A-aryl quaternary centres via asymmetric Vicarious Nucleophilic Substitution

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Contents Page

Acknowledgements i
Abstract ii
Abbreviations iii

1.1 Nucleophilic Aromatic Substitution 2
1.2 Oxidative Nucleophilic Substitution of Hydrogen (ONSH) 3
1.3 Conversion of the σH-adducts into Nitroso Compounds 4
1.4 Vicarious Nucleophilic Substitution of Hydrogen 5
1.5 Electrophilic Aromatic Substitution 8
1.6 Directed ortho-Metallation (DoM) 10
1.7 Palladium Catalysis 11
2.1 Review of VNS for the period 2000-2004 13
2.2 Asymmetric Vicarious Nucleophilic Substitution of Hydrogen 27
3.1 Aims 30
4.1 C-Arylation of Lactams and Pyrazolidinones via Vicarious Nucleophilic Substitution of Hydrogen 33
5.1 Asymmetric Vicarious Nucleophilic Substitution of Hydrogen 48
6.1 Synthesis of Diarylmethanes 71
6.2 The Synthesis of Diarylacetates via a Sequential VNS-S_NAr Three Component Coupling Reaction 72
6.3 Formation of Oxindoles 81
7.1 Cross-coupling of Nitrophenylacetates 88
8.1 Experimental 103
References 186
Appendix 195
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Abstract

This dissertation first describes a new method for the formation of α-aryl lactams based on the Vicarious Nucleophilic Substitution reaction. The route involves the three-component coupling of a nitroarene, an α-phenylsulfanyl lactam and an electrophile. The process incorporates various electrophiles and various N-substituted cyclic amides and has been developed for the most part using nitrobenzene. The process was also applied to α-phenylsulfanyl pyrazolidinones. The process also includes examples of amides possessing a removable nitrogen protecting group to give access to functionalised amides with a free NH group.

Secondly, an asymmetric version of the VNS reaction is described. The diastereoselectivity of the VNS-alkylation reaction of lactones was studied. For example using an α-phenylsulfanyl-γ-substituted butyrolactone, nitrobenzene and an alkyl halide, diastereoselectivities of greater than 7:1 were observed in some cases. The stereogenic centre at the γ position is clearly able to exert considerable control in the generation of the new stereogenic centre at the α-position.

The third area of research described involves capture of the intermediate VNS anion with aryl electrophiles. Activated electrophiles react in this way via an SNAr process. The VNS and SNAr reactions were combined to form an efficient one-pot three-component coupling process to give easy access to functionalised diarylmethanes. Reduction of the nitro group of selected products gave a quick and easy route to the oxindole structural motif.

The final chapter describes our attempts to react the intermediate VNS anion with unactivated aryl halides in a transition metal cross-coupling process. Unfortunately, we did not find conditions to effect the coupling of the anion derived from a VNS process with aryl halides. Nevertheless, the anion of nitrophenylacetates prepared via deprotonation participates in cross-coupling reactions with ease and provides an alternative way to prepare diarylmethanes. This has the potential to be extremely useful due to the lack of reports of nitroarenes in cross-coupling processes.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric Ammonium Nitrate</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-N,N-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMD</td>
<td>Dimethylidioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMG</td>
<td>Directing Metallating Group</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
</tr>
<tr>
<td>DOE</td>
<td>Design of Experiments</td>
</tr>
<tr>
<td>DoM</td>
<td>Directed ortho Metalation</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron Withdrawing Group</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethyl Phosphoramide</td>
</tr>
<tr>
<td>HOBr</td>
<td>Hydroxybenzotriazole</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl Alcohol</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium Hexamethyldisilazide</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxy Methyl</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>Sodium Hexamethyldisilazide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>ONSH</td>
<td>Oxidative Nucleophilic Substitution of Hydrogen</td>
</tr>
<tr>
<td>PDT</td>
<td>Photodynamic Therapy</td>
</tr>
<tr>
<td>S_NAr</td>
<td>Nucleophilic Aromatic Substitution</td>
</tr>
<tr>
<td>TASF</td>
<td>Tris(dimethylamino)sulfonium difluorotrimethylsilicate</td>
</tr>
<tr>
<td>TDA</td>
<td>Tris[2-(methoxyethoxy)ethylamine]</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMAI</td>
<td>Trimethylammonium Iodide</td>
</tr>
<tr>
<td>TMHI</td>
<td>Trimethylhydrazinium Iodide</td>
</tr>
<tr>
<td>TMSCI</td>
<td>Trimethylsilyl Chloride</td>
</tr>
</tbody>
</table>
\( p\text{-TsOH} \)  \textit{para}-Toluenesulfonic Acid

VNS Vicarious Nucleophilic Substitution
Chapter 1
The study of aromatic reactivity and synthesis has fascinated and occupied chemists since the very early days of the subject. Derivatives of benzene, both simple and complex, form the basis of a multitude of pharmaceuticals, agrochemicals, natural products, petrochemicals, synthetic polymers and materials. Methods designed to control the synthesis of new unexplored aryl derivatives remain as important as ever. This PhD develops one new method for arene synthesis. This introduction summarises some of the important ways by which arenes are prepared.

1.1 Nucleophilic Aromatic substitution (SnAr)

One of the most important methods is the addition of nucleophiles to the ring to form anionic σ-adducts. There are two ways in which this can happen, firstly addition to the ring in positions occupied with leaving groups such as halogens to form σ^X-adducts and secondly addition in positions occupied with hydrogen to form σ^H-adducts. The case of forming σ^H-adducts will be dealt with later in this Introduction.

The σ^X-adducts formed can undergo rapid elimination of X^−, to give products of nucleophilic aromatic substitution (SnAr). The mechanism of this reaction is shown in Scheme 1.

![Scheme 1](image)

The presence of electron withdrawing groups (such as nitro) ortho and para to the leaving group substantially enhance the rate of substitution. The reason they can do this is because they stabilize negative charge on adjacent groups at the ortho and para positions but not at the meta position.

The best leaving group in these reactions is fluoride (F). Attack at the carbon bearing fluorine is faster than that bearing chlorine or bromine in the rate determining step due to the difference in electronegativity. This process has been known for a long time and has been reviewed extensively.\(^1\)\(^-\)\(^4\)
1.2 Oxidative Nucleophilic Substitution of Hydrogen (ONSH)

Direct conversion of the $\sigma^H$-adducts into products does not occur due to hydride being a very poor leaving group. Without an additional reactant, the $\sigma^H$-adducts simply revert to the starting material. Even when the ortho or para positions are occupied with a good leaving group such as a halogen, it is well known that attack at a carbon-bearing hydrogen is much faster than that bearing halogen.\(^5\)\(^7\)

The hydride anion needs to be removed with an additional reactant in a process that is equivalent to oxidation. This process was termed oxidative nucleophilic substitution of hydrogen (ONSH).\(^8\)\(^-\)\(^11\)

One of the problems with the ONSH reactions is generally the high sensitivity of C-nucleophilic agents, such as carbanions or Grignard reagents towards oxidation. The introduction of carbon substituents can be carried out provided that the addition of the C-nucleophiles and the formation of the $\sigma^H$-adducts proceeds to completion, so amounts of the free nucleophile in the reaction vessel are negligible. Nucleophiles resistant towards oxidation are exemplified by the hydroxide anion and ammonia.

An example of an ONSH reaction is the addition of the 2-phenylpropionitrile carbanion (3) to nitrobenzene and its derivatives, carried out in liquid ammonia and THF at $-70^\circ$C. The nitroarenes are converted to the $\sigma^H$-adducts (4) almost quantitatively. These adducts are efficiently oxidized by external oxidants such as KMnO$_4$ in liquid ammonia (pathway a in Scheme 2) and dimethylidixirane (DMD) in THF-acetone (pathway b in Scheme 2).

Scheme 2

Oxidation with these two oxidants gave two different products leading to the assumption that they react with the $\sigma^H$-adducts at different places. Permanganate probably attacks the $\sigma^H$-
adduct at the addition site of the nucleophile, producing substituted nitroarene products of oxidative nucleophilic substitution of hydrogen (ONSH) (5).\textsuperscript{8-10} Oxidation with DMD proceeds at the carbon with the nitro group to give a substituted phenol 6 in which the nitro group has been replaced by the hydroxy group.\textsuperscript{12-13}

An alternative method was developed by RajanBabu and co-workers.\textsuperscript{14} This was the fluoride assisted nucleophilic addition of enol silyl ethers to aromatic nitro compounds. It is well established that the stable silyl enol ethers 7 can be activated using a source of fluoride.\textsuperscript{15} Oxidation of the resulting $\sigma^H$-adducts (8) with DDQ or bromine gave $\alpha$-nitroaryl carbonyl compounds 9 (Scheme 3).

Scheme 3

\[
\begin{align*}
\begin{array}{c}
\text{R} \\
\text{NO}_2
\end{array} & \text{R}_1 \text{OTMS} & \text{TASF} & \begin{array}{c}
\text{R} \\
\text{H} \\
\text{O} \\
\text{N}
\end{array} & \begin{array}{c}
\text{R} \\
\text{NO}_2 \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array} & \begin{array}{c}
\text{Br}_2 \\
\text{or} \\
\text{DDQ}
\end{array} & \begin{array}{c}
\text{R} \\
\text{NO}_2 \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array}
\end{align*}
\]

1.3 Conversion of the $\sigma^H$-adducts into Nitroso Compounds

Some $\sigma^H$-adducts can undergo spontaneous conversion into substituted nitroso compounds. This reaction can be considered an intramolecular redox process with release of hydroxide ion. This conversion usually takes place in protic solvents via protonation of the negatively charged $\text{NO}_2$ group of the $\sigma^H$-adducts and elimination of water and is often followed by further transformations of the nitroso compounds\textsuperscript{16-21} (Scheme 4).

Scheme 4

\[
\begin{align*}
\begin{array}{c}
\text{Cl} \\
\text{PhCH}_2\text{CN}
\end{array} & \text{KOH} & \text{EtOH} & \begin{array}{c}
\text{Cl} \\
\text{Ph}
\end{array} & \text{CN} & \text{CN} & \text{CN} & \text{CN} & \text{Cl} & \text{Ph}
\end{align*}
\]

Similar conversion can be promoted by treatment of $\sigma^H$-adducts with protic acids, Lewis acids,\textsuperscript{22-23} or silylating agents.\textsuperscript{24-27}
1.4 Vicarious Nucleophilic Substitution of Hydrogen (VNS)

Perhaps the most general and useful method for transforming $\sigma^H$-adducts into products of nucleophilic substitution is the process discovered by Mąkosza and co-workers in the late 1970's. This is a key reaction in this PhD study, so will be reviewed in detail. In this reaction, attack of the nucleophile occurs at carbon bearing hydrogen ortho or para to the nitro group in the same way as in the ONSH process. Instead of hydrogen, the leaving group connected with the carbanion departs by base induced $\beta$-elimination of HX (Scheme 5). Thus the leaving group is acting as a vicarious leaving group (in place of) and the reaction was therefore named Vicarious Nucleophilic Substitution of hydrogen. We call 11 (and 12) the post-VNS anion to avoid ambiguity when referring to other anions present in the reaction.

Scheme 5

Due to the fact that attack at carbons bearing hydrogen is significantly faster than at carbons bearing halogens, nucleophiles such as chloromethyl phenyl sulfone react with $p$-chloronitrobenzene exclusively at the ortho position to the nitro group.

Steric considerations are important in the VNS reaction; if the nucleophile (10) is a secondary carbanion, then a mixture of ortho and para substituted products will occur with nitrobenzene. If 10 is a tertiary carbanion, then exclusive para substitution will occur due to a steric clash with the nitro group (Figure 1). If the para position is blocked, exclusive ortho substitution will occur although with $p$-fluoronitrobenzene, the $S_N Ar$ pathway competes with the VNS process.

Figure 1
The conditions which favour VNS are sodium or potassium bases in solvents such as DMF, DMSO or liquid ammonia. Under these conditions the ortho/para ratio is governed by the kind of carbanion, i.e. the nature of the R group. If the base/solvent system is changed on the other hand to a t-BuOK/THF system, there is a unique opportunity with many secondary carbanions to afford selective ortho substitution even when there is a vacant para position. This effect is observed in the reaction of nitroarenes with chloromethyl phenyl sulfone and acetonitrile derivatives. In this base/solvent system, the carbanions are in the form of tight ion pairs with potassium cations which are attracted by the negatively charged oxygen atoms of the nitro groups. The σ-adducts are then formed ortho to the nitro group. To eliminate this effect, one equivalent of a crown ether can be added.

The main requirement for the carbanion is that it should contain a leaving group X connected directly to the carbanion centre. The leaving group must be capable of its elimination as HX from the intermediate σ-adduct. The general structure of the carbanion can be regarded as RCXY where X is the leaving group, Y the electron-withdrawing group and R the substituent (Scheme 6).

Scheme 6

\[
\begin{align*}
\text{NO}_2 & \quad \text{X} \quad \text{CHY} \\
& \quad \text{R} \\
\text{NO}_2 & \quad \text{R} \quad \text{CHY}
\end{align*}
\]

\[Y = \text{SO}_2\text{Ph, SO}_2\text{C(CH}_3)_2, \text{SO}_2\text{OPh, SO}_2\text{OCH}_3\text{C(CH}_3)_3, \]
\[\text{SO}_2\text{N(CH}_2\text{CH}_2)_2\text{O, SOPh, POPh}_2, \text{P(OEt)}_2, \text{CN, COOR', -N=C, PhS, Cl} \]
\[X = \text{Cl, PhS, Me}_2\text{NCCSS, PhO, CH}_3\text{O} \]
\[R = \text{H, alkyl, aryl, PhS, Cl} \]

Almost any combination of the leaving group (X), electron-withdrawing group (Y) and substituent (R) shown will produce a carbanion that will undergo VNS chemistry. However to achieve the best results the combination must be selected meticulously to avoid side reactions that compete with the VNS. One such example is the carbanion derived from methyl chloroacetate which rapidly undergoes self condensation leaving little or no VNS product.

The post VNS anion intermediates are usually highly coloured, a feature which can have some diagnostic value as to whether or not the VNS process has taken place. Below is a typically coloured post VNS anion intermediate (Figure 2).
There are a few examples that could be considered early examples of VNS; methylation of nitroarenes and heterocycles with dimsylsodium\(^3\) or with dimethyldisulfonium methyldide\(^4\) and dichloromethylation of \(p\)-halonitrobenzene with trichloromethylolithium.\(^5\) The mechanistic, synthetic value, and general character of these observed reactions were not, however, recognised.

Aromatic heterocycles bearing a nitro group can also be used in the VNS reaction. The VNS has been performed with 2- and 3-nitrothiophenes, 2-nitrofurans, particularly substituted at C-5, and \(N\)-alkylated 2- and 3-nitropyrrroles.\(^6\)

Previous research in the Lawrence group found that the post VNS anion can not only undergo a proton quench but can also undergo alkylation with electrophiles such as iodomethane. This gave a one-pot three-component coupling VNS/alkylation reaction (Scheme 7) to produce nitroarenes \(13\) bearing an adjacent quaternary stereogenic centre.\(^7\)

Scheme 7

The VNS/alkylation process was used in a racemic synthesis of Aminoglutethimide\(^8\) (Figure 3), an effective anti-cancer drug for the treatment of breast and prostate cancer.\(^9\)
Figure 3

(+/-)-Aminoglutethimide.

It was reported that α-aryl-α-hydroxyesters (14) could be formed during the reaction of the post VNS anion with aldehydes. The expected formation of the aldol product did not occur. On one occasion however, when air was inadvertently introduced into the reaction flask, the hydroxy ester 14 was obtained in 50% yield (Scheme 8). It was found that when three equivalents of the ester were used with respect to nitrobenzene the yield can be increased to 66%.

Scheme 8

1.5 Electrophilic Aromatic Substitution

This section will briefly discuss electrophilic aromatic substitution, an area of chemistry that has been known for a long time and has been extensively studied and is thoroughly documented. There are two fundamental sequential steps in an electrophilic aromatic substitution (Scheme 9) reaction, the first being the formation of a new sigma bond by attack of an electrophile by the aromatic ring. The second is the removal of the proton by breaking the C-H sigma bond and restoration of aromaticity.

Scheme 9
Substituents affect the reactivity of the aromatic ring. Electron donating substituents such as OH and NH$_2$ activate the ring making it more reactive than benzene. Electron-withdrawing substituents such as NO$_2$ deactivate the ring making it less reactive than benzene.

Substituents also affect the orientation of the reaction. The three possible disubstituted products- ortho, meta and para are not usually formed in equal amounts. The nature of the substituent already present on the benzene ring determines the position of the second substituent. Substituents can be classified into three groups: ortho/para directing activators, ortho/para directing deactivators and meta directing deactivators.

Reactivity and orientation in electrophilic aromatic substitutions are controlled by inductive and resonance effects. Nitration of anisole could occur either ortho, meta or para to the methoxy group. The intermediates from ortho and para attack are stabilized. Only in ortho and para attack are there resonance forms in which the positive charge is stabilized by donation of an electron pair from oxygen. The intermediate from meta attack has no such stabilization.

Toluene is ortho/para directing because these resonance forms can place the positive charge directly on the methyl substituted carbon, where it is a tertiary carbocation and can be stabilized by the electron donating effect of the methyl group. The halogens are deactivating because their stronger electron withdrawing inductive effect outweighs their weaker electron donating resonance effect. Though weak, that electron donating resonance effect is felt only at the ortho and para positions. Thus a halogen substituent can stabilize the positive charge of the carbocation intermediates from ortho and para attack in the same way that hydroxy and amino substituents do.

With electron-withdrawing substituents such as nitro, both ortho and para intermediates are destabilized because the resonance form places the positive charge on the carbocation intermediate directly on the ring carbon atom that bears the deactivating group. Reaction with an electrophile therefore occurs at the meta position. Below are some commonly used transformations (Scheme 10).
1.6 Directed ortho-Metalation (DoM)

This process has a distinct advantage over electrophilic aromatic substitution in that harsh reaction conditions are not required. It can also provide convenient access to 1,2,3- and 1,2,3,4-substituted aromatic systems which can be a daunting task with classical electrophilic aromatic substitution methods. Since its discovery by Gilman and Wittig, DoM took little time to establish itself as a powerful tool available to the organic chemist.

DoM requires the presence of a Directing Metalating Group (DMG) which is an inductively withdrawing atom or group that contains a lone pair of electrons. In the presence of a strong base, usually an alkyllithium, this functional group guides the alkyllithium, so that it attacks the adjacent protons. It does this by forming a complex with the Lewis-acidic metal ions, meaning only protons ortho to the functional group can be removed (Scheme 11).

DMG’s used include OMe, OMOM, and CO₂H among many others.
Palladium-catalysed reactions of aryl halides and triflates with ‘hard’ organometallic nucleophiles have been widely used over the past 30 years. Variants of these reactions have found widespread applications in modern organic chemistry. Variants include the Suzuki (boron-mediated), Corriu-Kumada-Tamao (magnesium-mediated), Stille (tin-mediated), Negishi (zinc-mediated), and Sonogashira (copper-mediated) coupling reactions.

The mechanism of palladium catalysis involves the oxidative addition of the halide or triflate to the initial palladium(0) complex to form a palladium(II) species. The key slow step is a transmetalation, so called because the nucleophile is transferred from the metal in the organometallic reagent to the palladium and the counterion moves in the opposite direction. The new palladium(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the palladium(0) catalyst ready for another cycle. This process is shown below (Scheme 12).

Scheme 12

The palladium catalysed coupling of soft nucleophiles has only been explored in the last 10 years. The studies of Buchwald and Hartwig have proved successful in a wide range of soft organometallic nucleophiles including oxygen, sulfur, phosphorus, boron and silicon based nucleophiles.

In recent years the cross-coupling at the α-position of carbonyl compounds such as ketones, esters and amides with aryl halides has been reported by the groups of Buchwald, Hartwig and Miura (Scheme 13).

Scheme 13
Chapter 2
2.1 Review of VNS for the period 2000-2004

Due to the numerous reviews\textsuperscript{30,83-84} covering VNS before 2000 already available, only VNS after 2000 will be reviewed in this chapter.

It was found by previous research in the Lawrence group that \(E\)-stilbenes could be synthesized efficiently \textit{via} a one pot Vicarious Nucleophilic Substitution/ Horner-Wittig reaction. This was achieved by generation of the anion of chloromethyl diphenylphosphinoyl oxide (15) with sodium hydride in DMSO and reaction with different nitro-substituted aromatics. The series of VNS products were used in a Horner-Wittig reaction by treatment of base and benzaldehyde derivatives. The desired \(E\)-stilbenes 17 were produced but only in modest yields. It was thought that the yields of the stilbene might be improved if the anion was used directly. In other words the post-VNS anion 16 was treated with the benzaldehyde derivatives in the same pot (Scheme 14). This approach effectively constitutes a one pot VNS-Horner Wittig reaction. The yields were significantly better than the two step process.\textsuperscript{39,85}

\textbf{Scheme 14}

\begin{center}
\includegraphics[width=\textwidth]{scheme14.png}
\end{center}

The post VNS anion undergoes a 1,4-conjugate addition (Michael reaction) with Michael acceptors.\textsuperscript{86} The post-VNS anion formed from nitrobenzene and ethyl 2-chloropropionate in a NaH/DMF base/solvent system could be quenched with methyl acrylate to give 18, which is the product of 1,4-conjugate addition (Scheme 15).

\textbf{Scheme 15}

\begin{center}
\includegraphics[width=\textwidth]{scheme15.png}
\end{center}

Derivatives of Indoprofen have been made by a 4-step synthesis that incorporates the VNS process (Scheme 16). Indoprofen (21a) is an arylpropionic acid non-steroidal anti-inflammatory drug.\textsuperscript{86} The first step in the synthesis was the VNS reaction of ethyl 2-chloropropionate and nitrobenzene in a NaH/DMF base/solvent system with either an acidic or electrophilic quench with methyl iodide to give the VNS products 19a and 19b. After the VNS process had been carried out, the product was reduced under hydrogenation conditions to give
the aniline 20a,b. The Takahashi protocol \(^{89-90}\) provided the method for obtaining the phthalimidine derivative from the aniline with 1,2,3-1H-benzotriazole, 2-mercaptoethanol and \(\alpha\)-phthalaldehyde. Saponification of the ester with sodium hydroxide gave Indoprofen 21a in a 24\% overall yield. An \(\alpha\)-methyl Indoprofen derivative 21b was also produced by a VNS/methylation reaction followed by the same condition as the Indoprofen approach.

Scheme 16

Palmisano’s synthesis of the natural product (-)-horsfiline (27) (Scheme 17) involved a VNS reaction. (-)-Horsfiline (27) is a tricyclic alkaloid, first isolated in 1990 from the leaves of *Horsfieldia superba*.\(^{89}\) In the first step of the synthesis 4-nitroanisole and 4-chlorophenoxy acetonitrile were treated with potassium tert-butoxide in DMF to give the required VNS product 22 (Scheme 17).\(^{90}\)

Scheme 17

The VNS product 22 was then converted to the ester 23 by methanolysis. On treatment of 23 with para-formaldehyde (10 equiv), in the presence of \(\mathrm{K}_2\mathrm{CO}_3\) and tris[2-(methoxyethoxy)ethyl]amine (TDA-1) as a solid-liquid phase-transfer catalyst in toluene at 85 °C for 3 hours, produced the acrylate product cleanly and in good yield. The ester was then
hydrolysed to the acid 24 which was then coupled to a chiral auxiliary to give 25. Treatment of this with sarcosine, \( p \)-formaldehyde, molecular sieves and toluene under reflux produced 26 which after reduction of the nitro group under hydrogenation conditions cyclised onto the ester bearing the chiral auxiliary to give (−)-horsfiline (27). Among the chiral auxiliaries tried, only Whitesell's (1S,2R)-2-phenyl-1-cyclohexanol\(^{90}\) provided an acceptable level of diastereoselectivity (86% de by HPLC).

A VNS-type process has also been used in the synthesis of the natural product (−)-Physostigmine (28) (Figure 4).\(^{93}\) The key step in the synthesis the author claimed was a VNS reaction between \( p \)-nitroanisole and a C-silylated derivative of \( N \)-methylpyrrolidinone 29 (Scheme 18) followed by oxidation with DDQ to give 30. This approach however was not strictly VNS but Oxidative Nucleophilic Substitution of Hydrogen (ONSH).

**Figure 4**

![MeHNOCO](image)

\((-\text{-Physostigmine (28)})\)

**Scheme 18**

![TASF/THF](image)

Vicarious Nucleophilic Substitution was used in the synthesis of 6,7-dihydroimidazo[4,5-\( d \)][1,3]diazepin-8(3\( H \))-one (31) (Figure 5), which is an important intermediate in organic synthesis.\(^{92}\) It has been used in the synthesis of natural products pentostatin,\(^{93-5}\) and coformycin\(^{96}\) which are both anti-cancer and anti-viral nucleosides.

**Figure 5**

![N](image)

6,7-dihydroimidazo[4,5-\( d \)][1,3]diazepin-8(3\( H \))-one (31)

The synthesis started with the commercially available 4-nitroimidazole. \( N \)-Benzylation gave a substrate 32 which could undergo the VNS process. It did so with the anion generated from chloroform and potassium tert-butoxide (Scheme 19) to give the expected VNS product 33.
When the VNS product 33 was treated with formic acid followed by NaClO2/NH2SO3H, the carboxylic acid 34 was obtained. This acid was then coupled with nitromethane using CDI to give the dinitroketone 35. The nitro groups were then reduced with Fe/HCl and the benzyl protecting group removed with Pd/HCO2NH4 to give 36. Treatment of the deprotected product with ethyl formate in DMSO gave the required product 37, which was isolated as a mono hydrochloride salt (Scheme 20).

Fused pyrimidines are of particular interest for the synthesis of purine derivatives 39. The synthesis starts from 4-nitroimidazole-5-carbaldehyde (38), readily available from 1-substituted 4-nitroimidazoles via VNS dichloromethylation (Scheme 21). This is an example of purine synthesis in which the 6-membered ring is constructed using an existing 5-membered imidazole ring, a strategy not commonly used in the synthesis of purines.

It has been recently reported that chloralkyloxazolines 40 and other chloroalkyl heterocycles under basic conditions react with nitroarenes to produce VNS products 41 (Scheme 22). 97-8
No success was achieved when trying to capture the post VNS anion with aldehydes. If instead of using chloromethylloxazolines 40, dichloromethylloxazoline 42 was used, quenching with benzaldehyde derivatives resulted in oxazolinyldiaryloxirane 44 as a single diastereoisomer (Scheme 23). 99

If the post VNS anion 43 was however left without an electrophilic quench, a mixture of E and Z 1,2-dioxolinyldi-1,2-di-p-nitrophenylethene (45) (Scheme 24) was formed. In this case, the post VNS anion 43, which has carbenoid character, undergoes homocoupling, followed by elimination of chloride to generate 45.

Attempts to trap the post VNS anion with ketones and imines resulted in no success with only 1,2-dioxolinyldi-1,2-di-p-nitrophenylethene (45) being formed. If THF was used as the solvent, the VNS reaction occurred exclusively at the carbon ortho to the nitro group, which when quenched with benzaldehyde derivatives also gave efficient access to oxiranes.

The mechanistic pathway of the formation of the σH-adducts formed in the VNS process was investigated by Mąkosza and Kwast. 100 The two possibilities considered were direct
nucleophilic addition of carbanions to nitroarenes *pathway a* (Scheme 24) and a two-step single electron transfer (SET) process *pathway b*. It was concluded on the basis of their observations of typical radical probes (α-halosulfones) with o-chloronitrobenzene that the intermediate σ^H-^-adduct is formed by a one step ionic process and not SET.

Scheme 25

Mąkosza has found that carbanions of halomethyl aryl sulfones react with substituted 1,2,4-triazine-4-oxides by at least three different processes (Scheme 26). Pathways a and b occur when R^1 is not H. Pathway a is the VNS process and Pathway b is deoxygenative replacement of the hydrogen in the 5-position. It was found that using α-haloaryl sulfones as the carbanion resulted predominantly in the products of deoxygenative replacement of hydrogen 47. Formation of the VNS product 46, all be it in small amounts, indicated that there are no large differences between the rates of the competing reactions. Changing the reaction conditions had no visible effect on the competition between the two processes.

Scheme 26
It was thought that instead of using an α-bromoaryl sulfone, but an α-chloroaryl sulfone the reaction would proceed via the VNS pathway because β-elimination of HBr should proceed much faster than HCl. This proved to be the case and the VNS process (pathway a) occurred predominantly. Pathway c occurs when the R¹ substituent is H which allows nucleophilic attack at this position followed by heterocyclic ring opening in the intermediate σ⁻H-adduct to produce 48.

The hydroxylation of nitroarenes proceeds conveniently by the addition of tert-butyl or cumyl hydroperoxides in the presence of strong bases. These conditions when used with azulenes however provided negative results. It appeared that due to the low nucleophilic activity of the t-BuOO⁻ anion, the σ⁻H-adduct is not formed. However, reaction with more electrophilic azulenes containing electron-withdrawing substituents in the 5 membered ring proceeded satisfactorily. It was found that 4-aminotriazole 50 is an efficient aminating agent of azulenes when the reaction is carried out in the presence of t-BuOK (Scheme 27). The products were of moderate stability so were isolated as the corresponding acetyl derivatives 51.

Scheme 27

A general method for specific para-hydroxylation of nitroarenes has been developed by Zhang. In basic aqueous media, the nucleophilic hydroxylation of nitronaphthalenes with cumene hydroperoxide led to specific para-hydroxylation (Scheme 28). The reaction took place very slowly in water due to the insolubility of the starting materials. When the reaction was carried out in anhydrous DMSO, a mixture of para- and ortho-regioisomers were formed. In a mixture of water (25%) and DMSO (75%), this nucleophilic substitution gave exclusively the product of para-hydroxylation 52.

Scheme 28

A series of tricyclic indole-2-carboxylic acid derivatives were synthesized by a route incorporating VNS (Scheme 29). Commercially available 4-iodonitrobenzene was treated with
tert-butyl chloroacetate under VNS conditions to give 53. Palladium catalysed cyanation was carried out using zinc cyanide to give 54. Reduction of 54 with BF$_3$OEt$_2$/B(OMe)$_3$ in THF followed by Boc protection and then reduction of the nitro group gave the aniline 55.

**Scheme 29**

Condensation of 56 with 57 followed by hydrolysis of the ester gave 58 which was obtained as the hydrochloride salt (Scheme 30). The tricyclic indole-2-carboxylic acid (58) was then evaluated by the radio-ligand binding assay and the anticonvulsant effects investigated in the mouse NMDA-induced seizure model.$^{107}$

**Scheme 30**

The direct amination of 1-substituted 3,5-dinitrobenzenes was successfully carried out by the use of 1,1,1-trimethylhydrazinium iodide (TMHI) in the presence of t-BuOK or NaOMe in DMSO (Scheme 31).$^{108}$

**Scheme 31**

With most substituents, the dinitroanilines 59 and 60 were obtained as a mixture in good yield with the ortho-isomer 59 being predominant (ortho with respect to the substituent X). When a sulfone was used as the substituent however, two equivalents of TMHI produced a mixture of diamines 62 and 63 (Scheme 32) in a 9:1 ratio. When only one equivalent of TMHI was used in the reaction another mixture of products was formed comprising a monosubstituted product.
64, a disubstituted product 63 as well as unreacted starting material was recovered in a 4:1:5 ratio. In the presence of strong base, deprotonation of TMHI occurs resulting in the formation of trimethylammonium iodide (TMAI). The TMAI adds to the nitroaromatic to either the ortho or para position relative to X to give a σ-adduct. Base induced β-elimination of trimethylamine then takes place. Protonation of the post VNS anion then gave the product 65 (Scheme 33).

Scheme 32

Nitrobenzyl quaternary salts of nitrogen mustards have been reported as hypoxia selective cytotoxins.\textsuperscript{109-110} The VNS process was used in the synthesis of a pyrazole analogue 66 that was evaluated as a hypoxia-selective cytotoxin (Scheme 34).\textsuperscript{111}

Scheme 33

Scheme 34
Nitroaromatic compounds are not the only ones to undergo the VNS process. Wojciechowski found that the VNS process could be used in the synthesis of novel isothiazolopyridine and quinoline derivatives 68 (Scheme 35).

**Scheme 35**

In the final step an intramolecular VNS process takes place. Deprotonation of the sulfone 67 followed by the formation of an intermediate in which base induced β-elimination of HCl takes place. Alternatively, instead of the pyridine N-oxide, quaternisation of the nitrogen atom with electrophiles such as methyl iodide produces substrates which undergo the VNS process.

**Scheme 36**

1,4-Naphthoquinones and derivatives also undergo the VNS process to give 70 (Scheme 36). These VNS reactions in 2-halo substituted naphthoquinones 69 are generally faster processes than Vinylic Nucleophilic Substitution of Halogen (SnV). The halogen substituent however does result in faster addition of the carbanion to the position occupied by hydrogen due to the increased electrophilic activity. Base induced β-elimination occurs and the expected VNS product 70 formed.

Selectively ortho-deuterated nitroarenes can be synthesized in high isotopic purity using a process that involves a VNS step. The method consists of electrophilic aromatic substitution of H for D in para-substituted anilines in the ortho position to the amino group which was carried out with DCI/D₂O. This was followed by oxidation of the aniline 71 to the nitro-compound 72 followed by a VNS process with N,N,N-trimethylhydrazonium iodide to give an ortho-nitroaniline 73. Diazotization and reduction of the diazonium salt gave selectively ortho-deuterated nitroarenes 74 in high isotopic purity (Scheme 37).
It has been found that the VNS process can be carried out upon 1-methyl-4-nitroimidazole (75) (Scheme 38), under mild conditions in the presence of sodium methoxide or potassium tert-butoxide to give the VNS product (76).115

The VNS C-amination does not occur with 2-methyl-4-nitroimidazole and 1,2-dimethyl-4-nitroimidazole. EPR spectroscopy shows that the VNS C-amination of 1-methyl-4-nitroimidazole is likely to follow a radical ion mechanism. The EPR signal of the reaction mixture of 1-methyl-4-nitroimidazole with N,N,N-trimethylhydrazinium iodide (TMHI) and t-BuOK/DMSO can be assigned as the radical ion of 1-methyl-4-nitroimidazole.

A practical procedure for the synthesis of 6-aminoadulene 79 has been reported using the VNS process. Amination of azulene (77) occurs using 4-amino-1,2,4-triazole (78) (Scheme 39).93

Amination with TMHI of more electrophilic derivatives, substituted at position 1 with CN or COPh, affords mixtures of 4-, 6- and 8-aminoadulenes (Figure 6).
A novel synthesis of 4-amino-3,5-dinitro-1H-pyrazole 81 was reported using the VNS process (Scheme 40). Reaction of 1,1,1-trimethylhydrazinium iodide with 3,5-dinitropyrazole (80) in DMSO produced 4-amino-3,5-dinitro-1H-pyrazole (81).

