.38(15) | | |

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **200**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| S(1) | 41(1) | 39(1) | 41(1) | 2(1) | 2(1) | -1(1) |
| O(1) | 72(1) | 45(1) | 60(1) | -12(1) | 12(1) | 2(1) |
| O(2) | 69(1) | 38(1) | 52(1) | 2(1) | 6(1) | -1(1) |
| O(3) | 41(1) | 65(1) | 65(1) | 8(1) | 6(1) | -3(1) |
| O(4) | 53(1) | 97(1) | 50(1) | 20(1) | 2(1) | -21(1) |
| O(5) | 36(1) | 62(1) | 52(1) | 6(1) | 3(1) | -4(1) |
| N(1) | 54(1) | 35(1) | 46(1) | 5(1) | 1(1) | -9(1) |
| C(1) | 42(1) | 36(1) | 44(1) | 0(1) | -2(1) | 1(1) |
| C(2) | 36(1) | 37(1) | 37(1) | 0(1) | 3(1) | -2(1) |
| C(3) | 40(1) | 35(1) | 37(1) | -1(1) | 5(1) | -6(1) |
| C(4) | 39(1) | 45(1) | 37(1) | 2(1) | 3(1) | -4(1) |
| C(5) | 41(1) | 49(1) | 37(1) | 7(1) | 0(1) | -8(1) |
| C(6) | 49(1) | 75(1) | 43(1) | 14(1) | 0(1) | -21(1) |
| C(7) | 50(1) | 111(2) | 46(1) | 8(1) | 12(1) | -16(1) |
| C(8) | 57(1) | 107(2) | 49(1) | -11(1) | 18(1) | 4(1) |
| C(9) | 52(1) | 63(1) | 48(1) | -8(1) | 9(1) | -3(1) |
| C(10) | 42(1) | 46(1) | 38(1) | 2(1) | 2(1) | -8(1) |
| C(11) | 40(1) | 44(1) | 45(1) | -1(1) | 3(1) | -5(1) |
| C(12) | 34(1) | 50(1) | 63(1) | -2(1) | 6(1) | -4(1) |
| C(13) | 57(1) | 57(1) | 123(2) | 7(1) | -6(1) | -14(1) |
| C(14) | 56(1) | 93(2) | 114(2) | -34(2) | 27(1) | -6(1) |
| C(15) | 45(1) | 115(2) | 81(2) | 18(2) | -7(1) | -4(1) |
| C(16) | 89(2) | 39(1) | 65(1) | 10(1) | -7(1) | -17(1) |
| C(17) | 57(1) | 53(1) | 38(1) | -3(1) | -4(1) | -4(1) |
| C(18) | 59(1) | 54(1) | 32(1) | 0(1) | 1(1) | -3(1) |
| C(19) | 77(2) | 65(1) | 61(1) | -1(1) | 19(1) | 2(1) |
| C(20) | 83(2) | 104(2) | 87(2) | -5(2) | 35(2) | 5(2) |
| C(21) | 86(2) | 134(3) | 71(2) | -12(2) | 33(2) | -29(2) |
| C(22) | 111(2) | 87(2) | 58(1) | 5(1) | 18(1) | -38(2) |
| C(23) | 82(2) | 62(1) | 49(1) | 8(1) | 6(1) | -7(1) |

**Table 5.** Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **200**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | 2251 | 4081 | 933 | 45 |
| H(3A) | 2620 | 3165 | -84 | 45 |
| H(6A) | 4565 | 5407 | -852 | 68 |
| H(7A) | 5065 | 4527 | -1726 | 82 |
| H(8A) | 4532 | 3275 | -1877 | 84 |
| H(9A) | 3467 | 2902 | -1166 | 65 |
| H(10A) | 1836 | 4583 | -696 | 51 |
| H(10B) | 1823 | 3833 | -1249 | 51 |
| H(13A) | -261 | 2724 | -137 | 122 |

| | | | | |
|---|---|---|---|---|
| H(13B) | -282 | 2496 | -1074 | 122 |
| H(13C) | -1119 | 2668 | -737 | 122 |
| H(14A) | -432 | 4105 | 254 | 129 |
| H(14B) | -1342 | 4083 | -248 | 129 |
| H(14C) | -713 | 4728 | -442 | 129 |
| H(15A) | -826 | 4360 | -1933 | 123 |
| H(15B) | -1536 | 3782 | -1776 | 123 |
| H(15C) | -776 | 3474 | -2171 | 123 |
| H(16A) | 3194 | 6340 | 311 | 99 |
| H(16B) | 3416 | 6208 | -583 | 99 |
| H(16C) | 4121 | 6170 | 199 | 99 |
| H(17A) | 3851 | 3661 | 2842 | 61 |
| H(17B) | 3474 | 4450 | 2464 | 61 |
| H(19A) | 2119 | 4771 | 2628 | 80 |
| H(20A) | 866 | 4476 | 3052 | 107 |
| H(21A) | 569 | 3206 | 3369 | 113 |
| H(22A) | 1523 | 2228 | 3266 | 102 |
| H(23A) | 2781 | 2518 | 2834 | 77 |

**Table 6.** Torsion angles [°] for **200**.

| | |
|---|---|
| C(5)-N(1)-C(1)-O(1)168.69(16) | C(4)-C(5)-C(6)-C(7)-0.4(3) |
| C(16)-N(1)-C(1)-O(1)-5.4(3) | N(1)-C(5)-C(6)-C(7)178.81(17) |
| C(5)-N(1)-C(1)-C(2)-13.3(2) | C(5)-C(6)-C(7)-C(8)-0.5(3) |
| C(16)-N(1)-C(1)-C(2)172.61(15) | C(6)-C(7)-C(8)-C(9)0.7(3) |
| O(1)-C(1)-C(2)-C(3)154.01(16) | C(7)-C(8)-C(9)-C(4)0.0(3) |
| N(1)-C(1)-C(2)-C(3)-24.0(2) | C(5)-C(4)-C(9)-C(8)-1.0(3) |
| O(1)-C(1)-C(2)-S(1)-81.44(18) | C(3)-C(4)-C(9)-C(8)176.53(17) |
| N(1)-C(1)-C(2)-S(1)100.51(15) | C(4)-C(3)-C(10)-C(11)170.97(14) |
| O(2)-S(1)-C(2)-C(1)-173.56(11) | C(2)-C(3)-C(10)-C(11)-67.98(18) |
| O(3)-S(1)-C(2)-C(1)-43.74(14) | C(12)-O(5)-C(11)-O(4)-1.7(3) |
| C(17)-S(1)-C(2)-C(1)70.47(13) | C(12)-O(5)-C(11)-C(10)179.77(14) |
| O(2)-S(1)-C(2)-C(3)-47.15(13) | C(3)-C(10)-C(11)-O(4)16.5(3) |
| O(3)-S(1)-C(2)-C(3)82.66(12) | C(3)-C(10)-C(11)-O(5)-164.98(14) |
| C(17)-S(1)-C(2)-C(3)-163.13(11) | C(11)-O(5)-C(12)-C(13)-56.7(2) |
| C(1)-C(2)-C(3)-C(4)48.02(18) | C(11)-O(5)-C(12)-C(14)67.2(2) |
| S(1)-C(2)-C(3)-C(4)-76.36(14) | C(11)-O(5)-C(12)-C(15)-175.62(18) |
| C(1)-C(2)-C(3)-C(10)-72.76(17) | O(2)-S(1)-C(17)-C(18)-49.49(16) |
| S(1)-C(2)-C(3)-C(10)162.86(11) | O(3)-S(1)-C(17)-C(18)-178.76(13) |
| C(2)-C(3)-C(4)-C(9)143.66(16) | C(2)-S(1)-C(17)-C(18)65.09(15) |
| C(10)-C(3)-C(4)-C(9)-93.79(19) | S(1)-C(17)-C(18)-C(19)-109.99(18) |
| C(2)-C(3)-C(4)-C(5)-38.8(2) | S(1)-C(17)-C(18)-C(23)72.2(2) |
| C(10)-C(3)-C(4)-C(5)83.72(17) | C(23)-C(18)-C(19)-C(20)0.0(3) |
| C(9)-C(4)-C(5)-C(6)1.1(3) | C(17)-C(18)-C(19)-C(20)-177.9(2) |
| C(3)-C(4)-C(5)-C(6)-176.45(15) | C(18)-C(19)-C(20)-C(21)0.1(4) |
| C(9)-C(4)-C(5)-N(1)-178.09(16) | C(19)-C(20)-C(21)-C(22)0.0(4) |
| C(3)-C(4)-C(5)-N(1)4.3(2) | C(20)-C(21)-C(22)-C(23)-0.2(4) |
| C(1)-N(1)-C(5)-C(6)-154.51(16) | C(19)-C(18)-C(23)-C(22)-0.2(3) |
| C(16)-N(1)-C(5)-C(6)19.5(2) | C(17)-C(18)-C(23)-C(22)177.69(18) |
| C(1)-N(1)-C(5)-C(4)24.7(2) | C(21)-C(22)-C(23)-C(18)0.3(3) |
| C(16)-N(1)-C(5)-C(4)-161.32(16) | |