**Scheme 40**

Two different procedures have been found as a route to 2-amino-5-nitropyridines 82 in moderate to good yields from the VNS process using 3-nitropyridines with either hydroxylamine or 4-amine 1,2,4-triazole as animating agents (Scheme 41). 2-Amino-5-nitropyridines 82 would be useful starting materials in the synthesis of biologically active compounds. The 2,5-substitution pattern of pyridine is the base for many pharmaceuticals and crop protecting agents. It has proved difficult in the past to obtain this substitution pattern with high regioselectivity. The use of hydroxylamine as the VNS animating agent provides a simpler and cheaper procedure. In large scale preparations, this procedure would be better because of the easy work up despite the process with 4-amine 1,2,4-triazole giving slightly better yields. The use of 4-amino-1,2,4-triazole demanded an inert atmosphere and DMSO as solvent.

**Scheme 41**

Some porphyrin derivatives are used as photosensitizers in photodynamic therapy (PDT). PDT is a treatment involving photosensitising drugs and light to kill neoplastic cells. This simple technique is currently being evaluated in multiple clinical trials with promising results. Nitration of meso-tetraphenyl porphyrin results in mono-nitration in a para-position on one of the phenyl rings. The transformation of the two NH centres in the macrocyclic ring into the metal complex 83, where the central metal cation (Zn$^{2+}$ or Cu$^{2+}$) is playing the role of a convenient protecting group allowed the VNS process to proceed to 84 in
good yield (Scheme 42). The metal cation offers very labile protection of the NH functions and can easily be removed after reaction if needed.

**Scheme 42**

A new range of TPP derivatives were synthesized, substituted with α-functionalized alkyl groups e.g. arylsulfonyl methyl, cyanomethyl and \( N,N \)-dimethylsulfonamide. Reactions with tertiary carbanions were unsuccessful due to steric hindrance.

**Figure 7**

Multiple attempts at utilizing unprotected nitro-\( \text{meso} \)-tetraphenylporphyrin derivatives however proved unsuccessful. Under the strong basic conditions associated with the VNS process deprotonation of the two NH groups occurs so the porphyrin should exist in the \( N \)-anionic form 85 (Figure 7). At low temperatures the rotation around the C-C bond should be limited, leaving the four \( \text{meso} \) aryl rings orthogonal, thus limiting the conjugation. This would then give the opportunity for VNS to take place on the nitroaromatic as the possibility of increasing the electron density on this ring has been much reduced.\(^{123}\) This was found to be the case. In \( t \)-BuOK/THF at \(-30\) °C to \(-40\) °C and \( t \)-BuOK/DMF at 0 °C the unprotected porphyrins underwent the VNS process to give the desired products in good yield.\(^{119}\) \( \alpha \)-Halomethyl aryl sulfones, \( \alpha \)-chloromethyl \( N,N \)-dialkylsulfonamide and \( p \)-chlorophenoxyacetanitride were all
used as the VNS nucleophile. The products obtained gave opportunity for further transformations.

When investigating the effect of halogens on reactions of carbanions with halonitroarenes, Makosza found that under certain conditions, the VNS reaction of chloromethyl phenyl sulfone with 2,4-dinitrochlorobenzene is accompanied by the formation of a considerable amount of (3,5-dichlorophenyl)methyl phenyl sulfone (86) (Scheme 43)."124

Scheme 43

![Diagram of Scheme 43](image)

The side-product was observed only when the reaction mixture was quenched after a very short time. It was formed by protonation of the intermediate $\sigma^H$-adduct followed by elimination of nitrous acid. The essential part of this $\sigma^H$-substitution was the acidic quench. When ammonium chloride or acetic acid were used, the starting materials were recovered. However, the products of $\sigma^H$-substitution 86 were obtained when protonation was performed using dilute strong acids such as HCl or H$_2$SO$_4$.

Reaction of 2-nitronaphthalene (87a) and 6-nitroquinoline (87b) with a secondary carbanion bearing a leaving group and electron withdrawing group such as chloromethyl phenyl sulfone in a NaH/THF base solvent system yielded the conventional products of vicarious nucleophilic substitution of hydrogen 88a and 88b (Scheme 44)."94

Scheme 44

![Diagram of Scheme 44](image)
However, when secondary and tertiary carbanions were used in a NaH/DMF base solvent system the reactants underwent direct cyclocondensation giving dihydroisoxazolo[4,3-\textit{f}]quinoline \(N\)-oxides (89a) and dihydronapth[2,1-\textit{c}]isoxazole \(N\)-oxides (89b) (Scheme 45).\(^9^4\)

**Scheme 45**

\[
\text{NO}_2 \quad \text{NaH/DMF} \quad \text{Cl} \quad R \quad \text{EWG} \quad \text{EWG} \quad \text{O} \quad X = N \quad 89a \quad \text{X = C} \quad 89b
\]

The reaction conditions were tried with \(m\)-dinitrobenzene as the substrate with secondary and tertiary carbanions but in this case the reaction afforded the VNS products and the desired 2,1-benzisoxazole \(N\)-oxides were not obtained.

2-Chloropyrimidine and 2,4-dichloropyrimidine react at low temperatures with trihalomethyl carbanions to give covalent \(\sigma^H\)-adducts and the VNS products in low yield. 4,5,6-Trichloropyrimidine in the reactions with carbanions such as \(X\text{CHSO}_2\text{Tol}\) and \(\text{CBr}_3\) and other nucleophiles such as \(t\)-\text{BuO} and \(\text{NH}_3\) give diverse substituted products of chlorine while in the reaction with \(\text{CCl}_3\) anion the VNS process takes place albeit in low yield (Scheme 46).\(^{1^2^5}\)

**Scheme 46**

\[
\text{Cl} \quad \text{CHCl}_3 \quad -65 ^\circ\text{C} \quad \text{t-BuOK/\text{NH}_3} \quad \text{ClH}_2\text{C} \quad \text{Cl}
\]

2.2 Asymmetric Vicarious Nucleophilic Substitution of Hydrogen

The VNS/alkylation process, in which the post-VNS anion was quenched with a variety of electrophiles to produce quaternary stereogenic centres was first reported by Lawrence and co-workers.\(^{3^8}\) An unprecedented asymmetric version of the VNS/alkylation reaction was then reported with the use of an appropriate auxiliary incorporated into the nucleophile (Scheme 47).\(^{1^2^0}\)
Menthol proved to be a poor auxiliary, since reaction of the VNS nucleophile 90a with the nitroarene followed by a quench with benzyl bromide gave a 1:1 mixture of diastereoisomers. The reaction of the VNS nucleophile 90b derived from (-)-8-phenylmenthol however was much more successful. Quenching with methyl iodide gave a 3:1 mixture of diastereoisomers while quenching with benzyl bromide gave a 8:1 mixture. Other auxiliaries were tried such as trans-2-phenylcyclohexan-1-ol since both enantiomeric forms are available from a variety of methods, most notably hydroboration or dihydroxylation-reduction of 1-phenylcyclohexene. The diastereoselectivity however with this auxiliary was poor.

More sterically demanding auxiliaries were also tried, with quenching of the post-VNS anion with methyl iodide and benzyl bromide, and the results are summarised below (Table 1).

Both products of the VNS reaction of trans-2-(2'-naphthyl)cyclohexylphenylsulfonyl acetate 90f were crystalline. X-ray crystallography showed the major isomer to be the (1RS, 2SR, aRS) diastereoisomer A.

### Table 1

<table>
<thead>
<tr>
<th>Auxiliary</th>
<th>91a</th>
<th>91b</th>
<th>91c</th>
<th>91d</th>
<th>91e</th>
<th>91f</th>
</tr>
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<tbody>
<tr>
<td>(-)-Menthol</td>
<td></td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
<td>3:2</td>
<td>3:1</td>
</tr>
<tr>
<td>(-)-8-Phenylmenthol</td>
<td></td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
<td>3:2</td>
<td>3:1</td>
</tr>
<tr>
<td>(-)-trans-2-Phenylcyclohexan-1-ol</td>
<td></td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
<td>3:2</td>
<td>3:1</td>
</tr>
<tr>
<td>(+/-)-trans-2-(4-Biphenyl)cyclohexan-1-ol</td>
<td></td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
<td>3:2</td>
<td>3:1</td>
</tr>
<tr>
<td>(+/-)-trans-2-(1'-Naphthyl)cyclohexan-1-ol</td>
<td></td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
<td>3:2</td>
<td>3:1</td>
</tr>
<tr>
<td>(+/-)-trans-2-(2'-Naphthyl)cyclohexan-1-ol</td>
<td></td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
<td>3:2</td>
<td>3:1</td>
</tr>
</tbody>
</table>

\[ R^1 = \text{Me} \quad R^1 = \text{Bn} \]
Chapter 3
3.1 Aims

This PhD thesis documents a possibility of applying the VNS process to lactams and thereby developing a new and versatile route to α-aryl lactams. The latter are potentially useful in drug discovery chemistry. They possess several points of structural diversity amenable to convenient derivatization thereby providing an important peptide-like scaffold.

The PhD study also set out to provide further insights into the asymmetric VNS alkylation process. We were keen to investigate the VNS reactions of chiral heterocyclic nucleophiles. The diastereoselectivity of VNS reactions was to be assessed first using an α-thiophenyl lactone possessing a γ-stereogenic centre such as 92 (Scheme 48).

Scheme 48

Reaction of the VNS nucleophile 92 with nitroarenes would generate the post-VNS anion in the usual way. Reaction of this anion with a variety of electrophiles would give the lactone 93 possessing an α-aryl quaternary stereogenic centre. It was expected that the electrophile would approach anti to the R group for primarily steric reasons (Scheme 49).

Scheme 49

We hoped to be able to apply this methodology to the total synthesis of Physostigmine, an alkaloid isolated from African Calabar seeds. It possesses interesting biological activity, it is a potent inhibitor of acetylcholinesterase and is used clinically to treat glaucoma and myasthenia gravis. Physostigmine and analogues are also being evaluated as treatments of Alzheimer’s disease and possess morphine-like analgesic properties. The proposed synthesis will commence with a VNS reaction of α-thiophenyl lactone 94 with p-methoxynitrobenzene followed by selective reaction of the post-VNS anion with iodomethane (Scheme 50). Catalytic hydrogenation of the nitro compound 95 will provide an aniline derivative, which
will ring-open the lactone, to give, after N-methylation an oxindole. Removal of the silyl protecting group will generate the diol 96.

**Scheme 50**

Treatment of the diol 96 with periodic acid will give the known aldehyde 97. Physostigmine 98 can be formed from this known aldehyde by sequential reaction with methylamine and LiAlH₄ followed by transformation of the methoxyl moiety to the N-methyl carbamate group (Scheme 51).

**Scheme 51**

The following chapters describe the results of my work in attempting to achieve these initial aims. Several additional areas were also studied as the programme of work developed. Most notably the treatment of the post-VNS anion with electron deficient aryl electrophiles 99 such as Sanger's reagent (R² = NO₂) was investigated as a possible route to the formation of diarylmethanes 100 and oxindoles 101 (Scheme 52).

**Scheme 52**
Chapter 4
4.1 C-Arylation of Lactams and Pyrazolidinones via Vicarious Nucleophilic Substitution of Hydrogen

We have been interested in applying the VNS process to lactams and thereby developing a new and versatile route to α-aryl lactams. The latter are potentially useful in drug discovery chemistry. They possess several points of structural diversity amenable to convenient derivatization thereby providing an important peptide-like scaffold. Such a scaffold has been incorporated into γ-lactam derived inhibitors of tumour necrosis factor α converting enzyme such as 102,130 and matrix metalloproteinase-13 inhibitor 103 131 (Figure 8).

Figure 8

It has been shown that the palladium-catalyzed intermolecular coupling of halides and keto enolates is a useful method for synthesizing α-aryl ketones75 and α-aryl esters.132 Arylation of other carboxylic acid derivatives such as amides are less common.132,133-6

Few examples of C-arylation of a cyclic amide moiety have been reported in the literature. Stewart and co-workers have utilized an excess of strong base (lithium isopropylcyclohexylamide, 3.2-8 equivalents) in the presence of aryl halides for arylation to proceed at the 3-position (Scheme 53).137 The reaction of 104 was thought to follow the benzyne mechanism, due to the products 105 and 106 being formed in equal amounts from the reaction of p-bromoanisole with NMP and excess LiCA.

Scheme 53

On the other hand, Alonso and co-workers138 have used 1-alkyl-2-pyrrolidinone enolate ions as nucleophiles to react with aryl halides under uv radiation (Scheme 54). The reaction of 104 apparently follows an $S_{RN1}$ mechanism and leads to a single product 108.
A further example of C-arylation of γ-lactams was reported involving the α-silylated derivative 109 of 1-methyl-2-pyrrolidinone (Scheme 55). The cleavage of the silyl group with fluoride leads to the generation of a stabilized enolate. This can then react reversibly with the electrophilic nitroarene to produce the σH-adduct 110 which can then be oxidized to the required product 111 with DDQ or Br₂. Different para substituted nitroaromatics were used including p-nitroanisole, p-nitrotoluene and p-bromonitrobenzene.

Scheme 55

The α-arylation of the zinc enolate of N-protected 2-piperidinones with aryl bromides in the presence of a palladium catalyst was reported by Cossy.¹³⁹ (Scheme 56). When N-tosylpiperidinone 112 was treated under the conditions used for the arylation of esters no arylation occurred. To increase the reactivity, a transmetallation with zinc chloride was carried out. The α-arylation of N-tosylpiperidinone 112 and N-benzylpiperidinones was achieved in good yields.

Scheme 56

An approach for the α-arylation of esters and amides using Reformatsky reagents under a microwave accelerated reaction and a Pd(PPh₃)₄ catalyst has been reported by Moloney¹⁴⁰ (Scheme 57).
We thought that a lactam or pyrazolidinone with a vicarious leaving group could undergo the VNS process with nitrobenzene to effect C-3 arylation. If successful this would allow us to develop an asymmetric version of the reaction. We now report that α-sulfanyllactams can be used in the VNS-alkylation reaction without a problem.

The VNS nucleophile 119 (Scheme 58) was formed by treating N-methylpyrrolidinone with 2 equivalents of LDA followed by phenyl disulfide (1 eq.) and HMPA. We found that DMPU could be used as a non-toxic alternative to HMPA without compromising the yield. N-Methyl pyrrolidinone was chosen since it is commercially available, cheap and a method of forming the VNS nucleophile with the α-sulfanylphenyl group was already available in the literature.

The VNS nucleophile 119 dissolved in a solution of DMF with nitrobenzene (1 eq.), was added to a sodium hydride/DMF base solvent system at 0 °C. This produced the normal bright purple intermediate which was quenched with methyl iodide (2 eq.) (Scheme 59). It was found that two equivalents of the electrophile were needed to maximize the yield due to the thiophenolate anion competing with the post-VNS anion for the electrophile. The required product 120 was isolated by column chromatography from the crude reaction mixture which contained unreacted nitrobenzene, mineral oil from the sodium hydride, methylated thiophenol and DMF.
The two doublets at δ 8.05 and 7.52 (J 8.9 Hz) in the $^1$H-NMR indicated the presence of the para substituted nitroaromatic. The N-methyl group appears as a singlet at δ 2.86 and the remaining methyl group appears as a singlet at δ 1.48. Multiplets (δ 3.24-3.36), (δ 2.31-2.37) and (δ 2.11-2.19) represent the four protons on the pyrrolidinone ring.

A further series of electrophiles were tried in this VNS/alkylation reaction (Scheme 60). The results are summarised below (Scheme 60, Table 2). The electrophiles were chosen due to them being readily available and highly reactive alkylating agents.

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>120a</strong> Methyl iodide</td>
<td>CH$_3$</td>
<td>65</td>
</tr>
<tr>
<td><strong>120b</strong> HCl</td>
<td>H</td>
<td>66</td>
</tr>
<tr>
<td><strong>120c</strong> Allyl bromide</td>
<td>Allyl</td>
<td>66</td>
</tr>
<tr>
<td><strong>120d</strong> Benzyl bromide</td>
<td>CH$_3$Ph</td>
<td>72</td>
</tr>
</tbody>
</table>

The 2 aromatic doublets in the $^1$H-NMR spectrum representing the para substituted nitroaromatic were present in the remaining compounds **120b-d**. The triplet at δ 3.7 (J 9.2 Hz) in the $^1$H-NMR of **120b** indicated a simple proton quench of the post-VNS anion had occurred to give the required product **120b**. The multiplets (δ 5.49-5.56) and (δ 5.00-5.05) along with a doublet at δ 2.57 (J 7.2 Hz) in the $^1$H-NMR spectrum indicated the presence of the allyl group in **120c**. The multiplets at (δ 7.16-7.19) and (δ 7.00-7.02) along with the 2 doublets at δ 3.23 and 2.96 (J = 13.3 Hz) indicated the presence of the benzyl group in compound **120d**. For full characterisation details see the experimental section.
To introduce extra diversity into the reaction, a VNS nucleophile was made from N-Boc-pyrrolidinone by the same method as the VNS nucleophile 119 was obtained (Scheme 61). Boc pyrrolidinone (122) was obtained by treating pyrrolidinone (121) with di-tert-butyl dicarbonate and DMPA in acetonitrile. The multiplets at (δ 7.22-7.25) and (δ 7.46-7.48) in the 1H-NMR spectrum along with the shift of the singlet representing the Boc group from 8 1.2 in Boc pyrrolidinone to 8 1.4 in the product indicated the required product had been formed. Also the appearance of the ABX system at δ 3.78, (2.30-2.29) and (1.89-1.98) indicated the required product had been formed.

Scheme 61

Use of the VNS nucleophile 123 in the VNS/alkylation reaction under the same conditions as those used with the VNS nucleophile 119 was not successful (Scheme 62). The 1H-NMR spectrum of the crude reaction product contained unreacted nitrobenzene, VNS nucleophile 124 that had been methylated at the C-3 position, DMF and mineral oil from the sodium hydride with no trace of the required product 125. Even though 124 was not isolated, its presence was indicated by the appearance of a singlet at δ 2.71 and the disappearance of the C-3 proton at δ 3.78 in the starting material 123.

Scheme 62

We explored the scope of the process by using a further series of pyrrolidinones in the VNS/alkylation process. The first of these was based on 1-phenyl-2-pyrrolidinone (128). This was prepared by treating γ-butyrolactone (126) with aniline (127). The VNS nucleophile 129 was then obtained by the usual method (Scheme 63).

Scheme 63
Multiplets (δ 7.81-7.84), (δ 7.59-7.64) and (δ 7.53-7.57) represented the required 10 aromatic protons. The C-3 proton of 129 appeared as a double doublet at δ 4.25 (J 6.0 & 8.6 Hz). Elemental analysis also indicated the required product. For full details see the experimental section.

The VNS nucleophile 129 was used in the VNS/alkylation process with a series of electrophiles. The results are summarised below (Scheme 64, Table 3).

Scheme 64

![Scheme 64](image)

**Table 3. Yields of Product Pyrrolidin-2-ones**

<table>
<thead>
<tr>
<th></th>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130a</td>
<td>HCl</td>
<td>H</td>
<td>75</td>
</tr>
<tr>
<td>130b</td>
<td>Methyl iodide</td>
<td>CH₃</td>
<td>68</td>
</tr>
<tr>
<td>130c</td>
<td>Allyl bromide</td>
<td>Allyl</td>
<td>65</td>
</tr>
<tr>
<td>130d</td>
<td>2,4-Dinitrofluorobenzene</td>
<td>2,4-DNB</td>
<td>58</td>
</tr>
</tbody>
</table>

The two aromatic doublets representing the *para*-substituted nitroaromatic were present in compounds 130a-d indicating VNS had been successful. The N-phenyl group was also present in each compound occurring as a doublet and two triplets. Five protons in the non-aromatic region for compound 130a indicated the correct product.

The presence of the methyl group in 130b was indicated by a singlet at δ 3.10. The presence of the allyl group in 130c was indicated by the multiplets at (δ 5.52-5.62), (δ 5.02-5.06) and (δ 2.65-2.67) giving a combined total of 5 protons. The presence of the 2,4-substituted aromatic at the C-3 position of 130d was indicated by the presence of a doublet at δ 8.55 (J 2.4 Hz), double doublet at δ 8.29 (J 2.4 & 8.7 Hz) and multiplet at (δ 7.47-7.50) which represented the required 3 protons. The aryl electrophile (2,4-dinitrofluorobenzene) was chosen to show the VNS-S₅Ar process mentioned later in this thesis could be extended to lactams with an α-phenylsulfanyl group as the vicarious leaving group.

The *ortho* selectivity of the VNS/alkylation process was tested with the VNS nucleophile 129 with *p*-nitroanisole (Scheme 65). The VNS process did not occur under the same conditions as the *para* selective version, since the bright purple intermediate solution, associated with the post-VNS anion not observed.
The $^1$H-NMR spectrum of the crude reaction mixture contained $p$-nitroanisole, the methylated VNS nucleophile 131, mineral oil and DMF. Although it was not isolated the presence of 131 was indicated by the presence of a singlet at $\delta$ 2.69 and the disappearance of the C-3 proton at $\delta$ 4.25. The reaction was repeated with a KOt-Bu/DMF base solvent system, which also resulted in no success. On this occasion, however, the bright purple colour associated with the post-VNS anion was observed. The problem with using $p$-nitroanisole as a VNS substrate is that it is much less electron-deficient than nitrobenzene, due to the electron-donating nature of the methoxy group. As an alternative to $p$-nitroanisole as the VNS substrate $p$-chloronitrobenzene was tried (Scheme 66) with the same outcome as the $p$-nitroanisole substrate. The steric clash of the tertiary carbanion with the nitro group is the most likely problem with this reaction (Scheme 66). The intermediates 134 and 135 are extremely sterically encumbered, and may therefore not form.

The next VNS nucleophile studied was based on 1-benzyl-2-pyrrolidinone (136). The VNS nucleophile was prepared by the same method as the previous ones (Scheme 67). This was chosen as it offered the opportunity for generating the NH pyrrolidinones that can then be further functionalised.
The VNS nucleophile 137 was used in the VNS/alkylation reaction with a series of electrophiles (Scheme 68) under identical conditions as discussed previously. The results are summarised below (Scheme 68, Table 4).

Table 4. Yields of Product Pyrrolidin-2-ones

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>138a</td>
<td>HCl</td>
<td>62</td>
</tr>
<tr>
<td>138b</td>
<td>Methyl iodide</td>
<td>CH₃</td>
</tr>
<tr>
<td>138c</td>
<td>Ethyl iodide</td>
<td>CH₂CH₃</td>
</tr>
</tbody>
</table>

The two aromatic doublets in the ¹H-NMR spectrum representing the para substituted nitroaromatic were present in compounds 138a-c indicating that the VNS had been successful. A triplet at δ 3.77 (J 9.1 Hz) in the ¹H-NMR spectrum of 138a represents the benzylic proton. A singlet at δ 1.54 indicates that the alkylation with methyl iodide had been successful. A triplet at δ 0.76 (J 7.4 Hz) and two double quartets at δ 1.95 (J 14.8 & 7.4 Hz) and δ 1.86 (J 13.9 & 7.4 Hz) indicated that the quench with ethyl iodide had been successful.

The next VNS nucleophile studied was based on 1-para-methoxyphenyl-2-pyrrolidinone (141) as this also offered the opportunity for deprotection and further functionalisation. The γ-lactam 141 was formed by treating 4-chlorobutyryl chloride (139) with p-anisidine and triethylamine (Scheme 69). The product 140 was then treated with sodium hydride to effect cyclization to the pyrrolidinone (Scheme 17).
The VNS nucleophile was then formed by the usual method (Scheme 70). Treatment of 141 with LDA (2 eq.) followed by phenyl disulfide and DMPU gave 142 in 68% yield

**Scheme 70**

The doublets at δ 7.41 and 6.91 (J 9.1 Hz) in the $^1$H-NMR spectrum of 142 indicates the presence of the para substituted anisole. The multiplets at (δ 7.60-7.62) and (δ 7.31-7.37) represents the aromatic group attached to sulfur. A double doublet at δ 4.01 (J 5.8 & 8.7) represents the C-3 proton adjacent to the carbonyl. The three remaining protons are represented by multiplets (δ 3.67-3.82), (δ 3.56-3.60) and (δ 2.60-2.65).

The VNS nucleophile 142 was used in the VNS/alkylation process with a series of electrophiles under identical conditions. The results are summarised below (Scheme 71, Table 5). The two aromatic doublets representing the para-substituted nitroaromatic were present in compounds 143a-c indicating that the VNS had been successful.

**Scheme 71**

<table>
<thead>
<tr>
<th>Table 5. Yields of Product Pyrrolidin-2-ones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrophi</td>
</tr>
<tr>
<td>143a</td>
</tr>
<tr>
<td>143b</td>
</tr>
<tr>
<td>143c</td>
</tr>
</tbody>
</table>

Having only used γ-lactams so far, we decided to try δ-lactams in the VNS/alkylation process. The VNS nucleophile 146 was prepared in the usual way after N-benzylation of commercially available δ-caprolactam (Scheme 72).
Scheme 72

\[
\begin{align*}
\text{NH} & \quad \text{N}^+ \quad \text{Ph} \\
\text{144} & \quad \text{NaH} & \quad \text{CH}_3I \\
\text{145} & \quad \text{LDA} & \quad \text{PhSSPh} \\
\text{96\%} & \quad \text{146} & \quad 67\%
\end{align*}
\]

The VNS nucleophile 146 was used in the VNS/alkylation process with nitrobenzene and a series of electrophiles under identical conditions as described earlier. The results are summarised below (Scheme 73, Table 6).

Scheme 73

\[
\begin{align*}
\text{PhS} & \quad \text{O} \\
\text{146} & \quad \text{1. PhNO}_2 & \quad \text{NaH/DMF} \\
\text{2. E}^+ & \quad \text{147} & \quad \text{O}_2\text{N}
\end{align*}
\]

Table 6. Yields of Product Piperidin-2-ones

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>147a HCl</td>
<td>H</td>
<td>64</td>
</tr>
<tr>
<td>147b Methyl iodide</td>
<td>CH$_3$</td>
<td>61</td>
</tr>
<tr>
<td>147c Ethyl iodide</td>
<td>CH$_2$CH$_3$</td>
<td>58</td>
</tr>
</tbody>
</table>

The two aromatic doublets in the $^1$H-NMR spectrum representing the para substituted nitroaromatic were present in 147a-c indicating that the VNS process had been successful. For full details see the experimental section.

As an alternative to the thiophenolate as the vicarious leaving group, a VNS nucleophile 149 with an α-chloro group was made by treatment of $N$-benzylated δ-valerolactam (148) with sec-BuLi followed by tosyl chloride (Scheme 74). This was done to give us a method where we could avoid the need for an excess of electrophile due to chloride ion being a poor nucleophile.

Scheme 74

\[
\begin{align*}
\text{PhN} & \quad \text{O} \\
\text{148} & \quad \text{sec-BuLi} & \quad \text{TsCl} \\
\text{149} & \quad 38\%
\end{align*}
\]

The VNS nucleophile 149 was then used in a VNS/alkylation reaction with nitrobenzene and methyl iodide (1 eq.) under identical conditions as previously described (Scheme 75).
The reaction proceeded, but in much lower yield. The α-chloro-N-methylpyrrolidinone (150) was made under the same conditions as the α-chloro N-benzylpiperidinone (149). This was also used in the VNS/alkylation process (Scheme 76). Again, this resulted in a much lower yield of the required VNS product 122a, as compared to using the equivalent VNS nucleophile 121.

We next tried a pyrazolidinone in the VNS/alkylation process. The 2-methylpyrazolidin-3-one 153 was prepared by methylation of the commercially available pyrazolidine 148 followed by the usual method of adding the vicarious leaving group (Scheme 77). A multiplet at (δ 3.89-3.96) and double doublet at δ 3.65 (J 11.3 & 14.5 Hz) in the ¹H-NMR spectrum of 153 represented the presence of the C-3 and two C-4 protons, indicating the required product. Ten protons were observed in the range δ 6.79-7.33, representing the two phenyl rings. The singlet for the methyl group appears at δ 2.97.

The VNS nucleophile 153 was then used in the VNS/alkylation process with nitrobenzene and a series of electrophiles, under the usual conditions. The results are summarised (Scheme 78, Table 7). The two aromatic doublets representing the para-substituted nitroaromatic were present in compounds 78a-b, indicating that the VNS process had been successful. For full characterisation details see the experimental section.

43
Scheme 78

\[ \text{PhS}^+\text{N} \xrightarrow{\text{1. } \text{Ph-NO}_2, \text{NaH/DMF}} \text{O}^+\text{N} \xrightarrow{\text{2. } E^+} \]

Table 7. Yields of Product Pyrazolidin-3-ones

<table>
<thead>
<tr>
<th></th>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>154a</td>
<td>HCl</td>
<td>H</td>
<td>69</td>
</tr>
<tr>
<td>154b</td>
<td>Methyl iodide</td>
<td>CH₃</td>
<td>47</td>
</tr>
<tr>
<td>154c</td>
<td>Benzyl bromide</td>
<td>CH₂Ph</td>
<td>61</td>
</tr>
</tbody>
</table>

The VNS products (143a-c) represent the opportunity for oxidative removal of the para-methoxy aromatic making the amide available for further functionalisation. This was achieved with ceric ammonium nitrate (Scheme 79). Treatment with ceric ammonium nitrate, according to the method of Giang, gave the amide in quantitative yield. The disappearance of the peaks corresponding to the anisole in the $^1$H-NMR spectrum indicated that deprotection had occurred successfully, as did the appearance of a singlet at $\delta$ 7.0 representing the NH of the amide. Further proof was given by an electrospray accurate mass measurement, which gave a (M + H)$^+$ peak at 207.0699 corresponding to the calculated mass of 207.0691.

Scheme 79

\[ \text{MeO-}^\text{N} \xrightarrow{\text{CAN, H}_2\text{O/CH}_3\text{CN, 1 h 0 °C}} ^\text{N} \xrightarrow{\text{H}_2, 10\% \text{Pd/C}} \]

The VNS products (138a-c and 147a-c) can also be deprotected and further functionalised by removal of the benzyl group under hydrogenation conditions (Scheme 80). Under such conditions it was anticipated that the nitro group would also be reduced (e.g. $138a \rightarrow 156$).

Scheme 80
Hydrogenation of 138a in ethyl acetate with activated catalyst (10% Pd on C) under an atmosphere of hydrogen for 24 hours did not proceed as desired. The crude product was checked by 1H-NMR spectroscopy, which showed unfortunately that the benzyl group was still present (Scheme 81) by a singlet at δ 4.44 and multiplet (δ 6.79-7.30). The nitro group was reduced as indicated by the two doublets δ 7.07 and 6.64 (J 8.4 Hz). The reaction probably needed to be done under pressure but the required facilities were not available to us.

**Scheme 81**

Summary and Conclusion

In summary, a useful procedure has been developed that can be used for the α-arylation of pyrrolidinones, piperidinones, and pyrazolidinones. Even allowing for the limited number of examples of α-arylation of cyclic amides reported, this is potentially of real value. Nitrogen protecting groups have been used successfully which allow for subsequent deprotection and further functionalisation of the amide. Pyrrolidinones, piperidinones and pyrazolidinones have been incorporated into the VNS/alkylation group by adding an α-phenylsulfanyl VNS leaving group and treating with base and nitrobenzene. Several different N-substituted protecting groups such as benzyl and p-methoxyphenyl have been incorporated in the VNS nucleophile successfully. The p-methoxyphenyl protecting group was successfully removed with eerie ammonium nitrate and although we weren't able to remove the benzyl group we were confident that under hydrogenation conditions above atmospheric pressure we would be able to thus providing the possibility for further functionalisation of the α-aryl lactam. Unfortunately, however using a N-Boc lactam resulted in the VNS/alkylation process not taking place.

Using chloride as the VNS leaving group we were hopeful would lead to a cleaner process due to chloride being a poorer nucleophile than thiophenolate so removing the need for two equivalents of the electrophile. Unfortunately however this resulted in a significant reduction in the yield of the reaction.

All the examples discussed in this chapter have undergone the VNS process at the para-position of the nitroarene. When using a para-substituted nitroarene to force the VNS
nucleophile onto the ortho-position resulted in no success. The most probable reason for this is the clash with the nitro-group (Scheme 66). In the case of the unsuccessful reactions the $^1$H-NMR spectra of the crude reaction mixtures indicated the presence of the alkylated VNS nucleophile and nitrobenzene.

In conclusion we have developed a simple one pot route to $\alpha$-aryl cyclic amides. This laid the foundations for the development of an asymmetric process using $\gamma$-substituted lactams and lactones as the VNS nucleophile. The lack of success with the ortho-selective VNS reaction was worrying as this would be important in the synthesis of Physostigmine (98).
Chapter 5
5.1 Asymmetric Vicarious Nucleophilic Substitution of Hydrogen

The biological world can be regarded as a chiral world in the chemical sense. It happens often in nature that one enantiomer exhibits biological activity whereas the other enantiomer does not. A number of biologically active natural products contain quaternary carbon atoms. Interest in synthesizing them in an optically active form is reflected in the explosive increase in the number of new development for the chiral construction of quaternary carbons that have been published in the last 15 years.

Asymmetric syntheses can be divided into two types, enantioselective syntheses and diastereoselective syntheses. According to Izumi, a reaction is described as enantioselective if the reaction is carried out on an achiral molecule using an enantioselective reagent or catalyst. In the case of diastereoselective synthesis, if a molecule contains a centre of chirality and a centre of prochirality and the reaction results in the conversion of the centre of prochirality into a new centre of chirality, the reagent may attack from either face with the result that diastereoisomers are formed. This definition proposed by Izumi has proven useful for organic and medicinal chemists for classifying asymmetric synthesis.

We decided to assess the diastereoselectivity of VNS reactions using an α-thiophenyl-γ-lactone possessing a γ-stereogenic centre to provide a further insight into the asymmetric VNS/alkylation process. As mentioned previously, a diastereoselective version of the VNS/alkylation reaction was reported in the Lawrence group using an auxiliary incorporated into the VNS nucleophile (Scheme 82).

Scheme 82

We thought that reaction of the VNS nucleophile with nitroarenes would generate the post-VNS anion in the usual way. Reaction of the post-VNS anion with a variety of electrophiles would hopefully give the lactone possessing an α-aryl quaternary stereogenic centre (Scheme 83).
It was expected that the electrophile would approach *anti* to the R group for primarily sterical reasons. In other words, the R group is shielding one face of the molecule from the incoming electrophile (Scheme 84). It is known that conventional alkylation of enolates derived from α-aryl-γ-lactones bearing a γ-stereogenic centre results in such 1,3-stereocontrol at acceptable levels.  

**Scheme 84**

The ultimate aim of this section was to develop an efficient synthesis to the natural product physostigmine (98) using an asymmetric VNS reaction to produce the required stereochemical arrangement of the molecule (Scheme 85).

**Scheme 85**

The first lactone to be studied 'dihydro-5-phenyl(3H)furan-2-one (160), was formed by reduction of 3-benzoylpropionic acid with sodium borohydride. The α-thiophenyl-γ-butryolactones *cis*-161 & *trans*-161 were prepared by a known process from γ-butyrolactone 160, LDA (1 eq.) and phenyldisulfide (Scheme 86) with a 6:4 ratio of the two diastereoisomers.
in overall 70% yield. This ratio matched that of the literature procedure. The isomers were separated by column chromatography. The diastereosomers were assigned in the literature procedure by nOe studies.

**Scheme 86**

The mixture of VNS nucleophiles trans-161 and cis-161 were dissolved in a solution of DMF containing nitrobenzene (1 eq) and added to a sodium hydride/DMF solvent system at 0 °C under nitrogen. After stirring at 0 °C for 2 hours the bright purple solution was quenched with methyl iodide at -78 °C. After work up and purification this left the required product in only 9% yield. It was found that if the post-VNS anion was allowed to warm to room temperature and stirred for 2 hours before the electrophilic quench the yield improved to 73% (Scheme 87) of the trans-162:cis-162 products (in an 88:12 ratio). The major product was isolated by column chromatography but unfortunately the minor diastereoisomer could not be isolated.

**Scheme 87**

The presence of the required product was indicated by the presence of doublets at δ 8.21 and 7.71 (J 8.9 Hz) in the ¹H-NMR spectrum indicating the presence of a para substituted nitroaromatic. The double doublets at δ 5.65 (J 9.9 & 6.1 Hz), 2.89 (J 13.0 & 6.1 Hz) and 2.63 (J 13.0 & 9.9 Hz) represent an ABX system consisting of the C-4 and C-5 protons. The phenyl group is represented by a multiplet (δ 7.33-7.41) and the methyl group as a singlet at δ 1.79.

Fortunately the major isomer was crystalline. A crystal suitable for X-ray analysis was grown by dissolving a small amount of sample in dichloromethane and then putting this vial into a pot containing hexane. This was then left covered in the dark until crystals were obtained. X-ray crystal structure determination was performed by Abdul Malik of Cardiff University. The
structure clearly reveals the relative stereochemical configuration of the product and shows that the major product is the trans isomer, as expected. The lactone 162 adopts an envelope conformation as shown in Figure 9.

Figure 9

Chem3D representation of the X-ray crystal structure of the trans-162

The ratio of the major:minor stereoisomers trans-162:cis-162 is based on analysis of the $^1$H-NMR spectrum of the crude reaction product. Because the minor isomer was present in only small quantities we were not confident that those peaks we were assigning as corresponding to the minor isomer were indeed those of the cis-isomer. A method had to be obtained to make the minor diastereoisomer so that we could accurately assign the peaks in the crude $^1$H-NMR spectrum and be totally confident of quoting an accurate figure for the diastereoselectivity.

The synthetic route chosen is illustrated in Scheme 88.

**Scheme 88**

Esterification of the commercially available 4-nitrophenylpropionic acid (163) with methanol and sulfuric acid and heating under reflux for 3 hours gave the ester 164 in 90% yield. The ester 164 was then treated with sodium hydride (1 eq.) followed by 2-bromoacetophenone at 0 °C to give 165 in 65% yield. The presence of the required product is indicated by the presence of a singlet at $\delta$ 1.85 in the $^1$H-NMR spectrum representing the methyl group at the quaternary centre. In the starting material 164, this methyl group appears as a doublet at $\delta$ 1.4 ($J$ 7.2 Hz). The doublets at $\delta$ 3.92 and 3.65 ($J$ 17.8 Hz) represent the CH$_2$ group next to the quaternary
centre. The methyl group of the ester appears as a singlet at $\delta 3.74$. The appearance of singlets at $\delta 196.3$ and $174.7$ in the $^{13}$C-NMR spectrum indicate the presence of two carbonyl groups. We hoped that reduction of the ketone to the alcohol would cause cyclization onto the ester to give the required lactone 162. This was achieved using sodium borohydride as the reducing agent although the reaction was capricious with the lactone being sometimes reduced in the process. Other reducing agents were attempted such as sodium acetoxyborohydride and tetramethyldisiloxane/TBAF with little success.

The sodium borohydride method did however eventually give the two required diastereoisomeric products in a 1:1 ratio and overall yield of 83%. These two products were the same products formed in the VNS reaction but formed in a different ratio. The two diastereoisomers were then separated by column chromatography. Doublets at $\delta 8.15$ and $7.67$ ($J 8.8$ Hz) in the $^1$H-NMR spectrum indicated the presence of a para-substituted nitroaromatic. The ABX system was represented by double doublets at $\delta 5.17$ ($J 5.4$ & $10.6$ Hz), $3.08$ ($J 5.4$ & $13.3$ Hz) & $2.46$ ($J 10.6$ & $13.3$ Hz). The phenyl group appeared as a multiplet ($\delta 7.29-7.37$) and the methyl group as a singlet at $\delta 1.69$. Comparing with the $^1$H-NMR spectrum of the crude reaction product 162 prepared earlier we could deduce which peaks belonged to the minor diastereoisomer cis-162 and the ratio of the two products had therefore been accurately calculated. An X-ray structure was obtained of the minor diastereoisomer (Figure 10): This was done by growing a crystal under the same conditions as mentioned previously for the major product in the VNS reaction. The structure clearly reveals the relative stereochemical configuration of the product and shows that the product is indeed in the cis form (cis defined as a cis relationship between the methyl and phenyl groups).

**Figure 10**

![Chem3D representation of the X-ray crystal structure of the cis-162](image)

A further series of electrophiles were used in the VNS reaction with nitrobenzene and 5-phenyl-3-phenylsulfanylfuran-2-one (92) under identical conditions (Scheme 89). The results are summarised below (Table 8).
Scheme 89

Table 8. Yields of Product Furan-2-ones

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)</th>
<th>Ratio trans: cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>162a</td>
<td>HCl</td>
<td>73</td>
<td>73:27</td>
</tr>
<tr>
<td>162b</td>
<td>Allyl bromide</td>
<td>CH₂CH₂⁻</td>
<td>67</td>
</tr>
<tr>
<td>162c</td>
<td>Benzyl bromide</td>
<td>PhCH₂⁻</td>
<td>65</td>
</tr>
<tr>
<td>162d</td>
<td>2-Bromoacetophenone</td>
<td>PhCH₂(CO)⁻</td>
<td>67</td>
</tr>
</tbody>
</table>

The doublets representing the 1,4-disubstituted aromatic were present in compounds 162a-d indicating that the VNS process had been successful. The double doublet at $\delta$ 5.50 ($J$ 10.7 & 5.5 Hz) in the $^1$H-NMR spectrum of 162a indicated a proton quench of the post-VNS anion had taken place. The allyl group in the $^1$H-NMR spectrum of 162b is represented by multiplets ($\delta$ 5.49-5.68) and ($\delta$ 5.09-5.17) and a doublet at $\delta$ 2.73 ($J$ 7.4 Hz). The benzyl group in the $^1$H-NMR spectrum of 162c is represented by doublets at $\delta$ 3.63 and 3.16 ($J$ 13.2 Hz) along with a multiplet ($\delta$ 7.19-7.45). The presence of the acetophenone group in the $^1$H-NMR spectrum of 162d is indicated by doublets at $\delta$ 3.81 and 3.65 ($J$ 18.1 Hz).

To be confident of quoting an accurate ratio of diastereoisomers again, the minor diastereoisomers were again required. This was done by a similar method as described previously (Scheme 90).

Scheme 90
Again chemoselective reduction of the ketone 168 proved to be capricious, but the required product was eventually isolated, giving a 1:1 mixture of the two diastereoisomers 162a. However, separation by column chromatography proved to be difficult but the $^1H$-NMR spectrum of the crude reaction still gave the position of signals of the minor diastereoisomer. From this the accurate ratio of the two diastereoisomers 162a (cis-162a: trans-162a 73:27), obtained from the VNS process of 92 with a proton quench could be quoted.

Scheme 91

![Scheme 91](image)

The minor diastereoisomer of compound 162b was formed again based on the same method (Scheme 91). Deprotonation of methyl 4-nitrophenylacetate (167) with sodium hydride at 0 °C followed by quenching with allyl bromide (1 eq) gave 168 in 93% yield. Treatment of 168 with sodium hydride followed by quenching with 2-bromoacetophenone (1 eq.) gave 169 in 86% yield. The presence of 169 was indicated by the disappearance of the benzylic proton of the starting material at $\delta$ 3.78 in the crude $^1H$-NMR spectrum and the appearance of doublets at $\delta$ 3.82 and 3.74 ($J$ 18.0 Hz). Doublets at $\delta$ 8.16 and 7.89 ($J$ 8.9 Hz) represent the para substituted nitroaromatic. The phenyl group is represented by a triplet at $\delta$ 7.41 ($J$ 7.9 Hz) and multiplet ($\delta$ 7.49-7.55). The allyl group is represented by multiplets ($\delta$ 5.28-5.36 & 4.85-4.93 & 2.94-3.07). The singlet representing the methyl group appeared at $\delta$ 3.63.

Reduction of 169 with sodium borohydride gave the two diastereoisomers of 162b in a 1:1 ratio in 62% overall yield. The doublets at $\delta$ 8.28 and 7.72 ($J$ 8.9 Hz) in the $^1H$-NMR spectrum of the cis product represent the para-substituted nitroaromatic. The phenyl group appears as a multiplet ($\delta$ 7.33-7.43), the allyl group appears as multiplets ($\delta$ 5.61-5.70 & 5.02-5.18 & 2.68-2.80). The three protons on the ring appear as an ABX system at $\delta$ 5.22 ($J$ 5.4 & 10.9 Hz), 3.01 ($J$ 5.4 & 13.6 Hz) and 2.56 ($J$ 10.9 & 13.6 Hz). From this data an accurate ratio of the two diastereoisomers was calculated.
To make the minor diastereoisomer of compound 162c, the same route was followed (Scheme 92). Deprotonation of methyl 4-nitrophenylacetate (167) with sodium hydride at 0 °C followed by an electrophilic quench with benzyl bromide (1 eq) gave 171 in 76% yield. Treatment of 171 with sodium hydride followed by an electrophilic quench with 2-bromoacetophenone (1 eq) gave 172 in 87% yield. The presence of 172 was indicated by the presence of a doublet at δ 8.20 (J 8.9 Hz) and multiplet (δ 7.45-7.51) representing the para-substituted nitroaromatic. A doublet at δ 3.58 (J 13.7 Hz) and multiplet (δ 3.68-3.72) represent the two CH₂ groups. A singlet at δ 3.72 represents the methyl group. The remaining aromatic protons are represented by doublets at δ 7.95 (J 7.5 Hz) and 6.52 (J 7.4 Hz), triplets at δ 7.62 (J 7.5 Hz), 7.14 (J 7.4 Hz) and 7.05 (J 7.4 Hz) and a multiplet (δ 7.45-7.51). As before the selective reduction of compound 172 proved capricious but this time the required products could not be isolated.

The minor diastereoisomer of compound 162d was not formed by this method due to the precursor having two identical carbonyl groups of which we only want to reduce the one. Nevertheless in these last two cases, we are not unduly concerned that the ratio we quote in Scheme 89 does not represent the true level of diastereoselectivity.

It was expected that the larger the electrophile, the higher the level of selectivity which would be obtained. The lowest level of selectivity achieved was with a simple proton quench of the post-VNS anion with HCl. Using methyl iodide as the electrophile however produced slightly better stereoselectivity than using allyl bromide as the electrophile. However, all the alkyl halides produced very similar results of stereoselectivity.
To study the diastereoselectivity in an ortho-selective VNS reaction, p-chloronitrobenzene was used as the VNS substrate (Scheme 93). Compound 173 was formed in an overall yield of 51% with a 80:20 ratio of trans:cis diastereoisomers. The presence of the required compound 173 was indicated by the presence of a singlet at δ 1.69 in the 1H-NMR spectrum representing the methyl group. An ABX system at δ 5.29 (J 9.2 & 6.8 Hz), 2.69 (J 13.6 & 6.8 Hz) and 2.49 (J 13.6 & 9.2 Hz) represents the three protons on the lactone ring. The three protons on the nitroaromatic ring are represented by doublets at δ 8.35 (J 8.9 Hz) & 8.01 (J 1.1 Hz) and a double doublet at δ 7.89 (J 1.1 & 8.9 Hz). The remaining aromatic protons are represented by a multiplet (δ 7.31-7.45). The major diastereoisomer was isolated by column chromatography.

From the results of the previous asymmetric VNS reaction using nitrobenzene, we were confident that the major diastereoisomer could be assigned as the trans product.

All the examples of asymmetric VNS discussed so far have produced racemic products. The next stage was to develop the protocol to incorporate a chiral lactone to produce an enantiomerically pure product. The chiral lactone we chose to try was made by the following route (Scheme 94), that has been developed by Herdeis, Tse, Drioh and Hanessian. 155-8

Scheme 94

To check that the lactone 177 was enantiomerically enriched the αD was measured (+35.3, c = 1.09 in EtOH) and compared to the literature value (+ 35.5 c = 1.09 in EtOH). 172 The first step of the synthesis involves diazotisation of glutamic acid (174). The process involves diazotisation of the amine group followed by cyclisation of the adjacent acid that involves an S_N2 inversion. The resulting α-lactone 179 is ring-opened by attack of the other acid to give
the γ-lactone 180. Due to the two consecutive Sn2 reactions the reaction takes place in an overall retention of configuration (Scheme 95).

Scheme 95

![Scheme 95 Diagram]

Esterification of 180 with EtOH/p-TsOH/benzene gave the ester 175. Reduction of the ester with sodium borohydride gave the alcohol 176. Protection of the alcohol with tert-butyl diphenylchlorosilane gave the required product 177. Treatment of 177 with LDA (2 eq.), phenyl disulfide (1 eq.) and DMPU (1 eq.) gave the VNS nucleophiles (trans-181 & cis-181) (Scheme 96). These were then separated by column chromatography.

Scheme 96

![Scheme 96 Diagram]

The VNS nucleophiles trans-181 & cis-181 were used in the VNS/alkylation process under the conditions developed previously, namely sodium hydride, nitrobenzene and methyl iodide (Scheme 97).

Scheme 97

![Scheme 97 Diagram]

Despite numerous attempts to get this reaction to work, all were unsuccessful. Using sodium hydride as the base resulted in no brightly coloured intermediate being observed. In the 1H-NMR spectrum of the crude reaction mixture nitrobenzene was observed along with the α-
methylated VNS nucleophile 183 although attempts to isolate this compound failed. Changing the base/solvent system to KOt-Bu/DMF resulted in the usual bright purple solution. The $^1$H-NMR spectrum of the crude reaction mixture however showed no sign of the required VNS product. Nitrobenzene was observed as well as a singlet at $\delta$ 0.95 along with aromatic protons at ($\delta$ 7.41-7.55). There was no indication of the product lactone in the $^1$H-NMR spectrum, and also no indication of the starting material 181.

An alternative protecting group was then attempted. This was formed under the same conditions as the previous lactone but using TBDMS-Cl instead of TBDPS-Cl (Scheme 98). The protected lactone 184 was then treated with LDA (2 eq.), DMPU and phenyl disulfide to give the cis and trans diastereoisomers in a 1:1 ratio (Scheme 98). The two diastereoisomers were separated by column chromatography.

**Scheme 98**

\[
\begin{align*}
\text{HO} & \quad \to \quad \text{PhS}^\text{SSPh}^\text{PhS} \quad \text{trans-185} \quad \text{cis-185} \\
\text{TBDMSO} & \quad \to \quad \text{TBDMSO} \quad \text{TBDMSO} \\
\text{DMAP} & \quad \text{LDA} \quad \text{PhSSPh} \quad \text{DMPU} \\
\text{NEt}_3 & \quad \text{DCM} \quad \text{DCM} \\
\end{align*}
\]

The presence of the required products was indicated by the presence of a double doublet at $\delta$ 4.05 ($J$ 7.4 & 9.3 Hz) in one diastereoisomer and a triplet at $\delta$ 3.89 ($J$ 10.2 Hz) in the other diastereoisomer representing the C-3 protons. The VNS nucleophiles trans-185 & cis-185 were studied in the asymmetric VNS reaction under the previous conditions using both sodium hydride and potassium tert-butoxide as the base. Using sodium hydride as the base resulted in no VNS product 186, but only nitrobenzene and the $\alpha$-methylated VNS nucleophile 187 present in the $^1$H-NMR spectrum of the crude reaction mixture (Scheme 99).

**Scheme 99**

\[
\begin{align*}
\text{PhS} & \quad \to \quad \text{PhNO}_2 \quad \text{trans-185} \\
\text{TBDMSO} & \quad \to \quad \text{TBDMSO} \\
\text{NaH/DMF} & \quad \text{CH}_3\text{I} \\
\end{align*}
\]

Using potassium tert-butoxide as the base again it looked as if the protecting group was being removed by the base as a singlet at $\delta$ 0.82 and doublet at 0.00 ($J$ 3.7 Hz) was observed in the
$^1$H-NMR of the crude reaction mixture. Nitrobenzene was also present although there was no sign of the peaks associated to a lactone.

A further VNS nucleophile was studied with a trityl protecting group. This was formed from the commercially available lactone 188 and treatment with LDA (2 eq.), DMPU and phenyl disulfide in THF (Scheme 100) to produce the cis and trans VNS nucleophiles although these could not be separated by column chromatography.

Scheme 100

These nucleophiles were studied in the VNS reaction under the same conditions as before. Using sodium hydride as the base resulted in nitrobenzene and the α-methylated VNS nucleophile 191 being observed in the $^1$H-NMR spectrum of the crude reaction mixture with no trace of the required product 190 (Scheme 101). The same result was observed when potassium tert-butoxide was used as the base instead of sodium hydride.

Scheme 101

A possible reason as to why these reactions failed is that in formation of the σ1-adduct causes the large PhS group to be forced cis to the large protecting group making the reaction highly unfavourable (Scheme 102). One possible solution is looking for a smaller VNS leaving group.

Scheme 102
Despite the lack of success with nitrobenzene an attempt was made to study the VNS nucleophile 181 in the VNS reaction with \textit{para}-substituted nitroaromatics to obtain the \textit{ortho}-VNS product (Scheme 103) as this would be important in the synthesis of physostigmine (98). The same conditions were used as in the earlier attempts with nitrobenzene.

\textbf{Scheme 103}

Unfortunately this also resulted in no success with the \textit{para}-substituted nitroaromatic and only the \textit{\alpha}-methylated VNS nucleophile 183 was observed in the \textsuperscript{1}H-NMR spectrum of the crude reaction mixture. A possible problem with the \textit{para}-nitroanisole is the electron-donating nature of the methoxy group.

As an alternative to the VNS/alkylation process, we considered Hartwig’s palladium-catalysed \textit{\alpha}-arylation of esters by forming a silyl ketene acetal 195 and then forming the enolate by treatment with a fluoride source (Scheme 104).\textsuperscript{82} If we could successfully apply this methodology to effect C-arylation of the lactone, we could obtain the same products as the VNS process which could then be protonated and quenched with electrophiles to carry out a diastereoselective alkylation process. This would hopefully allow us to obtain the substrate required to continue with the proposed synthesis of the natural product physostigmine (98).

\textbf{Scheme 104}

The silyl ketene acetal 197 was formed by treatment of the lactone with LiHMDS followed by chlorotrimethylsilane at \(-78^\circ\text{C}\) (Scheme 105). Purification of the product proved to be problematic, so the crude product was used directly in a cross-coupling process with \textit{p}-chloronitrobenzene (Scheme 105).
To probe the reactivity of the system, the silyl ketene acetal 197, P(r-Bu)$_3$, Pd$_2$(dba)$_3$, zinc fluorine and bromobenzene were heated in DMF for 12 hours at 80 °C. The process however also resulted in no success, with the starting materials recovered. 3-Bromo-4-nitroanisole (201) was also used in this method as an alternative electrophile. This was prepared by treatment of 3-bromophenol (199) with sulphuric acid and sodium nitrate (Scheme 106).\(^{159-160}\) The product was then methylated with K$_2$CO$_3$ and methyl iodide to give the 3-bromo-4-nitroanisole (201) in 86% yield.\(^{161}\)

The electrophile 201 was then studied in the cross-coupling of the silyl ketene acetal 197 under Hartwig's conditions (Scheme 107). If this proved successful, it would give us the required substrate to continue with the physostigmine synthesis.

This attempt also resulted in no success with the starting materials being recovered. Silyl ketene acetals of different lactones were also attempted (Scheme 108) as a test to see if the
problem was with the sterically hindered lactone 188. Again this resulted in the starting materials being recovered.

**Scheme 108**

![Scheme 108 Diagram]

An attempt was made to use the enolate generated from a silyl ketene acetal in a $S_{N}Ar$ reaction (Scheme 109) as an alternative method to effect C-arylation of the lactone. This again proceeded without success, with the starting materials recovered. 3-Fluoro-4-nitroanisole was also used as an electrophile in this attempted $S_{N}Ar$ reaction (Scheme 109). This also resulted in the starting materials being recovered.

Buchwald's method of cross-coupling esters with aryl bromides was also attempted as a further alternative for forming a C-3 arylation of the lactone. We chose bromobenzene as our electrophile as a test as there was no successful reactions with a nitroaromatic reported by Buchwald (Scheme 110).[^162] However this method also resulted in recovery of the starting materials.

[^162]: Reference number
Due to the failure of the cross-coupling and SNAr approaches, we wondered if we could use an \( \alpha \)-carbonyloxylactone 210 and decarboxylate to give the required product 211 (Scheme 111). This again would be an alternative route to get through to the substrate we needed to continue with the synthesis of physostigmine. An \( \alpha \)-carbonyloxylactone provides a stabilized enolate similar to that of a malonate which are known to successfully undergo the SNAr process.

Firstly, we needed to know if a malonate substituted at the carbon between the two carbonyl groups would undergo the SNAr process. The commercially available malonate 212 was treated with sodium hydride (1 eq.) in DMF at 0 °C and then 2,4-dinitrofluorobenzene before being allowed to warm to room temperature (Scheme 112). This reaction proceeded in 83% yield.
Due to the success of this reaction we decided to form an α-carbonyloxylactone from the lactone. This was done by treating the lactone 214 with LDA followed by dimethyl carbonate (Scheme 113).\textsuperscript{163} This reaction proceeded in 73\% yield. The product 215 was treated with sodium hydride at 0 °C followed by 2,4-dinitrofluorobenzene and allowed to warm to room temperature (Scheme 113).

**Scheme 113**

\[
\begin{array}{c}
\text{214} \\
\text{1. LDA} \\
\text{2. MeO-CO-Me} \\
\text{215} 73\% \\
\text{1. NaH} \\
\text{2.} \text{NO}^\cdot \\
\text{216} 86\% \\
\end{array}
\]

This reaction proceeded in 86\% yield. The presence of the required product was indicated by a triplet at δ 3.43 (J 8.4 Hz) in the starting material disappearing. Doublets at δ 8.86 (J 2.4 Hz) and 7.64 (J 8.4 Hz) and a double doublet at δ 8.44 (J 2.4 & 8.4 Hz) indicated the presence of the aryl group. We took the product 216 and attempted to decarboxylate using Krapcho conditions (Scheme 114).\textsuperscript{164} The product 216 was heated in a flask at 180 °C containing DMSO, sodium chloride and water.

**Scheme 114**

\[
\begin{array}{c}
\text{216} \\
\text{NaCl/H}_2\text{O/DMSO} \\
\text{217} \\
\end{array}
\]

The required product 217 was not formed in this reaction and no starting materials were recovered. The crude $^1$H-NMR spectrum was no help as it was extremely complicated. We thought that maybe a competing process was taking place as a lactone is a cyclic ester and the C-5 position is unhindered it could be susceptible to attack by the chloride which could then ring open the lactone (eg 218$\rightarrow$219) (Scheme 115). Unfortunately no products could be isolated by column chromatography. Use of LiI instead of water and NaCl resulted in no improvement to the process. We thought that the problem could be avoided, however, if the lactone was substituted at the γ-position which would undergo the competing process more slowly.
\( \gamma \)-Methyl-\( \gamma \)-butyrolactone 220 was treated with LDA followed by dimethyl carbonate (Scheme 116). This reaction proceeded in 75% yield. A 1:1 mixture of diastereoisomers was observed. This mixture was treated with sodium hydride at 0 °C followed by 2,4-dinitrofluorobenzene to give 223 (Scheme 116). However the stereochemistry of the lactone was not assigned due to the chiral centre being destroyed in the next step. Nevertheless it is highly likely that the aryl group is trans to the methyl group.

Scheme 116

\[
\begin{align*}
\text{Scheme 115} & \\
\text{Scheme 116} & \\
\text{Scheme 117} &
\end{align*}
\]

The reaction proceeded in 80% yield. Only one product 221 was observed. The product 221 was then treated under Krapcho conditions to undergo decarboxylation (Scheme 117). Unfortunately, however, this process did not occur cleanly, with the \(^1\)H-NMR spectrum of the crude reaction product being extremely complex.

Scheme 117

A further alternative method for forming the required product was treating the enolate of an ester with an epoxide. Despite there being few examples of ester enolates reacting with epoxides in the literature we were hopeful that the nitrophenyl acetates would be more successful due to the similar pK\(_a\) of malonates. Malonates readily undergo reactions with epoxides.\(^{165}\) Isopropyl 2-nitrophenylacetate (225) was treated with sodium hydride at 0 °C to
form the enolate followed by an electrophilic quench with allyl glycidyl ether as a simple test. The epoxide was chosen as it was readily available at hand (Scheme 118). Unfortunately, however this resulted in the starting materials being recovered. The reaction was tried several times with heating but all with no success.

Scheme 118

Due to this lack of success we tried treating 4-nitrophenylacetic acid (166) with 2 equivalents of base, followed by treatment with the allyl glycidyl ether 226 (Scheme 119) This was tried due to precedent of carboxylic acids reacting with epoxides with 2 equivalents of base to produce a γ-lactone. This however also resulted in the starting materials being recovered.

Scheme 119

We wondered if oxidative nucleophilic substitution of hydrogen would provide an alternative process to get through to the same products. γ-Phenyl-γ-butyrolactone (160) was treated with potassium tert-butoxide and 4-chloronitrobenzene followed by DDQ (Scheme 120). ONSH had already been used in the synthesis of physostigmine using the enolate of N-methyl pyrrolidinone as mentioned previously. However again this resulted only in the recovery of the starting materials.

Scheme 120
We decided to try a chiral lactam as a VNS nucleophile due to the success with the lactams in the previous chapter. This would hopefully give us a valuable method for forming α-aryl quaternary centres in high selectivity, which as mentioned previously possesses a scaffold with several points of diversity amenable to convenient derivatization thereby providing an important peptide-like scaffold. The chiral lactam was made from commercially available L-pyroglutamic acid (230) (Scheme 121) according to the method of Thottathil.167

**Scheme 121**

The pyroglutamic acid 230 was esterified with ethanol and sulphuric acid. The ester 231 was then reduced to the primary alcohol 232 with sodium borohydride. The alcohol 232 was protected with trityl chloride, a bulky group required to shield one side of the lactam in the asymmetric VNS alkylation process. Triethylamine and trityl chloride were added to a solution of 5-hydroxymethylpyrrolidin-2-one (232) in dichloromethane. The amide nitrogen was then methylated with sodium hydride and methyl iodide at 0 °C to give the required product 233. To prove no racemisation had occurred at the chiral centre the aD was measured (+28.4 c = 1.71 in ethanol) and compared with the literature value (+28.9 c = 1.71 in ethanol).168

The lactam 234 was then treated with LDA (2 eq) followed by phenyl disulfide (1 eq.) and DMPU (1 eq.) to give the VNS nucleophile 235 (Scheme 122). This process occurred in 55% yield with only the one diastereoisomer observed. The stereochemistry of the lactam was not assigned due to the chiral centre being destroyed in the next step. Nevertheless it is highly likely that the thiophenyl group is trans to the trityl group. The presence of the desired product was indicated by a presence of a triplet at δ 4.00 (J 8.3 Hz). This was then used in the VNS/alkylation process with sodium hydride and nitrobenzene (Scheme 123). The required product was not observed in the crude 1H-NMR spectrum with only nitrobenzene and the α-methylated VNS nucleophile observed. Potassium tert-butoxide was tried as a base but also with no success.
An alternative lactam was also tried in the VNS/alkylation process. This was formed by treatment of succinimide with methylmagnesium iodide followed by treatment of the intermediate with sodium cyanoborohydride (Scheme 123). \(^{169-170}\)

**Scheme 123**

\[
\begin{align*}
1. \text{PhMgl} & \quad \text{NaH} \\
2. \text{NaCNBH}_3 & \quad \text{CH}_3\text{I}
\end{align*}
\]

N-Methylation of the resulting product 238 with sodium hydride and methyl iodide at 0 °C gave 239. Treatment of 239 with LDA (2 eq.) followed by phenyl disulfide (1 eq.) and DMPU (1 eq.) at -78 °C gave 240 (Scheme 124). A mixture of the two diastereoisomers were formed which proved difficult to separate by column chromatography. The lactam 240 was used in the VNS/alkylation process (Scheme 124). However this resulted in no VNS product, with nitrobenzene and the α-methylated lactam 241 being recovered.

**Scheme 124**

**Summary and Conclusion**

In conclusion, the one pot asymmetric VNS alkylation was developed successfully using Dihydro-5-phenyl-3-(phenylthio)(3H)furan-2-one (161) as the VNS nucleophile. Significant diastereoselectivities were observed using 161 as the VNS nucleophile. The method provided
diastereoselectivities of greater than 7:1. The ortho-selective VNS reaction was successful using 167 and p-chloronitrobenzene, this was important as it gave us hope that the proposed route to physostigmine could be carried out using this method.

Attempting to use a silyl protected lactone resulted in deprotection of the alcohol and loss of the lactone in the work up. Changing to a trityl group also resulted in no success. We considered the possibility that in forming the φH-adduct the large PhS group is forced cis to the large protecting group making the reaction highly unfavourable (Scheme 102). A possible solution would be to use a smaller VNS leaving group or another solution would be to use a smaller alcohol protecting group although this would probably compromise on the level of diastereoselectivity. The advantage of the PhS VNS leaving group was that it was easy to add to the lactone. An α-chloro lactone is more difficult to form.

We concluded that due to the difficulties associated with getting the conditions right for the VNS reaction an alternative process for the VNS step might be more favourable. We considered Hartwig’s cross-coupling of silyl ketene acetals, Buchwald’s cross-coupling of esters, the use of an α-carbonyloxylactone followed by decarboxylation and finally treating the enolate of an ester with an epoxide. Hartwig’s cross-coupling of silyl ketene acetals and Buchwald’s method for cross-coupling of esters both resulted in the recovery of starting materials. The Krapcho decarboxylation of an α-carbonyloxylactone resulted in a complicated 1H-NMR spectrum with a possible competing process occurring (Scheme 115). The asymmetric VNS/alkylation of lactams was also studied but again with no success. Clashes of the large PhS group with the protecting group could again be the problem when the PhS group is forced cis on forming the φH-adduct.

We conclude that in our efforts to obtain high diastereoselectivities that we under estimated the sensitivity of the VNS reaction to steric effects, and should not have used such a bulky directing group. We should have started with a much smaller alcohol protecting group. Future work will be to investigate a smaller VNS leaving group in the reaction to try and avoid the problem of a steric clash between the VNS leaving group and the bulky protecting group (Scheme 102) and also try different alcohol protecting groups in the reaction.
Chapter 6
6.1 Synthesis of Diarylmethanes

Diarylmethanes and diarylacetates are extremely useful synthetic intermediates\textsuperscript{173-5} and the diarylmethyl motif is found in many pharmacologically important agents\textsuperscript{176-9} such as Tolterodine (242) and Nomifensine (243) (Figure 11). A versatile route to this important scaffold incorporating several points of diversity is potentially useful.

Figure 11

A synthesis of (p-nitroaryl)diarylmethanes via VNS of hydrogen has been reported by Katritzky (Scheme 125).\textsuperscript{180} (Diarylmethyl)benzotriazoles 245 were prepared from benzotriazole and diarylmethanols 244 in the presence of a catalytic amount of \textit{p} toluenesulfonic acid (PTSA) in benzene with azeotropic removal of water. In these compounds, the benzotriazoyl moiety serves as a carbon-stabilizing and leaving group, in the course of the VNS reaction. (Diarylmethyl)benzotriazoles 245 were reacted with a series of \textit{o}- and \textit{m}-substituted nitrobenzenes. An equimolar mixture of 245 and the nitroarene were added to a solution of potassium \textit{tert}-butoxide in dry THF to give a deep red reaction mixture. Upon quenching with saturated ammonium chloride solution, (nitroaryl)diarylmethanes 248 were obtained.

Scheme 125

A synthesis of (p-nitroaryl)diarylmethanes via VNS of hydrogen was also reported by Makosza (Scheme 126).\textsuperscript{181} This process used the carbanions of benzhydryl sulfides 249. These reacted
with nitroarenes in the usual way to produce $\sigma^H$-adducts 250 from which base induced $\beta$-elimination can take place to give the VNS product 252. The benzhydryl sulfides 249 were prepared from the reaction of diarylcchloromethanes 253 with $p$-chlorothiophenol (254) in $K_2CO_3/acetone$ in yields close to quantitative (Scheme 127). The $p$-chlorophenyl sulfides 249 were used as the VNS nucleophile due to $p$-chlorophenylthiolate being a better leaving group than thiophenolate ($pK_a (H_2O)$ is 10 compared to the $pK_a$ $p$-chlorophenylthiolate is 8.1). 182

Scheme 126

Scheme 127

6.2 The Synthesis of Diarylacetates via a Sequential VNS-$SNAr$ Three Component Coupling Reaction

It has been shown that the VNS nucleophiles exhibit reactivity similar to that of the malonate anion. This is not surprising given that other properties such as acidity are similar. For example, the $pK_a$ (DMSO) of ethyl $p$-nitrophenylacetate is 15.1 183 while that of diethyl malonate is 16.4. 184 Malonate is an excellent nucleophile for many $SNAr$ reactions 185-6 and some examples of the use of nitrophenylacetates in the $SNAr$ reaction have been reported. 187-9

We were therefore hopeful that the anion derived from the VNS reaction (Scheme 128), would react with activated aryl electrophiles such as 255 to give products such as 256.