X-ray data of **201**

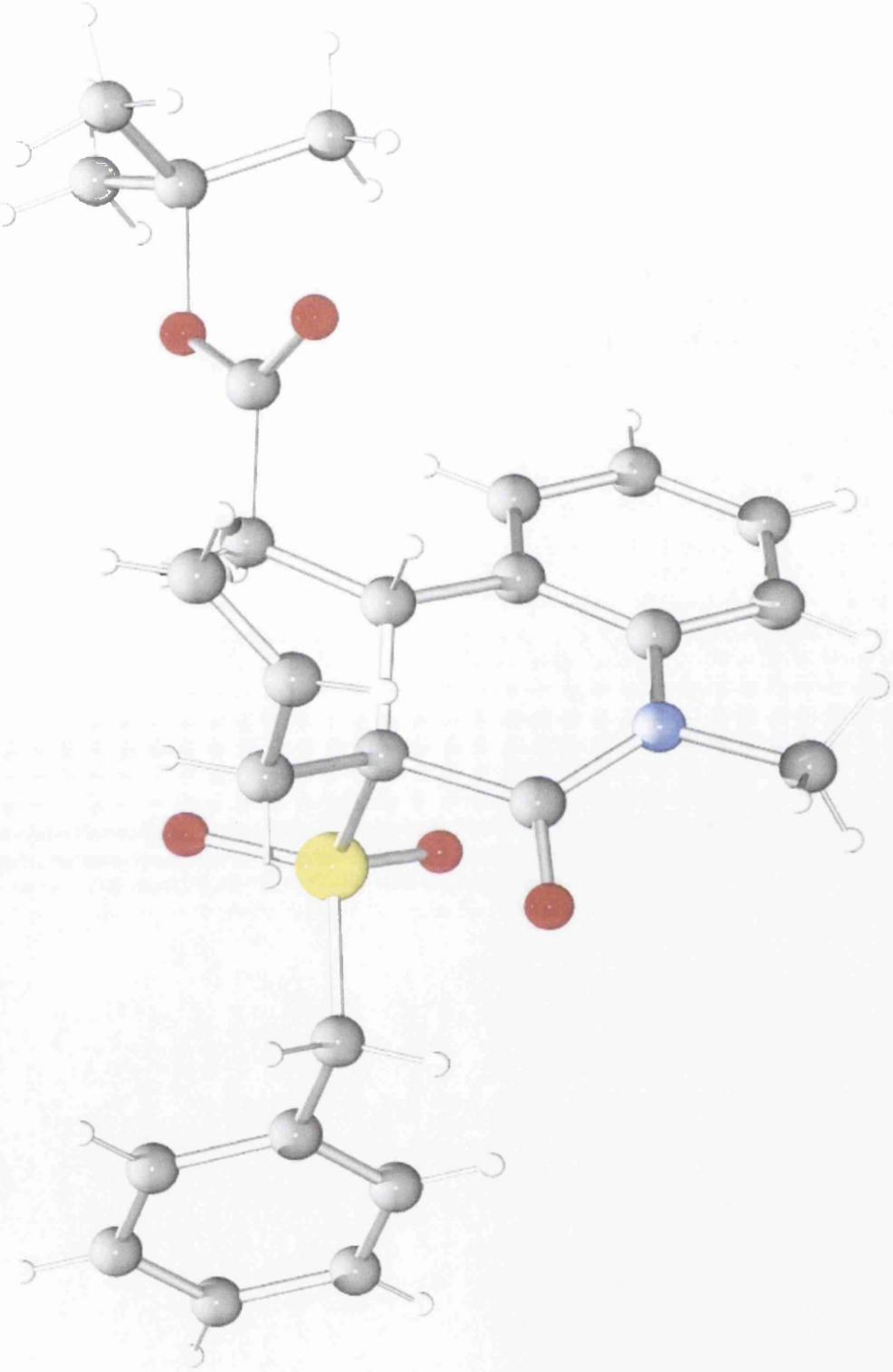

**Table 1.** Crystal data and structure refinement for **201**.

| | | |
|---|---|---|
| Identification code | **201** | |
| Empirical formula | C26 H31 N O5 S | |
| Formula weight | 469.58 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 10.8283(13) Å | α= 103.161(2)°. |
| | b = 11.0456(13) Å | β= 113.007(2)°. |
| | c = 12.277(2) Å | γ = |
| 103.9230(10)°. | | |
| Volume | 1223.8(3)Å$^3$ | |
| Z | 2 | |
| Density (calculated) | 1.274 Mg/m$^3$ | |
| Absorption coefficient | 0.169 mm$^{-1}$ | |
| F(000) | 500 | |
| Crystal size | 0.35 x 0.25 x 0.08 mm$^3$ | |
| Theta range for data collection | 1.93 to 26.36 °. | |
| Index ranges | 13<=h<=12, -13<=k<=13, -11<=l<=15 | |
| Reflections collected | 6960 | |
| Independent reflections | 4833 [R(int) = 0.0423] | |
| Completeness to theta = 26.36° | 96.5 % | |
| Max. and min. transmission | 0.9866 and 0.9433 | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 4833 / 0 / 302 | |
| Goodness-of-fit on F$^2$ | 0.879 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0395, wR2 = 0.0798 | |
| R indices (all data) | R1 = 0.0641, wR2 = 0.0851 | |
| Largest diff. peak and hole | 0.419 and -0.363 e.Å$^{-3}$ | |

**Table 2.** Atomic coordinates ( x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$)for **201**. U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | -545(1) | 7014(1) | 7016(1) | 18(1) |
| O(1) | -1489(1) | 6209(1) | 7355(1) | 25(1) |
| O(2) | -461(1) | 8361(1) | 7175(1) | 26(1) |
| O(3) | 2250(1) | 7078(1) | 6520(1) | 22(1) |
| O(4) | 1178(1) | 7951(1) | 12044(1) | 22(1) |
| O(5) | 3220(1) | 7999(1) | 11921(1) | 23(1) |
| N(1) | 3142(2) | 9027(2) | 8157(1) | 19(1) |
| C(1) | -2548(2) | 6045(2) | 4539(2) | 19(1) |
| C(2) | -2786(2) | 7000(2) | 4015(2) | 24(1) |
| C(3) | -4174(2) | 6858(2) | 3207(2) | 31(1) |
| C(4) | -5332(2) | 5759(2) | 2931(2) | 30(1) |
| C(5) | -5105(2) | 4809(2) | 3459(2) | 27(1) |
| C(6) | -3722(2) | 4941(2) | 4252(2) | 23(1) |

| | | | | |
|---|---|---|---|---|
| C(7) | -1045(2) | 6157(2) | 5388(2) | 21(1) |
| C(8) | 1267(2) | 7047(2) | 7957(2) | 16(1) |
| C(9) | 1838(2) | 7840(2) | 9380(2) | 16(1) |
| C(10) | 2200(2) | 9316(2) | 9652(2) | 18(1) |
| C(11) | 1935(2) | 10149(2) | 10494(2) | 21(1) |
| C(12) | 2439(2) | 11518(2) | 10801(2) | 28(1) |
| C(13) | 3209(2) | 12063(2) | 10259(2) | 32(1) |
| C(14) | 3451(2) | 11263(2) | 9383(2) | 29(1) |
| C(15) | 2944(2) | 9891(2) | 9073(2) | 20(1) |
| C(16) | 2255(2) | 7726(2) | 7475(2) | 17(1) |
| C(17) | 4163(2) | 9594(2) | 7732(2) | 29(1) |
| C(18) | 984(2) | 7281(2) | 10009(2) | 19(1) |
| C(19) | 1944(2) | 7788(2) | 11434(2) | 18(1) |
| C(20) | 1901(2) | 8510(2) | 13454(2) | 22(1) |
| C(21) | 625(2) | 8499(2) | 13700(2) | 34(1) |
| C(22) | 2608(2) | 7602(2) | 13989(2) | 26(1) |
| C(23) | 2950(2) | 9925(2) | 13925(2) | 28(1) |
| C(24) | 1209(2) | 5598(2) | 7729(2) | 19(1) |
| C(25) | 2630(2) | 5519(2) | 8502(2) | 24(1) |
| C(26) | 2885(3) | 4988(2) | 9375(2) | 43(1) |

**Table 3.** Bond lengths [A] and angles [°] for **201**.

| | | | |
|---|---|---|---|
| (1)-O(2) | 1.4332(13) | C(8)-C(9) | 1.549(2) |
| S(1)-O(2) | 1.4306(14) | C(9)-C(10) | 1.504(2) |
| S(1)-O(1) | 1.4395(13) | C(9)-C(18) | 1.529(2) |
| S(1)-C(7) | 1.7969(19) | C(9)-H(9) | 0.98 |
| S(1)-C(8) | 1.8335(18) | C(10)-C(11) | 1.387(3) |
| O(3)-C(16) | 1.224(2) | C(10)-C(15) | 1.402(2) |
| O(4)-C(19) | 1.334(2) | C(11)-C(12) | 1.382(3) |
| O(4)-C(20) | 1.487(2) | C(11)-H(11) | 0.93 |
| O(5)-C(19) | 1.207(2) | C(12)-C(13) | 1.369(3) |
| N(1)-C(16) | 1.359(2) | C(12)-H(12) | 0.93 |
| N(1)-C(15) | 1.421(2) | C(13)-C(14) | 1.381(3) |
| N(1)-C(17) | 1.468(2) | C(13)-H(13) | 0.93 |
| C(1)-C(2) | 1.379(3) | C(14)-C(15) | 1.384(3) |
| C(1)-C(6) | 1.392(3) | C(14)-H(14) | 0.93 |
| C(1)-C(7) | 1.506(2) | C(17)-H(17A) | 0.96 |
| C(2)-C(3) | 1.385(3) | C(17)-H(17B) | 0.96 |
| C(2)-H(2) | 0.93 | C(17)-H(17C) | 0.96 |
| C(3)-C(4) | 1.382(3) | C(18)-C(19) | 1.518(3) |
| C(3)-H(3) | 0.93 | C(18)-H(18A) | 0.97 |
| C(4)-C(5) | 1.375(3) | C(18)-H(18B) | 0.97 |
| C(4)-H(4) | 0.93 | C(20)-C(23) | 1.512(3) |
| C(5)-C(6) | 1.379(3) | C(20)-C(22) | 1.517(3) |
| C(5)-H(5) | 0.93 | C(20)-C(21) | 1.524(3) |
| C(6)-H(6) | 0.93 | C(21)-H(21A) | 0.96 |
| C(7)-H(7A) | 0.97 | C(21)-H(21B) | 0.96 |
| C(7)-H(7B) | 0.97 | C(21)-H(21C) | 0.96 |
| C(8)-C(16) | 1.539(2) | C(22)-H(22A) | 0.96 |
| C(8)-C(24) | 1.542(3) | C(22)-H(22B) | 0.96 |

| | | | |
|---|---|---|---|
| C(22)-H(22C) | 0.96 | C(10)-C(9)-C(18) | 113.79(15) |
| C(23)-H(23A) | 0.96 | C(10)-C(9)-C(8) | 111.84(14) |
| C(23)-H(23B) | 0.96 | C(18)-C(9)-C(8) | 116.58(15) |
| C(23)-H(23C) | 0.96 | C(10)-C(9)-H(9) | 104.3 |
| C(24)-C(25) | 1.496(3) | C(18)-C(9)-H(9) | 104.3 |
| C(24)-H(24A) | 0.97 | C(8)-C(9)-H(9) | 104.3 |
| C(24)-H(24B) | 0.97 | C(11)-C(10)-C(15) | 118.27(18) |
| C(25)-C(26) | 1.304(3) | C(11)-C(10)-C(9) | 124.62(17) |
| C(25)-H(25) | 0.93 | C(15)-C(10)-C(9) | 116.97(17) |
| C(26)-H(26A) | 0.93 | C(12)-C(11)-C(10) | 121.31(19) |
| C(26)-H(26B) | 0.93 | C(12)-C(11)-H(11) | 119.3 |
| O(2)-S(1)-O(1) | 118.67(8) | C(10)-C(11)-H(11) | 119.3 |
| O(2)-S(1)-C(7) | 108.16(9) | C(13)-C(12)-C(11) | 119.4(2) |
| O(1)-S(1)-C(7) | 108.28(9) | C(13)-C(12)-H(12) | 120.3 |
| O(2)-S(1)-C(8) | 108.41(8) | C(11)-C(12)-H(12) | 120.3 |
| O(1)-S(1)-C(8) | 106.60(8) | C(12)-C(13)-C(14) | 121.0(2) |
| C(7)-S(1)-C(8) | 106.04(9) | C(12)-C(13)-H(13) | 119.5 |
| C(19)-O(4)-C(20) | 120.39(14) | C(14)-C(13)-H(13) | 119.5 |
| C(16)-N(1)-C(15) | 123.27(15) | C(13)-C(14)-C(15) | 119.6(2) |
| C(16)-N(1)-C(17) | 116.30(16) | C(13)-C(14)-H(14) | 120.2 |
| C(15)-N(1)-C(17) | 119.38(16) | C(15)-C(14)-H(14) | 120.2 |
| C(2)-C(1)-C(6) | 119.13(18) | C(14)-C(15)-C(10) | 120.32(18) |
| C(2)-C(1)-C(7) | 121.44(17) | C(14)-C(15)-N(1) | 121.53(18) |
| C(6)-C(1)-C(7) | 119.42(17) | C(10)-C(15)-N(1) | 118.14(17) |
| C(1)-C(2)-C(3) | 120.49(19) | O(3)-C(16)-N(1) | 122.21(17) |
| C(1)-C(2)-H(2) | 119.8 | O(3)-C(16)-C(8) | 119.54(17) |
| C(3)-C(2)-H(2) | 119.8 | N(1)-C(16)-C(8) | 118.21(16) |
| C(4)-C(3)-C(2) | 119.9(2) | N(1)-C(17)-H(17A) | 109.5 |
| C(4)-C(3)-H(3) | 120.1 | N(1)-C(17)-H(17B) | 109.5 |
| C(2)-C(3)-H(3) | 120.1 | H(17A)-C(17)-H(17B) | 109.5 |
| C(5)-C(4)-C(3) | 119.98(19) | N(1)-C(17)-H(17C) | 109.5 |
| C(5)-C(4)-H(4) | 120 | H(17A)-C(17)-H(17C) | 109.5 |
| C(3)-C(4)-H(4) | 120 | H(17B)-C(17)-H(17C) | 109.5 |
| C(4)-C(5)-C(6) | 120.21(19) | C(19)-C(18)-C(9) | 109.87(15) |
| C(4)-C(5)-H(5) | 119.9 | C(19)-C(18)-H(18A) | 109.7 |
| C(6)-C(5)-H(5) | 119.9 | C(9)-C(18)-H(18A) | 109.7 |
| C(5)-C(6)-C(1) | 120.31(19) | C(19)-C(18)-H(18B) | 109.7 |
| C(5)-C(6)-H(6) | 119.8 | C(9)-C(18)-H(18B) | 109.7 |
| C(1)-C(6)-H(6) | 119.8 | H(18A)-C(18)-H(18B) | 108.2 |
| C(1)-C(7)-S(1) | 109.95(13) | O(5)-C(19)-O(4) | 125.92(17) |
| C(1)-C(7)-H(7A) | 109.7 | O(5)-C(19)-C(18) | 123.51(17) |
| S(1)-C(7)-H(7A) | 109.7 | O(4)-C(19)-C(18) | 110.57(15) |
| C(1)-C(7)-H(7B) | 109.7 | O(4)-C(20)-C(23) | 109.52(15) |
| S(1)-C(7)-H(7B) | 109.7 | O(4)-C(20)-C(22) | 110.13(15) |
| H(7A)-C(7)-H(7B) | 108.2 | C(23)-C(20)-C(22) | 113.03(17) |
| C(16)-C(8)-C(24) | 108.28(15) | O(4)-C(20)-C(21) | 101.34(15) |
| C(16)-C(8)-C(9) | 110.10(15) | C(23)-C(20)-C(21) | 110.82(17) |
| C(24)-C(8)-C(9) | 111.52(14) | C(22)-C(20)-C(21) | 111.38(16) |
| C(16)-C(8)-S(1) | 107.71(12) | C(20)-C(21)-H(21A) | 109.5 |
| C(24)-C(8)-S(1) | 108.95(12) | C(20)-C(21)-H(21B) | 109.5 |
| C(9)-C(8)-S(1) | 110.18(13) | H(21A)-C(21)-H(21B) | 109.5 |

| | | | |
|---|---|---|---|
| C(20)-C(21)-H(21C) | 109.5 | H(23B)-C(23)-H(23C) | 109.5 |
| H(21A)-C(21)-H(21C) | 109.5 | C(25)-C(24)-C(8) | 112.99(15) |
| H(21B)-C(21)-H(21C) | 109.5 | C(25)-C(24)-H(24A) | 109 |
| C(20)-C(22)-H(22A) | 109.5 | C(8)-C(24)-H(24A) | 109 |
| C(20)-C(22)-H(22B) | 109.5 | C(25)-C(24)-H(24B) | 109 |
| H(22A)-C(22)-H(22B) | 109.5 | C(8)-C(24)-H(24B) | 109 |
| C(20)-C(22)-H(22C) | 109.5 | H(24A)-C(24)-H(24B) | 107.8 |
| H(22A)-C(22)-H(22C) | 109.5 | C(26)-C(25)-C(24) | 125.0(2) |
| H(22B)-C(22)-H(22C) | 109.5 | C(26)-C(25)-H(25) | 117.5 |
| C(20)-C(23)-H(23A) | 109.5 | C(24)-C(25)-H(25) | 117.5 |
| C(20)-C(23)-H(23B) | 109.5 | C(25)-C(26)-H(26A) | 120 |
| H(23A)-C(23)-H(23B) | 109.5 | C(25)-C(26)-H(26B) | 120 |
| C(20)-C(23)-H(23C) | 109.5 | H(26A)-C(26)-H(26B) | 120 |
| H(23A)-C(23)-H(23C) | 109.5 | | |

Symmetry transformations used to generate equivalent atoms:

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **201**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| S(1) | 14(1) | 21(1) | 14(1) | 3(1) | 5(1) | 5(1) |
| O(1) | 17(1) | 33(1) | 19(1) | 7(1) | 9(1) | 3(1) |
| O(2) | 21(1) | 22(1) | 24(1) | 3(1) | 3(1) | 10(1) |
| O(3) | 21(1) | 28(1) | 17(1) | 5(1) | 11(1) | 9(1) |
| O(4) | 19(1) | 30(1) | 14(1) | 6(1) | 9(1) | 6(1) |
| O(5) | 21(1) | 30(1) | 21(1) | 11(1) | 11(1) | 10(1) |
| N(1) | 18(1) | 21(1) | 18(1) | 6(1) | 10(1) | 3(1) |
| C(1) | 19(1) | 24(1) | 12(1) | 2(1) | 8(1) | 9(1) |
| C(2) | 25(1) | 26(1) | 21(1) | 6(1) | 12(1) | 8(1) |
| C(3) | 38(1) | 34(1) | 24(1) | 12(1) | 13(1) | 21(1) |
| C(4) | 21(1) | 40(1) | 20(1) | 2(1) | 4(1) | 15(1) |
| C(5) | 21(1) | 30(1) | 21(1) | -2(1) | 10(1) | 5(1) |
| C(6) | 25(1) | 24(1) | 19(1) | 5(1) | 11(1) | 9(1) |
| C(7) | 20(1) | 26(1) | 16(1) | 5(1) | 10(1) | 9(1) |
| C(8) | 14(1) | 17(1) | 15(1) | 5(1) | 6(1) | 4(1) |
| C(9) | 13(1) | 20(1) | 13(1) | 4(1) | 5(1) | 4(1) |
| C(10) | 15(1) | 19(1) | 15(1) | 5(1) | 4(1) | 5(1) |
| C(11) | 19(1) | 24(1) | 18(1) | 7(1) | 7(1) | 8(1) |
| C(12) | 31(1) | 25(1) | 22(1) | 1(1) | 8(1) | 12(1) |
| C(13) | 38(1) | 17(1) | 29(1) | 4(1) | 9(1) | 6(1) |
| C(14) | 32(1) | 23(1) | 25(1) | 9(1) | 12(1) | 1(1) |
| C(15) | 18(1) | 20(1) | 15(1) | 3(1) | 4(1) | 4(1) |
| C(16) | 13(1) | 23(1) | 16(1) | 9(1) | 5(1) | 8(1) |
| C(17) | 20(1) | 34(1) | 25(1) | 10(1) | 11(1) | -2(1) |
| C(18) | 20(1) | 19(1) | 17(1) | 4(1) | 10(1) | 4(1) |
| C(19) | 20(1) | 16(1) | 21(1) | 8(1) | 10(1) | 6(1) |
| C(20) | 26(1) | 24(1) | 14(1) | 5(1) | 11(1) | 6(1) |
| C(21) | 37(1) | 43(2) | 25(1) | 9(1) | 21(1) | 14(1) |
| C(22) | 35(1) | 23(1) | 19(1) | 8(1) | 14(1) | 7(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(23) | 34(1) | 25(1) | 20(1) | 6(1) | 11(1) | 9(1) |
| C(24) | 21(1) | 18(1) | 19(1) | 5(1) | 11(1) | 6(1) |
| C(25) | 26(1) | 21(1) | 27(1) | 7(1) | 13(1) | 11(1) |
| C(26) | 41(1) | 55(2) | 50(2) | 32(1) | 24(1) | 31(1) |

**Table 5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **201**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | -2008 | 7745 | 4206 | 29 |
| H(3) | -4327 | 7502 | 2851 | 37 |
| H(4) | -6265 | 5662 | 2389 | 36 |
| H(5) | -5886 | 4075 | 3280 | 32 |
| H(6) | -3573 | 4290 | 4597 | 27 |
| H(7A) | -370 | 6644 | 5160 | 25 |
| H(7B) | -1007 | 5271 | 5277 | 25 |
| H(9) | 2774 | 7758 | 9807 | 20 |
| H(11) | 1408 | 9780 | 10859 | 26 |
| H(12) | 2257 | 12065 | 11371 | 34 |
| H(13) | 3574 | 12986 | 10485 | 39 |
| H(14) | 3951 | 11643 | 9003 | 35 |
| H(17A) | 4458 | 8913 | 7390 | 43 |
| H(17B) | 4993 | 10310 | 8439 | 43 |
| H(17C) | 3706 | 9931 | 7090 | 43 |
| H(18A) | 162 | 7556 | 9827 | 23 |
| H(18B) | 627 | 6311 | 9671 | 23 |
| H(21A) | 155 | 9026 | 13295 | 51 |
| H(21B) | 962 | 8867 | 14597 | 51 |
| H(21C) | -46 | 7596 | 13363 | 51 |
| H(22A) | 1951 | 6690 | 13534 | 40 |
| H(22B) | 2856 | 7839 | 14870 | 40 |
| H(22C) | 3466 | 7703 | 13900 | 40 |
| H(23A) | 3724 | 9912 | 13730 | 42 |
| H(23B) | 3333 | 10321 | 14827 | 42 |
| H(23C) | 2459 | 10439 | 13519 | 42 |
| H(24A) | 498 | 5127 | 7932 | 23 |
| H(24B) | 896 | 5150 | 6837 | 23 |
| H(25) | 3389 | 5875 | 8349 | 29 |
| H(26A) | 2153 | 4621 | 9555 | 51 |
| H(26B) | 3800 | 4976 | 9817 | 51 |