Scheme 128
The post VNS anion was generated by addition of nitrobenzene and ethyl 2-chloropropionate in DMF to a suspension of sodium hydride in DMF at -50 °C. This generated the usual brightly coloured intermediate, which after warming to room temperature was cooled back to -50 °C then was quenched with 2,4-dinitrofluorobenzene. The desired diarylacetaate 257 was isolated after column chromatography in 77% yield (Scheme 129). The two doublets at δ 8.22 and 7.68 (J 9.0 Hz) in the $^1$H-NMR spectrum indicated the presence of a 1,4-disubstituted aryl group. Doublets at δ 8.80 (J 2.4 Hz) and 7.16 (J 8.7 Hz) along with a double doublet at δ 8.30 (J 2.4 and 8.7 Hz) indicates the presence of a 1,2,4-trisubstituted aryl group. The methyl group appears as a singlet at δ 2.26 indicating that it was attached to a quaternary centre.

Scheme 129

To investigate whether this was a general process the reaction was repeated with several other electrophiles under the same conditions as described. The electrophiles were chosen due to their highly reactive nature and because they were commercially available.

Scheme 130

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>257a</td>
<td>CF₃</td>
<td>NO₂</td>
<td>73%</td>
</tr>
<tr>
<td>257b</td>
<td>NO₂</td>
<td>NO₂</td>
<td>77%</td>
</tr>
<tr>
<td>257c</td>
<td>NO₂</td>
<td>CN</td>
<td>88%</td>
</tr>
<tr>
<td>257d</td>
<td>NO₂</td>
<td>CF₃</td>
<td>89%</td>
</tr>
</tbody>
</table>

Diarylacetaate 257a was formed using the conditions described above (Scheme 130). The seven aromatic protons representing the two aryl groups appear as a multiplet (δ 8.20-8.23) along with doublets at δ 7.72 (J 8.4 Hz) (H-5"), 7.67 (J 9.0 Hz) (H-2' & H-6') and 7.06 (J 8.4 Hz) (H-6†). The methyl group appears as a singlet at 2.25 indicating the presence of a quaternary centre.

Diarylacetaate 257c was formed in 88% yield using slightly different conditions, instead of using just the one equivalent of ethyl 2-chloropropionate increasing to two equivalents to
increase the yield based on nitrobenzene. This was discovered by previous research in the Lawrence group. The excess nucleophile undergoes self condensation. It was also found that there was no need to cool the reaction mixture to -50 °C for the electrophilic quench. Cooling to 0 °C was sufficient. Diarylacetae 262d was formed in 89% yield also using two equivalents of ethyl 2-chloropropionate and cooling to 0 °C for the electrophilic quench. The 1H-NMR spectra for both these compounds were consistent with what was observed in diarylacettes 257a and 257b. The products were characterized in foil (see Experimental section).

It was decided to investigate different nucleophiles in the VNS-\textit{S\textsubscript{N}Ar} process. Methyl 2-chloropropionate was investigated as the nucleophile as it was commercially available (Scheme 131).

\begin{scheme}
1. NaH, DMF
\[
\text{Me}_2\text{C} \overset{\text{CO}_2\text{Me}}{\text{Cl}} \rightarrow \text{Me}_2\text{C} \overset{\text{CO}_2\text{Me}}{\text{Cl}} \rightarrow \text{Me}_2\text{C} \overset{\text{CO}_2\text{Me}}{\text{Cl}}
\]

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>257e</td>
<td>CF\textsubscript{3}</td>
<td>NO\textsubscript{2}</td>
</tr>
<tr>
<td>257f</td>
<td>NO\textsubscript{2}</td>
<td>NO\textsubscript{2}</td>
</tr>
<tr>
<td>257g</td>
<td>NO\textsubscript{2}</td>
<td>CN</td>
</tr>
<tr>
<td>257h</td>
<td>NO\textsubscript{2}</td>
<td>CF\textsubscript{3}</td>
</tr>
</tbody>
</table>

Diarylacetae 257e was formed in 69% yield using one equivalent of methyl 2-chloropropionate. The reaction was also cooled to -50 °C for the electrophilic quench. One of the two doublets in the 1H-NMR spectrum representing the 1,4-disubstituted aryl group overlaps with one of the signals from the second aryl group to give a multiplet (δ 8.19-8.23). The other doublet of the 1,4-disubstituted aryl group appears at δ 7.68 (J 8.9 Hz). Doublets at δ 7.72 (J 8.3 Hz) and 7.09 (J 8.3 Hz) represent the other two protons on the second aryl group. The methyl group appears as a singlet at δ 2.25 indicating the presence of a quaternary centre.

The process was applied to 257f, 257g and 257h. The products were obtained in good yields (Scheme 7). Diarylacetae 257f was formed using one equivalent of methyl 2-chloropropionate and the electrophilic quench at -50 °C. Diarylacettes 257g and 257h were formed using two equivalents of methyl 2-chloropropionate and the electrophilic quench carried out at 0 °C. The products were characterized in full (see experimental section).

The next nucleophile investigated was methyl 2-chlorobutanoate (259) to give us access to butanoates as well as propionates. This was prepared by esterification of chlorobutyric acid (258) (Scheme 132).
Methyl 2-chlorobutanoate was used in the VNS-S_N_Ar process with a series of electrophiles (Scheme 133). The process was used to make 257i, 257j and 257k. The products were obtained in good yields (Scheme 133). Diarylacetate 257i was formed using one equivalent of methyl 2-chlorobutanoate and the electrophilic quench at 0 °C. 257j and 257k were formed using two equivalents of methyl 2-chlorobutanoate under the same conditions. The products were characterized in full (see Experimental section).

**Scheme 133**

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>257i</td>
<td>CF₃</td>
<td>NO₂</td>
<td>60%</td>
</tr>
<tr>
<td>257j</td>
<td>NO₂</td>
<td>NO₂</td>
<td>80%</td>
</tr>
<tr>
<td>257k</td>
<td>NO₂</td>
<td>CF₃</td>
<td>69%</td>
</tr>
</tbody>
</table>

The results clearly indicate that the process is general and efficient. The efficiency of the S_N_Ar process is high, as the yields are close to that expected for protonation of the post-VNS anion. The use of activated arenes allows the S_N_Ar reaction to proceed conveniently at ambient temperature, avoiding the need for heating. Heating can be problematic for sodium hydride in DMF when the reaction is performed on a large scale. To overcome the problems associated with the NaH/DMF base/solvent system, we next showed the process has potential for scale up using potassium tert-butoxide as the base (Scheme 134).

**Scheme 134**

Diarylacetate 257b was formed in 57% yield using potassium tert-butoxide as the base with one equivalent of ethyl 2-chloropropionate. The reaction was cooled to -50 °C and allowed to warm to -20 °C before cooling back to -50 °C for the electrophilic quench. It was important to
use a maximum of two equivalents of potassium tert-butoxide and a slight excess of the electrophile as a side reaction also took place with the tert-butoxide anion reacting with the electrophile, as indicated by LC-MS (Scheme 135). Diarylacate 257d was formed in 69% yield using the same conditions as described earlier.

Scheme 135

The process is not limited to the use of fluoronitroarenes. 2,4-Dinitrochlorobenzene was used in place of 2,4-dinitrofluorobenzene to give 257b in 69% yield (Scheme 136). This reaction was carried out with one equivalent of ethyl 2-chloropropionate and cooling to -50 °C. Similarly the VNS-SNAr reaction with 4-chloro-3-nitrobenzonitrile as the electrophile gave the required product 2571 in 72% yield using one equivalent of ethyl 2-chloropropionate and cooling to -50 °C. The doublets at δ 8.15 and 7.58 (J 9.0 Hz) in the 1H-NMR spectrum indicate the presence of a 1,4-disubstituted aryl group. The doublets at δ 8.17 (J 1.8 Hz) and 6.97 (J 8.7 Hz) along with a double doublet at δ 7.66 (J 1.8 & 8.7 Hz) represent the three protons on the second aryl group. The methyl group appears as a singlet at 2.16 indicating the presence of a quaternary centre.

Scheme 136

The less activated 4-fluoronitrobenzene proved sufficiently reactive to enter the VNS-SNAr process to give 257m in 74% yield (Scheme 136). This was performed using two equivalents of ethyl 2-chloropropionate and cooling to 0 °C for the electrophilic quench. The two aryl groups were identical so the presence of doublets at δ 8.10 and 7.33 (J 8.9 Hz) in the 1H-NMR spectrum when compared to the integration of the methyl group indicates the presence of two
1,4-disubstituted aryl groups. The methyl group appears as a singlet at δ 1.93 indicating that the electrophilic quench had been successful.

Scheme 137

Scheme 137

The use of 2-fluoronitrobenzene as the electrophile did not result in the required product. Instead the post VNS anion underwent a coupling reaction with another post VNS anion to give the dimer 264 as a 1:1 mixture of diastereoisomers presumably by a radical pathway (Scheme 138). This process has been observed by previous work in the group. The 2-fluoronitrobenzene (263) must be acting as an oxidising agent. The doublets at δ 8.01 7.92, 7.02 and 6.99 (J 8.8 Hz) in the ¹H-NMR spectrum indicated the presence of two 1,4-disubstituted aryl groups. The multiplet (δ 4.02-4.21) and two triplets at 1.15 and 1.17 (J 7.4 Hz) represent the two ethyl groups. Singlets at δ 1.88 and 1.60 represent the other two methyl groups. As far as we can tell this is a novel process.

Scheme 138

Scheme 138

Branched esters behaved well in the reaction although the reaction only proceeded with potassium tert-butoxide as base and not sodium hydride. The isopropyl ester 266 was prepared by esterification of 2-chloropropionic acid in 69% yield (Scheme 139).
The isopropyl ester was used in the VNS process with nitrobenzene and 4-fluoro-3-nitrobenzotrifluoride as the electrophile (Scheme 140). Using sodium hydride as the base produced no VNS product with nitrobenzene being recovered. Using potassium tert-butoxide as the base and keeping the temperature of the reaction mixture between -50 °C and -20 °C gave the VNS product 268 in 64% yield.

Scheme 140

One of the two doublets in the $^1$H-NMR spectrum representing the 1,4-disubstituted aryl group overlaps with one of the signals from the second aryl group to give a multiplet ($\delta$ 8.13-8.16). The other doublet of the 1,4-disubstituted aryl group appears at $\delta$ 7.60 ($J$ 9.0 Hz). A double doublet at $\delta$ 7.64 ($J$ 1.7 and 8.5 Hz) and a doublet at 7.00 ($J$ 8.5 Hz) represent the other two protons on the second aryl group. The methyl group appears as a singlet at $\delta$ 2.16 indicating the presence of a quaternary centre.

The tert-butyl ester 270 was obtained in 52% yield by treatment of 2-chloropropionyl chloride (269) with tert-butanol and triethylamine (Scheme 141). The tert-butyl ester 270 was used in the VNS-S$_{N}$Ar process (Scheme 142) with potassium tert-butoxide as the base and using conditions identical to those used with the isopropyl ester nucleophile. The required VNS product was formed but we had trouble removing excess 2,4-dinitrofluorobenzene from the product.

Scheme 141
To remove this excess 2,4-dinitrofluorobenzene, we considered the use of a scavenger. We thought that a polymer-supported amine would be successful. As a test, we added benzylamine (1 eq.) to a solution of 2,4-dinitrofluorobenzene in ethyl acetate (Scheme 143) and left the solution to stir overnight. The reaction produced the required product 273 as the HF salt of the amine in quantitative yield.

As this test was successful, the contaminated VNS product 271 was dissolved in a small amount of ethyl acetate and added to a small filter syringe containing poly(styrene-co-divinylbenzene)amino methylated polymer (0.75 g) (2.0-3.5 mmol/g) and the mixture were shaken for 24 hours (Scheme 144). The solution was filtered and the solvent removed on a rotary evaporator to leave the pure product 271 in 61% yield.

To further expand the scope of this reaction we attempted to use activated pyridines and pyrimidines in the VNS-S_NAr process (Scheme 145). Pyridines and pyrimidines are important heterocyclic compounds. Several examples of these class of compounds are well known as important biologically active compounds for example 2-(benzylamino)pyrimidine is an antihistaminic agent. 2-Chloro-3-nitropyridine (272) and 2-chloropyrimidine (274) were
chosen as they were commercially available and known to undergo the S\textsubscript{N}Ar process. For example 2-chloropyrimidine readily reacts with thiophenolates, phenolates and anilines.\textsuperscript{195} These examples were chosen to extend the methodology so that heterocyclic rings could be utilized, which are important in many drugs. There were also literature examples of these electrophiles undergoing C-arylation with enolates.\textsuperscript{196-8} The bright purple colour associated with the post VNS anion was observed as expected, but the electrophilic quench with both electrophiles did not occur at room temperature. Careful heating of the reaction mixture to 50 °C also resulted in no success. In both cases the protonated post-VNS anion (ethyl 4-nitrophenylpropionate) was recovered.

**Scheme 145**

To provide some examples of the ortho selectivity of the VNS-S\textsubscript{N}Ar process, chloromethyl phenyl sulfone was chosen as the VNS nucleophiles, and p-chloronitrobenzene as the substrate (Scheme 146 and Table 9).

**Scheme 146**
Table 9. Yields of Product Sulfones

<table>
<thead>
<tr>
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<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>276a</td>
<td>Cl</td>
<td>NO₂</td>
<td>CF₃</td>
<td>75</td>
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<tr>
<td>276b</td>
<td>Cl</td>
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<td>NO₂</td>
<td>74</td>
</tr>
<tr>
<td>276c</td>
<td>Cl</td>
<td>CN</td>
<td>NO₂</td>
<td>74</td>
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<tr>
<td>276d</td>
<td>Cl</td>
<td>CF₃</td>
<td>NO₂</td>
<td>75</td>
</tr>
<tr>
<td>276e</td>
<td>CF₃</td>
<td>NO₂</td>
<td>CF₃</td>
<td>79</td>
</tr>
<tr>
<td>276f</td>
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<td>276g</td>
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<tr>
<td>276h</td>
<td>CF₃</td>
<td>CF₃</td>
<td>NO₂</td>
<td>78</td>
</tr>
</tbody>
</table>

Sulfone 276a was obtained in 75% yield by adding a mixture of chloromethyl phenyl sulfone (1 eq.) and p-chloronitrobenzene in DMF to a suspension of sodium hydride in DMF at 0 °C. This produced a bright purple solution which was allowed to warm to room temperature, stirred for 30 minutes and then cooled back to 0 °C for the electrophilic quench with 4-fluoro-3-nitrobenzotrifluoride. The doublets at δ 8.53 (J 8.3 Hz), 8.23 (J 1.3 Hz) and double doublet at δ 8.02 (J 1.3 and 8.3 Hz) in the ¹H-NMR spectrum indicate the presence of a trisubstituted aryl group. The doublets at 8.30 (J 2.2 Hz), 7.93 (J 8.8 Hz) and double doublet at 7.55 (J 2.2 & 8.8 Hz) indicate the presence of a second trisubstituted aryl group. The mono substituted aryl group was represented by a doublet at δ 7.69 (J 7.6 Hz) and triplets at δ 7.64 (J 7.6 Hz) and 7.48 (J 7.6 Hz). The benzylic proton appears as a singlet at δ 7.40.

The same process was then applied to a range of electrophiles and nitroarenes, to produce 276b-h in good yield (see Table 2). The nitroarenes p-chloronitrobenzene and p-trifluoromethyl nitrobenzene were chosen as the VNS substrates as they were both commercially available and it is known that they undergo the VNS process exclusively at the ortho position with no competitive S₅Ar observed. The products were characterized in full (see Experimental section).

6.3 Formation of Oxindoles

The oxindole moiety is a common motif in many alkaloids and is also found in a number of marketed drugs (Figure 12). Ziprasidone (277) is a serotonin and dopamine antagonist, and effective as an antipsychotic drug. Many currently available antipsychotropic drugs have the side effect of inducing significant weight gain, which is distressing and stigmatising to
patients and increases the risk of cardiovascular complications, but ziprasidone avoids this side effect.

**Figure 12**

![Chemical structures of Ziprasidone and Ropinirole](image)

Ziprasidone™ (277) Ropinirole™ (278)

Parkinson's disease causes the brain to lose dopamine, which results in stiffness and rigidity of the muscles, slowness in movement and the tremor of the arms and legs. Levodopa, the main treatment for the disease, is metabolised to the brain as dopamine. The brain's ability to metabolise and store levodopa diminishes after time and it becomes more dependant on the external supply of levodopa. Eventually most patients experience fluctuations when the medication is working and when it is not working in the body.

Ropinirole (278) is a direct dopamine receptor agonist that works by minimising the actions of dopamine in the brain and thereby reducing the symptoms of Parkinson's disease.

Because of the very potent and diverse biological activity exhibited by various oxindole derivatives, this heterocyclic system has attracted considerable attention in chemistry, biology and medicine.

Previous methods for the synthesis of the oxindole motif include Lewis acid mediated cyclization of α-haloacetanilides, cyclization of (o-aminophenyl)acetic acid derivatives and the Gassman procedure (Scheme 147). In the Gassman procedure, 3-methylthio-2-oxindoles are produced. The methodology of choice is dependent on the nature of the aromatic ring. When electron withdrawing groups are present, the oxindole can be synthesized by treatment of the aniline with a methylthioacetate ester to furnish an azasulfonium salt (Scheme 147, Method A). Electron-donating groups destabilize the intermediate 281, and thus give diminished yields of the oxindole 282. A second method of generation of this salt by reaction of the chlorosulfonium salt 280 with an appropriate aniline (Scheme 147, Method B) gives better yields of the 3-methylthio-2-oxindoles 282.
Buchwald reported a novel variant of the Friedel-Crafts procedure using palladium catalysed C-H functionalisation, avoiding the need for harsh reaction conditions (Scheme 148). The combination of catalytic amounts of palladium acetate, 2-(di-tert-butylphosphino)biphenyl (284) as a ligand, triethylamine as base and α-chloroacetanilides (283) can be smoothly converted to oxindoles in good yields with high levels of regioselectivity. The process is most likely initiated by oxidative addition of the α-chloroamide to Pd(0), resulting in a Pd(II) enolate. The formation of the carbon-carbon bond may proceed by an electrophilic aromatic substitution to give a six-membered palladacycle, which undergoes reductive elimination to afford the product oxindole 285 and regenerate the Pd(0) species.

One of the most attractive and general methods for the synthesis of oxindoles is the reductive cyclization of α-nitroaryl carbonyl compounds (Scheme 149). Reduction of the nitroarene 286 to aniline 287 furnishes a nucleophilic nitrogen atom. This can then attack the electrophilic ester to promote cyclization to the oxindole 288.
This reaction has been one of the oldest methods for the synthesis of oxindoles even though the availability of the starting materials has been limited. Rajanbabu reported a synthesis of oxindoles based on an oxidative nucleophilic substitution of hydrogen (ONSH) reaction followed by reductive cyclization (Scheme 150). Addition of the silyl ketene acetal 289 to the nitro-aromatic in the presence of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) followed by oxidation of the resulting σH-adduct gave an α-nitroarylester 290. Cyclization to the oxindole 291 occurred after hydrogenation of the nitro group of 290.

The diarylacettes 257a-m synthesized by our VNS-SNAr process with an ortho-nitro group provided the opportunity for formation of 3,3-substituted oxindoles by reduction of the nitro group. This was achieved by hydrogenation (Method A)\textsuperscript{204} or Sn(II)-mediated reduction\textsuperscript{205} (Scheme 151).
Oxindole 292a was formed (method A) by adding 5% Pd/C to a solution of 257b dissolved in an ethyl acetate/acetic acid mixture in a multi-Parr reaction vessel. While stirring, the mixture was purged with nitrogen and then hydrogen. The reaction mixture was then left stirring under a hydrogen atmosphere (50 psi) for 16 hours. The product was then filtered through a celite plug and the solvent removed on a rotary evaporator to leave the crude product. The crude product was then washed with chloroform to leave the pure product in 54% yield. The doublets at δ 7.05 and 6.70 (J 8.6 Hz) in the 1H-NMR spectrum indicate the presence of a 1,4-disubstituted aryl group. The doublets at δ 6.87 (J 8.0 Hz) and 6.56 (J 2.0 Hz) along with a double doublet at δ 6.46 (J 2.0 and 8.0 Hz) indicate the presence of a trisubstituted aryl group. The methyl group appears as a singlet at δ 1.66.

As an alternative method (method B), the ester was dissolved in an ethanol:ethyl acetate 4:1 mixture. Tin(II) chloride dihydrate and a few drops of hydrochloric acid were added and the mixture was heated under reflux for 36 hours. Following an aqueous work up the solvent was removed on a rotary evaporator to leave the crude product. Washing the crude product with chloroform left the pure product 292a in 71% yield.

Both methods were applied to 257a and 257l to give the products 292b and 292c. Both methods led to the N-hydroxyoxindole being exclusively formed. This was formed because cyclisation of the hydroxylamine was faster than reduction to form the aniline. We found that under the hydrogenation conditions the acid was crucial to forming exclusively the N-hydroxyoxindole. Without the acid, a mixture of the oxindole and the N-hydroxyoxindole occurred.

Other nitro groups present in the molecules were also reduced under these conditions providing additional points for further functionalization and incorporation of extra diversity. The ester 257b cleanly gives the oxindole 292a by both methods of reduction of the nitro group. However, reduction of both 257a and 257l gave the 1-hydroxy-oxindoles 292b and 292c. It seems that the presence of the electron-withdrawing group impedes reduction of the intermediate hydroxylamine such that cyclization to form the hydroxyoxindole occurs faster.
The formation of the oxindoles involves first reduction of the less hindered nitro group at position 4. Sodium disulfite$^{179}$ has been used to reduce similar nitro esters to oxindoles. However when applied to diarylacettes $257a$ & $I$ the starting materials remained untouched.

**Summary and Conclusion**

In conclusion we have therefore shown that intriguing one-pot VNS$_{Ar}$-SnAr combination of two types of nucleophilic substitution reaction can be integrated to provide an excellent synthesis of diarylacette derivatives. The process has been shown to tolerate activated fluoro electrophiles bearing electron withdrawing groups such as cyano, nitro and trifluoromethyl. Chloro electrophiles have also been shown to undergo the SnAr process with the post VNS anion. The use of 2-fluoronitrobenzene however the post VNS anion underwent a homo coupling reaction to give a dimmer (264) as a 1:1 mixture of diastereoisomers presumably by a radical pathway. The 2-fluoronitrobenzene must be acting as an oxidizing agent.

Unfortunately our attempts to use activated pyridines and pyrimidines met with no success with just the VNS product being formed, the post VNS anion did not undergo the SnAr process.

Due to the problems associated with the sodium hydride/DMF base solvent system a potassium tert-butoxide/DMF base solvent system was shown to be acceptable so the process could be conveniently carried out on a large scale. Due to a side with the tert-butoxide anion reacting with the electrophile an excess of the electrophile is required. In the case of 271 the excess electrophile could not be separated from the product. We therefore developed a process to scavenge for the excess electrophile using poly(styrene-co-divinylbenzene)amino methylated polymer.

The VNS/SnAr process was shown to proceed with chloromethyl phenyl sulfone as the VNS nucleophile, para-substituted nitroarenes and aryl electrophiles. This provided examples of the ortho selectivity of the VNS-SnAr process.

The diarylacettes $257a-m$ provide convenient access to the oxindole motif by reductive cyclization of the nitrogroup. Reduction of the nitro group proceeded of hydrogen (50 psi) over a palladium on carbon catalyst and also using a tin(II)chloride dihydrate and acid. Cyclisation then occurred to produce the required oxindole or the $N$-hydroxy oxindole. The latter being formed because cyclisation of the $N$-hydroxylamine occurred faster than reduction of the $N$-hydroxylamine to the aniline. The only product to go to the required oxindole was $257b$ which had a second nitro group present on the second aromatic ring. This would presumably be reduced before the nitro group undergoing the cyclisation due to it being unhindered. As cyclisation the nitro group would be present as the aniline, so therefore an
electron donating group. It seemed that the ring with electron withdrawing groups give the \(N\)-hydroxyoxindole while those with an electron donating group give the required oxindole. Future work would be to adapt the conditions of the reductive cyclization so that we could get through to the oxindole without the need to reduce the hydroxyoxindole. Possible options include changing the hydrogenation catalyst or finding an additional method for reduction of nitro groups.
Chapter 7
7.1 Cross-coupling of Nitrophenylacetates

The VNS-SnAr process covered in Chapter 6 provided a convenient one step process for the formation of diaryl acetates and sulfones. The process is limited to the use of an electron-deficient arene as the electrophile. The least electron-deficient electrophile which was successfully used was \( p \)-fluoronitrobenzene, which only has one electron-withdrawing group in addition to the leaving group. Electron-rich electrophiles can not be used in this process.

We considered the possibility that the VNS process could be extended to a VNS cross-coupling process (Scheme 152). This would give the opportunity to add electron-rich aromatic rings to the post-VNS anion.

Scheme 152

![Scheme 152](image)

There are very few examples of nitro compounds in transition metal-catalysed cross-coupling reactions. The area of cross-coupling in organic synthesis has been reviewed by Prim\(^\text{206}\), Miura\(^\text{207-8}\) and Hartwig\(^\text{209}\). One of the few examples was carried out by Miura\(^\text{210}\) who reported that \( p \)-nitrotoluene could effectively react with aryl bromides at its benzylic position in the presence of catalytic amounts of Pd(\( \text{OAc} \))\(_2\) and PPh\(_3\) with cesium carbonate as a base to give the corresponding mono and/or di-arylated products 293 and 294 (Scheme 153).

Scheme 153

![Scheme 153](image)

Palladium-catalysed coupling of esters and derivatives was first carried out in the groups of Buchwald\(^\text{162}\) and Hartwig\(^\text{79}\). The synthesis of \( \alpha \)-aryl esters and their derivatives is extremely important in the synthesis of useful pharmaceutical products. The \( \alpha \)-aryl carboxylic acid structure is of particular interest as it forms part of the structure of several marketed drugs such as Ibuprofen, Naproxen and Ketoprofen (Figure 13). These compounds have anti-inflammatory and analgesic properties.
The palladium-catalysed α-arylation of ketones was reported in 1997 by the groups of Buchwald,\textsuperscript{75} Hartwig\textsuperscript{79} and Miura.\textsuperscript{211} Buchwald subsequently reported a significant improvement on the initial system based on the use of electron rich, bulky o-biphenyl phosphines 114, 296 and 297 (Figure 14).\textsuperscript{78}

This catalyst system demonstrated a good functional group tolerance and a high selectivity for ketones with two enolizable positions where the less substituted position is arylated. Buchwald also reported an asymmetric version of the ketone arylation system using a Pd/(S)-BINAP catalyst (298→299) (Scheme 154)\textsuperscript{76}.

Buchwald took the conditions for the ketone arylation to explore the palladium-catalysed arylation of esters. The initial attempts using 1-bromo-4-tert-butylbenzene with tert-butyl acetate using NaHMDS and a catalyst derived from 295 and Pd(OAc)$_2$ gave a mixture of mono and di-arylated products 300 and 301 along with significant amounts of the Claisen product 302 (Scheme 155). No nitro-containing substrates were included in this protocol.
To search for better conditions, a number of reaction variables were tried including temperature, base and ligands. It was found that with a combination of 114 as the ligand, LiHMDS as base and toluene as the solvent it was possible to carry out the reaction at room temperature which suppressed the formation of the diarylated product (Scheme 156). The limitation with this method is the necessity to use 2.3 equivalents of ester and 2.5 equivalents of base to affect complete conversion of the aryl bromide.\textsuperscript{162}

Hartwig also reported a procedure for the palladium-catalysed $\alpha$-arylation of esters\textsuperscript{212} using palladium catalysts ligated by P(t-Bu)$_3$ or the hindered carbene precursor SiPr (304) (Figure 15) in the presence of 2 equivalents of LiHMDS or NaHMDS. Reactions of tert-butyl acetate or tert-butyl propionate with a range of aryl bromides proceeded at room temperature with fast rates and high selectivity for monoarylation. No nitro groups were included in this protocol however.

Use of the stronger hindered amide base LiNCy$_2$ and generation of the enolate prior to the addition of the palladium catalyst and aryl halide provided even more efficient couplings of tert-butyl acetate and $\alpha,\alpha$-disubstituted esters (Scheme 157).\textsuperscript{213} Lower catalyst loadings and only a slight excess of ester and base were required.
Hartwig also reported two procedures for the α-arylation of esters and amides under more neutral conditions. The first procedure involved the use of zinc enolates and rests upon the development of catalysts bearing the hindered pentaphenyl ferrocenyldi-tert-butylphosphine (Qphos) (308) or the highly reactive dimeric Pd(I) complex [P(t-Bu)_3(PdBr)_2]. No nitro groups were included in this protocol.

The catalysts above also catalysed the coupling of Reformatsky reagents prepared from activated zinc and α-bromo esters with a variety of base sensitive substrates (Scheme 158). ortho-nitrobromobenzene and para-nitrobromobenzene were successfully used as electrophiles in this process.

Hartwig also reported the palladium-catalysed arylation of trimethylsilyl enolates of esters (or silyl ketene acetals) with zinc fluoride as a co-catalyst (Scheme 159). This protocol incorporated nitro groups in the electrophile. p-Bromonitrobenzene and p-chloronitrobenzene were successfully cross-coupled with esters using this procedure.\(^{214}\)

It was therefore clear that a general method for the cross-coupling of haloarenes and arylacetates possessing nitro substituents would be valuable. Modification of such a process to allow the direct cross-coupling of a nitroaryleacetate anion derived from a VNS reaction would
be a second aim. To find suitable conditions for a VNS cross-coupling process, we first attempted to cross-couple the preformed VNS product 311 with bromobenzene (Scheme 160) under the same conditions as used by Miura in the cross-coupling of 4-nitrotoluene with bromobenzene which were heating at 140 °C for 1 hour in DMF. The preformed VNS substrate 311 was formed from commercially available p-nitrophenylacetic acid (166) by heating under reflux in ethanol with 3 drops of H$_2$SO$_4$. The cross-coupling reaction however was unsuccessful, with the starting materials being recovered and no trace of 312. An attempt to repeat the same reaction carried out by Miura’s group to validate the procedure also proved unsuccessful with the starting materials being recovered and a tiny trace of product observed by LC-MS.

**Scheme 160**

As an alternative approach cesium carbonate (dried) was added to a two necked round bottom flask fitted with a condenser and nitrogen bubbler. This approach was adapted from a method used by Buchwald who cross-coupled ethyl phenyl acetate with aryl bromides. Anhydrous 1,4-dioxane was added to the cesium carbonate. A solution of ethyl 4-nitrophenylacetate in dioxane was then added followed by bromobenzene, palladium acetate and tri(i-butyl)phosphine. The mixture was then heated at 100 °C for 24 hours. After cooling to room temperature ethyl acetate was added to the reaction mixture which was then filtered through a silica gel plug. Removal of the solvent on a rotary evaporator gave the crude product which was purified by column chromatography to leave the pure product in 46% yield (Scheme 161). The benzylic proton appears as a singlet at δ 5.10 compared to 3.73 in the starting material. The mono substituted aryl group is represented by a multiplet (δ 7.28-7.37). Using an Electron Ionisation mass-spectrometry technique a molecular ion was found at 285.1014 which corresponds to the calculated molecular ion at 285.1001 indicating that the required product had been formed.
Using potassium phosphate as the base under identical conditions resulted in a slight improvement with the required product being formed in 56% yield. In order to make the process more efficient a different ligand was tried. This was the sterically hindered biphenyl 295 (Figure 14) which was used in the Buchwald group in the cross coupling of the enolates of esters with aryl halides.\textsuperscript{162} This was first attempted using the previous conditions (Scheme 162) to produce the required product 312 in 71% yield.

It was important, if we were to establish methodology for the one-pot VNS cross-coupling reaction, that this process could be performed with typical bases that are used in the VNS reaction such as sodium hydride and potassium tert-butoxide. The experiments we carried out with this aim provided very encouraging results. The yields were better than anything encountered previously when potassium tert-butoxide was employed as the base. (Scheme 163).
As we had found good conditions for the cross coupling of the nitrophenylacetate, we then needed to find out if these conditions could be transferred to the cross coupling of nitrophenyl propionates. The parent ester 311 cannot be prepared exclusively in a VNS reaction. The use of a secondary carbanion would result in a mixture of ortho and para phenylacetates. Different conditions were tried to cross-couple the nitrophenylpropionate 313 with aryl halides as summarised (Scheme 164), but all without success. The starting materials were recovered after the reaction every time.

Scheme 164

Since the nitrophenylpropionates could not be cross-coupled with aryl halides, an attempt to cross-couple the preformed ortho-VNS product 315 with aryl halides was made (Scheme 165).

Scheme 165

The reaction failed with the starting materials being recovered. The reaction was repeated changing the solvent to 1,4-dioxane, DMF and acetonitrile, all resulting in no success. The reaction time was increased to 48 hours and the reaction temperature increased to the boiling point of the individual solvents. After continuous heating the starting materials decomposed when using THF and 1,4-dioxane as the solvent. The crown ether 18-crown-6 was tried in the reaction due to a literature precedent in which it was used in the alkylation with methyl iodide, but this also resulted in no success. Different bases were also tried: potassium carbonate, potassium phosphate, sodium tert-butoxide, sodium hydride and cesium carbonate but all with no success. Iodobenzene was tried instead of bromobenzene also with the same result. A transmetallation with ZnCl₂ was also tried with no success.

Despite the lack of success in the cross-coupling of the preformed VNS substrate 313, the one-pot VNS cross-coupling reaction was attempted. Using a KOt-Bu/THF base/solvent system we expected the VNS process to proceed exclusively at the ortho position due to tight ion pairs.
being formed. This reaction was carried out and the required product 318 isolated in 47% yield.

Scheme 166

\[
\begin{align*}
\text{NO}_2 & \quad \text{Cl} \quad \text{CO}_2\text{-t-Bu} \\
\text{317} & \quad \text{1. KOt-Bu, THF, -20 °C} \\
\text{NO}_2 & \quad \text{Cl} \quad \text{CO}_2\text{-t-Bu} \\
\text{318} & \quad \text{2. HCl}
\end{align*}
\]

The one-pot VNS cross-coupling process was then attempted but without success with the VNS product 323 being isolated in 43% yield and no sign of the required product 321. Nitrobenzene and bromobenzene were also present in the crude reaction mixture.