**Table 6.** Torsion angles [°] for **201**.

| | | | |
|---|---|---|---|
| C(6)-C(1)-C(2)-C(3) | -0.5(3) | C(7)-C(1)-C(6)-C(5) | -178.92(17) |
| C(7)-C(1)-C(2)-C(3) | 178.16(18) | C(2)-C(1)-C(7)-S(1) | 91.94(19) |
| C(1)-C(2)-C(3)-C(4) | 0.6(3) | C(6)-C(1)-C(7)-S(1) | -89.42(19) |
| C(2)-C(3)-C(4)-C(5) | 0.0(3) | O(2)-S(1)-C(7)-C(1) | -65.51(15) |
| C(3)-C(4)-C(5)-C(6) | -0.8(3) | O(1)-S(1)-C(7)-C(1) | 64.29(15) |
| C(4)-C(5)-C(6)-C(1) | 0.9(3) | C(8)-S(1)-C(7)-C(1) | 178.38(13) |
| C(2)-C(1)-C(6)-C(5) | -0.2(3) | O(2)-S(1)-C(8)-C(16) | -59.27(14) |

O(1)-S(1)-C(8)-C(16)171.90(12)
C(7)-S(1)-C(8)-C(16)56.67(15)
O(2)-S(1)-C(8)-C(24)-176.51(12)
O(1)-S(1)-C(8)-C(24)54.66(14)
C(7)-S(1)-C(8)-C(24)-60.57(14)
O(2)-S(1)-C(8)-C(9) 60.84(14)
O(1)-S(1)-C(8)-C(9) -67.99(14)
C(7)-S(1)-C(8)-C(9) 176.78(12)
C(16)-C(8)-C(9)-C(10)47.5(2)
C(24)-C(8)-C(9)-C(10)167.75(15)
S(1)-C(8)-C(9)-C(10)-71.12(16)
C(16)-C(8)-C(9)-C(18)-179.11(15)
C(24)-C(8)-C(9)-C(18)-58.9(2)
S(1)-C(8)-C(9)-C(18)62.23(18)
C(18)-C(9)-C(10)-C(11)6.4(3)
C(8)-C(9)-C(10)-C(11)141.14(18)
C(18)-C(9)-C(10)-C(15)-178.05(15)
C(8)-C(9)-C(10)-C(15)-43.3(2)
C(15)-C(10)-C(11)-C(12)-2.7(3)
C(9)-C(10)-C(11)-C(12)172.79(17)
C(10)-C(11)-C(12)-C(13)0.3(3)
C(11)-C(12)-C(13)-C(14)2.0(3)
C(12)-C(13)-C(14)-C(15)-1.9(3)
C(13)-C(14)-C(15)-C(10)-0.6(3)
C(13)-C(14)-C(15)-N(1)178.65(18)
C(11)-C(10)-C(15)-C(14)2.8(3)
C(9)-C(10)-C(15)-C(14)-173.04(17)
C(11)-C(10)-C(15)-N(1)-176.46(16)
C(9)-C(10)-C(15)-N(1)7.7(2)
C(16)-N(1)-C(15)-C(14)-154.23(18)
C(17)-N(1)-C(15)-C(14)13.6(3)
C(16)-N(1)-C(15)-C(10)25.0(3)
C(17)-N(1)-C(15)-C(10)-167.21(16)
C(15)-N(1)-C(16)-O(3)164.44(17)
C(17)-N(1)-C(16)-O(3)-3.7(3)
C(15)-N(1)-C(16)-C(8)-17.6(2)
C(17)-N(1)-C(16)-C(8)174.26(15)
C(24)-C(8)-C(16)-O(3)36.6(2)
C(9)-C(8)-C(16)-O(3)158.81(16)
S(1)-C(8)-C(16)-O(3)-81.03(18)
C(24)-C(8)-C(16)-N(1)-141.38(16)
C(9)-C(8)-C(16)-N(1)-19.2(2)
S(1)-C(8)-C(16)-N(1)100.95(16)
C(10)-C(9)-C(18)-C(19)-70.3(2)
C(8)-C(9)-C(18)-C(19)157.25(16)
C(20)-O(4)-C(19)-O(5)3.6(3)
C(20)-O(4)-C(19)-C(18)-176.73(15)
C(9)-C(18)-C(19)-O(5)-33.5(3)
C(9)-C(18)-C(19)-O(4)146.89(15)
C(19)-O(4)-C(20)-C(23)63.2(2)
C(19)-O(4)-C(20)-C(22)-61.7(2)
C(19)-O(4)-C(20)-C(21)-179.71(16)
C(16)-C(8)-C(24)-C(25)65.61(19)
C(9)-C(8)-C(24)-C(25)-55.7(2)
S(1)-C(8)-C(24)-C(25)-177.51(13)
C(8)-C(24)-C(25)-C(26)116.6(2)

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Symmetry transformations used to generate equivalent atoms:

X-data data of **202**

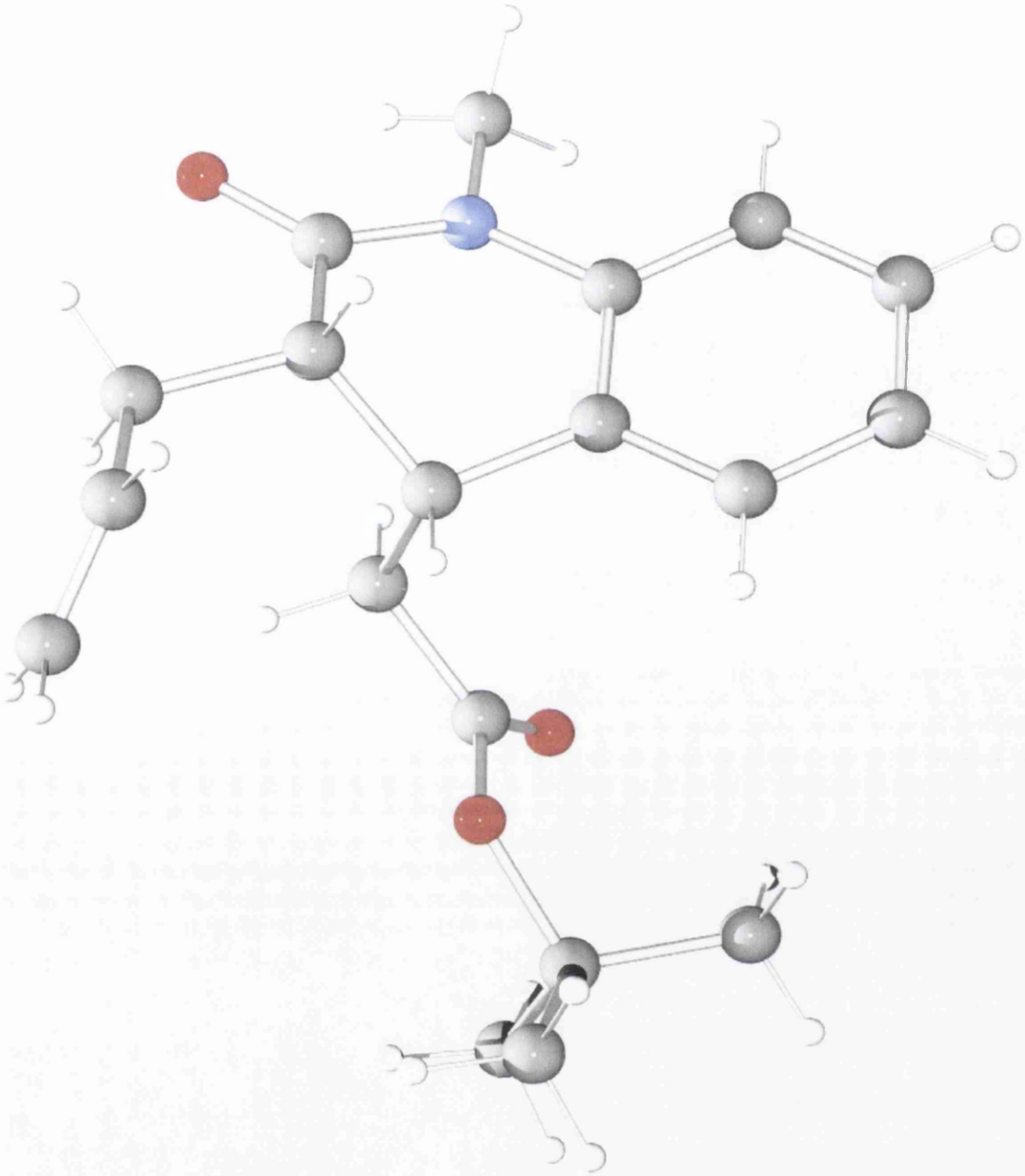


**Table 1.** Crystal data and structure refinement for **202.**

| | | |
|---|---|---|
| Identification code | **202** | |
| Empirical formula | C19 H25 N O3 | |
| Formula weight | 315.40 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 14.9879(17)Å | α= 90 °. |
| | b = 13.5965(16) Å | β= 95.950(2) °. |
| | c = 8.7184(10) Å | γ = 90 °. |
| Volume | 1767.1(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.186 $Mg/m^3$ | |
| Absorption coefficient | 0.079 $mm^{-1}$ | |
| F(000) | 680 | |
| Crystal size | 0.60 x 0.50 x 0.50 $mm^3$ | |
| Theta range for data collection | 2.03 to 26.38 °. | |
| Index ranges | -13<=h<=18, -17<=k<=15, -10<=l<=10 | |
| Reflections collected | 9922 | |
| Independent reflections | 3584 [R(int) = 0.0246] | |
| Completeness to theta = 26.36° | 99.1 % | |
| Max. and min. transmission | 0.9613 and 0.9539 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3584 / 0 / 212 | |
| Goodness-of-fit on $F^2$ | 1.028 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0446, wR2 = 0.1063 | |
| R indices (all data) | R1 = 0.0658, wR2 = 0.1167 | |
| Largest diff. peak and hole | 0.213 and -0.170 $e.Å^{-3}$ | |

**Table 2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)for **202.** U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7816(1) | 6387(1) | -3684(1) | 54(1) |
| O(2) | 7004(1) | 4450(1) | 2374(1) | 34(1) |
| O(3) | 8082(1) | 3538(1) | 1456(1) | 41(1) |
| N(1) | 8901(1) | 6167(1) | -1707(1) | 36(1) |
| C(1) | 8048(1) | 6386(1) | -2285(2) | 41(1) |
| C(2) | 7405(1) | 6632(1) | -1107(2) | 39(1) |
| C(3) | 7593(1) | 5973(1) | 327(2) | 31(1) |
| C(4) | 8552(1) | 6147(1) | 952(2) | 27(1) |
| C(5) | 8830(1) | 6245(1) | 2518(2) | 27(1) |
| C(6) | 9719(1) | 6433(1) | 3030(2) | 30(1) |
| C(7) | 10341(1) | 6522(1) | 1969(2) | 33(1) |
| C(8) | 10082(1) | 6424(1) | 406(2) | 33(1) |
| C(9) | 9190(1) | 6246(1) | -104(2) | 30(1) |
| C(10) | 9570(2) | 5982(1) | -2782(2) | 49(1) |

| | | | | |
|---|---|---|---|---|
| C(11) | 6434(1) | 6631(1) | -1845(2) | 51(1) |
| C(12) | 5801(2) | 6954(2) | -740(3) | 84(1) |
| C(13) | 5143(2) | 6445(3) | -326(3) | 121(2) |
| C(14) | 7413(1) | 4876(1) | -58(2) | 34(1) |
| C(15) | 7555(1) | 4205(1) | 1328(2) | 30(1) |
| C(16) | 6991(1) | 3877(1) | 3823(2) | 38(1) |
| C(17) | 7889(1) | 3953(2) | 4783(2) | 51(1) |
| C(18) | 6734(1) | 2821(1) | 3448(2) | 43(1) |
| C(19) | 6271(2) | 4402(2) | 4604(2) | 66(1) |

**Table 3.** Bond lengths [Å] and angles [°] for **202**.

| | | | |
|---|---|---|---|
| O(1)-C(1) | 1.2335(18) | C(16)-C(18) | 1.514(2) |
| O(2)-C(15) | 1.3340(19) | C(17)-H(17A) | 0.98 |
| O(2)-C(16) | 1.4857(18) | C(17)-H(17B) | 0.98 |
| O(3)-C(15) | 1.2012(19) | C(17)-H(17C) | 0.98 |
| N(1)-C(1) | 1.358(2) | C(18)-H(18A) | 0.98 |
| N(1)-C(9) | 1.4232(19) | C(18)-H(18B) | 0.98 |
| N(1)-C(10) | 1.464(2) | C(18)-H(18C) | 0.98 |
| C(1)-C(2) | 1.517(3) | C(19)-H(19A) | 0.98 |
| C(2)-C(11) | 1.529(3) | C(19)-H(19B) | 0.98 |
| C(2)-C(3) | 1.540(2) | C(19)-H(19C) | 0.98 |
| C(2)-H(2) | 1 | C(15)-O(2)-C(16) | 120.89(12) |
| C(3)-C(4) | 1.502(2) | C(1)-N(1)-C(9) | 121.80(14) |
| C(3)-C(14) | 1.547(2) | C(1)-N(1)-C(10) | 118.75(14) |
| C(3)-H(3) | 1 | C(9)-N(1)-C(10) | 118.86(15) |
| C(4)-C(5) | 1.391(2) | O(1)-C(1)-N(1) | 121.75(17) |
| C(4)-C(9) | 1.402(2) | O(1)-C(1)-C(2) | 122.35(18) |
| C(5)-C(6) | 1.384(2) | N(1)-C(1)-C(2) | 115.89(13) |
| C(5)-H(5) | 0.95 | C(1)-C(2)-C(11) | 111.03(14) |
| C(6)-C(7) | 1.385(2) | C(1)-C(2)-C(3) | 110.23(13) |
| C(6)-H(6) | 0.95 | C(11)-C(2)-C(3) | 115.29(15) |
| C(7)-C(8) | 1.384(2) | C(1)-C(2)-H(2) | 106.6 |
| C(7)-H(7) | 0.95 | C(11)-C(2)-H(2) | 106.6 |
| C(8)-C(9) | 1.386(2) | C(3)-C(2)-H(2) | 106.6 |
| C(8)-H(8) | 0.95 | C(4)-C(3)-C(2) | 106.89(13) |
| C(10)-H(10A) | 0.98 | C(4)-C(3)-C(14) | 111.73(13) |
| C(10)-H(10B) | 0.98 | C(2)-C(3)-C(14) | 111.85(12) |
| C(10)-H(10C) | 0.98 | C(4)-C(3)-H(3) | 108.8 |
| C(11)-C(12) | 1.487(3) | C(2)-C(3)-H(3) | 108.8 |
| C(11)-H(11A) | 0.99 | C(14)-C(3)-H(3) | 108.8 |
| C(11)-H(11B) | 0.99 | C(5)-C(4)-C(9) | 118.67(14) |
| C(12)-C(13) | 1.287(4) | C(5)-C(4)-C(3) | 123.34(14) |
| C(12)-H(12) | 0.95 | C(9)-C(4)-C(3) | 117.96(13) |
| C(13)-H(13A) | 0.95 | C(6)-C(5)-C(4) | 120.99(14) |
| C(13)-H(13B) | 0.95 | C(6)-C(5)-H(5) | 119.5 |
| C(14)-C(15) | 1.511(2) | C(4)-C(5)-H(5) | 119.5 |
| C(14)-H(14A) | 0.99 | C(5)-C(6)-C(7) | 119.55(14) |
| C(14)-H(14B) | 0.99 | C(5)-C(6)-H(6) | 120.2 |
| C(16)-C(17) | 1.512(2) | C(7)-C(6)-H(6) | 120.2 |
| C(16)-C(19) | 1.513(3) | C(8)-C(7)-C(6) | 120.55(16) |

| | | | |
|---|---|---|---|
| C(8)-C(7)-H(7) | 119.7 | C(3)-C(14)-H(14B) | 108.8 |
| C(6)-C(7)-H(7) | 119.7 | H(14A)-C(14)-H(14B) | 107.7 |
| C(7)-C(8)-C(9) | 119.77(15) | O(3)-C(15)-O(2) | 124.97(14) |
| C(7)-C(8)-H(8) | 120.1 | O(3)-C(15)-C(14) | 124.50(15) |
| C(9)-C(8)-H(8) | 120.1 | O(2)-C(15)-C(14) | 110.52(13) |
| C(8)-C(9)-C(4) | 120.45(14) | O(2)-C(16)-C(17) | 110.27(14) |
| C(8)-C(9)-N(1) | 120.92(14) | O(2)-C(16)-C(19) | 101.97(14) |
| C(4)-C(9)-N(1) | 118.63(15) | C(17)-C(16)-C(19) | 110.71(17) |
| N(1)-C(10)-H(10A) | 109.5 | O(2)-C(16)-C(18) | 109.83(13) |
| N(1)-C(10)-H(10B) | 109.5 | C(17)-C(16)-C(18) | 112.11(15) |
| H(10A)-C(10)-H(10B) | 109.5 | C(19)-C(16)-C(18) | 111.52(16) |
| N(1)-C(10)-H(10C) | 109.5 | C(16)-C(17)-H(17A) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 | C(16)-C(17)-H(17B) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 | H(17A)-C(17)-H(17B) | 109.5 |
| C(12)-C(11)-C(2) | 111.76(15) | C(16)-C(17)-H(17C) | 109.5 |
| C(12)-C(11)-H(11A) | 109.3 | H(17A)-C(17)-H(17C) | 109.5 |
| C(2)-C(11)-H(11A) | 109.3 | H(17B)-C(17)-H(17C) | 109.5 |
| C(12)-C(11)-H(11B) | 109.3 | C(16)-C(18)-H(18A) | 109.5 |
| C(2)-C(11)-H(11B) | 109.3 | C(16)-C(18)-H(18B) | 109.5 |
| H(11A)-C(11)-H(11B) | 107.9 | H(18A)-C(18)-H(18B) | 109.5 |
| C(13)-C(12)-C(11) | 125.6(3) | C(16)-C(18)-H(18C) | 109.5 |
| C(13)-C(12)-H(12) | 117.2 | H(18A)-C(18)-H(18C) | 109.5 |
| C(11)-C(12)-H(12) | 117.2 | H(18B)-C(18)-H(18C) | 109.5 |
| C(12)-C(13)-H(13A) | 120 | C(16)-C(19)-H(19A) | 109.5 |
| C(12)-C(13)-H(13B) | 120 | C(16)-C(19)-H(19B) | 109.5 |
| H(13A)-C(13)-H(13B) | 120 | H(19A)-C(19)-H(19B) | 109.5 |
| C(15)-C(14)-C(3) | 113.67(12) | C(16)-C(19)-H(19C) | 109.5 |
| C(15)-C(14)-H(14A) | 108.8 | H(19A)-C(19)-H(19C) | 109.5 |
| C(3)-C(14)-H(14A) | 108.8 | H(19B)-C(19)-H(19C) | 109.5 |
| C(15)-C(14)-H(14B) | 108.8 | | |

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **202**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 106(1) | 35(1) | 18(1) | 2(1) | -5(1) | -11(1) |
| O(2) | 44(1) | 35(1) | 25(1) | 4(1) | 5(1) | 5(1) |
| O(3) | 41(1) | 35(1) | 47(1) | 7(1) | 11(1) | 6(1) |
| N(1) | 68(1) | 26(1) | 16(1) | 0(1) | 11(1) | -4(1) |
| C(1) | 81(1) | 21(1) | 19(1) | 2(1) | 0(1) | -5(1) |
| C(2) | 65(1) | 25(1) | 24(1) | 0(1) | -8(1) | 5(1) |
| C(3) | 45(1) | 27(1) | 20(1) | -1(1) | 0(1) | 3(1) |
| C(4) | 42(1) | 17(1) | 20(1) | 1(1) | 4(1) | 3(1) |
| C(5) | 41(1) | 22(1) | 18(1) | 1(1) | 7(1) | 2(1) |
| C(6) | 44(1) | 24(1) | 22(1) | 2(1) | 2(1) | 1(1) |
| C(7) | 42(1) | 24(1) | 34(1) | 3(1) | 6(1) | 1(1) |
| C(8) | 51(1) | 21(1) | 31(1) | 3(1) | 17(1) | 1(1) |
| C(9) | 55(1) | 17(1) | 19(1) | 1(1) | 9(1) | 1(1) |
| C(10) | 92(2) | 32(1) | 26(1) | -7(1) | 27(1) | -17(1) |
| C(11) | 74(1) | 43(1) | 33(1) | -4(1) | -18(1) | 15(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(12) | 76(2) | 108(2) | 59(1) | -40(1) | -40(1) | 60(2) |
| C(13) | 54(2) | 227(4) | 78(2) | -45(2) | -9(2) | 64(2) |
| C(14) | 46(1) | 31(1) | 24(1) | -2(1) | 1(1) | -2(1) |
| C(15) | 34(1) | 28(1) | 28(1) | -3(1) | 0(1) | -4(1) |
| C(16) | 49(1) | 40(1) | 24(1) | 6(1) | 5(1) | -3(1) |
| C(17) | 72(1) | 48(1) | 31(1) | 10(1) | -11(1) | -21(1) |
| C(18) | 47(1) | 45(1) | 35(1) | 8(1) | -1(1) | -15(1) |
| C(19) | 91(2) | 71(2) | 41(1) | 7(1) | 29(1) | 12(1) |