Scheme 167

\[
\begin{align*}
\text{NO}_2 & \quad \text{Cl} \quad \text{CO}_2\text{-t-Bu} \\
\text{317} & \quad \text{1. KOt-Bu, THF, -20 °C} \\
\text{NO}_2 & \quad \text{Cl} \quad \text{CO}_2\text{-t-Bu} \\
\text{318} & \quad \text{2. Pd(OAc)}_2 (5 \text{ mol%}) \\
& \quad \text{ligand 114 (10 mol%)} \\
& \quad \text{Ph-Br, 80 °C, 24 hours}
\end{align*}
\]

The process was repeated but using chloromethyl phenyl sulfone (322) as the VNS nucleophile (Scheme 168). This reaction also resulted in no success. The \(^1\)H-NMR showed the VNS product, bromobenzene and nitrobenzene. A very small amount of the VNS cross coupling product 323 was observed by LC-MS. Different bases and solvents were also used in this reaction, however none gave a positive result.

Scheme 168

\[
\begin{align*}
\text{NO}_2 & \quad \text{Cl} \quad \text{SO}_2\text{Ph} \\
\text{322} & \quad \text{1. KOt-Bu, THF -20 °C} \\
\text{NO}_2 & \quad \text{Ph} \quad \text{SO}_2\text{Ph} \\
\text{323} & \quad \text{2. Bromobenzene} \\
& \quad \text{Pd(OAc)}_2 (5 \text{ mol%}) \\
& \quad \text{Buchwald ligand 114} (10 \text{ mol%}) \\
& \quad 80 °C, 24 hours
\end{align*}
\]

In the VNS reaction the base is normally present in a slight excess. To determine whether this excess of the base would be a problem in the cross-coupling part of the reaction a cross-coupling reaction of ethyl 4-nitrophenylacetate with bromobenzene was carried out using 1.5 equivalents of potassium tert-butoxide (Scheme 169).
When the same reaction was carried out with 1 equivalent of base the product 312 was obtained in 90% yield. Using 1.5 equivalents of potassium tert-butoxide however resulted in the yield for the reaction dropping to 38%. This was a problem for any possible one-pot VNS cross-coupling process as at least 2 equivalents of base are required for the VNS reaction but the reaction never runs to completion so there would always be excess potassium tert-butoxide around to lower the yield for the cross-coupling part of the process.

Different aryl electrophiles were also used in the cross-coupling with nitrophenylacetates under identical conditions (Scheme 170).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>R</th>
<th>R’</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>324a</td>
<td>Dioxane</td>
<td>H</td>
<td>OMe</td>
</tr>
<tr>
<td>324a</td>
<td>DMF</td>
<td>H</td>
<td>OMe</td>
</tr>
<tr>
<td>324b</td>
<td>Dioxane</td>
<td>CF₃</td>
<td>H</td>
</tr>
<tr>
<td>324c</td>
<td>Dioxane</td>
<td>CN</td>
<td>H</td>
</tr>
</tbody>
</table>

Changing the solvent to DMF improved the yield of 324a to 59%. Doublets at δ 8.16 and 7.48 (J 8.8 Hz) in the ¹H-NMR spectrum indicated the presence of a 1,4-disubstituted aryl group. Accurate mass data for 324a was also consistent with the assigned structure.

The next electrophile attempted was 3-bromobenzotrifluoride, as it was much more electron deficient. This produced the required product 324b, which was shown by a doublet at δ 8.21 (J 8.8 Hz) and multiplets (δ 7.57-7.60 & 7.48-7.51) representing the required number of aromatic protons. The benzylic proton appears as a singlet at δ 5.15. Accurate mass spectrometry was consistent with the assigned structure.

A further example 324c was found with the use of 3-bromobenzonitrile. The ¹H-NMR spectrum was consistent with what was expected, as was the accurate mass data.

Using 1-iodo-2-nitrobenzene as the electrophile, the reaction did not proceed with the nitrophenylacetate and nitrobenzene being recovered. Presumably, the catalyst undergoes oxidative insertion into the C-I bond but cannot react with the enolate so the electrophile is
reduced to nitrobenzene. Using 1-bromo-2-nitrobenzene as the electrophile also resulted in no success this time with both starting materials being recovered although a trace amount of the desired product was observed by LC-MS.

**Scheme 171**

The effect of bromo electrophiles was then compared with the chloro and iodo equivalents under identical conditions (Scheme 171). As can be seen, bromobenzene was the most efficient with the iodo equivalent being only slightly less efficient. Even chlorobenzene gave the required product in good yield.

We attempted to cross-couple the meta-nitrophenylacetate 326 with an aryl halide, even though these products could not be formed by a VNS reaction. The meta-nitrophenylacetate 326 was formed by esterification of the commercially available acid 325. The cross-coupling of the nitrophenylacetate 326 with bromobenzene proceeded in 69% yield (Scheme 172) to give the desired product 327.

**Scheme 172**

Doublets at $\delta$ 8.12 and 7.48 ($J$ 8.3 Hz) along with a triplet at $\delta$ 7.67 ($J$ 8.3 Hz) and a singlet at $\delta$ 8.21 in the $^1$H-NMR spectrum indicate the presence of a 1,3-disubstituted aryl group. The mono substituted aryl group is represented by a multiplet ($\delta$ 7.28-7.36). The benzylic proton occurs as a singlet at $\delta$ 5.11. Using an electron spray mass-spec technique a (M + H)$^+$ peak was found at 303.1342 which corresponded to the calculated (M + H)$^+$ peak of 303.1339 indicating the correct product had been obtained.

We thought that since the cross-coupling of ortho substituted nitrophenylacetates with aryl halides did not proceed (Scheme 165), an intramolecular process might be more favourable.
This is based on Hartwig's report of an intramolecular method for the formation of \( N \)-substituted oxindoles (Scheme 173).\(^{132}\)

**Scheme 173**

![Scheme 173 Diagram]

The substrate 332 was formed by addition of 2-nitrophenylacetic acid (330), dichloromethane, carbonyldiimidazole (CDI) and 2-chloro-\( N \)-methylaniline (331) to a two neck round bottom flask fitted with a condenser and nitrogen bubbler. The mixture was heated under reflux to give the required product in 49% yield after column chromatography (Scheme 174). Doublets at \( \delta 8.07 \) (\( J 8.1 \text{ Hz} \)) assigned to the proton adjacent to the nitro group and \( 7.29 \) (\( J 8.4 \text{ Hz} \)) along with multiplets (\( \delta 7.53-7.57 \) and \( 7.38-7.42 \)) in the \(^1\)H-NMR spectrum indicate the presence of two disubstituted aryl groups. Doublets at \( \delta 3.97 \) and \( 3.45 \) (\( J 16.6 \text{ Hz} \)) show the presence of the two benzylic protons, while the methyl group appears as a singlet at \( \delta 3.25 \).

**Scheme 174**

![Scheme 174 Diagram]

The substrate 332 was added to a solution of potassium \textit{tert}-butoxide in 1,4-dioxane followed by palladium acetate and tricyclohexylphosphine (Scheme 175). The reaction mixture was then heated at 100 °C for 2 hours. After cooling to room temperature, the reaction mixture was filtered through a silica gel plug to remove the palladium and then purified by column chromatography to give the required oxindole 333 in 67% yield. Doublets at \( \delta 8.09 \) (\( J 8.3 \text{ Hz} \)) assigned to the proton adjacent to the nitro group and \( 7.27 \) (\( J 8.3 \text{ Hz} \)) along with multiplets (\( \delta 7.52-7.57 \) and \( 7.40-7.45 \)) indicate the presence of the two disubstituted aryl groups. A singlet at \( \delta 5.19 \) represents the benzylic proton and the methyl group is observed as a singlet at \( \delta 3.22 \).
Summary and Conclusion

To conclude, a method for the cross coupling of nitrophenylacetates with aryl halides has been developed. This is potentially very useful due to the lack of palladium cross-coupling reactions for compounds containing a nitro group. Aryl electrophiles with electron withdrawing groups and electron donating groups have been shown to proceed in the reaction. Attempts to extend the process to nitrophenylpropionates met with no success with the starting materials being recovered. Presumably this failed due to the propionates being more sterically hindered than the acetates.

Unfortunately the reaction only proceeded with para and meta-nitrophenylacetates, and the method for the cross-coupling of ortho-nitrophenylacetates remains elusive. Different reaction conditions were tried to get the cross-coupling of ortho nitrophenylacetates to proceed such as different solvents, ligands and bases but all with no success. Presumably the problem is due to a steric clash with the nitro group but could also be due to the electronic nature of the nitrogroup. This is unfortunate as this process would provide convenient access to the oxindole structural motif.

An intramolecular cross-coupling process to form N-methyloxindoles was successfully carried out. The intramolecular process is more thermodynamically favourable than the intermolecular equivalent but due to the success with the intramolecular process we were hopeful that conditions could be found to get the intermolecular process to proceed.

The one-pot VNS cross-coupling process however proved more difficult, and remains a challenge. The problems we encountered were the lack of success with the nitrophenylpropionates in the cross-coupling process. If we used a secondary carbanion to generate the equivalent post VNS anion a mixture of ortho and para-substituted VNS products would be formed. We therefore needed a tertiary carbanion to get exclusively the para-substituted product. The post VNS anion would then be too hindered to undergo the cross-coupling process.

With an excess of potassium tert-butoxide present in the reaction mixture, this produced lower yields, presumably because the tert-butoxide anion is adding to the catalyst by oxidative addition. This was a problem as an excess of base is always present in the VNS reaction due to...
the reaction never going to completion. Suitable conditions would have to be found to minimize this excess.

Even if we used a para-substituted nitroaromatic and secondary carbanion to generate the ortho VNS product exclusively we had no success in getting the preformed product to undergo the cross-coupling process.

We conclude that it is going to be very difficult to get the one-pot VNS/cross-coupling process to work. The excess of base in the VNS reactions is a serious problem. Possible future work would be to find conditions to cross-couple the ortho-nitrophenylacetates with aryl halides and possibly get the one-pot VNS cross-coupling reaction to proceed. This could perhaps be achieved by a different catalyst/ligand system or maybe a base/solvent system we have not tested. A DoE (Design of Experiments) test could perhaps provide the answer in which different catalysts, ligands and bases are screened against each other to attempt to find the ideal conditions.
Chapter 8
8.1 Experimental

General Considerations: Anhydrous \(N,N\)-dimethylformamide was purchased from Aldrich in a Sure/Seal™ bottle. All other reagents were purchased from commercial suppliers except those described below and used without further purification.

Thin layer chromatography was performed using Merck silica gel 60 F\(_{254}\) plates. Column chromatography was performed using silica gel 60 (220-440 mesh). Melting points were obtained using an Electrothermal digital melting point apparatus model 9100. IR spectra was obtained for all previously unreported compounds using a Perkin Elmer 1600 series FTIR instrument. Elemental analyses were performed by the Analytical Department of the School of Chemistry; \(^1\)H NMR and \(^{13}\)C NMR spectra were obtained on a Bruker 400 MHz spectrometer; chemical shifts for \(^1\)H NMR are referenced to tetramethylsilane (TMS) as an internal standard while chemical shifts for \(^{13}\)C NMR are referenced to the solvent used. Low resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument. High resolution mass spectroscopy was carried out by the EPSRC National Mass Spectrometry Service Centre at Swansea University.

\[
\begin{align*}
\text{O} & \quad \text{DMAP, CH}_3\text{N} \\
\text{N-H} & \quad \text{(Boc)}_2\text{O} \\
\text{O} & \quad \text{N-Boc}
\end{align*}
\]

1-tert-Butyloxycarbonyl-pyrrolidin-2-one\(^{142}\) (122)—To a solution of 2-pyrrolidinone (5.0 g, 58.74 mmol) in acetonitrile (100 ml) at 0 °C was added 4-dimethylaminopyridine (0.72 g, 58.74 mmol) and di-tert-butyldicarbonate (25.64 g, 117 mmol) with stirring. The reaction was slowly allowed to warm to room temperature overnight. The solvent was removed on a rotary evaporator to give the crude product (12.41 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.4 (silica, hexane:ethyl acetate; 1:1) to give the pure product (10.75 g, 99%) as a yellow oil. \(\nu_{\text{max}}\) (neat, NaCl plates/ cm\(^{-1}\)) 3619 (s), 3544 (s), 2980 (s), 2880 (m), 1786 (s) (C=O), 1560 (w), 1478 (s); \(\delta_{\text{H}}\) (400 MHz; CDCl\(_3\)) 3.46 (2H, t, \(J\) 7.1 Hz, H-5) 2.22 (2H, t, \(J\) 8.1 Hz, H-3), 1.68-1.76 (2H, m, H-4), 1.23 (9H, s, Boc); \(\delta_{\text{C}}\) (100 MHz; CDCl\(_3\)) 174.8 (s) (C=O), 150.3 (s) (C=O), 82.7 (s) (C-(CH\(_3\))\(_3\)), 46.7 (s) (C-5), 33.1 (s) (C-3), 28.2 (s) (3 x CH\(_3\)), 17.6 (s) (C-4); \(m/z\) (APCI) 186.0 [(M + H)]\(^+\), 100%.

General Method for N-Alkylation—To a slurry of sodium hydride (60% dispersion in oil) (100 mmol) in anhydrous DMF (50 ml) under an inert atmosphere at 0 °C was added the cyclic amide (100 mmol) dropwise. The solution was slowly allowed to warm to room temperature

103
and stirred for 1 hour. After cooling to 0 °C the electrophile (100 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured onto ice/HCl (1M solution). The product was extracted with dichloromethane (3 × 100 ml). The organic solution was then washed with water (5 × 100 ml) and dried over Na₂SO₄. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product.

1-Benzyl-piperidin-2-one¹⁴⁷ (145)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (4.04 g, 100 mmol), DMF (50 ml), piperidin-2-one (10.0 g, 100 mmol) and benzyl bromide (12.0 ml, 100 mmol) to give the crude product (20.9 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.4 (silica, hexane:ethyl acetate; 1:1) to give the pure product (18.1 g, 96%) as a yellow oil. \( \nu_{\text{max}} \) (neat, NaCl plates/cm⁻¹) 3483 (s), 2946 (s), 2967 (m), 2356 (m), 1618 (s), 1495 (s), 1451 (s), 1418 (s), 1353 (s), 1263 (s), 1177 (s), 1073 (m), 993 (m); \( \delta_{\text{H}} \) (400 MHz; CDCl₃) 7.10-7.20 (5H, m, Ph) 4.43 (2H, s, CH₂-Ph), 3.04 (2H, t, J 5.7 Hz, H-6), 2.32 (2H, t, J 6.3 Hz, H-3), 1.55-1.68 (4H, m, H-4 & H-5); \( \delta_{\text{C}} \) (100 MHz; CDCl₃) 170.0 (s) (C=O), 137.5 (s) (C, Ar), 128.8 (s) (2 × CH, Ar), 128.4 (s) (2 × CH, Ar), 127.5 (s) (CH, Ar), 50.2 (s) (CH₂), 47.4 (s) (CH₂), 32.6 (s) (CH₂), 23.3 (s) (CH₂), 21.6 (s) (CH₂); m/z (APCI) 190.0 [M+H]+, 100%.

1-Phenyl-2-methylpyrazolidin-3-one¹⁴⁸ (152)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (2.0 g, 49.6 mmol), 1-phenyl-pyrazolidin-3-one (151) (8.0 g, 49.6 mmol) and methyl iodide (6.24 ml, 99.2 mmol) to give the crude product (9.84 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.3 (silica, hexane:ethyl acetate; 1:1) to give the pure product 152 (8.01 g, 92%) as a yellow oil. \( \nu_{\text{max}} \) (neat, NaCl plates/cm⁻¹) 2981 (s), 1691 (s), 1401 (m); \( \delta_{\text{H}} \) (400 MHz; CDCl₃) 7.30 (2H, app. t, J 7.6 Hz, Ph) 7.08 (1H, app. t, J 7.6 Hz, Ph), 6.95 (2H, app. t, J 7.6 Hz, Ph), 3.79 (2H, t, J 7.5 Hz, H-4), 3.03 (3H, s, CH₃), 2.50 (2H, t, J 7.5 Hz, H-3); \( \delta_{\text{C}} \) (100 MHz; CDCl₃)
172.6 (s) (C=O), 149.7 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 124.0 (s) (CH, Ar), 119.0 (s) (2 × CH, Ar), 55.6 (s) (CH₂), 30.6 (s) (CH₃), 29.4 (s) (CH₂); m/z (APCI) 177.0 [(M+H)+, 100%].

4-Chloro-N-(4-methoxyphenyl)butyramide

4-Chloro-N-(4-methoxyphenyl)butyramide (140)—Triethylamine (20.4 ml) was added to a solution of p-anisidine in dry THF (150 ml) at 0 °C. The solution was then stirred at 0 °C for 30 minutes. The acid chloride (10.2 ml, 122 mmol) was then added dropwise at 0 °C over a 10 minute period. The solution was then stirred at 0 °C for 1 hour. The solution was then allowed to warm to room temperature and stirred for a further 2 hours. Water (150 ml) was then added to the reaction mixture and the crude product was extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were then washed with sodium bicarbonate. The solution was then dried over MgSO₄ and the solvent removed on a rotary evaporator to give the crude product as a brown crystalline solid. M.p. 83-85 °C (lit. 85 °C); ν_max (nujol, NaCl plates/cm⁻¹) 2981 (s), 1665 (s), 1625 (m), 1517 (s); δ_H (400 MHz; CDCl₃) 8.10 (1H, s, NH), 7.39 (2H, d, J 8.3 Hz, H-2 & H-6), 6.81 (2H, d, J 8.3 Hz, H-3 & H-5), 3.76 (3H, s, OCH₃), 3.58 (2H, t, J 6.2 Hz, CH₂CONH) 2.48 (2H, t, J 7.2 Hz, CH₂Cl), 2.13 (2H, tt, J 7.2 & 6.2 Hz, CH₂CH₂Cl); δ_C (100 MHz; CDCl₃) 169.9 (s) (C=O), 156.4 (s) (C, Ar), 130.7 (s) (C, Ar), 121.8 (s) (2 × CH, Ar), 114.1 (s) (2 × CH, Ar), 55.4 (s) (O-CH₃), 44.5 (s) (CH₂), 33.9 (s) (CH₂), 27.9 (s) (CH₂); m/z (APCI) 228.0 [(M+H)+, 100%].

1-(4-Methoxyphenyl)pyrrolidin-2-one

1-(4-Methoxyphenyl)pyrrolidin-2-one (141)—A solution of 4-chloro-N-(4'-methoxyphenyl)butyramide (140) (5.0 g, 21.98 mmol) dissolved in anhydrous THF (20 ml) was slowly added to a suspension of sodium hydride (60% dispersion in oil) (0.87 g, 21.98, mmol) in anhydrous THF (20 ml) at 0 °C. The solution was then stirred at room temperature for 24 hours. The solution was then poured into saturated ammonium chloride (100 ml) and extracted with ethyl acetate (3 × 75 ml). The combined organic extracts were then dried over Na₂SO₄. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product (4.26 g) as a brown crystalline solid. The crude product was the
recrystallised from ethanol to give the pure product 141 (3.7 g, 88%) as a brown crystalline solid. M.p. 107-109 °C (lit. 108 °C); νmax (nujol, NaCl plates/ cm⁻¹) 2980 (s), 1678 (s), 1612 (m), 1514 (s); δH(400 MHz; CDCl₃) 7.48 (2H, d, J 8.4 Hz, H-2 & H-6), 6.81 (2H, d, J 8.4 Hz, H-3 & H-5), 3.80 (2H, t, J 8.1 Hz, H-5), 3.78 (3H, s, OCH₃), 2.56 (2H, t, J 8.1 Hz, H-3) 2.12 (2H, tt, J 8.1 & 7.0 Hz, H-4); δc(100 MHz; CDCl₃) 173.8 (s) (C=O), 156.4 (s) (C, Ar), 132.5 (s) (C, Ar), 121.7 (s) (2 × CH, Ar), 114.0 (s) (2 × CH, Ar), 55.4 (s) (O-CH₃), 49.1 (s) (CH₂), 33.4 (s) (CH₂), 18.0 (s) (CH₂); m/z (APCI) 192.0 [(M+H)+, 100%].

**General Method for α-phenylsulfanylation**—To a solution of diisopropylamine (54 mmol), in dry THF (25 ml) was added n-butyllithium (2.5 M in hexanes) (54 mmol) at 0°C. The reaction was allowed to stir at this temperature for 10 minutes before cooling to -78°C with an acetone/dry ice cooling bath. The cyclic amide (26 mmol) dissolved in dry THF (10 ml) was added dropwise to the reaction mixture. The mixture was then stirred at -78 °C for 35 minutes. Phenyl disulfide (26 mmol) dissolved in dry THF (20 ml) containing DMPU (26 mmol) was then added dropwise to the reaction mixture over a 20 minute period. The mixture was then left to stir at -78 °C for another 35 minutes. The mixture was then slowly left to warm to room temperature over an hour and a half. The reaction mixture was then poured into water (200 ml) and then extracted with diethyl ether (3 × 150 ml). The ether extracts were combined and washed consecutively with 10% sodium hydroxide (100 ml), water (100 ml), 10% hydrochloric acid (100 ml) and finally water (100 ml). The solvent was then dried over sodium sulfate. The drying agent was filtered off and the solvent was removed on a rotary evaporator to give the crude product

1-Methyl-3-phenylsulfanyl-pyrrolidin-2-one^{118} (119) — This was prepared by the General Method using diisopropylamine (7.6 ml, 54 mmol), n-butyllithium (2.5 M in hexanes) (21.6 ml, 54 mmol), 1-methyl-2-pyrrolidinone (104) (5.0 g, 27 mmol), phenyl disulfide (5.7 g, 26 mmol) and DMPU (3.14 ml, 26 mmol) to give the crude product (2.63 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.42 (silica, diethyl ether) to give the pure product (2.63 g, 60%) as a yellow oil. νmax (neat, NaCl plates/ cm⁻¹) 3549 (br, st), 3055 (w), 2933 (s), 2880 (m), 1706 (s) (C=O), 1582 (m), 1488 (m), 1437 (s), 1402 (m), 1300 (s), 1273 (s), 1107 (m), 1026 (w), 984 (w); δH(400 MHz; CDCl₃) 7.26-7.31 (2H, m, Ph), 7.04-7.08
(3H, m, Ph), 3.56 (1H, dd, J 5.8 & 8.8 Hz, H-3), 2.93-2.99 (1H, m, H-5α), 2.76-2.82 (1H, m, H-5β), 2.18-2.27 (1H, m, H-4α), 1.74-1.82 (1H, m, H-4β); δC(100 MHz; CDCl3) 172.2 (s) (C=O), 133.4 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 47.9 (s) (N-CH3), 47.5 (s) (C-3), 30.4 (s) (CH2), 26.8 (s) (CH2); m/z (APCI) 209.0 [(M+H)+, 100%].

1-Butyloxy carbonyl-3-phenylsulfanylpurrolidin-2-one (123)—This was prepared by the General Method using diisopropylamine (7.9 ml, 56 mmol), n-butyllithium (2.5M in hexanes) (22.4 ml, 56 mmol), 1-boc-2-pyrrolidinone (122) (5.0 g, 27 mmol), phenyl disulfide (5.9 g, 27 mmol), DMPU (3.26 ml, 27 mmol) to give the crude product (4.15 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.20 (silica, ethyl acetate:hexane; 1:3) to give the pure product (3.7 g, 47%) as a yellow oil. υmax (neat, NaCl plates/ cm−1) 2979 (s), 2251 (w), 2933 (s), 1783 (s), 1748 (s), 1717 (s), 1583 (m), 1477 (m), 1437 (m), 1368 (s), 1301 (s), 1257 (s), 1151 (s), 1088 (m), 1041 (w), 1014 (s), 909 (s), 849 (s), 779 (s); δ(400 MHz; CDCl3) 7.46-7.48 (2H, m, Ph), 7.22-7.25 (3H, m, Ph), 3.78 (1H, dd, J 6.3 & 8.4 Hz, H-3), 3.46-3.58 (2H, m, H-5), 2.30-2.39 (1H, m, H-4α), 1.89-1.98 (1H, m, H-4β), 1.44 (9H, s, H-Boc); δC(100 MHz; CDCl3) 171.9 (s) (C=O), 150.4 (s) (C=O), 133.6 (s) (2 × CH, Ar), 132.8 (s) (C, Ar), 129.5 (s) (2 × CH, Ar), 128.6 (s) (CH, Ar), 83.6 (s) (C-(CH3)3), 49.7 (s) (CH-S), 44.7 (s) (C-5), 28.4 (s) (3 × CH3), 25.9 (s) (C-4); m/z (APCI) 209.0 [(M+H)+, 100%].

1-Phenyl-3-phenylsulfanylpurrolidin-2-one (129)—This was prepared by the General Method using diisopropylamine (8.72 ml, 62.2 mmol, n-butyllithium (2.5 M in hexanes) (24.88 ml, 62.2 mmol), 1-phenyl-2-pyrrolidinone (5.0 g, 31.1 mmol), phenyl disulfide (6.79 g, 31.1 mmol), DMPU (3.75 ml, 31.1 mmol) to give the crude product (5.59 g) as an orange powder. The crude product was then recrystallized from ethanol to give the pure product (5.8 g, 69%) as a slightly brown powder. m.p. 82.5-83.5 °C; (Found C, 71.31; H, 5.63; N 5.20. C16H15SNO requires C, 71.35; H, 5.61; N, 5.20%); υmax (nujol, NaCl plates/ cm−1) 2912 (s), 1682 (s), 1599
(w), 1457 (s), 1379 (s), 1302 (s), 1115 (w), 895 (m); δH (400 MHz; CDCl3) 7.81-7.84 (4H, m, Ph), 7.59-7.64 (2H, m, Ph), 7.53-7.57 (3H, m, Ph), 7.42 (1H, t, J 7.4 Hz, Ph), 4.25 (1H, dd, J 6.0 & 8.6 Hz, H-3), 3.95-4.01 (1H, m, H-5α), 3.84-3.90 (1H, m, H-5β), 2.81-2.91 (1H, m, H-4α), 2.40-2.49 (1H, m, H-4β); δC (100 MHz; CDCl3) 171.8 (s) (C=O), 139.5 (s) (C, Ar), 133.7 (s) (2 x CH, Ar), 133.2 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.5 (s) (CH, Ar), 125.3 (s) (CH, Ar), 120.4 (s) (CH, Ar), 49.7 (s) (C-3), 46.9 (s) (C-5), 26.7 (s) (C-4); m/z (APCI) 270.1 [(M+H)+, 100%] 203.2 (14); (Found: (M + H)+ (ES+), 270.0953 C16H13NOS requires (M + H)+ 220.0947).

1-Benzyl-3-phenylsulfanylpyrrolidin-2-one (137)—This was prepared by the General Method using diisopropylamine (8.97 ml, 64.0 mmol, n-butyllithium (2.5 M in hexanes) (25.60 ml, 64.0 mmol), 1-benzyl-2-pyrrolidinone (5.0 ml, 32.0 mmol), phenyl disulfide (6.99 g, 32.0 mmol), DMPU (3.83 ml, 32.0 mmol) to give the crude product (7.46 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.20 (silica, ethylacetate:hexane; 1:3) to give the pure product (5.4 g, 60%) as a yellow oil. νmax (neat, NaCl plates/cm⁻¹) 2901 (s), 1684 (s), 1600 (w); δH (400 MHz; CDCl3) 7.51 (2H, d, J 7.9 Hz, Ph), 7.19-7.35 (8H, m, Ph), 4.56 (1H, d, J 14.5 Hz, HCH), 4.45 (1H, d, J 14.5 Hz, HCH), 4.21 (1H, dd, J 5.9 & 8.1 Hz, H-3), 3.93-3.99 (1H, m, H-5α), 3.83-3.89 (1H, m, H-5β), 2.77-2.89 (1H, m, H-4α), 2.39-2.46 (1H, m, H-4β); δC (100 MHz; CDCl3) 173.9 (s) (C=O), 135.3 (s) (C, Ar), 133.4 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 131.1 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 127.5 (s) CH, Ar), 50.9 (s) (CH2), 47.4 (s) (C-3), 30.1 (s) (CH2), 26.7 (s) (CH2); m/z (APCI) 284.0 [(M+H)+, 100%].

2-Methyl-1-Phenyl-4-pyrazolidin-3-one (153)—This was prepared by the General Method using diisopropylamine (3.18 ml, 22.72 mmol, n-butyllithium (2.5 M in hexanes) (9.1 ml, 22.72 mmol), 2-methyl-1-phenyl pyrazolidin-3-one (2.0 g, 11.36 mmol), phenyl disulfide (2.48 g, 11.36 mmol), DMPU (1.37 ml, 11.36 mmol) to give the crude product (2.54 g) as a yellow
oil. The crude product was then purified by column chromatography Rf 0.45 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (1.59 g, 49%) as a yellow oil; υ_{max} (neat, NaCl plates/ cm\(^{-1}\)) 3058 (s), 2922 (s), 2244 (w), 1951 (w), 1875 (w), 1690 (s) (C=O), 1597 (s), 1490 (s), 1388 (s), 1284 (m), 1112 (m); δ_{H}(400 MHz; CDCl\(_3\)) 7.31-7.33 (2H, m, Ph), 7.19 (2H, app. t, J 7.8 Hz, Ph), 7.11-7.12 (2H, m, Ph), 6.97 (1H, app. t, J 7.3 Hz, Ph), 6.79 (2H, app. d, J 7.8 Hz, Ph), 3.89-3.96 (2H, m, H-4 or H-5), 3.65 (1H, dd, J 11.3 & 14.5 Hz, H-4 or H-5), 2.97 (3H, s, N-CH\(_3\)); δ_{C}(100 MHz; CDCl\(_3\)) 170.1 (s) (C=O), 149.4 (s) (C, Ar), 132.9 (s) (C, Ar), 132.8 (s) (2 × CH, Ar), 129.8 (s) (2 × CH, Ar), 128.9 (s) (2 × CH, Ar), 127.4 (s) (CH, Ar), 124.2 (s) (CH, Ar), 118.7 (s) (2 × CH, Ar), 61.7 (s) (C-5), 47.0 (s) (C-5), 31.8 (s) (N-CH\(_3\)); m/z (APCI) 285.5 [(M+H)+, 100%] 112.7 (33) (Found: (M + H)+ (ES+), 285.1056 C\(_{16}\)H\(_{16}\)N\(_2\)OS requires (M + H)+ 285.1056).

1-Benzyl-3-Phenylsulfanyl-piperidin-2-one\(^{219}\) (146)—This was prepared by the General Method using diisopropylamine (4.45 ml, 31.72 mmol, n-butyllithium (2.5M in hexanes) (12.69 ml, 31.72 mmol), 1-benzylpiperidin-2-one (145) (3.0 g, 15.86 mmol), phenyl disulfide (3.46 g, 15.86 mmol), DMPU (1.92 ml, 15.86 mmol) to give the crude product (3.81 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.25 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (3.15 g, 67%) as a yellow oil; υ_{max} (neat, NaCl plates/ cm\(^{-1}\)) 3059 (m), 2948 (s), 2862 (m), 1952 (w), 1650 (s) (C=O), 1582 (m), 1488 (s), 1438 (s), 1350 (s), 1255 (s), 1177 (s); δ_{H}(400 MHz; CDCl\(_3\)) 7.55 (2H, app. d, J 7.8 Hz Ph), 7.21-7.31 (8H, m, Ph), 4.7 (1H, d, J 14.6 Hz, CH\(_2\)-Ph), 4.46 (1H, d, J 14.6 Hz, CH\(_2\)-Ph), 3.93 (1H, t, J 5.6 Hz, H-3), 3.13-3.18 (2H, m, H-6), 1.88-2.11 (3H, m, H-4α, 2 × H-5), 1.61 (1H, m, H-4β); δ_{C}(100 MHz; CDCl\(_3\)) 168.7 (s) (C=O), 137.3 (s) (C, Ar), 134.9 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 128.5 (s) (2 × CH, Ar), 128.0 (s) (CH, Ar), 127.9 (s) (CH, Ar), 51.0 (s) (CH\(_2\)), 49.4 (s) (CH), 47.6 (s) (CH\(_2\)), 28.8 (s) (CH\(_2\)), 20.7 (s) (CH\(_2\)); m/z (APCI) 298 [(M+H)+, 100%].
1-(4-Methoxyphenyl)-3-pyrrolidin-2-one (142)—This was prepared by the general method using diisopropylamine (4.40 ml, 31.42 mmol, n-butyllithium (2.5 M in hexanes) (12.58 ml, 31.42 mmol), 1-(4-methoxyphenyl)-pyrrolidin-2-one (141) (3.0 g, 15.71 mmol), phenyl disulfide (3.43 g, 15.71 mmol), DMPU (1.89 ml, 15.71 mmol) to give the crude product (4.3 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.45 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (3.21 g, 68%) as a yellow crystalline solid. M.p. °C; νmax (nujol, NaCl plates/ cm⁻¹) 2912 (s), 1677 (s) (C=O), 1514 (m), 1417 (s), 1350 (s); δH(400 MHz; CDCl₃) 7.60-7.62 (2H, m, Ph), 7.47 (2H, d, J 9.1 Hz, Ph), 7.31-7.33 (3H, m, Ph), 6.91 (2H, d, J 9.1 Hz, Ph), 4.01 (1H, dd, J 5.8 & 8.7 Hz, H-3), 3.67-3.82 (1H, m, H-5α), 3.56-3.60 (1H, m, H-5β), 2.60-2.65 (1H, m, H-4α), 2.18-2.24 (1H, m, H-4β); δC(100 MHz; CDCl₃) 171.1 (s) (C=O), 156.8 (s) (C, Ar), 133.3 (s) (2 × CH, Ar), 132.9 (s) (C, Ar), 132.3 (s) (C, Ar), 129.0 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 121.9 (s) (2 × CH, Ar), 114.0 (s) (2 × CH, Ar), 55.5 (s) (O-CH₃), 49.2 (s) (C-3), 47.0 (s) (C-5), 26.4 (s) (C-4); m/z (APCI) 300 [(M+H)+, 100%] 191 (10); (Found: (M + H)+ (ES+), 300.1057 Ci requires (M + H)+ 300.1053).

General Method for VNS-Alkylation of Lactams—Sodium hydride (60% dispersion in oil) (14.4 mmol) in anhydrous DMF (5 ml) was flushed with nitrogen and cooled to 0 °C. Nitrobenzene (4.8 mmol) and the VNS nucleophile (4.8 mmol) dissolved in anhydrous DMF (5 ml) was added dropwise to the sodium hydride slurry. The mixture was left to stir at 0 °C for 30 minutes before being allowed to warm to room temperature. The purple reaction mixture was left to stir at room temperature for 2 hours before cooling back down to 0 °C. The electrophile (9.6 mmol) was then added drop-wise to the reaction mixture. The mixture was then allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then poured onto ice/hydrochloric acid (1M solution). The product was then extracted with dichloromethane (3 × 100 ml), washed with water (5 × 100 ml), sodium bicarbonate (3 × 100 ml) and dried over sodium sulfate. The drying agent was then filtered off and the solvent removed on a rotary evaporator to give the crude product.
1,3-Dimethyl-3-(4'-nitrophenyl)pyrrolidin-2-one (120b)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.58 g, 14.4 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (119) (1.0 g, 4.8 mmol), nitrobenzene (0.50 ml, 4.8 mmol) and iodomethane (0.45 ml, 7.2 mmol) to give 2.2 g of crude product as a brown oil. The crude product was then purified by column chromatography Rf 0.30 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.73 g, 65%) as a brown oil. νmax (neat, NaCl plates/ cm⁻¹) 3463 (br, st), 3077 (m), 2910 (s), 2455 (w), 1689 (s) (C=O); δH(400 MHz; CDCl₃) 8.05 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.52 (2H, d, J 8.9 Hz, H-2' & H-5'), 3.24-3.36 (2H, m, H-5), 2.86 (3H, s, N-CH₃), 2.31-2.37 (1H, m, H-4α), 2.11-2.19 (1H, m, H-4β), 1.48 (3H, s, CH₃); δC(100 MHz; CDCl₃) 176.5 (s) (C=O), 152.1 (s) (C, Ar), 146.8 (s) (C, Ar), 127.7 (s) (2 × CH, Ar), 123.9 (s) (2 × CH, Ar), 49.1 (s) (C, quaternary), 46.3 (s) (N-CH₂), 35.2 (s) (CH₂), 30.5 (s) (N-CH₃), 25.1 (s) (CH₃); m/z (APCI) 235.0[(M+H)+, 100%]; (Found: (M + H)+, 235.1078. C₁₂H₁₄N₂O₃ requires (M + H)+ 235.1077).

1-Methyl-3-(4'-nitrophenyl)pyrrolidin-2-one (120a)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.29 g, 7.2 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (119) (0.50 g, 2.4 mmol), nitrobenzene (0.25 ml, 2.4 mmol). No electrophile was added and the mixture was poured onto a mixture of ice and hydrochloric acid (1M) to give the crude product (2.2 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.34 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.73 g, 65%) as an orange crystalline solid. M.p. 74-76 °C; νmax (nujol, NaCl plates/ cm⁻¹) 2917 (s), 1672 (m), 1599 (w), 1518 (w), 1461 (s), 1376 (s), 1092 (w), 850 (w); δH(400 MHz; CDCl₃) 8.10 (2H, d, J 8.7 Hz, H-3' & H-5'), 7.38 (2H, d, J 8.7 Hz, H-2' & H-5'), 3.71 (1H, t, J 9.2 Hz, H-3), 3.40-3.44 (2H, m, H-5), 2.87 (3H, s, N-CH₃), 2.48-2.56 (1H, m, H-4α), 2.02-2.12 (1H, m, H-4β); δC(100 MHz; CDCl₃) 173.8 (s) (C=O), 147.9 (s) (C, Ar), 147.2 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 48.2 (s) (C-3), 47.9 (s) (C-5), 30.5 (s) (N-CH₃), 28.0 (s) (C-4); m/z (APCI) 220.8[(M+H)+, 100%]; (Found: (M + NH₄)+, 238.1186. C₁₁H₁₂N₂O₃ requires (M + NH₄)+ 238.1186).
3-Allyl-1-methyl-3-(4'-nitrophenyl)pyrrolidin-2-one (120c)—This was prepared by the general method used in the previous compound using sodium hydride (60% dispersion in oil) (0.29 g, 7.2 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (119) (0.50 g, 2.4 mmol), nitrobenzene (0.25 ml, 2.4 mmol) and allyl bromide (0.41 ml, 4.8 mmol) to give the crude product (1.46 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.37 g, 66%) as a yellow oil. £max (neat, NaCl plates/ cm⁻¹) 3075 (m), 2922 (s), 1682 (s), 1640 (w), 1602 (s), 1514 (s), 1435 (s), 1403 (s), 1346 (s), 1101 (s) 1014 (s), 922 (s), 853 (s), 729 (s); δH(400 MHz; CDCl₃) 8.10 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.63 (2H, d, J 8.9 Hz, H-2' & H-5'), 5.49-5.56 (1H, m, CH), 5.00-5.05 (2H, m, =CH₂), 3.21-3.31 (2H, m, H-5), 2.84 (3H, s, N-CH₃) 2.57 (2H, d, J 7.2 Hz, H₂C=CH-CH₂-), 2.28-2.39 (2H, m, H-4); δC(100 MHz; CDCl₃) 175.1 (s) (C=O), 150.3 (s) (C, Ar), 146.9 (s) (C, Ar), 133.3 (s) (H₂C=CH-), 128.1 (s) (2 × CH, Ar), 123.8 (s) (2 × CH, Ar), 119.8 (s) (H₂C=), 52.4 (s) (C, quaternary), 47.0 (s) (CH₂), 43.8 (s) (C-5), 30.5 (s) (C-4), 30.4 (s) (N-CH₃); m/z (APCI) 260.9[(M+H)+, 100%], 205.8 (14); (Found: (M + H)+, 261.1234. C₁₄H₁₆N₂O₃ requires (M + H)+ 261.1236).

3-Benzyl-1-methyl-3-(4'-nitrophenyl)pyrrolidin-2-one (120d)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.29 g, 7.2 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (119) (0.50 g, 2.4 mmol), nitrobenzene (0.25 ml, 2.4 mmol) and benzyl bromide (0.57 ml, 4.8 mmol) to give the crude product (2.0 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.55g, 72%) as an orange crystalline solid. M.p. 113-115°C; £max (nujolt, NaCl plates/ cm⁻¹) 2852 (s), 1668 (s), 1598 (m), 1515 (m), 1377 (m), 1347 (m), 1312 (m); δH(400 MHz; CDCl₃) 8.11 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.68 (2H, d, J 8.9 Hz, H-2' & H-6'), 7.16-7.19 (3H, m Ph), 7.00-7.02 (2H, m, Ph), 3.23 (1H, d, J 13.3 Hz, HCH-Ph), 2.99-3.03 (1H, m, H-4α), 2.96 (1H, d, J 13.3 Hz, HCH-Ph), 2.70 (3H, s, N-CH₃), 2.47-
2.53 (1H, m, H-4β), 2.25-2.40 (2H, m, H-5); δC(100 MHz; CDCl₃) 175.2 (s) (C=O), 150.9 (s) (C, Ar), 147.1 (s) (C, Ar), 136.6 (s) (C, Ar), 130.5 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.2 (s) (2 × CH, Ar), 127.5 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 53.8 (s) (C, quartenary), 46.4 (s) (CH₂), 46.1 (s) (CH₂), 30.1 (s) (N-CH₃), 30.5 (s) (CH₂); m/z (APCI) 311.3 [(M+H)+ , 100%]; (Found: (M + H)+ , 311.1390 CI₈H₁₈N₂O₃ requires (M + H)+ 311.1390).

1-Phenyl-3-(4'-nitrophenyl)pyrrolidin-2-one (130a)—This was prepared by the general method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (129) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) to give the crude product (0.70 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.39 g, 75%) as an orange crystalline solid. M.p. 117-119 °C; v_max (nujol, NaCl plates/ cm⁻¹) 2916 (s), 1690 (s), 1596 (m), 1513 (w), 1463 (s), 1377 (s), 1303 (m); δH(400 MHz; CDCl₃) 8.08 (2H, d, J 8.7 Hz, H-3' & H-5'), 7.56 (2H, app. d, J 8.0 Hz, Ph), 7.42 (2H, d, J 8.7 Hz, H-2' & H-6'), 7.28 (2H, app. t, J 8.0 Hz, Ph), 7.08 (1H, app. t, J 8.0 Hz, Ph), 3.79-3.90 (3H, m, H-3 & H-4), 2.53-2.61 (1H, m, H-5α), 2.13-2.23 (1H, m, H-5β), δC(100 MHz; CDCl₃) 173.0 (s) (C=O), 147.4 (s) (C, Ar), 147.0 (s) (C, Ar), 144.5 (s) (C, Ar), 129.6 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 125.4 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 120.3 (s) (2 × CH, Ar), 49.7 (s) (CH), 47.1 (s) (CH₂), 27.7 (s) (CH₂); m/z (APCI) 283.5 [(M+H)+ , 16 %]; (Found: (M + H)+ , 283.1079 CI₆H₁₄N₂O₃ requires (M + H)+ 283.1077).

3-Methyl-3-(4'-nitrophenyl)-1-phenylpyrrolidin-2-one (130b)—This was prepared by the general method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (129) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and iodomethane (0.23 ml, 3.72 mmol) to give the crude product (0.8 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.61 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.38 g, 68%) as a yellow crystalline solid. (Found C,
68.81; H, 5.39; N 9.57. C_{17}H_{16}N_{2}O_{3} requires C, 68.91; H, 5.44; N, 9.45%). M.p. 160-162°C; 
u_{\text{max}} (nujol, NaCl plates/ cm^{-1}) 2921 (s), 1686 (s) (C=O), 1592 (m), 1456 (s), 1378 (s); \delta_{\text{H}}(400 MHz; CDCl_{3}) 8.12 (2H, d, J 8.7 Hz, H-3' & H-5'), 7.31-7.35 (4H, m, Ar), 7.10 (2H, app. d, J 7.4 Hz, Ph), 6.95 (2H, app. d, J 7.6 Hz, Ar), 3.29-3.39 (2H, m, H-5), 2.93 (3H, s, N-CH_{3}), 2.38 (1H, tdd, J 13.7 Hz & 11.9 Hz & 2.01 Hz, H-4\alpha), 2.19 (1H, tdd, J 13.7 Hz & 11.9 Hz & 2.01 Hz, H-4\beta); \delta_{C}(100 MHz; CDCl_{3}) 171.6.(s) (C=O), 149.3 (s) (C, Ar), 147.7 (s) (C, Ar), 143.9 (s) (C, Ar), 130.1 (s) (2 x CH, Ar), 129.9 (s) (2 x CH, Ar), 125.0 (s) (CH, Ar), 124.3 (s) (2 x CH, Ar), 119.3 (s) (2 x CH, Ar), 77.7 (s) (C, q), 63.6 (s) (C-5), 45.9 (s) (C-4), 31.6 (s) (CH_{3}); m/z (APCI) 297.3 [(M+H)^{+}, 100 %]; (Found: (M + H)^{+}, 297.1235. C_{17}H_{16}N_{2}O_{3} requires (M + H)^{+} 297.1234).

3-Allyl-3-(4'-nitrophenyl)-1-phenylpyrrolidin-2-one (130c)—This was prepared by the general method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (129) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and allyl bromide (0.32 ml, 3.72 mmol) to give the crude product (1.40 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.5 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.39 g, 65%) as a yellow crystalline solid. M.p. 62-63°C; \nu_{\text{max}} (nujol, NaCl plates/ cm^{-1}) 3076 (m), 2979 (m), 2892 (m), 2249 (w), 1943 (w), 1861 (w), 1686 (s) 1596 (s) 1502 (s), 1394 (s) 1346 (s); \delta_{\text{H}}(400 MHz; CDCl_{3}) 8.09 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.65 (2H, d, J 8.9 Hz, H-2' & H-6'), 7.55 (2H, app. d, J 8.0 Hz, Ph), 7.29 (2H, app. t, J 8.0 Hz, Ph), 7.08 (1H, app. t, J 8.0 Hz, Ph), 5.52-5.62 (1H, m, H_{2}C=CH-), 5.02-5.06 (2H, m, H_{2}C=), 3.72-3.78 (1H, m, H-5\alpha), 3.66 (1H, dd, J 7.4 & 17.1 Hz, H-5\beta), 2.65-2.67 (2H, m, =CH-CH_{2}), 2.39-2.53 (2H, m, 2 x H-4); \delta_{C}(100 MHz; CDCl_{3}) 174.5.(s) (C=O), 149.2 (s) (C, Ar), 147.3 (s) (C, Ar), 139.5 (s) (C,Ar), 133.1 (s) (CH, Ar), 129.4 (s) (2 x CH, Ar), 128.2 (s) (2 x CH, Ar), 125.4 (s) (CH, Ar), 124.0 (s) (2 x CH, Ar), 120.4 (s) (2 x CH, Ar), 120.2 (s) (CH, Ar), 54.0 (s) (C, q), 45.7 (s) (CH_{2}), 44.0 (s) (CH_{2}), 30.0 (s) (CH_{2}); m/z (APCI) 323.3 [(M+H)^{+}, 100 %]; (Found: (M + H)^{+}, 323.1390. C_{19}H_{18}N_{2}O_{3} requires (M + H)^{+} 323.1390).
2) 2,4-dinitrofluorobenzene

3-(2''',4'''-dinitrophenyl)-3-(4'-nitrophenyl)-1-phenylpyrrolidin-2-one (130d)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (129) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and 2,4-dinitrofluorobenzene (0.47 ml, 3.72 mmol) to give the crude product (1.42 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.19 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.48 g, 58%) as an orange oil. \( \nu_{\text{max}} \) (nujol, NaCl plates/cm\(^{-1}\)) 3071 (m), 2892 (m), 1681 (s), 1487 (s); \( \delta_t \) (400 MHz; CDCl\(_3\)) 8.55 (1H, d, \( J = 2.4 \) Hz, H-3'''), 8.29 (1H, dd, \( J = 2.4 \) & 8.7 Hz, H-5'''), 8.14 (2H, d, \( J = 8.9 \) Hz, H-3' & H-5'), 7.60 (2H, d, \( J = 8.9 \) Hz, H-2' & H-6'), 7.47-7.50 (3H, m, H-6'' & Ph), 7.3 (2H, app. t, \( J = 7.6 \) Hz, Ph), 7.13 (1H, t, \( J = 7.6 \) Hz, Ph), 3.98-4.09 (2H, m, H-4a & H-40), 3.38 (1H, ddd, \( J = 2 \) & 6.5 & 13.9 Hz, H-5 a), 2.98 (1H, m, 2.94-3.02, H-5b); \( \delta_C \) (100 MHz; CDCl\(_3\)) 170.8 (s) (C=O), 150.6 (s) (C, Ar), 148.1 (s) (C, Ar), 147.3 (s) (C, Ar), 144.4 (s) (C, Ar), 144.1 (s) (C, Ar), 138.8 (s) (C, Ar), 133.8 (s) (CH, Ar), 129.5 (s) (2 \( \times \) CH, Ar), 129.0 (s) (CH, Ar), 126.8 (s) (CH, Ar), 126.3 (s) (CH, Ar), 124.4 (s) (2 \( \times \) CH, Ar), 121.2 (s) (CH, Ar), 120.8 (CH, Ar), 58.9 (s) (C, q), 46.3 (s) (CH\(_2\)), 31.9 (s) (CH\(_2\)); \( m/z \) (APCI) 449 [(M+H)\(^+\), 65%]; (Found: (M + NH\(_4\))^+ 466.1358 C\(_{22}\)H\(_{16}\)N\(_4\)O\(_7\) requires (M + NH\(_4\))^+ 466.1357).

1-Benzyl-3-(4'-nitrophenyl)pyrrolidin-2-one (138a)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (137) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and hydrochloric acid (1 M) (2 ml) to give the crude product (3.34 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.40 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.34 g, 62%) as a white crystalline solid M.p. 91-93°C; \( \nu_{\text{max}} \) (nujol, NaCl plates/cm\(^{-1}\)) 2907 (s), 1675 (s), 1601 (m), 1514 (m), 1456 (s), 1377 (w), 115
1347 (s), 1285 (m); δH (400 MHz; CDCl3) 8.12 (2H, d, J 8.7 Hz, H-3’ & H-5’), 7.38 (1H, d, J 8.7 Hz, H-2’ & H-6’), 7.19-7.31 (5H, m, Ph), 4.51 (1H, d, J 14.6 Hz, HCH), 4.41 (1H, d, J 14.6 Hz, HCH), 3.77 (1H, t, J 9.1 Hz, H-3), 3.25-3.31 (2H, m, H-5), 2.44-2.52 (1H, m, H-4α), 2.04 (1H, ddd, J 8.6 & 13.0 & 17.1 Hz, H-4β); δC (100 MHz; CDCl3) 173.7 (s) (C=O), 147.6 (s) (C, Ar), 147.4 (s) (C, Ar), 136.5 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 48.3 (s) (CH), 47.6 (s) (CH2), 45.2 (s) (CH2), 27.9 (s) (CH2); m/z (APCI) 297 [(M+H)+, 100%]; (Found: (M + H)+ (ES+), 297.1234). C17H16N2O3 requires M + H)+ 297.1234).

3-Methyl-1-benzyl-3-(4’-nitrophenyl)pyrrolidin-2-one (138b)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (137) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and methyl iodide (0.23 ml, 3.72 mmol) to give the crude product (2.21 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.21 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.34 g, 66%) as a yellow oil. νmax (neat, NaCl plates/ cm⁻¹) 3506 (w), 3064 (s), 2967 (m), 2967 (m), 2927 (w), 2872 (w), 1686 (s) (C=O), 1603 (m), 1520 (s), 1495 (m), 1454 (m), 1429 (m), 1348 (s), 1270 (s); δH (400 MHz; CDCl3) 8.09 (2H, d, J 8.9 Hz, H-3’ & H-5’), 7.53 (2H, d, J 8.9 Hz, H-2’ & H-6’), 6.70-7.27 (5H, m, Ph), 4.45 (2H, s, CH2-Ph), 3.10-3.22 (2H, m, H-5), 2.28-2.34 (1H, m, H-4α), 2.08-2.16 (1H, m, H-4β), 1.54 (3H, s, CH3); δC (100 MHz; CDCl3) 176.5 (s) (C=O), 151.9 (s) (C, Ar), 147.0 (s) (C, Ar), 136.5 (s) (C, Ar), 129.8 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar), 128.6 (s) (CH, Ar), 128.2 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 49.3 (s) (C, quaternary), 47.5 (s) (CH2), 43.6 (s) (CH2), 35.2 (s) (CH2), 24.9 (s) (CH3); m/z (APCI) 311 [(M+H)+, 100%]; (Found: (M + H)+ (ES+), 311.1392 C18H18N2O3 requires M + H)+ 311.1390).
3-Ethyl-1-benzyl-3-(4'-nitrophenyl)pyrrolidin-2-one (138c)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (137) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and ethyl iodide (0.28 ml, 3.50 mmol) to give the crude product (1.04 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.21 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.35 g, 61%) as a yellow crystalline solid. M.p. 110-111 °C; ν_\text{max} (neat, NaCl plates/ cm\(^{-1}\)) 3480 (s), 2932 (s), 1666 (s), 1602 (m), 1515 (m), 1454 (s), 1378 (s), 1106 (m), 855 (m); δ_\text{H}(400 MHz; CDCl_3) 8.10 (2H, d, 7.89 Hz, H-3' & H-5'), 7.63 (2H, d, J 8.9 Hz, H-2' & H-6'), 7.19-7.24 (3H, m, Ph), 7.12 (2H, app. d, J 7.8 Hz, Ph), 4.48 (1H, d, J 14.6 Hz, HCH), 4.37 (1H, d, J 14.6 Hz, HCH), 3.08-3.19 (2H, m, H-5), 2.35 (1H, dt, J 7.4 & 12.9 Hz, H-4α), 2.20 (1H, dt, J 7.4 & 12.9 Hz, H-4β), 1.95 (1H, dq, J 14.8 & 7.4 Hz, HCH-CH₃), 1.86 (1H, dq, J 13.9 & 7.4 Hz, HCH-CH₃), 0.76 (3H, t, J 7.4 Hz, CH₃); δ_C (100 MHz; CDCl₃) 175.6 (s) (C=O), 150.3 (s) (C, Ar), 147.1 (s) (C, Ar), 136.6 (s) (C, Ar), 129.2 (s) (2 x CH, Ar), 128.5 (s) (2 x CH, Ar), 128.1 (s) (2 x CH, Ar), 123.9 (s) (2 x CH, Ar), 53.2 (s) (C, quaternary), 47.4 (s) (CH₂), 43.7 (s) (CH₂), 32.3 (s) (CH₂), 30.7 (s) (CH₂), 9.4 (s) (CH₃); m/z (APCI) 325 [(M+H)+, 100%]; (Found: (M + H)^+ (ES^+), 325.1553 C₁₉H₂₀N₂O₃ requires (M + H)^+ 325.1547).

l-(4'-methoxyphenyl)-3-(4''-nitrophenyl)pyrrolidin-2-one (143a)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), l-(4'-methoxyphenyl)-3-phenylsulfanyl-pyrrolidin-2-one (142) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and saturated ammonium chloride (0.50 ml) to give the crude product (1.85 g) as brown oil. The crude product was then purified by column chromatography Rf 0.20 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.38 g, 73%) as a yellow crystalline solid. M.p. 157-159 °C; ν_\text{max} (nujol, NaCl plates/ cm\(^{-1}\)) 2909 (s), 2360 (s), 1694 (s), 1603 (m), 1514 (m), 1492 (s), 1377 (s), 1346 (m), 1252 (m); δ_\text{H}(400 MHz; CDCl₃) 8.14 (2H, d, 7.86 Hz, H-3' & H-5'), 7.48 (2H, d, J 9.0 Hz, H-2'' & H-6''), 7.44 (2H, d, J 8.6 Hz, H-2' & H-6'), 6.85 (2H, d, J 9.0 Hz, H-3'' & H-5''), 3.80-3.95 (3H, m, H-3 & H-5), 3.73 (3H, s, O-CH₃), 2.57-2.67 (1H, m, H-4α), 2.17-2.27 (1H, m, H-4β); δ_C(100 MHz; CDCl₃) 172.6 (s) (C=O), 157.3 (s) (C, Ar), 147.5 (s) (C, Ar), 147.1 (s) (C, Ar), 132.6 (s) (C, Ar), 129.5 (s) (2 x CH, Ar), 124.3 (s) (2...
× CH, Ar), 122.1 (s) (CH, Ar), 114.5 (s) (2 × CH, Ar), 55.9 (s) (O-CH₃), 49.5 (s) (CH), 47.5 (s) (CH₂), 27.8 (s) (CH₂); m/z (APCI) 313 [(M+H)+, 100%]; (Found: (M + H)+ (ES⁺) 313.1184. C₁₇H₁₈N₂O₄ requires (M + H)+ 313.1183).

3-Methyl-1-(4'-methoxyphenyl)-3-(4"-nitrophenyl)pyrrolidin-2-one (143b)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-(4-methoxyphenyl)-3-phenylsulfanyl-pyrrolidin-2-one (142) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and methyl iodide (0.21 ml, 3.34 mmol) to give the crude product (1.41 g) as brown oil. The crude product was then purified by column chromatography Rf 0.19 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.45 g, 83%) as a yellow crystalline solid. M.p. 84-85 °C; vₘₚₙₐₓ (nujol, NaCl plates/ cm⁻¹) 2922 (s), 1688 (s), 1603 (m), 1463 (s), 1377 (m), 1296 (w), 1244 (w), 1024 (w), 840 (m); δᵣᵣᵣᵣ (400 MHz; CDCl₃) 8.10 (2H, d, J 8.7 Hz, H-3' & H-5'), 7.58 (2H, d, J 8.7 Hz, H-2' & H-6'), 7.48 (2H, d, J 8.9 Hz, H-2" & H-6"), 6.84 (2H, d, J 8.9 Hz, H-3" & H-5"), 3.73-3.78 (1H, m, H-5α), 3.72 (3H, s, O-CH₃), 3.62-3.68 (1H, m, H-5β), 2.47-2.57 (1H, m, H-4α), 2.25-2.31 (1H, m, H-4β), 1.58 (3H, s, CH₃); δₜₜₜₜ (100 MHz; CDCl₃) 175.4 (s) (C=0), 157.2 (s) (C, Ar), 151.4 (s) (C, Ar), 147.1 (s) (C, Ar), 132.8 (s) (C, Ar), 127.8 (s) (2 × CH, Ar), 124.1 (s) (2 × CH, Ar), 122.1 (s) (2 × CH, Ar), 114.5 (s) (2 × CH, Ar), 55.9 (s) (O-CH₃), 50.5 (s) (C, quaternary), 45.9 (s) (CH₂), 34.8 (s) (CH₂), 25.6 (s) (CH₃); m/z (APCI) 327 [(M+H)+, 100%]; (Found: (M + H)+ (ES⁺) 327.1337. C₁₈H₁₈N₂O₄ requires (M + H)+ 327.1339).

3-Benzyl-1-(4'-methoxyphenyl)-3-(4"-nitrophenyl)-pyrrolidin-2-one (143c)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-(4-methoxyphenyl)-3-phenylsulfanyl-pyrrolidin-2-one (142) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and benzyl bromide (0.40 ml, 3.34 mmol) to give the crude product (2.60 g) as brown oil. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.44 g, 66%) as an orange
oil. \( \text{\( \nu \text{max (neat, NaCl plates/ cm}^{-1}) \)} \) 2956 (s), 1681 (s), 1453 (s), 1110 (s); \( \delta_{H}(400 \text{ MHz; CDCl}_3 \) 8.20 (2H, d, \( J 8.9 \text{ Hz, H-3' & H-5'} \)), 7.80 (2H, d, \( J 8.9 \text{ Hz, H-2' & H-6'} \)), 7.40 (2H, d, \( J 9.0 \text{ Hz, H-2'' & H-6''} \)), 7.24-7.28 (3H, m, Ph), 7.10-7.12 (2H, m, Ph), 6.91 (2H, d, \( J 9.0 \text{ Hz, H-3'' & H-5''} \)), 3.81 (3H, s, O-CH\(_3\)), 3.50 (1H, dt, \( J 7.0 \text{ & 9.5 Hz, H-5a} \)), 3.43 (1H, d, \( J 13.4 \text{ Hz, HCH-Ph} \)), 3.21-3.27 (1H, m, H-5β), 3.15 (1H, d, \( J 13.4 \text{ Hz, HCH-Ph} \)), 2.51-2.57 (2H, m, H-4); \( \delta_{C}(100 \text{ MHz; CDCl}_3 \) 174.1 (s) (C=O), 157.3 (s) (C, Ar), 150.0 (s) (C, Ar), 147.2 (s) (C, Ar), 136.6 (s) (C, Ar), 132.5 (s) (C, Ar), 130.6 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 127.6 (s) (CH, Ar), 123.9 (s) (2 × CH, Ar), 122.5 (s) (2 × CH, Ar), 114.4 (s) (2 × CH, Ar), 55.9 (s) (O-CH\(_3\)), 55.0 (s) (C, quaternary), 46.1 (s) (CH\(_2\)), 46.0 (s) (CH\(_2\)), 30.0 (s) (CH\(_3\)); m/z (APCI) 403 [(M+H)\(^+\), 100\%]; (Found: (M + H)\(^+\) (ES\(^+\)) 403.1581 C\(_{18}\)H\(_{18}\)N\(_2\)O\(_4\) requires (M + H)\(^+\) 403.1580).

1-Benzyl-3-(4'-nitrophenyl)piperidin-2-one (147a)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-benzyl-3-phenylsulfanyl-piperidin-2-one (146) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and saturated ammonium chloride (2.0 ml) to give the crude product (1.80 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.33 g, 64\%) as a yellow crystalline solid. M.p. 104-105 °C; \( \nu \text{max (nujol, NaCl plates/ cm}^{-1}) \) 3458 (s), 3029 (s), 2940 (s), 2240 (m), 1710 (s), 1627 (s), 1518 (s), 1452 (s), 1348 (s), 1249 (m), 1195 (m), 1108 (m), 1015 (m); \( \delta_{H}(400 \text{ MHz; CDCl}_3 \) 8.11 (2H, d, \( J 8.8 \text{ Hz, H-3' & H-5'} \)), 7.31 (2H, d, \( J 8.8 \text{ Hz, H-2' & H-6'} \)), 7.21-7.29 (5H, m, Ph), 4.59 (3H, s, CH\(_2\)), 3.76 (1H, dd, \( J 6.1 \text{ & 9.2 Hz, H-3} \)), 3.24-3.36 (2H, m, H-6), 2.09-2.17 (1H, m, H-4a), 1.73-1.93 (3H, m, H-4β & H-5); \( \delta_{C}(100 \text{ MHz; CDCl}_3 \) 169.8 (s) (C=O), 149.7 (s) (C, Ar), 147.1 (s) (C, Ar), 137.4 (s) (C, Ar), 129.8 (s) (2 × CH, Ar), 129.1 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 124.1 (s) (2 × CH, Ar), 51.0 (s) (CH\(_2\)), 49.2 (s) (CH), 47.6 (s) (CH\(_2\)), 30.3 (s) (CH\(_2\)), 21.4 (s) (CH\(_2\)); m/z (APCI) 311 [(M+H)\(^+\), 100\%]; (Found: (M + H)\(^+\) (ES\(^+\)) 311.1388 C\(_{18}\)H\(_{18}\)N\(_2\)O\(_3\) requires (M + H)\(^+\) 311.1390).
3-Methyl-1-benzyl-3-(4"-nitrophenyl)piperidin-2-one (147b)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.16 g, 4.05 mmol), 1-Benzyl-3-phenylsulfanyl-piperidin-2-one (146) (0.40 g, 1.35 mmol), nitrobenzene (0.14 ml, 1.35 mmol) and methyl iodide (0.17 ml, 2.70 mmol) to give the crude product (1.30 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.10 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.27 g, 61%) as a yellow oil. $\nu_{\text{max}}$ (neat, NaCl plates/cm$^{-1}$) 3460 (s), 3027 (s), 2938 (s), 1701 (s), 1637 (s), 1518 (s), 1453 (s), 1350 (s), 1249 (m), 1199 (m), 1101 (m); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 8.08 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.41 (2H, d, J 8.9 Hz, H-2' & H-6'), 7.19-7.30 (5H, m, Ph), 4.73 (1H, d, J 14.4 Hz, HCH-Ph), 4.45 (1H, d, J 14.4 Hz, HCH-Ph) 3.19-3.27 (2H, m, H-6), 2.11-2.18 (1H, m, H-4a), 1.87-1.96 (1H, m, H-4β), 1.63-1.71 (1H, m, H-5a), 1.44-1.55 (1H, m, H-5β), 1.58 (3H, s, CH$_3$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 173.0 (s) (C=O), 153.9 (s) (C, Ar), 146.8 (s) (C, Ar), 137.6 (s) (C, Ar), 129.1 (s) (2 x CH, Ar), 128.7 (s) (2 x CH, Ar), 128.0 (s) (2 x CH, Ar), 127.8 (s) (2 x CH, Ar), 124.0 (s) (2 x CH, Ar), 51.2 (s) (CH$_2$), 48.5 (s) (C, quaternary), 48.1 (s) (CH$_2$), 37.0 (s) (CH$_2$), 27.9 (s) (CH$_3$), 19.6 (s) (CH$_3$); $m/z$ (APCI) 325 [(M+H)$^+$, 100%]; (Found: (M + H)$^+$ (ES$^+$) 325.1551. C$_{19}$H$_{20}$N$_2$O$_3$ requires (M + H)$^+$ 325.1547).

3-Ethyl-1-benzyl-3-(4"-nitrophenyl)piperidin-2-one (147c)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.04 mmol), 1-benzyl-3-phenylsulfanyl-piperidin-2-one (146) (0.50 g, 1.68 mmol), nitrobenzene (0.18 ml, 1.68 mmol) and ethyl iodide (0.52 g, 3.36 mmol) to give the crude product (1.43 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.27 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.33 g, 58%) as a yellow oil. $\nu_{\text{max}}$ (neat, NaCl plates/cm$^{-1}$) 2929 (s), 1618 (s), 2938 (s), 1494 (s), 1377 (m), 1194 (m); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 8.07 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.47 (2H, d, J 8.9 Hz, H-2' & H-6'), 7.19-7.27 (5H, m, Ph); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 172.0 (s) (C=O), 152.7 (s) (C, Ar), 146.8 (s) (C, Ar), 137.6 (s) (C, Ar), 129.7 (s) (2 x CH, Ar), 129.1 (s) (2 x CH, Ar), 128.6 (s) (2 x CH, Ar), 128.0 (s) (CH, Ar), 123.9 (s) (2 x CH, Ar), 52.4 (s) (C, quaternary), 51.2 (s) (CH$_2$), 48.0 (s) (CH$_2$), 34.3 (s) (CH$_2$), 31.3 (s) (CH$_3$), 19.0 (s) (CH$_3$), 9.6 (s) (CH$_3$); $m/z$ (APCI) 339 [(M+H)$^+$, 100%]; (Found: (M + H)$^+$ (ES$^+$) 339.1708. C$_{20}$H$_{22}$N$_2$O$_3$ requires (M + H)$^+$ 339.1703).
1-Phenyl-2-methyl-4-(4”-nitrophenyl)pyrazolidin-3-one (154a)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.21 g, 5.28 mmol), 1-phenyl-2-methyl-4-phenylsulfanyl-pyrazolidin-3-one (153) (0.50 g, 1.76 mmol), nitrobenzene (0.18 ml, 1.76 mmol) and saturated ammonium chloride (2.0 ml) to give the crude product (1.01 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.14 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.36 g, 69%) as a yellow crystalline solid. M.p. 170-172 °C; νmax (nujol, NaCl plates/ cm⁻¹) 2918 (s), 1699 (s), 1595 (m), 1513 (m), 1462 (s), 1377 (m); δH(400 MHz; CDCl₃) 7.97 (2H, d, J 8.8 Hz, H-3‘ & H-5’), 7.17-7.23 (4H, m, H-2’, H-6’, H-3” & H-5”), 6.96 (1H, app. t, J 7.5 Hz, H-4”), 6.81 (2H, d, J 7.5 Hz, H-2” & H-6”), 3.76-3.96 (3H, m, H-3 & H-4), 2.96 (3H, s, CH₃); δC(100 MHz; CDCl₃) 171.6.(s) (C=O), 149.3 (s) (C, Ar), 147.6 (s) (C, Ar), 143.9 (s) (C, Ar), 130.1 (s) (2 × CH, Ar), 129.9 (s) (2 × CH, Ar), 125.0 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 119.2 (s) (2 × CH, Ar), 63.6 (s) (CH₂), 45.9 (s) (CH₃ or CH), 31.6 (s) (CH₃ or CH); m/z (APCI) 298 [(M+H)⁺, 100%]; (Found: (M + H)⁺ (ES⁺) 298.1181. C₁₄H₁₅N₃O₃ requires (M + H)⁺ 298.1186).