**Table 5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **202**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | 7543 | 7321 | -761 | 47 |
| H(3) | 7194 | 6183 | 1118 | 37 |
| H(5) | 8404 | 6181 | 3246 | 32 |
| H(6) | 9900 | 6501 | 4101 | 36 |
| H(7) | 10952 | 6652 | 2318 | 40 |
| H(8) | 10514 | 6478 | -314 | 40 |
| H(10A) | 9276 | 5696 | -3735 | 73 |
| H(10B) | 10024 | 5524 | -2312 | 73 |
| H(10C) | 9859 | 6603 | -3019 | 73 |
| H(11A) | 6380 | 7077 | -2748 | 62 |
| H(11B) | 6271 | 5960 | -2215 | 62 |
| H(12) | 5890 | 7591 | -302 | 101 |
| H(13A) | 5029 | 5805 | -735 | 145 |
| H(13B) | 4770 | 6710 | 390 | 145 |
| H(14A) | 6786 | 4804 | -531 | 40 |
| H(14B) | 7814 | 4664 | -829 | 40 |
| H(17A) | 8351 | 3640 | 4233 | 77 |
| H(17B) | 7856 | 3620 | 5773 | 77 |
| H(17C) | 8040 | 4647 | 4966 | 77 |
| H(18A) | 6181 | 2807 | 2740 | 64 |
| H(18B) | 6636 | 2472 | 4400 | 64 |
| H(18C) | 7217 | 2499 | 2961 | 64 |
| H(19A) | 6441 | 5093 | 4772 | 99 |
| H(19B) | 6206 | 4088 | 5598 | 99 |
| H(19C) | 5701 | 4366 | 3947 | 99 |

X-ray data of **205**

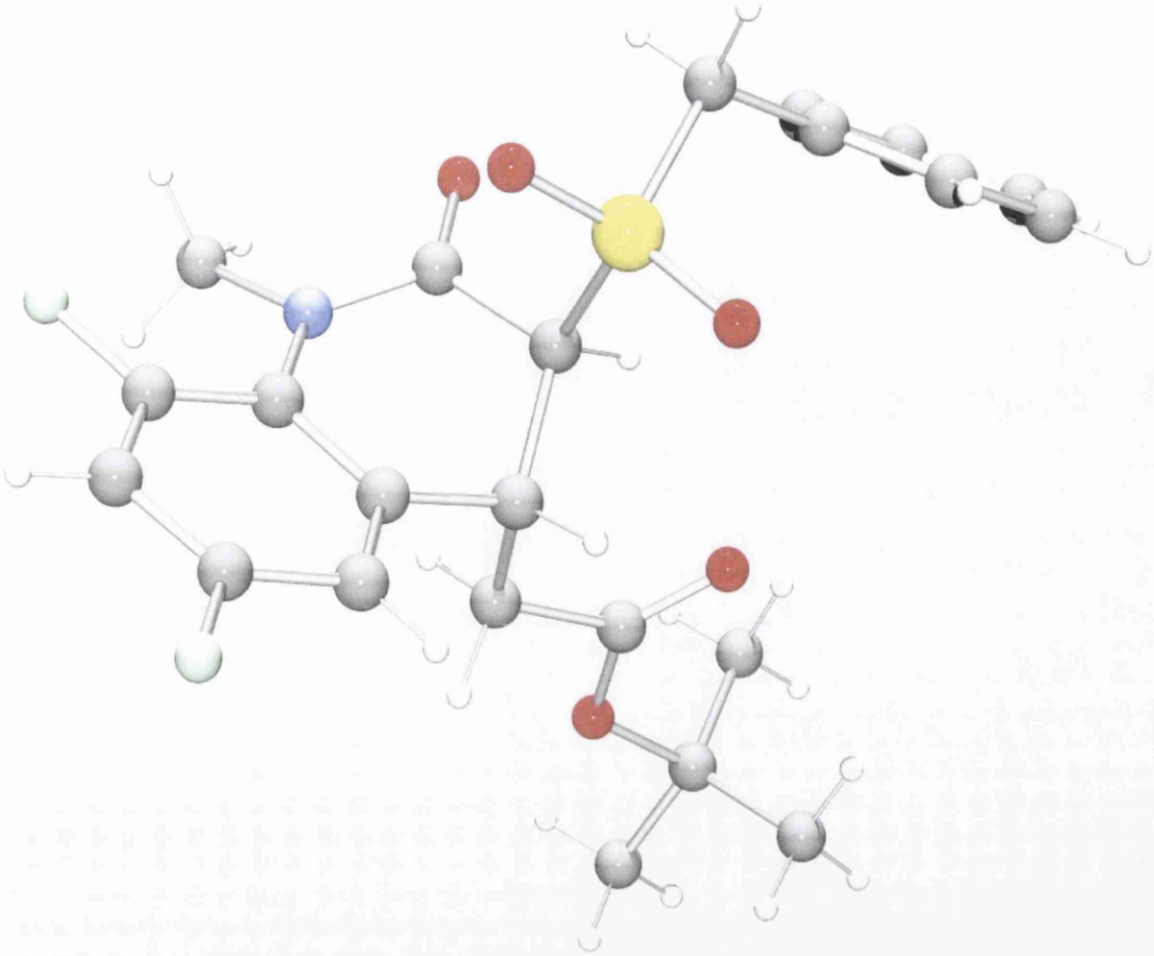


**Table 1.** Crystal data and structure refinement for **205**.

| | | |
|---|---|---|
| Identification code | **205** | |
| Empirical formula | C23 H25 F2 N O5 S | |
| Formula weight | 465.50 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073Å | |
| Crystal system | Monoclinic | |
| Space group | C2/c | |
| Unit cell dimensions | a = 17.2061(8) Å | α= 90 °. |
| | b = 16.3253(8) Å | β= 102.6910(10) °. |
| | c = 16.2379(8) Å | γ = 90 °. |
| Volume | 4449.7(4) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.390 $Mg/m^3$ | |
| Absorption coefficient | 0.197 $mm^{-1}$ | |
| F(000) | 1952 | |
| Crystal size | 0.50 x 0.30 x 0.30 $mm^3$ | |
| Theta range for data collection | 1.74 to 26.39 °. | |
| Index ranges | -21<=h<=21, -20<=k<=20, -20<=l<=20 | |
| Reflections collected | 17514 | |
| Independent reflections | 4555 [R(int) = 0.0224] | |
| Completeness to theta = 26.36° | 99.9 % | |
| Max. and min. transmission | 0.9432 and 0.9078 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4555 / 0 / 293 | |
| Goodness-of-fit on $F^2$ | 1.032 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0339, wR2 = 0.0896 | |
| R indices (all data) | R1 = 0.0390, wR2 = 0.0935 | |
| Largest diff. peak and hole | 0.453 and -0.292e.$Å^{-3}$ | |

**Table 2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)for **201**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | 3498(1) | 1389(1) | 1510(1) | 17(1) |
| F(1) | 4682(1) | 1663(1) | -1691(1) | 29(1) |
| F(2) | 4428(1) | -929(1) | -558(1) | 22(1) |
| O(1) | 3359(1) | 2254(1) | 1374(1) | 23(1) |
| O(2) | 4255(1) | 1056(1) | 1446(1) | 24(1) |
| O(3) | 2685(1) | -482(1) | 1373(1) | 22(1) |
| O(4) | 1094(1) | 1653(1) | 215(1) | 28(1) |
| O(5) | 441(1) | 1053(1) | -995(1) | 22(1) |
| N(1) | 3177(1) | -390(1) | 190(1) | 17(1) |
| C(1) | 2569(1) | 1389(1) | 2714(1) | 19(1) |
| C(2) | 2408(1) | 2219(1) | 2812(1) | 23(1) |
| C(3) | 1699(1) | 2456(1) | 3006(1) | 27(1) |
| C(4) | 1141(1) | 1874(1) | 3111(1) | 30(1) |
| C(5) | 1297(1) | 1049(1) | 3016(1) | 30(1) |

| | | | | |
|---|---|---|---|---|
| C(6) | 2006(1) | 808(1) | 2813(1) | 23(1) |
| C(7) | 3348(1) | 1117(1) | 2527(1) | 19(1) |
| C(8) | 2714(1) | 857(1) | 784(1) | 16(1) |
| C(9) | 2610(1) | 1215(1) | -109(1) | 17(1) |
| C(10) | 3292(1) | 932(1) | -482(1) | 17(1) |
| C(11) | 3671(1) | 1456(1) | -942(1) | 19(1) |
| C(12) | 4288(1) | 1151(1) | -1267(1) | 21(1) |
| C(13) | 4538(1) | 349(1) | -1164(1) | 20(1) |
| C(14) | 4160(1) | -150(1) | -689(1) | 18(1) |
| C(15) | 3538(1) | 116(1) | -339(1) | 16(1) |
| C(16) | 2869(1) | -63(1) | 823(1) | 17(1) |
| C(17) | 3169(1) | -1289(1) | 114(1) | 22(1) |
| C(18) | 1818(1) | 937(1) | -679(1) | 19(1) |
| C(19) | 1088(1) | 1268(1) | -418(1) | 19(1) |
| C(20) | -367(1) | 1338(1) | -948(1) | 22(1) |
| C(21) | -876(1) | 992(1) | -1753(1) | 43(1) |
| C(22) | -390(1) | 2261(1) | -952(1) | 39(1) |
| C(23) | -603(1) | 985(1) | -178(1) | 47(1) |