4-Methyl-1-phenyl-2-methyl-4-(4”-nitrophenyl)pyrazolidin-3-one (154b)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.21 g, 5.28 mmol), 1-phenyl-2-methyl-4-phenylsulfanyl-pyrazolidin-3-one (153) (0.50 g, 1.76 mmol), nitrobenzene (0.18 ml, 1.76 mmol) and methyl iodide (0.22 ml, 3.52 mmol) to give the crude product (1.22 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.50 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.26 g, 47%) as a yellow crystalline solid. M.p. 200 °C dec; νmax (nujol, NaCl plates/ cm⁻¹) 3383 (s), 2923 (s), 2455 (w), 1939 (m), 1462 (m), 1376 (m); δH(400 MHz; CDCl₃) 7.96 (2H, d, J 8.8 Hz, H-3‘ & H-5’), 7.42 (2H, d, J 8.8 Hz, H-2’ & H-6”), 7.13 (2H, app. t, J 8.1 Hz, Ph), 6.89 (1H, app. t, J 8.1 Hz, Ph), 6.73 (2H, app. d, J 8.1 Hz, Ph), 4.20 (1H, d, J 11.7 Hz, HCH), 3.95 (1H, d, J 11.7 Hz, HCH), 3.07 (3H, s, N-CH₃), 1.44 (3H, s, CH₃); δC(100 MHz; CDCl₃) 174.3.(s) (C=O), 149.7 (s) (C, Ar), 149.6 (s)
(C, Ar), 147.0 (s) (C, Ar), 129.7 (s) (2 x CH, Ar), 128.6 (s) (2 x CH, Ar), 124.0 (s) (CH, Ar), 123.9 (s) (2 x CH, Ar), 118.1 (s) (2 x CH, Ar), 67.8 (s) (CH2), 49.4 (s) (C, quaternary), 32.1 (s) (CH3), 25.4 (s) (CH3); m/z (APCI) 312.0 [(M+H)+, 100%; (Found: (M + H)+ (ES+) 312.1340 C_{17}H_{27}N_{3}O requires (M + H)+ 312.1343).

4-Benzyl-1-phenyl-2-methyl-4-(4'-nitrophenyl)pyrazolidin-3-one (154c)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-phenyl-2-methyl-4-phenylsulfanyl-pyrazolidin-3-one (153) (0.50 g, 1.76 mmol), nitrobenzene (0.18 ml, 1.76 mmol) and benzyl bromide (0.40 ml, 3.34 mmol) to give the crude product (2.60 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane/ethyl acetate; 3:1) to give the pure product (0.41 g, 61%) as a yellow crystalline solid. v_max (nujol, NaCl plates/ cm⁻¹) 2920 (s), 2440 (w), 1921 (w), 1690 (s), 1595 (m), 1507 (m), 1462 (s); δ_H (400 MHz; CDCl₃) 7.97 (2H, d, J 8.8 Hz, H-3' & H-5'), 7.39 (2H, d, J 8.8 Hz, H-2' & H-6'), 7.21-7.29 (3H, m, Ph), 7.15 (2H, app. t, J 8.0 Hz, Ph), 7.10-7.13 (2H, m, Ph), 6.91 (1H, t, J 8.0 Hz, Ph), 6.70 (2H, app. d, J 8.0 Hz, Ph), 4.19 (1H, d, J 11.9 Hz, HCH), 3.93 (1H, d, J 11.9 Hz, HCH), 3.41 (1H, d, J 13.1 Hz, HCH-Ph), 3.13 (1H, d, J 13.1 Hz, HCH-Ph), 3.10 (3H, s, N-CH₃); δ_C (100 MHz; CDCl₃) 173.7 (s) (C=O), 149.9 (s) (C, Ar), 149.7 (s) (C, Ar), 146.9 (s) (C, Ar), 130.0 (s) (2 x CH, Ar), 128.5 (s) (2 x CH, Ar), 127.9 (s) (CH, Ar), 127.0 (s) (2 x CH, Ar), 126.7 (s) (2 x CH, Ar), 123.9 (s) (CH, Ar), 123.7 (s) (2 x CH, Ar), 117.9 (s) (2 x CH, Ar), 67.9 (s) (CH₂), 49.9 (s) (C, quaternary), 43.0 (s) (CH₂), 32.2 (s) (CH₃); m/z (APCI) 388.0 [(M+H)+, 100%; (Found: (M + H)+ (ES+) 388.1586 C_{17}H_{27}N_{3}O requires (M + H)+ 388.1583).

3-(4''-Nitrophenyl)-pyrrolidin-2-one (155)—Cerium ammonium nitrate (0.53 g, 0.96 mmol) was dissolved in water (6.0 ml) and added to a solution of 1-(4'-methoxyphenyl)-3-(4''-nitrophenyl)-pyrrolidin-2-one (143a) (200 mg, 0.32 mmol) in acetonitrile (12.0 ml) at 0 °C. After stirring for 1 hour excess solid sodium sulfite was added. The solvent was then removed.
on a rotary evaporator. Ethyl acetate (20.0 ml) was then added to the organic residue. The solution was then washed with brine, dried over magnesium sulfate and the solvent removed on a rotary evaporator to leave the crude product (0.21 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.10 (silica, hexane:ethyl acetate; 1:1) to give the pure product (98 mg, 81%) as a yellow crystalline solid. M.p. 168-170 °C; \( \nu_{\text{max}} \) (nujol, NaCl plates/ cm\(^{-1}\)) 2922 (s), 1676 (s), 1598 (m), 1528 (m), 1464 (s), 1377 (m), 1346 (s); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 8.15 (2H, d, \( J = 8.8 \) Hz, H-3' & H-5'), 7.41 (2H, d, \( J = 8.8 \) Hz, H-2' & H-6'), 7.0 (1H, s, NH), 3.73 (1H, t, \( J = 9.4 \) Hz, H-3), 3.41-3.46 (2H, m, H-5), 2.55-2.64 (1H, m, H-4a), 2.15-2.25 (1H, m, H-4\( \beta \)); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 177.9 (s) (C=O), 147.5 (s) (C, Ar), 147.0 (s) (C, Ar), 129.5 (s) (2 \( \times \) CH, Ar), 124.4 (s) (2 \( \times \) CH, Ar), 47.7 (s) (CH), 41.0 (s) (CH\(_2\)), 30.8 (s) (CH\(_2\)); \( m/z \) (APCI) 207 [(M+H)+, 100%]; (Found: (M + H)+ (ES+) 207.0699 C\(_{10}\)H\(_{10}\)N\(_2\)O\(_3\) requires (M + H)+ 207.0691).

**General Method for \( \alpha \)-chlorination of Lactams**—To a stirred solution of the lactam (31.26 mmol) in dry THF (30 ml) at \(-78^\circ\)C under an inert atmosphere was added sec-Buli (34.3 mmol) (1.4 M in cyclohexanes) and the reaction mixture was stirred for 30 minutes. \( p \)-Toluenesulfonyl chloride (50 mmol) dissolved in dry THF (25 ml) was added dropwise to the reaction mixture, which was then allowed to warm to room temperature. After stirring for 16 hours the resulting suspension was quenched with saturated ammonium chloride (100 ml) and the aqueous layer was washed with ethyl acetate (3 x 50 ml). The organic layers were combined, washed with water (50 ml), dried over Na\(_2\)SO\(_4\), the solvent removed on a rotary evaporator to give the crude product.

![Chemical Structure](https://example.com/structure.png)

**1-Methyl-3-chloro-pyrrolidin-2-one\(^{220} \)** (150)—This was prepared by the General Method using 1-methyl-2-pyrrolidinone (104) (3.0 ml, 31.26 mmol), sec-BuLi (25.0 ml, 35 mmol) (1.4 M in cyclohexanes), and \( p \)-toluenesulfonyl chloride (9.1 g, 50.1 mmol) to give the crude product as an orange oil. The crude product was then purified by column chromatography Rf 0.037 (silica, dichloromethane:ethyl acetate; 1:1) to give the pure product (2.09 g, 50%) as a yellow oil. \( \nu_{\text{max}} \) (neat, NaCl plates/ cm\(^{-1}\)) 1698 (s), 1513 (m), 1344 (m); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 4.29 (1H, dd, \( J = 4.6 \) & 7.7 Hz, H-3), 3.40-3.51 (1H, m, H-5\( \alpha \)), 3.22-3.33 (1H, m, H-5\( \beta \)), 2.81 (3H, s, CH\(_3\)), 2.42-2.60 (1H, m, H-4\( \alpha \)), 2.06-2.21 (1H, m, H-4\( \beta \)); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\))
169.1 (s) (C=O), 56.9 (s) (C-3), 48.4 (s) (N-CH₃), 47.8 (s) (C-5), 32.1 (s) (C-4); m/z (APCI) 134.0 [(M+H)+, 100%].

1-Benzyl-3-chloro-piperidin-2-one (149) — This was prepared by the General Method using 1-benzyl-piperidin-2-one (145) (1.3 g, 6.87 mmol), sec-Buli (5.5 ml, 7.7 mmol) (1.4 M in cyclohexanes), and p-toluenesulfonyl chloride (2.0 g, 11.0 mmol) to give the crude product as a yellow oil. The crude product was then purified by column chromatography Rf 0.10 (silica, hexane:ethyl acetate; 3:2) to give the pure product (0.58 g, 38%) as a yellow crystalline solid. M.p. 71-73 °C (lit. 72-73 °C), υmax (nujol, NaCl plates/ cm⁻¹) 2956 (s), 2240 (w), 1657 (s), 1493 (s), 1452 (s), 1353 (s), 1173 (s), 1079 (m), 951 (m); δH (400 MHz; CDCl₃) 7.12-7.24 (5H, m, Ph), 4.61 (1H, d, J 14.6 Hz, HCH-Ph), 4.40 (1H, t, J 4.4 Hz, H-3), 4.33 (1H, d, J 14.6 Hz, HCH-Ph), 3.08-3.19 (2H, m, H-6), 1.99-2.14 (3H, m, H-5 & H-4 a), 1.62-1.67 (1H, m, H-4β); δC (100 MHz; CDCl₃) 173.6 (s) (C=O), 136.9 (s) (C, Ar), 130.3 (s) (2 × CH, Ar), 129.0 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 55.6 (s) (CH), 50.8 (s) (CH₂), 47.4 (s) (CH₂), 31.4 (s) (CH₂), 19.0 (s) (CH₂); m/z (APCI) 224.0 [(M+H)+, 100%].

3-Methyl-1-benzyl-3-(4'-aminophenyl)pyrrolidin-2-one (156) — In a two necked round bottom flask was added 10% palladium on carbon (25 mg) and ethyl acetate (2 ml). The catalyst was activated by flushing with hydrogen 3 times. 3-Methyl-1-benzyl-3-(4'-nitrophenyl)pyrrolidin-2-one (138a) was added to the flask. The mixture was flushed with hydrogen and then left to stir under hydrogen at atmospheric pressure for 24 hours. The reaction mixture was then filtered through celite and then reduced on a rotary evaporator to give the crude product (210 mg) as a brown oil. The crude product was then purified by column chromatography Rf 0.20 (silica, hexane: ethyl acetate 1:3) as a yellow oil. υmax (neat, NaCl plates/ cm⁻¹) 3489 (s), 3410 (s), 2981 (s), 1691 (s); δH (400 MHz; CDCl₃) 7.07 (2H, d, J 8.4 Hz, H-2' & H-6'), 6.79-7.30 (5H, m, Ph), 6.64 (2H, d, J 8.4 Hz, H-3' & H-5'), 4.44 (2H, s, CH₂-Ph), 3.49 (2H, s, CH₃), 3.09-3.21 (2H, m, H-5), 2.23-2.29 (1H, m, H-4α), 2.03-2.11 (1H, m, H-4β), 1.52 (3H, s, CH₃); δC (100 MHz; CDCl₃) 177.1 (s) (C=O), 149.2 (s) (C, Ar), 146.3 (s) (C, Ar), 135.7 (s) (C, Ar),
129.5 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 128.0 (s) (2 × CH, Ar), 123.5 (s) (2 × CH, Ar),
119.8 (s) (2 × CH, Ar), 49.7 (s) (C, quaternary), 47.4 (s) (CH₂), 43.2 (s) (CH₂), 35.1 (s) (CH₂),
24.8 (s) (CH₃); m/z (APCI) 281.0 [(M+H)⁺, 100%].

**Dihydro-5-phenyl(3H)furan-2-one**

Dihydro-5-phenyl(3H)furan-2-one

3-Benzoylpropionic acid (2.0 g, 11.2 mmol) was dissolved in ethanol (50 ml). A solution of sodium borohydride (0.85 g, 22.4 mmol) in ethanol (25 ml) was slowly added at 0 °C. Following the addition the reaction mixture was stirred at room temperature for four hours. The reaction was followed by TLC. After acidification with 10% HCl most of the ethanol was removed on a rotary evaporator. The resulting mixture was cooled to room temperature and extracted with dichloromethane (3 × 50 ml). The dichloromethane was removed on a rotary evaporator to give the crude product (1.70 g) as a white solid. The product was then purified by column chromatography Rf 0.25 (silica, hexane:ethyl acetate 3:1) to give the pure product (1.39 g, 51%) as a white crystalline solid. M.p.35-37 °C (lit. 37-38 °C).

υmax (nujol on NaCl plates/ cm⁻¹) 2921 (s), 1794 (s) (C=O), 1459 (s), 1376 (s), 1170 (m), 939 (w), 698 (w), δh(400 MHz; CDCl₃) 7.25-7.45 (5H, m, aromatic), 5.5, (1H, m, CH-O), 2.80 (3H, m, CH₂-C=O + HCH), 2.25 (1H, m, HCH), δc(400 MHz; CDCl₃) 177.0 (s) (C=O), 139.4 (s) (C, Ar), 128.8 (s) (2 × CH, Ar), 128.5 (s) (CH, Ar), 125.3 (s) (2 × CH, Ar), 81.2 (s) (Ph-C-O), 31.0 (s) (C=C=O), 29.0 (s) (CH₂-CH₂-CH₂) m/z (APCI) 162.9 [(M + H)⁺, 100%].

(3SR,5RS) & (3RS,5RS)-Dihydro-5-phenyl-3-(phenylthio)(3H)furan-2-one

(3SR,5RS) & (3RS,5RS)-Dihydro-5-phenyl-3-(phenylthio)(3H)furan-2-one

To a solution of di-isopropylamine (0.33 ml, 2.35 mmol) in dry THF (10 ml) was added n-
butyllithium (0.67 ml, 2.35 mmol) at −78 °C under nitrogen. The mixture was stirred for half an hour at this temperature. The lactone 166 (0.35 g, 2.35 mmol) was dissolved in dry THF (5 ml), cooled to −78 °C and added to the LDA solution. The reaction mixture was stirred at −78 °C for a further half hour. Phenyl disulfide (0.55 g, 2.56 mmol) was dissolved in dry THF (5
ml) at -78 °C and added dropwise to the reaction mixture. The mixture was stirred at -78 °C for three hours. The reaction was then quenched with saturated aqueous ammonium chloride (2 ml). The organic product was extracted with chloroform (3 x 25 ml) and washed with water (3 x 25 ml), sodium, bicarbonate (25 ml) and the solvent was dried (magnesium sulfate) and removed to give the crude product (0.63 g) as a yellow crystalline solid. The product was then purified by column chromatography (silica, hexane:ethyl acetate 3:1) to give the cis and trans products (0.40 g, 70% overall yield). Cis-161 (0.24 g) as a white crystalline solid: Rf (Hexane:Ethyl acetate 3:1) 0.28, M.p. 92-94 °C (lit. 94 °C)\textsuperscript{171}; \nu_{\text{max}} (nujol; NaCl plates/ cm\textsuperscript{-1}) 2926 (s), 1772 (s), 1457 (m), 1376 (w), 1176 (m), 1017 (m), 940 (m), 756 (m); \delta_{\text{n}}(400 MHz; CDCl\textsubscript{3}) 7.48-7.51 (2H, m. aromatic), 7.26-7.35 (6H, m, aromatic), 7.05-7.08 (2H, m, aromatic), 5.30 (1H, dd, J 10.0 & 6.1 Hz, H-5), 4.08 (1H, dd, J 11.5 & 8.7 Hz, H-3), 2.97 (1H, ddd, J 13.4, 8.9 & 6.3 Hz, H-4\alpha), 2.20 (1H, ddd, J 13.4, 11.5 & 10.1 Hz, H-4\beta); \delta_{\text{c}}(400 MHz; CDCl\textsubscript{3}) 174.5 (s) (C=O), 138.5 (s) (C, Ar), 134.5 (s)(C, Ar), 132.0 (s) (C, Ar), 129.5 (s) (C, Ar), 129.0 (s) (C, Ar), 128.5 (s) (C, Ar), 126.5 (s) (C, Ar) 126.0 (s) (C, Ar), 79.0 (s) (C-O), 47.0 (s) (C-S), 39.0 (s) (CH\textsubscript{2}) m/z (APCI) 271.0 [(M+H)+, 100%]; Trans-161 (0.16 g) as a white crystalline solid: Rf (Hexane:ethyl acetate) 0.32, M.p. 80-81 °C (lit. 81-82 °C)\textsuperscript{250}; \nu_{\text{max}} (nujol; NaCl plates/ cm\textsuperscript{-1}) 2928 (s), 1769 (s), 1460 (m), 1372 (w), 1177 (m), 1020 (m), 755 (m); \delta_{\text{n}}(400 MHz; CDCl\textsubscript{3}) 7.49-7.51 (2H, m, aromatic), 7.20-7.35 (8H, m, aromatic), 5.39 (1H, t, J 7.6 Hz, H-5), 3.96 (1H, dd, J 8.0 & 4.2 Hz, H-3), 2.56 (2H, m, H-4\alpha & H-4\beta); \delta_{\text{c}}(400 MHz; CDCl\textsubscript{3}) 174.0 (s) (C=O), 137.5 (s) (C, Ar), 133.0 (s) (C, Ar), 131.0 (s) (C, Ar), 129.0 (s) (C, Ar), 128.0 (s) (C, Ar), 127.5 (s) (C, Ar), 124.5 (s) (C, Ar), 78.5 (s) (C-O), 44.0 (s) (C-S), 37.5 (s) (CH\textsubscript{2}); m/z (APCI) 271 [(M+H)+, 100%].

**General Method for Asymmetric VNS**—Sodium hydride (60% dispersion in oil) (4.6 mmol) was added to anhydrous DMF (3 ml) and the mixture flushed with nitrogen and cooled to 0 °C. The thiophenylated lactone 167 (4.6 mmol) and nitrobenzene (4.6 mmol) were dissolved in anhydrous DMF (5 ml) and added dropwise to the sodium hydride slurry. The reaction was stirred at 0 °C for thirty minutes before being allowed to warm to room temperature and stirred at this temperature for two hours. The reaction was then cooled to -50 °C using a methanol/cardice cooling bath. The electrophile (9.2 mmol) was added to the solution. The solution was then allowed to warm to room temperature and stirred at this temperature for two hours. The reaction mixture was poured onto ice/hydrochloric acid (1 M solution) (50 ml). The product was then extracted with dichloromethane (5 x 50 ml) and then washed with water
(5 x 50 ml), sodium bicarbonate (3 x 50 ml) and dried (sodium sulfate). The solvent was removed on a rotary evaporator to give the crude product.

(3SR,5RS)-3-Methyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (162)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone 161 (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and iodomethane (0.24 ml, 3.7 mmol) to give the crude product (0.62 g) an orange oil. The crude product was purified using column chromatography (silica, hexane:ethyl acetate 3:1 Rf 0.20) to give the pure product (0.41g, 73%) as a white crystalline solid. M.p. 122-124 °C; (Found C, 68.8; H, 4.9; N 4.8% C_{17}H_{13}NO_{4} requires C, 68.7; H, 5.1; N, 4.7%); ν_{max} (nujol on NaCl plates/ cm\(^{-1}\)) 2918 (m), 1758 (s) (C=O), 1344 (m), 1177 (m), 848 (m), 732 (m), 694 (m), δ_{H} (400 MHz; CDCl\(_3\)), 8.21 (2H, d, J 8.9 Hz, H-3' and H-5'), 7.71 (2H, d, J 8.9 Hz, H-2' and H-6'), 7.33-7.41 (5H, m, Ph), 5.65 (1H, dd, J 9.9 & 6.1 Hz, H-5), 2.89 (1H, dd, J 13.0 & 6.1 Hz, H-4a), 2.63 (1H, dd, J 13.0 & 9.9 Hz, H-4β), 1.79 (3H, s, CH\(_3\)); δ_{C} (100 MHz; CDCl\(_3\)), 178.5 (s) (C=O), 149.5 (s) N(C, Ar), 147.4 (s) (C, Ar), 138.7 (s) (C, Ar), 129.3 (s) (2 x CH, Ar), 129.2 (s) (CH, Ar), 127.8 (s) (2 x CH, Ar), 125.8 (s) (2 x CH, Ar), 124.2 (s) (2 x CH, Ar), 78.4 (s) (C-5), 49.0 (s) (C-3), 46.6 (s) (CH\(_2\)), 25.6 (s) (CH\(_3\)); m/z (APCI) 298.0 [(M + H\(^{+}\)), 100 %], 282.0 (24), 252.0 (24), 220.9 (7), 219.9 (62), 192.0 (8), 79.2 (9); (Found: (M + NH\(_4\))\(^{+}\) (ES\(^{+}\)), 315.1348. C_{17}H_{13}NO_{4} requires (M + NH\(_4\))\(^{+}\) 315.1345).

(3SR,5RS)-Dihydro-3-(4'-nitrophenyl)-5-phenyl(3H)furan-2-one (162a)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone
161 (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and saturated aqueous ammonium chloride (2.0 ml) to give the crude product (0.94 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.28 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 73%) as a white crystalline solid. M.p. 117-119 °C; (Found C, 67.93; H, 4.87; N 4.86%. C_{16}H_{13}NO_4 requires C, 67.8; H, 4.6; N, 4.9%); \nu_{\text{max}} \text{ (nujol on NaCl plates/ cm}^{-1}) 2917 (m), 1759 (s) (C=O), 1367 (m), 1321 (w), 1172 (m), 848 (m), 732 (m); \delta_{\text{H}} \text{(400 MHz; CDCl}_3\text{)} 8.16 (2H, d, J 8.8 Hz, H-3' \& H-5'), 7.46 (2H, d, J 8.8 Hz, H-2' \& H-6'), 7.27-7.38 (5H, m, Ph), 5.50 (1H, dd, J 10.7 & 5.5 Hz, H-5), 4.11 (1H, dd, J 12.8 & 8.4 Hz, H-3), 3.03-3.10 (1H, m, H-4a), 2.30-2.39 (1H, m, H-4b); \delta_{\text{C}} (100 MHz; CDCl}_3\text{)} 177.7 (s) (C=O), 149.2 (s) (C, Ar), 147.7 (s) (C, Ar), 138.9 (s) (C, Ar), 129.3 (s) (2 \times CH, Ar), 129.0 (s) (CH, Ar), 127.9 (s) (2 \times CH, Ar), 125.7 (s) (2 \times CH, Ar), 124.3 (s) (2 \times CH, Ar), 78.7 (s) (C-5), 50.9 (s) (C-3), 46.4 (s) (C-4); \text{m/z (APCI)} 284.0 [(M + H)^{+}, 100 \%]; (Found: (M + H)^{+} (APCI) 283.0846 C_{16}H_{13}NO_4 requires (M + H)^{+} 283.0845.

(3SR,5RS)-3-Allyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (162b)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone 161 (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and allyl bromide (0.16 ml, 1.85 mmol) to give the crude product (1.0 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.28 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 67%) as a white crystalline solid. M.p. 124-126 °C; (Found C, 70.71; H, 5.22; N 4.03. C_{19}H_{17}NO_4 requires C, 70.6; H, 5.3; N, 4.3%); \nu_{\text{max}} \text{ (nujol on NaCl plates/ cm}^{-1}) 2919 (m), 1760 (s) (C=O), 1341 (m), 1173 (m), 840 (m); \delta_{\text{H}} \text{(400 MHz; CDCl}_3\text{)} 8.12 (2H, d, J 9.0 Hz, H-3' \& H-5'), 7.67 (2H, d, J 9.0 Hz, H-2' \& H-6'), 7.21 (5H, m, Ph), 5.49-5.68 (2H, m, H-4 \& -CH=CH_2), 5.09-5.17 (2H, m, CH_2=CH-_), 2.98 (1H, dd, J 6.7 & 13.2 Hz, H-3\alpha), 2.73 (2H, d, J 7.40 Hz, -CH_2=CH-), 2.55 (1H, dd, J 9.2 & 13.2 Hz, H-3\beta); \delta_{\text{C}} (100 MHz; CDCl}_3\text{)} 177.0 (s) (C=O), 147.4 (s) (C, Ar), 147.0 (s) (C, Ar), 138.6 (s) (C, Ar), 128.9 (s) (CH), 128.8 (s) (2 \times CH, Ar), 127.8 (s) (2 \times CH, Ar), 125.9 (s) (C, Ar), 125.3 (s) (2 \times CH, Ar), 123.5 (s) (2 \times CH, Ar), 121.1 (s) (CH_2), 77.8 (s) (C-5), 51.9 (s) (C, quaternary), 43.7 (s) (CH_2), 42.0 (s)
(CH2); m/z (APCI) 324.0 [(M + H)+, 100%], 296.0 (19), 279.0 (9), 105.1 (5), 71.4 (4); (Found: (M + H)+ (APCI), 324.1236 C19H17NO4 requires (M + H)+ 324.1236).

(3SR,5RS)-3-Benzyl-3-(4'-nitrophenyl)-5-phenylidihydro(3H)furan-2-one (162c)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone 161 (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and benzyl bromide (0.32 g, 1.85 mmol) to give the crude product (0.95 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.46 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.34 g, 65%) as a white crystalline solid. M.p. 139-141 °C; (Found C, 74.17; H, 5.23; N 3.60%. C23H19NO4 requires C, 74.0; H, 5.1; N, 3.75%); \text{v}_{\text{max}}\text{ (nujol on NaCl plates/ cm}^{-1})\text{ 2918 (s), 1759 (s) (C=O), 1671 (w), 1595 (m), 1501 (w), 1462 (s), 1373 (m), 1353 (m); \delta_H\text{ (400 MHz; CDCl}_3\text{)} 8.19 (2H, d, J 8.8 Hz, H-3’ & H-5’), 7.69 (2H, d, J 8.8 Hz, H-2’ & H-6’), 7.19-7.45 (10H, m, Ph), 5.58 (1H, dd, J 10.0 & 6.2 Hz, H-5), 3.63 (1H, d, J 13.2 Hz, HCH-Ph), 3.16 (1H, d, J 13.2 Hz, HCH-Ph), 2.94 (1H, dd, J 7.4 & 14.1 Hz, H-4α), 2.48 (1H, dd, J 9.0 & 14.1 Hz, H-4β); \delta_C\text{ (100 MHz; CDCl}_3\text{)} 178.1 (s) (C=O), 149.0 (s) (C, Ar), 147.6 (s) (C, Ar), 140.2 (s) (C, Ar), 138.9 (s) (C, Ar), 129.7 (s) (2 × CH, Ar), 129.3 (s) (CH, Ar), 127.7 (s) (2 × CH, Ar), 125.5 (s) (2 × CH, Ar), 125.3 (s) (CH, Ar), 125.0 (s) (2 × CH, Ar), 124.3 (s) (2 × CH, Ar), 123.6 (s) (2 × CH, Ar), 78.0 (s) (C-5), 48.7 (s) (C-3), 46.1 (s) (CH2), 44.7 (s) (CH2); m/z (APCI) 374.0 [(M + H)+, 100%]; (Found: (M + H)+ (APCI) 373.1316 C23H19NO4 requires (M + H)+ 373.1314).
(3SR,5RS)-3-(2-oxo-2-phenylethyl)-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (162d)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone 161 (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and 2-bromoacetophenone (0.37 g, 1.85 mmol) to give the crude product (1.2 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.42 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 67%) as a white crystalline solid. M.p. 152-154 °C; \( \nu_{\text{max}} \) (nujol on NaCl plates/ cm\(^{-1}\)) 2918 (s), 1765 (s) (C=O), 1673 (m), 1596 (m), 1510 (m), 1462 (s), 1377 (m), 1348 (m), 1203 (w); \( \delta \) (400 MHz; CDCl\(_3\)) 8.05 (2H, d, \( J \) 8.9 Hz, H-3’ & H-5’), 7.84 (2H, app. d, \( J \) 8.0 Hz, Ph), 7.61 (2H, d, J 8.9 Hz, H-2’ & H-6’), 7.53 (1H, app. t, J 7.3 Hz, Ph), 7.39 (2H, app. t, J 7.8 Hz, Ph), 7.17-7.24 (3H, m, Ph), 7.08-7.14 (2H, m, Ph), 5.83 (1H, dd, J 5.8 & 8.4 Hz, H-5), 3.81 (1H, d, J 18.1 Hz, HCH), 3.65 (1H, d, J 18.1 Hz, HCH), 3.29 (1H, dd, J 8.5 & 13.6 Hz, H-4a), 2.81 (1H, dd, J 5.8 & 13.6 Hz, H-4b); \( \delta \) (100 MHz; CDCl\(_3\)) 196.4 (s) (C=O), 178.0 (s) (C=O), 148.5 (s) (C, Ar), 147.4 (s) (C, Ar), 140.0 (s) (C, Ar), 136.2 (s) (C, Ar), 134.5 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 129.1 (s) (2 × CH, Ar), 128.7 (s) (CH, Ar), 128.5 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 125.5 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 78.8 (s) (C-5), 50.1 (s) (C, quaternary), 48.5 (s) (CH\(_2\)), 42.1 (s) (CH\(_2\)); \( m/z \) (ES\(^+\)) 402.0 [(M + H\(^+\)], 100%); (Found: (M + H\(^+\) (ES\(^+\)), 402.1337. C\(_{22}\)H\(_{19}\)NO\(_5\) requires (M + H\(^+\)) 402.1335).

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\text{NO}_2
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\begin{array}{c}
\text{Cl} \\
\text{PhS} \\
\text{O} \\
\text{O} \\
\text{Ph}
\end{array}
\]

1. NaH, DMF
2. CH\(_3\)-I

(3SR,5RS)-3-Methyl-3-(5'-chloro-2'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (173)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone 161 (0.50 g, 1.85 mmol), 4-chloronitrobenzene (0.29 g, 1.85 mmol) and methyl iodide (0.25 ml, 1.85 mmol) to give the crude product (1.2 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.37 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.28 g, 51%) as a white crystalline solid. M.p. 179-181 °C; (Found C, 61.65; H, 4.30; N 4.19%. C\(_{17}\)H\(_{14}\)ClNO\(_4\) requires C, 61.55; H, 4.25; N, 4.22%); \( \nu_{\text{max}} \) (nujol on NaCl plates/ cm\(^{-1}\)) 2918 (s), 1762 (s) (C=O), 1666 (w), 1592 (m), 1496 (w);
δ\(_{\text{H}}\) (400 MHz; CDCl\(_3\)) 8.35 (1H, d, \(J 8.9\) Hz, H-3'), 8.01 (1H, d, \(J 1.1\) Hz, H-6'), 7.89 (1H, dd, \(J 1.1\) & 8.9Hz, H-4'), 7.31-7.45 (5H, m, Ph), 5.29 (1H, dd, \(J 9.2\) & 6.8 Hz, H-5), 2.69 (1H, dd, \(J 13.6\) & 6.8 Hz, H-4\(\alpha\)), 2.49 (1H, dd, \(J 13.6\) & 9.2 Hz, H-4\(\beta\)), 1.69 (3H, s, CH\(_3\)); δ\(_{\text{C}}\) (100 MHz; CDCl\(_3\)), 174.6 (s) (C=O), 148.1 (s) (C, Ar), 139.9 (s) (C, Ar), 138.2 (s) (C, Ar), 136.9 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.1 (s) (CH, Ar), 127.9 (s) (CH, Ar), 125.3 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 122.8 (s) (CH, Ar), 80.4 (s) (C-5), 49.8 (s) (C-3), 44.6 (s) (CH\(_2\)), 23.6 (s) (CH\(_3\)); m/z (APCI) 332.0 [(M + H)+, 100%]; (Found: (M + H)+ (APCI), 336.0614. C\(_{17}\)H\(_{14}\)ClNO\(_4\) requires (M + H)+ 331.0611).

**General Method for Alkylation of Nitrophenylacetates/propionates**—Sodium hydride (60% dispersion in oil) (1 eq.) was added to anhydrous DMF and the mixture flushed with nitrogen and cooled to 0 °C. Methyl 4-nitrophenyl propionate (173) (24.4 mmol) dissolved in DMF (20 ml) was then added and the solution was stirred at 0 °C for one hour. The electrophile (24.4 mmol) dissolved in DMF (10 ml) was added dropwise to the solution at -50 °C. The solution was then allowed to warm to room temperature and stirred for a further two hours. The reaction mixture was then poured onto ice/hydrochloric acid (1M solution) and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed well with water (5 × 50 ml), sodium bicarbonate (3 × 50 ml), dried (sodium sulfate) and the solvent removed on a rotary evaporator to give the crude product.

**Methyl (2-methyl-2-(4'-nitrophenyl)-4-oxo-4-phenyl)butyrate** (165)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.98 g, 24.4 mmol, methyl 4-nitrophenylpropionate (164) (5.1 g, 24.4 mmol) and 2-bromoacetophenone (4.86 g, 24.4 mmol) to give the crude product (5.6 g) as an orange crystalline solid. The crude product was recrystallized from ethanol to give the pure product (5.2 g, 65%) as a yellow crystalline solid. R.f. 0.40 (silica, 3:1 hexane:ethyl acetate). M.p.134-136 °C; (Found C, 66.61; H, 4.5.32; N 4.11%. C\(_{18}\)H\(_{17}\)NO\(_5\) requires C, 66.1; H, 5.2; N, 4.3%); \(\nu_{\text{max}}\) (nujol, NaCl plates/cm\(^{-1}\)) 2974 (s), 1726 (C=O) (m), 1684 (C=O) (m), 1596 (m), 1460, 1377 (m), 854 (m). δ\(_{\text{H}}\) (400 MHz; CDCl\(_3\)) 8.19 (2H, d, \(J 9.0\) Hz, H-3' & H-5'); 7.95 (2H, app. d, \(J 7.6\) Hz, aromatic), 7.57-7.63 (3H, m,
aromatic), 7.45 (2H, app. t, J 7.6 Hz, aromatic), 3.92 (1H, d, J 17.8 Hz, HCH), 3.74 (3H, s, OCH₃) 3.65 (1H, d, J 17.8 Hz, HCH), 1.85 (3H, s, CH₃). δ_C(400 MHz; CDCl₃) 196.3 (s) (C=O), 174.7 (s) (C=O), 150.4 (s) (C, Ar), 146.9 (s) (C, Ar), 136.5 (s) (C, Ar), 133.6 (s) (CH, Ar), 128.7 (s) (2 × CH, Ar), 128.0 (s) (2 × CH, Ar), 127.1 (s) (2 × CH, Ar), 123.8 (s) (2 × CH, Ar), 52.7 (s) (O-CH₃), 48.3 (s) (C, quaternary), 47.7 (s) (CH₂), 23.6 (s) (CH₃). m/z (APCI) 328.0 [(M + H)+, 100 %], 296.0 (58), 279.0 (11), 263.0 (3), 105.1 (18); (Found: (M + H)⁺ (ES⁺), 328.1187. C₁₈H₁₇NO₅ requires (M + H)+ 328.1185).