**Table 3.** Bond lengths [Å] and angles [°] for **205**.

| | | | |
|---|---|---|---|
| S(1)-O(2) | 1.4365(10) | C(9)-C(10) | 1.5084(18) |
| S(1)-O(1) | 1.4401(10) | C(9)-C(18) | 1.5368(18) |
| S(1)-C(7) | 1.7833(13) | C(9)-H(9) | 1 |
| S(1)-C(8) | 1.8061(13) | C(10)-C(11) | 1.3880(19) |
| F(1)-C(12) | 1.3560(16) | C(10)-C(15) | 1.4017(18) |
| F(2)-C(14) | 1.3539(15) | C(11)-C(12) | 1.378(2) |
| O(3)-C(16) | 1.2210(16) | C(11)-H(11) | 0.95 |
| O(4)-C(19) | 1.2021(17) | C(12)-C(13) | 1.376(2) |
| O(5)-C(19) | 1.3347(17) | C(13)-C(14) | 1.380(2) |
| O(5)-C(20) | 1.4846(16) | C(13)-H(13) | 0.95 |
| N(1)-C(16) | 1.3655(17) | C(14)-C(15) | 1.3876(19) |
| N(1)-C(15) | 1.4273(17) | C(17)-H(17A) | 0.98 |
| N(1)-C(17) | 1.4711(16) | C(17)-H(17B) | 0.98 |
| C(1)-C(6) | 1.390(2) | C(17)-H(17C) | 0.98 |
| C(1)-C(2) | 1.3981(19) | C(18)-C(19) | 1.5120(18) |
| C(1)-C(7) | 1.5050(19) | C(18)-H(18A) | 0.99 |
| C(2)-C(3) | 1.380(2) | C(18)-H(18B) | 0.99 |
| C(2)-H(2) | 0.95 | C(20)-C(22) | 1.508(2) |
| C(3)-C(4) | 1.387(2) | C(20)-C(23) | 1.509(2) |
| C(3)-H(3) | 0.95 | C(20)-C(21) | 1.514(2) |
| C(4)-C(5) | 1.389(2) | C(21)-H(21A) | 0.98 |
| C(4)-H(4) | 0.95 | C(21)-H(21B) | 0.98 |
| C(5)-C(6) | 1.388(2) | C(21)-H(21C) | 0.98 |
| C(5)-H(5) | 0.95 | C(22)-H(22A) | 0.98 |
| C(6)-H(6) | 0.95 | C(22)-H(22B) | 0.98 |
| C(7)-H(7A) | 0.99 | C(22)-H(22C) | 0.98 |
| C(7)-H(7B) | 0.99 | C(23)-H(23A) | 0.98 |
| C(8)-C(16) | 1.5239(18) | C(23)-H(23B) | 0.98 |
| C(8)-C(9) | 1.5365(17) | C(23)-H(23C) | 0.98 |
| C(8)-H(8) | 1 | O(2)-S(1)-O(1) | 118.80(6) |

| | | | |
|---|---|---|---|
| O(2)-S(1)-C(7) | 106.90(6) | F(1)-C(12)-C(13) | 118.01(12) |
| O(1)-S(1)-C(7) | 109.51(6) | F(1)-C(12)-C(11) | 119.02(13) |
| O(2)-S(1)-C(8) | 109.26(6) | C(13)-C(12)-C(11) | 122.96(13) |
| O(1)-S(1)-C(8) | 107.25(6) | C(12)-C(13)-C(14) | 117.15(12) |
| C(7)-S(1)-C(8) | 104.19(6) | C(12)-C(13)-H(13) | 121.4 |
| C(19)-O(5)-C(20) | 121.81(11) | C(14)-C(13)-H(13) | 121.4 |
| C(16)-N(1)-C(15) | 121.18(11) | F(2)-C(14)-C(13) | 117.18(12) |
| C(16)-N(1)-C(17) | 117.10(11) | F(2)-C(14)-C(15) | 119.78(12) |
| C(15)-N(1)-C(17) | 121.60(11) | C(13)-C(14)-C(15) | 123.04(12) |
| C(6)-C(1)-C(2) | 119.13(13) | C(14)-C(15)-C(10) | 117.42(12) |
| C(6)-C(1)-C(7) | 119.74(12) | C(14)-C(15)-N(1) | 122.80(12) |
| C(2)-C(1)-C(7) | 121.11(13) | C(10)-C(15)-N(1) | 119.70(11) |
| C(3)-C(2)-C(1) | 120.32(14) | O(3)-C(16)-N(1) | 122.44(12) |
| C(3)-C(2)-H(2) | 119.8 | O(3)-C(16)-C(8) | 120.80(12) |
| C(1)-C(2)-H(2) | 119.8 | N(1)-C(16)-C(8) | 116.66(11) |
| C(2)-C(3)-C(4) | 120.40(14) | N(1)-C(17)-H(17A) | 109.5 |
| C(2)-C(3)-H(3) | 119.8 | N(1)-C(17)-H(17B) | 109.5 |
| C(4)-C(3)-H(3) | 119.8 | H(17A)-C(17)-H(17B) | 109.5 |
| C(3)-C(4)-C(5) | 119.65(14) | N(1)-C(17)-H(17C) | 109.5 |
| C(3)-C(4)-H(4) | 120.2 | H(17A)-C(17)-H(17C) | 109.5 |
| C(5)-C(4)-H(4) | 120.2 | H(17B)-C(17)-H(17C) | 109.5 |
| C(6)-C(5)-C(4) | 120.13(15) | C(19)-C(18)-C(9) | 114.00(11) |
| C(6)-C(5)-H(5) | 119.9 | C(19)-C(18)-H(18A) | 108.8 |
| C(4)-C(5)-H(5) | 119.9 | C(9)-C(18)-H(18A) | 108.8 |
| C(5)-C(6)-C(1) | 120.37(14) | C(19)-C(18)-H(18B) | 108.8 |
| C(5)-C(6)-H(6) | 119.8 | C(9)-C(18)-H(18B) | 108.8 |
| C(1)-C(6)-H(6) | 119.8 | H(18A)-C(18)-H(18B) | 107.6 |
| C(1)-C(7)-S(1) | 115.39(9) | O(4)-C(19)-O(5) | 125.99(13) |
| C(1)-C(7)-H(7A) | 108.4 | O(4)-C(19)-C(18) | 125.03(13) |
| S(1)-C(7)-H(7A) | 108.4 | O(5)-C(19)-C(18) | 108.98(11) |
| C(1)-C(7)-H(7B) | 108.4 | O(5)-C(20)-C(22) | 109.64(11) |
| S(1)-C(7)-H(7B) | 108.4 | O(5)-C(20)-C(23) | 110.39(12) |
| H(7A)-C(7)-H(7B) | 107.5 | C(22)-C(20)-C(23) | 111.98(15) |
| C(16)-C(8)-C(9) | 113.33(10) | O(5)-C(20)-C(21) | 102.06(11) |
| C(16)-C(8)-S(1) | 110.40(9) | C(22)-C(20)-C(21) | 111.08(14) |
| C(9)-C(8)-S(1) | 110.41(9) | C(23)-C(20)-C(21) | 111.26(15) |
| C(16)-C(8)-H(8) | 107.5 | C(20)-C(21)-H(21A) | 109.5 |
| C(9)-C(8)-H(8) | 107.5 | C(20)-C(21)-H(21B) | 109.5 |
| S(1)-C(8)-H(8) | 107.5 | H(21A)-C(21)-H(21B) | 109.5 |
| C(10)-C(9)-C(8) | 108.86(11) | C(20)-C(21)-H(21C) | 109.5 |
| C(10)-C(9)-C(18) | 109.42(10) | H(21A)-C(21)-H(21C) | 109.5 |
| C(8)-C(9)-C(18) | 111.14(11) | H(21B)-C(21)-H(21C) | 109.5 |
| C(10)-C(9)-H(9) | 109.1 | C(20)-C(22)-H(22A) | 109.5 |
| C(8)-C(9)-H(9) | 109.1 | C(20)-C(22)-H(22B) | 109.5 |
| C(18)-C(9)-H(9) | 109.1 | H(22A)-C(22)-H(22B) | 109.5 |
| C(11)-C(10)-C(15) | 121.02(12) | C(20)-C(22)-H(22C) | 109.5 |
| C(11)-C(10)-C(9) | 121.79(12) | H(22A)-C(22)-H(22C) | 109.5 |
| C(15)-C(10)-C(9) | 117.18(12) | H(22B)-C(22)-H(22C) | 109.5 |
| C(12)-C(11)-C(10) | 118.37(13) | C(20)-C(23)-H(23A) | 109.5 |
| C(12)-C(11)-H(11) | 120.8 | C(20)-C(23)-H(23B) | 109.5 |
| C(10)-C(11)-H(11) | 120.8 | H(23A)-C(23)-H(23B) | 109.5 |

| | | | |
|---|---|---|---|
| C(20)-C(23)-H(23C) | 109.5 | H(23A)-C(23)-H(23C) | 109.5 |

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **205**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| S(1) | 18(1) | 17(1) | 15(1) | -1(1) | 2(1) | 0(1) |
| F(1) | 30(1) | 29(1) | 33(1) | 8(1) | 15(1) | -3(1) |
| F(2) | 24(1) | 18(1) | 25(1) | -2(1) | 5(1) | 6(1) |
| O(1) | 30(1) | 17(1) | 21(1) | 0(1) | 5(1) | -3(1) |
| O(2) | 20(1) | 27(1) | 25(1) | -3(1) | 4(1) | 1(1) |
| O(3) | 29(1) | 19(1) | 20(1) | 2(1) | 8(1) | 0(1) |
| O(4) | 26(1) | 33(1) | 23(1) | -7(1) | 2(1) | 10(1) |
| O(5) | 16(1) | 23(1) | 25(1) | -5(1) | 4(1) | 1(1) |
| N(1) | 22(1) | 13(1) | 17(1) | 0(1) | 4(1) | 1(1) |
| C(1) | 25(1) | 20(1) | 11(1) | 0(1) | 2(1) | 1(1) |
| C(2) | 31(1) | 20(1) | 15(1) | -1(1) | 2(1) | 0(1) |
| C(3) | 40(1) | 23(1) | 18(1) | -2(1) | 5(1) | 9(1) |
| C(4) | 31(1) | 36(1) | 25(1) | -1(1) | 10(1) | 8(1) |
| C(5) | 31(1) | 32(1) | 29(1) | 0(1) | 11(1) | -3(1) |
| C(6) | 30(1) | 20(1) | 20(1) | -2(1) | 7(1) | -1(1) |
| C(7) | 24(1) | 19(1) | 13(1) | 1(1) | 1(1) | 0(1) |
| C(8) | 17(1) | 16(1) | 15(1) | -1(1) | 2(1) | 1(1) |
| C(9) | 20(1) | 15(1) | 15(1) | 0(1) | 3(1) | 2(1) |
| C(10) | 18(1) | 17(1) | 13(1) | -1(1) | 1(1) | 1(1) |
| C(11) | 22(1) | 18(1) | 17(1) | 1(1) | 1(1) | 0(1) |
| C(12) | 21(1) | 24(1) | 17(1) | 2(1) | 3(1) | -4(1) |
| C(13) | 18(1) | 26(1) | 17(1) | -3(1) | 4(1) | 1(1) |
| C(14) | 20(1) | 16(1) | 16(1) | -3(1) | -1(1) | 3(1) |
| C(15) | 19(1) | 16(1) | 13(1) | -1(1) | 0(1) | -1(1) |
| C(16) | 17(1) | 17(1) | 17(1) | 0(1) | 1(1) | 0(1) |
| C(17) | 31(1) | 14(1) | 22(1) | 0(1) | 8(1) | 0(1) |
| C(18) | 20(1) | 18(1) | 17(1) | -1(1) | 2(1) | 3(1) |
| C(19) | 21(1) | 15(1) | 19(1) | 2(1) | 3(1) | 3(1) |
| C(20) | 16(1) | 21(1) | 29(1) | 0(1) | 6(1) | 2(1) |
| C(21) | 19(1) | 58(1) | 50(1) | -23(1) | 2(1) | -2(1) |
| C(22) | 22(1) | 22(1) | 68(1) | 4(1) | -3(1) | 4(1) |
| C(23) | 30(1) | 62(1) | 53(1) | 28(1) | 22(1) | 16(1) |

**Table 5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **205**.

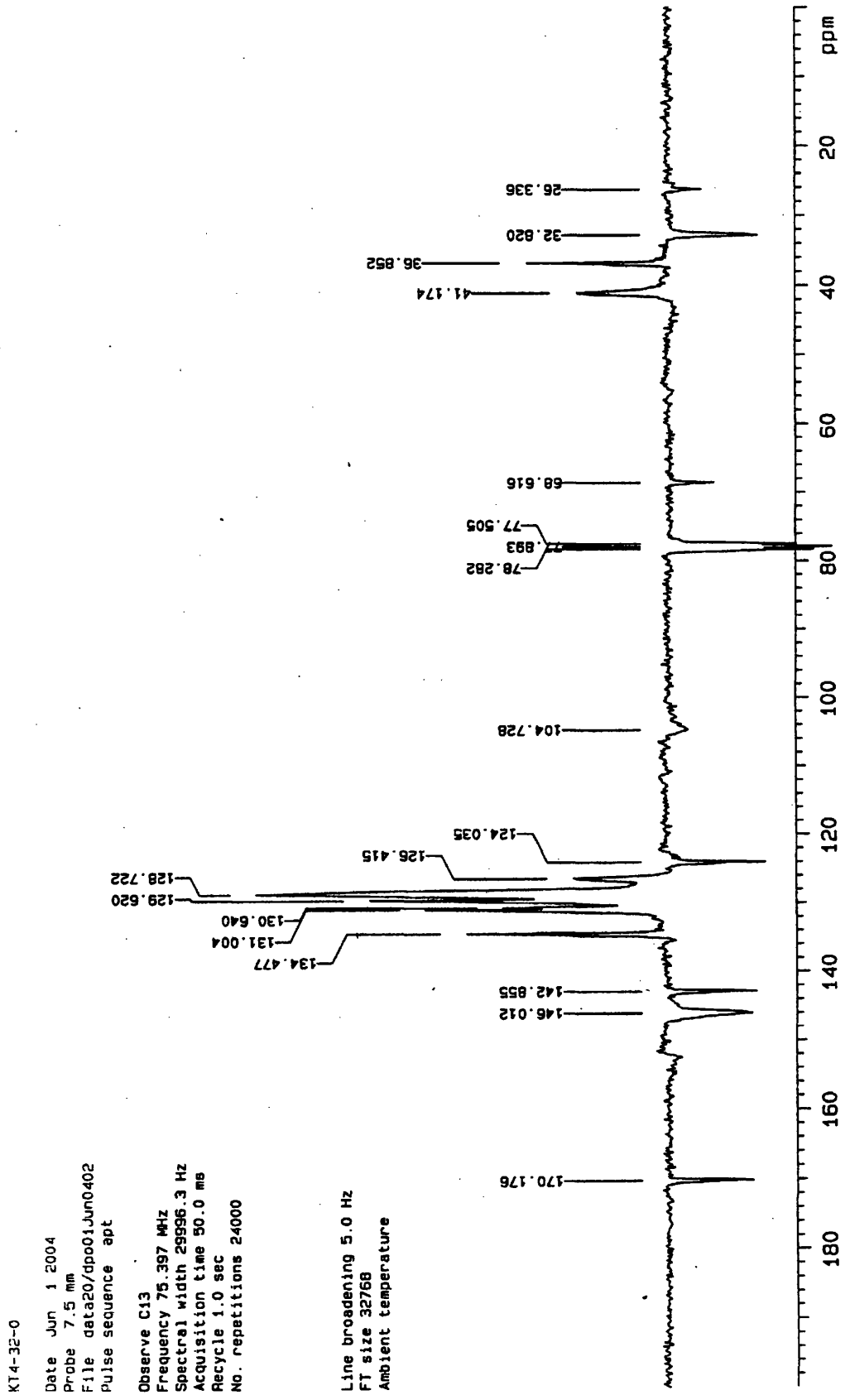
| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | -2008 | 7745 | 4206 | 29 |
| H(2) | 2788 | 2621 | 2745 | 27 |
| H(3) | 1593 | 3021 | 3067 | 33 |
| H(4) | 655 | 2039 | 3248 | 36 |
| H(5) | 917 | 648 | 3089 | 36 |

| | | | | |
|---|---|---|---|---|
| H(6) | 2107 | 244 | 2742 | 28 |
| H(7A) | 3384 | 513 | 2585 | 23 |
| H(7B) | 3787 | 1354 | 2959 | 23 |
| H(8) | 2206 | 955 | 974 | 19 |
| H(9) | 2617 | 1826 | -73 | 20 |
| H(11) | 3509 | 2011 | -1030 | 23 |
| H(13) | 4953 | 149 | -1410 | 24 |
| H(17A) | 3676 | -1510 | 431 | 33 |
| H(17B) | 3094 | -1442 | -482 | 33 |
| H(17C) | 2731 | -1512 | 342 | 33 |
| H(18A) | 1806 | 1114 | -1264 | 22 |
| H(18B) | 1797 | 331 | -676 | 22 |
| H(21A) | -719 | 1241 | -2241 | 65 |
| H(21B) | -1438 | 1113 | -1774 | 65 |
| H(21C) | -801 | 397 | -1765 | 65 |
| H(22A) | -57 | 2470 | -426 | 59 |
| H(22B) | -940 | 2447 | -1002 | 59 |
| H(22C) | -188 | 2467 | -1432 | 59 |
| H(23A) | -580 | 386 | -198 | 70 |
| H(23B) | -1146 | 1158 | -169 | 70 |
| H(23C) | -235 | 1183 | 332 | 70 |

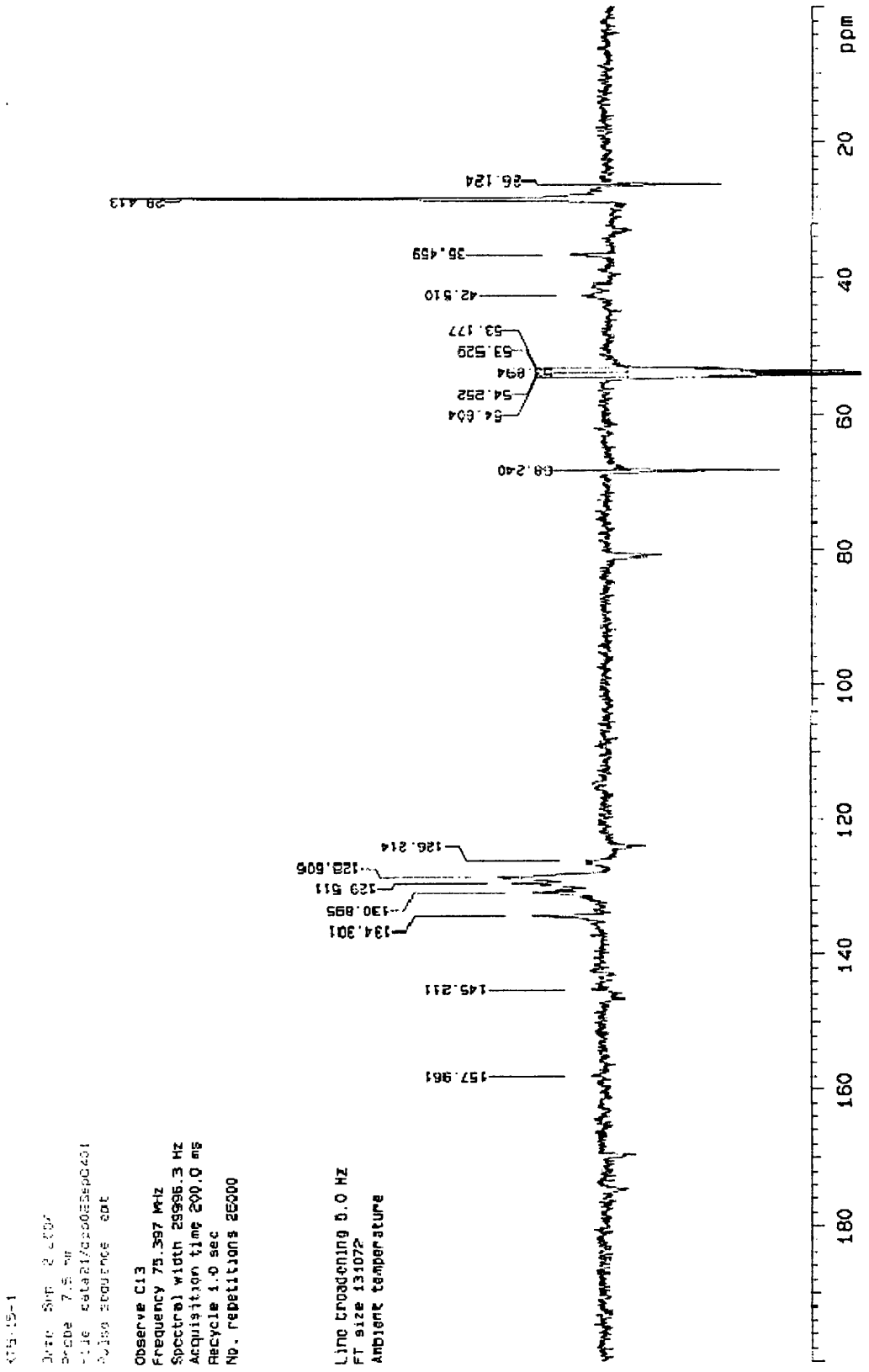
# APPENDIX II

## MAS NMR of resin-bound intermediates

APT spectrum of **216**. Plotted with CH/$CH_2$ positive and $_qC$/$CH_3$ negative



APT spectrum of **217**. Plotted with CH/$CH_3$ positive and $_qC$/$CH_2$ negative.



APPENDIX III

A solid phase approach to tetrahydroquinolones using a sulfur linker cleaved by $SmI_2$

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