**General Method for Reduction of Ketones**—The ester (1.53 mmol) was dissolved in chloroform (10 ml). A solution of sodium borohydride (3.06 mmol) in methanol (10 ml) was slowly added to the solution at 0 °C. Following the addition the reaction mixture was stirred at room temperature for four hours. The reaction was monitored by TLC. After acidification with 10% hydrochloric acid most of the methanol was removed on a rotary evaporator. The resulting mixture was cooled to room temperature and extracted with dichloromethane (3 × 25 ml). The dichloromethane was washed with water (3 × 20 ml), sodium bicarbonate (20 ml) and dried (sodium sulfate) to give the crude product.

(3SR,5RS) & (3RS,5RS)-3-Methyl-3-(4'-nitrophenyl)-5-phenylidihydro(3H)furan-2-one (162)—This was prepared by the General Method using methyl (2-methyl-2-(4'-nitrophenyl)-4-oxo-4-phenyl)butyrate (165) (1.00 g, 3.06 mmol) and sodium borohydride (232 mg, 6.12 mmol) to give the crude product (0.83 g, 83%) as a 1:1 mixture of the two diastereoisomers. The two diastereoisomers were then separated by column chromatography (silica, 3:1, hexane:ethyl acetate, v/v).Cis isomer (0.41 g): Rf 0.28 (silica, hexane:ethyl acetate 3:1); M.p. 129-132 °C; (Found C, 68.55; H, 4.99; N 4.88, C₁₇H₁₅NO₄ requires C, 68.7; H, 5.1; N, 4.7%); ν_max (nujol on NaCl plates/ cm⁻¹) 2920 (m), 1761 (s) (C=O), 1343(m), 1178 (m), 848 (m), 731 (m); δ_H(400 MHz; CDCl₃) 8.15 (2H, d, J 8.8 Hz, H-3' & H-5'), 7.67 (2H, d, J 8.8 Hz, H-2' & H-6'), 7.31-7.41 (5H, m, aromatic), 5.17 (1H, dd, J 5.4 & 10.6 Hz, H-5), 3.08 (1H, dd, J 5.4 & 13.3 Hz, H-4α), 2.46 (2H, dd, J 10.7 & 13.3 Hz, H-4β), 1.69 (3H, s, CH₃); δ_C (400 MHz;
Methyl (2-(4′-nitrophenyl)-4-oxo-4-phenyl)butyrate (168)—This was prepared by the General Method using sodium hydride (1.03 g, 25.62 mmol), methyl 4-nitrophenylacetate (167) (5.0 g, 25.62 mmol) and 2-bromoacetophenone (5.10 g, 25.62 mmol) to give the crude product (7.9 g) as a yellow crystalline solid. The crude product recrystallised from hot ethanol to give the pure product as a yellow crystalline solid (6.05 g, 75%). M.p. 161-163 °C; ν_max (nujol on NaCl plates/ cm⁻¹) 2926 (s), 1725 (s) (C=O), 1681 (s) (C=O), 1594 (m), 1519 (s), 1462 (s), 1377 (m), 1348 (m), 1259 (m), 1234 (m), 1205 (m), 1163 (m), 1110 (m), 997 (m), 964 (m), 866 (m), 834 (m), 762 (m), 736 (m), 690 (m); δ_H(400 MHz; CDCl₃) 8.22 (2H, d, J 8.7 Hz, H-3′ & H-5′), 7.97 (2H, d, J 8.7 Hz, H-2′ & H-6′), 7.41-7.61 (5H, m, Ph), 4.44 (1H, dd, J 5.0 & 9.4 Hz, CH), 3.95 (1H, dd, J 9.4 & 18.0 Hz, HCH), 3.72 (3H, s, OCH₃), 3.36 (1H, dd, J 5.0 & 18.0 Hz, HCH); δ_C(400 MHz; CDCl₃) 196.7 (s) (C=O), 172.7 (s) (O-C=O), 148.0 (s) (C, Ar), 145.6 (s) (C, Ar), 136.0 (s) (C, Ar) 133.7 (s) (CH, Ar), 129.0 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 124.1 (s) (2 × CH, Ar), 52.8 (s) (C-O), 46.2 (s) (Ph-CH), 42.2 (s) (CH₂); m/z (APCI) 314.0 [(M + H)⁺, 100 %], 283.0 (2), 282.0 (42), 60.4 (8) (Found: (M + H)⁺ (ES⁺), 314.0953. C₁₇H₁₅NO₅ requires (M + H)⁺ 314.0950).
(3SR,5RS) & (3RS,5RS)-3-(4'-Nitrophenyl)-5-phenylidihydro(3H)furan-2-one (162a)—This was prepared by the General Method using sodium borohydride (60 mg, 1.60 mmol), 2-(4'-nitrophenyl)-4-oxo-4-phenyl butyric acid methyl ester (168) (0.50 g, 1.60 mmol), ethanol (20 ml) and chloroform (10 ml) to give the crude product as a 1:1 mixture of diastereoisomers (0.63 g) as a yellow oil. Trans-162a: M.p. 117-119 °C; (Found C, 67.93; H, 4.87; N 4.96%). C_{16}H_{13}NO_{4} requires C, 67.8; H, 4.6; N, 4.9%); ν_{max} (nujol on NaCl plates/ cm^{-1}) 2917 (m), 1759 (s) (C=O), 1367 (m), 1321 (w), 1172 (m), 907 (m), 848 (m), 732 (m); δ_{H}(400 MHz; CDCl_{3}) 8.16 (2H, d, J 8.8 Hz, H-3' & H-5'), 7.46 (2H, d, J 8.8 Hz, H-2' & H-6'), 7.27-7.38 (5H, m, Ph), 5.50 (1H, dd, J 10.7 & 5.5 Hz, H-5), 4.11 (1H, dd, J 12.8 & 8.4 Hz, H-3), 3.03-3.10 (1H, m, H-4α), 2.30-2.39 (1H, m, H-4β); δ_{C} (100 MHz; CDCl_{3}) 177.7 (s) (C=O), 149.2 (s) (C, Ar), 147.7 (s) (C, Ar), 138.9 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 129.0 (s) (CH, Ar), 127.9 (s) (2 × CH, Ar), 125.7 (s) (2 × CH, Ar), 124.3 (s) (2 × CH, Ar), 78.7 (s) (C-5), 50.9 (s) (C-3), 46.4 (s) (C-4); m/z (APCI) 284.0 [(M + H)^{+}, 100 %]; (Found: (M + H)^{+} (APCI) 283.0845. C_{16}H_{13}NO_{4} requires (M + H)^{+} 283.0845. It was not possible to isolate the cis diastereoisomer from the crude products.

\[
\begin{align*}
\text{NO}_2 & \quad \text{CO} \\
\text{O} & \quad \text{OMe} \\
\end{align*}
\]

1. NaH, DMF  
2. Allyl Bromide

Methyl (2-(4'-nitrophenyl)pent-4-enoate (168)—This was prepared by the General Method using sodium hydride (0.14 g, 10.3 mmol), methyl 4-nitrophenylacetate (167) (2.0 g, 10.3 mmol) and allyl bromide (0.89 ml, 10.3 mmol) to give the crude product (2.98 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.30 (silica, hexane:ethyl acetate; 3:1) to give the pure product (2.25 g, 93%) as a yellow oil. ν_{max} (neat, NaCl plates/ cm^{-1}) 2925 (s), 1736 (s) (C=O), 1685 (s) (C=C), 1596 (s), 1518 (s), 1461 (s), 1376 (s), 1344 (s), 1254 (m), 1168 (s), 1110 (m), 1053 (m); δ_{H}(400 MHz; CDCl_{3}) 8.18 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.49 (2H, d, J 8.9 Hz, H-2' & H-6'), 5.63-5.73 (1H, m, H_{2}C=CH-), 5.01-5.09 (2H, m, H_{2}C=C), 3.78 (1H, t, J 7.7 Hz, CH-Ar), 3.69 (3H, s, OCH_{3}), 2.82-2.90 (1H, m, HCH-C-Ar), 2.51-2.58 (1H, m, HCH-C-Ar); δ_{C} (100 MHz; CDCl_{3}) 173.0 (s) (C=O), 147.6 (s) (C, Ar), 146.1 (s) (C, Ar), 134.5 (s) (CH), 129.4 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 118.3
Methyl (2-(4-nitrophenyl)-2-(2-oxo-2-phenyl-ethyl)pent-4-enoate (169)—This was prepared by the General Method using sodium hydride (0.08 g, 2.13 mmol), methyl ester 168 (0.5 g, 2.13 mmol) and 2-bromoacetophenone (0.42 g, 2.13 mmol) to give the crude product (0.74 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.30 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.65 g, 86%) as a yellow crystalline solid. M.p. 152-154 °C; \( \nu \text{max} \) (nujol on NaCl plates/ cm\(^{-1} \)) 3080 (s), 2952 (s), 2854 (m), 2455 (m), 1931 (m), 1737 (s), 1642 (s), 1604 (s), 1517 (s), 1435 (s), 1435 (s), 1109 (s), 995 (s); \( \delta \)H(400 MHz; CDCl\(_3 \)) 8.16 (2H, d, \( J \) 8.9 Hz, H-3' & H-5'), 7.89 (2H, d, \( J \) 8.9 Hz, H-2' & H-6'), 7.49-7.55 (3H, m, Ph), 7.41 (2H, app. t, \( J \) 7.9 Hz, Ph), 5.28-5.36 (1H, m, H2 C=CH-), 4.85-4.93 (2H, m, H2 C=), 3.82 (1H, d, \( J \) 18.0 Hz, O=C-HCH), 3.74 (1H, d, \( J \) 18.0 Hz, O=C-HCH), 3.63 (3H, s, OCH\(_3 \)), 2.94-3.07 (2H, m, H2 C=CH-CH2-); \( \delta \)C(100 MHz; CDCl\(_3 \)) 196.5 (s) (C=O), 174.1 (s) (C=O), 148.5 (s) (C, Ar), 146.9 (s) (C, Ar), 136.6 (s) (C, Ar) 134.0 (s) (CH), 132.6 (s) (CH), 128.9 (s) (2 × CH, Ar) 128.2 (s) (2 × CH, Ar) 127.6 (s) (2 × CH, Ar), 123.7 (s) (2 × CH, Ar), 120.0 (s) (CH\(_2 \)), 54.1 (s) (O-CH\(_3 \)), 51.6 (s) (C, quaternary), 42.5 (s) (CH\(_2 \)), 40.5 (s) (CH\(_2 \)); m/z (APCI) 354.0 [(M + H\(^{+} \)), 100 %], 322 (88); (Found: (M + NH\(_4 \))\(^{+} \) (ES\(^{+} \)) 371.1611 C\(_{20}\)H\(_{19}\)NO\(_5\) requires (M + NH\(_4 \))\(^{+} \) 371.1607).
(3SR,5RS) & (3RS,5RS)-3-Allyl-3-(4'-nitrophenyl)-5-phenylidihydro(3H)furan-2-one (162b)—This was prepared by the General Method using sodium borohydride (80 mg, 2.17 mmol), methyl (2-(4-nitrophenyl)-2-(2-oxo-2-phenylethyl))pent-4-enoate (169) (0.64 g, 2.17 mmol), ethanol (10 ml) and chloroform (5 ml) to give the crude product as a 1:1 mixture of diastereoisomers (0.60 g) as an orange oil. The two diastereoisomers were then separated by column chromatography (silica, 3:1, hexane:ethyl acetate, v/v) (62% overall yield). Cis isomer (0.30 g) Rf 0.34 (silica, hexane:ethyl acetate; 3:1) M.p. 127-130 °C; \( \nu_{\text{max}} \) (nujol on NaCl plates/ cm\(^{-1}\)) 2918 (m), 1758 (s) (C=O), 1339 (m), 1172 (m), 843 (m); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 8.28 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.72 (2H, d, J 8.9 Hz, H-2' & H-6'), 7.33-7.43 (5H, m, Ph), 5.61-5.70 (1H, m, -CH=CH2 ), 5.22 (1H, dd, J 5.4 & 10.9 Hz, H-5), 5.02-5.18 (2H, m, CH\(_2\)=CH-), 3.01 (1H, dd, J 5.4 & 13.6 Hz, H-3-alpha), 2.68-2.80 (2H, m, -CH\(_2\)-CH=CH2 ), 2.56 (1H, dd, J 10.9 & 13.6 Hz, H-3-beta); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 176.9 (s) (C=O), 147.5 (s) (C, Ar), 146.9 (s) (C, Ar), 138.0 (s) (C, Ar), 131.8 (s) (CH), 128.9 (s) (2 x CH, Ar), 128.8 (s) (CH), 127.6 (s) (2 x CH, Ar), 125.6 (s) (C, Ar), 124.2 (s) (2 x CH, Ar), 120.7 (s) (CH\(_2\)), 77.3 (s) (C-5), 54.0 (s) (C, quaternary), 43.7 (s) (CH\(_2\)), 41.8 (s) (CH\(_2\)); \( m/z \) (APCI) 324 [(M + H)+, 100%]; (Found: (M + H)+ (APCI) 324.1236. C\(_{19}\)H\(_{17}\)NO\(_4\) requires (M + H)+ 324.1236).

Methyl (2-(4-nitrophenyl)-3-phenyl)propionate\(^{223}\) (171)—This was prepared by the General Method using sodium hydride (0.14 g, 10.3 mmol), methyl 4-nitrophenylacetate (167) (2.0 g, 10.3 mmol) and benzyl bromide (1.22 ml, 10.3 mmol) to give the crude product (2.80 g) as an orange crystalline solid. The crude product was then recrystallized from ethanol to give the pure product (2.22 g, 76%) as a yellow crystalline solid. M.p. 59-60 °C (lit. 60-61 °C)\(^{223}\); \( \nu_{\text{max}} \) (nujol on NaCl plates/ cm\(^{-1}\)) 2921 (s), 1741 (s) (C=O), 1596 (m), 1458 (s), 1346 (m); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 8.15 (2H, d, J 8.8 Hz, H-3' & H-5'), 7.44 (2H, d, J 8.8 Hz, H-2' & H-6'), 7.17-7.26 (3H, m, Ph), 7.06 (2H, app. d, J 8.3 Hz, Ph), 3.97 (1H, t, J 7.8 Hz, CH), 3.64 (3H, s, OCH\(_3\)), 3.44 (1H, dd, J 13.8 & 7.8 Hz, HCH), 3.04 (1H, dd, J 13.8 & 7.8 Hz, HCH); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 172.7 (s) (C=O), 147.2 (s) (C, Ar), 145.6 (s) (C, Ar), 137.8 (s) (C, Ar), 129.1 (s)
(2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 128.5 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 53.4 (s) (O-CH₃), 52.4 (s) (CH,Ar), 39.6 (CH₂); m/z (APCi) 286.0 [(M + H)+, 100%].

\[
\text{NO} \quad \text{OMe}
\]

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1. \text{NaH, DMF}
\]

2. Bromoacetophenone

\[
\text{Methyl (2-benzyl-2-(4-nitrophenyl)-4-oxo-4-phenylbutyrate (172)—This was prepared by the General Method using sodium hydride (67 mg, 1.79 mmol), methyl (2-(4-nitrophenyl)-3-phenyl)propionate (171) (0.5 g, 1.79 mmol) and 2-bromoacetophenone (0.36g, 1.79 mmol) to give the crude product (0.74 g) as a yellow crystalline solid. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.63 g, 87%) as a yellow crystalline solid. M.p. 170-171 \nu_{\text{max}} (\text{nujol on NaCl plates/cm}^{-1}) 2929 (s), 1716 (s), 1687 (m), 1595 (m), 1521 (m), 1464 (s), 1376 (m), 1349 (m), 1219 (m), 1062 (m), 860 (m); \delta_{\text{H}} (400 MHz; CDCl₃) 8.20 (2H, d, J 8.9 Hz, H-3' & H-5'), 7.95 (2H, app. d, J 7.5 Hz, Ph), 7.62 (1H, app. t, J 7.5 Hz, Ph), 7.45-7.51 (4H, m, Ph), 7.14 (1H, app. t, J 7.4 Hz, Ph), 7.05 (2H, app. t, J 7.4 Hz, Ph), 6.52 (2H, d, J 7.4 Hz, Ph), 3.72 (3H, s, O-CH₃), 3.68-3.72 (3H, m, CH₂ & HCH), 3.58 (1H, d, J 13.7 Hz, HCH); \delta_{\text{C}} (100 MHz; CDCl₃) 197.2 (s (C=O), 174.7 (s (C=O), 149.2 (s) (C, Ar), 147.3 (s) (C, Ar), 137.0 (s) (C, Ar) 136.4 (s) (C, Ar), 134.0 (s) (CH, Ar), 130.5 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar) 128.6 (s) (2 × CH, Ar), 128.4 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 127.4 (s) (CH, Ar), 124.0 (s) (2 × CH, Ar), 53.1 (s (O-CH₃), 53.0 (s) (C, quaternary), 42.5 (s) (CH₂), 42.0 (s) (CH₂); m/z (APCi) 404.0 [(M + H)+, 100 %], 372 (40); (Found: (M + H)+ (APCi), 404.1500. C₂₄H₂₁NO₅ requires (M + H)+ 404.1498).}

\[
\text{H₂O₂-C} \quad \text{NH₂}
\]

\[
1. \text{NaNO₂/H}^+\]

2. p-TsOH/Ph-H/EtOH

\[
\text{OEt}
\]
(S)-Dihydro-5-carboethoxy(3H)furan-2-one$^{156}$ (175)—To a solution of L-glutamic acid (174) (90.0 g, 0.61 mol) in water (240 ml) and conc. hydrochloric acid (126 ml) was added slowly over a period of 6 hours at 0 °C a solution of sodium nitrite (63.0 g, 0.91 mol) in water (135 ml). The clear solution was then stirred at room temperature overnight. Evaporation to dryness gave a pale yellow oil. Ethyl acetate (300 ml) was added to the oil, the insoluble material was filtered off and the organic solution dried over Na$_2$SO$_4$. The solvent was then removed on a rotary evaporator to leave a pale yellow syrup (80.6 g). Ethanol (130 ml), benzene (300 ml) and p-TsOH (2.0 g) were added to the yellow syrup. The solution was then heated under reflux for 5 hours using a Dean-stark apparatus. The solvents were removed under reduced pressure. Benzene (100 ml) was added and the solution was washed with water (100 ml), Na$_2$CO$_3$ (100 ml) and water (100 ml) before drying over Na$_2$SO$_4$. Removal of the solvent left the crude product as a colourless oil (92.3 g, 95%). $\nu_{\text{max}}$ (neat, NaCl plates/cm$^{-1}$) 1784 (s) (C=O), 1747 (s) (C=O); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 4.91-4.97 (1H, m, H-5), 4.31 (2H, q, $J$ 7.0 Hz, O-CH$_2$), 2.20-2.80 (4H, m, H-3 & H-4), 1.34 (3H, t, $J$ 7.0 Hz, CH$_3$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 177.9 (s) (C=O), 88.9 (s) (C-5), 59.5 (s) (CH$_2$), 35.2 (s) (C-3), 17.7 (s) (C-4), 13.6 (s) (CH$_3$); $m/z$ (APCI) 159.0 [(M + H)$^+$, 100%].

\[ \text{OEt} \quad \overset{\text{NaBH}_4}{\longrightarrow} \quad \text{OH} \]

(S)-(−)-5-Hydroxymethyldihydro(3H)furan-2-one$^{224}$ (176)—A solution of dihydro-5-carboethoxy(3H)furan-2-one (175) (53.12 g, 0.34 mol) in ethanol (300 ml) was added dropwise to a stirred suspension of sodium borohydride (8.3 g, 0.22 mol) in ethanol (180 ml). The solution was stirred at room temperature for 90 minutes before being acidified to pH 3 with 10% aq. HCl at 0 °C. The resulting white precipitate was filtered off and the filtrate was evaporated under vacuum. Methanol (100 ml) was added to the residue and evaporated under vacuum (4 times) to give the crude product (28.8 g) as a clear oil. The crude product was then purified by column chromatography Rf 0.35 (silica, ethanol:chloroform; 7:93) to give the pure product (19.8 g, 51%) as a clear oil. $\nu_{\text{max}}$ (neat, NaCl plates/cm$^{-1}$) 3403 (s) (O-H), 1767 (s) (C=O), 1190 (s); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 4.58-4.62 (1H, m, H-5), 3.84 (1H, dd, $J$ 3.2 & 12.8 Hz, O-HCH), 3.61 (1H, dd, $J$ 4.4 & 12.8 Hz, O-HCH), 3.53 (1H, s, O-H), 2.46-2.63 (2H, m, H-3),
2.19-2.28 (1H, m, H-4a), 2.10-2.15 (1H, m, H-4β); δC(100 MHz; CDCl₃) 178.3 (s) (C=O), 81.1 (s) (CH₂), 63.9 (s) (CH), 28.5 (s) (CH₂), 23.1 (s) (CH₂); m/z (APCI) 117.0 [(M + H)+, 100%].

**General Method for Silyl protection of Alcohols**—A mixture of alcohol (155 mmol), triethylamine (43.0 ml), silyl chloride (155 mmol), DMAP (15.5 mmol) and dichloromethane (200 ml) were stirred together for 24 hours. The reaction mixture was then poured into water (200 ml) and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were then dried over sodium sulfate. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product.

![Chemical Structure](image)

**((S)-(+)-5-(tert-Butyldiphenylsilanyloxymethyl)-dihydro(3H)furan-2-one** (177)—This was prepared by the General Method using ((S)-(+)-γ-hydroxymethyl-γ-butyrolactone (176) (18.0 g, 155 mmol), DMAP (1.89 g, 15.5 mmol), TBDPS-Cl (40.35 g, 155 mmol), triethylamine (43 ml, 313 mmol) and dichloromethane to give the crude product (51.9 g) as a black oil. The crude product was then purified by column chromatography Rf 0.18 (silica, ethyl acetate:hexane; 1:3) to give the pure product (30.2 g, 55%) as a white crystalline solid. [α]D +35.3° [α]D (c 1.09 in ethanol) (lit. +35.5° c 1.09 in ethanol) 158; M.p. 74-75 °C (lit. 75-77 °C) 255; νmax (nujol, NaCl plates/ cm⁻¹) 2966 (s), 1769 (s) (C=O), 1457 (s), 1377 (s), 1266 (m), 1170 (s); δH(400 MHz; CDCl₃) 7.56 (2H, app. d, J 7.5 Hz, Ph), 7.26-7.32 (3H, m, Ph), 4.46 (1H, ddd, J 3.1 & 5.7 & 8.3 Hz, H-5), 3.76 (1H, dd, J 3.1 & 11.4 Hz, O-HCH), 3.55 (1H, dd, J 3.1 & 11.4 Hz, H-5), 2.54 (1H, ddd, J 7.2 & 10.1 & 17.5 Hz, H-3α), 2.36 (1H, ddd, J 6.7 & 9.9 & 16.7 Hz, H-3β), 2.02-2.19 (2H, m, H-4), 0.95 (9H, s, (CH₃)₃); δC(100 MHz; CDCl₃) 178.0 (s) (C=O), 136.1 (s) (CH, Ar), 136.0 (s) (CH, Ar), 133.3 (s) (C, Ar), 132.9 (s) (C, Ar), 130.4 (s) (CH, Ar), 128.3 (s) (CH, Ar), 80.4 (s) (CH), 65.9 (s) (CH₂), 29.1 (s) (CH₂), 27.2 (s) (CH₃), 24.0 (s) (CH₂), 19.6 (s) C, quaternary; m/z (APCI) 355.0 [(M + H)+, 100%].
(S)-(+)\text{-}5-(\text{tert-Butyl-dimethylsilyloxymethyl})\text{dihydro}(3\text{H})\text{furan-2-one} \text{ 225 (184)—This was prepared by the General Method using (S)-(+)\text{-}\gamma\text{-}hydroxymethyl-\gamma\text{-}butyrolactone (176) (2.53 g, 21.78 mmol), DMAP (0.27 g, 21.7 mmol), TBDMS-CI (3.28 g, 21.78 mmol), triethylamine (6.04 ml, 44.0 mmol) and dichloromethane (50 ml) to give the crude product (4.89 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.20 (silica, ethyl acetate:hexane; 1:3) to give the pure product (3.62 g, 73%) as a colourless oil. \([\alpha]_D -10.7^\circ (c 0.5 \text{ in CHCl}_3) \text{ (lit. } -11.0^\circ \text{ c 0.5 in ethanol)}^2; \nu_{\text{max}} \text{ (nujol, NaCl plates/ cm}^{-1}) 2931 \text{ (s), 2857 (s), 1778 (s), 1462 (s), 1361 (m), 1257 (s); } \delta_{\text{H}}(400 \text{ MHz; CDCl}_3) 4.52 \text{ (1H, ddd, } J 3.2 & 5.2 & 8.0 \text{ Hz, Ph), 3.79 (1H, dd, } J 3.2 & 11.2 \text{ Hz, O-HCH), 3.55 (1H, dd, } J 3.2 & 11.2 \text{, HCH), 2.52 (1H, ddd, } J 7.2 & 9.9 & 17.5 \text{ Hz, H-3}\alpha), 2.37 (1H, ddd, } J 6.7 & 9.9 & 16.7 \text{ Hz, H-3}\beta), 2.05-2.25 (2H, m, H-4), 0.81 (9H, s, (CH}_3)_3), 0.00 (6H, d, } J 3.6 \text{ Hz, } 2 \times (\text{CH}_3); \delta_{\text{C}}(100 \text{ MHz; CDCl}_3) 178.0 \text{ (s) (C=O), 80.5 (s) (CH, Ar), 65.2 (s) (CH}_2), 28.9 \text{ (s) (CH}_2), 26.1 \text{ (s) (CH}_3), 23.9 \text{ (s) (CH}_2), 18.6 \text{ (s) (C, quaternary); } m/z \text{ (APCI) 231.0 [(M + H)}^+, 100\%)]

**General Method for \(\alpha\)-phenylsulfanylation of lactones**—A solution of diisopropylamine (28.2 mmol) in dry THF (5 ml) was cooled to 0 °C and flushed with nitrogen. \(\text{n-Butyllithium} \text{ (28.2 mmol) (2.5 M in hexanes) was added dropwise to the reaction mixture. The mixture was stirred at 0 °C for 10 minutes before cooling to } -78 \text{ °C in a dry ice/acetone cooling bath. The lactone (14.1 mmol.) dissolved in dry THF (5 ml) was added dropwise to the solution. The mixture was stirred at } -78 \text{ °C for 35 minutes. Phenyl disulfide (14.12 mmol) and DMPU (14.12 mmol) dissolved in dry THF (5 ml) was added dropwise to the reaction mixture. The mixture was stirred at } -78 \text{ °C for a further 35 minutes before being allowed to warm to room temperature. The reaction mixture was then poured into water (100 ml) and extracted with ether (3 \times 100 \text{ ml}). The combined organic extracts were then washed successively with 10% NaOH (100 ml), water (100 ml), 10% HCl (100 ml) and water (100 ml). The organic solution was then dried over Na}_2\text{SO}_4. \text{ The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product.}
(3R,SS) & (3S,SS)-5-(tert-Butyldiphenylsilyloxyethyl)-3-phenylsulfanyldihydro(3H)furan-2-one \(^{226}\)(181)—This was prepared by the General Method using diisopropylamine (3.96 ml, 28.2 mmol, \textit{n}-butyllithium (2.5 M in hexanes) (11.3 ml, 28.24 mmol), the lactone 178 (5.0 g, 14.12 mmol), phenyl disulfide (3.08 g, 14.12 mmol), DMPU (1.71 ml, 14.12 mmol) to give the crude product (6.40 g) as an orange oil. The crude product was then purified by column chromatography (silica, ethyl acetate:hexane; 1:3) to give the two diastereoisomers (4.96 g, 76\%) in a \textit{cis:trans} ratio of 3:7 as colourless oils. \textit{Cis} product (1.49 g): Rf 0.28 (ethyl acetate: hexane 1:3) \(\nu_{\text{max}}\) (neat, NaCl plates/ cm\(^{-1}\)) 2928 (s), 1771 (s), 1457 (m), 1376 (m), 1180 (m), 1020 (m); \(\delta\)(400 MHz; CDCl\(_3\)) 7.51-7.55 (4H, m, Ph), 7.44-7.47 (2H, m, Ph), 7.28-7.35 (6H, m, Ph), 7.21-7.25 (3H, m, Ph), 4.35 (1H, ddd, \(J\) 2.9 & 4.9 & 7.6 Hz, H-5), 4.04 (1H, dd, \(J\) 7.4 & 9.3 Hz, H-3), 3.78 (1H, dd, \(J\) 2.8 & 11.5 Hz, HCH-O), 3.53 (1H, dd, \(J\) 2.8 & 11.5 Hz, HCH-O), 2.55-2.63 (1H, m, H-4\(\alpha\)), 2.17-2.26 (1H, m, H-4\(\beta\)), 0.94 (9H, s, (CH\(_3\))\(_3\)); \(\delta\)(100 MHz; CDCl\(_3\)) 175.1 (s) (C=O), 136.1 (s) (CH, Ar), 136.0 (s) (CH, Ar), 135.3 (s) (CH, Ar), 133.7 (s) (C, Ar), 133.6 (s) (C, Ar), 133.3 (s) (C, Ar), 130.5 (s) (CH, Ar), 129.7 (s) (CH, Ar), 128.8 (s) (CH, Ar), 128.4 (s) (CH, Ar), 78.6 (s) (C-5), 64.8 (s) (CH\(_2\)), 46.3 (s) (CH), 31.6 (s) (CH\(_2\)), 27.2 (s) (CH\(_3\)), 19.7 (s) (C); \(m/z\) (APCI) 463.0 [(M + H\(^{+}\)], 100\%]; \textit{trans} product (3.47 g): Rf 0.32 (ethyl acetate: hexane 1:3) \(\nu_{\text{max}}\) (neat, NaCl plates/ cm\(^{-1}\)) 2928 (s), 1769 (s), 1458 (m), 1376 (m), 1179 (m), 1017 (m); \(\delta\)(400 MHz; CDCl\(_3\)) 7.51-7.56 (4H, m, Ph), 7.39-7.44 (2H, m, Ph), 7.25-7.35 (6H, m, Ph), 7.15-7.19 (3H, m, Ph), 4.38 (1H, ddd, \(J\) 4.5 & 6.4 & 8.9 Hz, H-5), 3.88 (1H, t, \(J\) 10.2 Hz, H-3), 3.65 (1H, dd, \(J\) 3.9 & 11.5 Hz, HCH-O), 3.53 (1H, dd, \(J\) 4.6 & 11.5 Hz, HCH-O), 2.49 (1H, ddd, \(J\) 6.6 & 9.3 & 15.9 Hz, H-4\(\alpha\)), 2.07-2.16 (1H, m, H-4\(\beta\)), 0.93 (9H, s, (CH\(_3\))\(_3\)); \(\delta\)(100 MHz; CDCl\(_3\)) 174.6 (s) (C=O), 135.7 (s) (CH, Ar), 135.6 (s) (CH, Ar), 133.2 (s) (CH, Ar), 132.9 (s) (C, Ar), 132.7 (s) (C, Ar), 132.5 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.2 (s) (CH, Ar), 128.4 (s) (CH, Ar), 127.8 (s) (CH, Ar), 78.1 (s) (C-5), 64.4 (s) (CH\(_2\)), 45.9 (s) (CH), 31.3 (s) (CH\(_2\)), 26.7 (s) (CH\(_3\)), 19.2 (s) (C); \(m/z\) (APCI) 463.0 [(M + H\(^{+}\)], 100\%].
(3R,5S) & (3S,5S)-5-(tert-Butyldimethylsilyloxymethyl)-3-phenylsulfanyldihydro(3H)furan-2-one (185)—This was prepared by the General Method using diisopropylamine (1.23 ml, 8.68 mmol), n-butyllithium (2.5 M in hexanes) (3.47 ml, 8.68 mmol), the lactone 177 (1.0 g, 4.34 mmol), phenyl disulfide (0.95 g, 4.34 mmol), DMPU (0.52 ml, 4.34 mmol) to give the crude product (1.19 g) as a yellow oil. The crude product was then purified by column chromatography (silica, ethyl acetate:hexane; 1:3) to give the two diastereo isomers (0.88 g, 60%) in a cis:trans ratio of 1:1 as colourless oils. cis product (0.44 g): νmax (neat, NaCl plates/cm⁻¹) 2927 (s), 1772 (m), 1377 (m), 1183 (m), 1021 (m); δH(400 MHz; CDCl₃) 7.27-7.30 (2H, m, Ph), 7.03-7.09 (3H, m, Ph), 4.36 (1H, ddd, J 3.0 & 4.9 & 7.6 Hz, H-5), 4.05 (1H, dd, J 7.4 & 9.3Hz, H-3), 3.78 (1H, dd, J 2.9 & 11.5 Hz, HCH-O), 3.53 (1H, dd, J 2.9 & 11.5 Hz, HCH-O), 2.54-2.62 (1H, m, H-4α), 2.16-2.25 (1H, m, H-4β), 0.80 (9H, s, (CH₃)₃), 0.00 (6H, d, J 3.6 Hz, 2 × (CH₃)); δC(100 MHz; CDCl₃) 175.0 (s) (C=O), 133.7 (s) (C, Ar), 133.1 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.0 (s) (CH, Ar), 78.5 (s) (C-5), 64.7 (s) (CH₂), 46.2 (s) (CH), 31.6 (s) (CH₂), 27.2 (s) (CH₃), 19.7 (s) (C); m/z (APCI) 339.0 [(M + H)+, 100%];
trans product (0.44 g): νmax (neat, NaCl plates/cm⁻¹) 2928 (s), 1774 (s), 1458 (m), 1376 (m), 1181 (m), 1020 (m); δH(400 MHz; CDCl₃) 7.26-7.29 (2H, m, Ph), 7.04-7.10 (3H, m, Ph), 4.39 (1H, ddd, J 4.5 & 6.4 & 9.0 Hz, H-5), 3.89 (1H, t, J 10.2 Hz, H-3), 3.66 (1H, dd, J 3.9 & 11.5 Hz, HCH-O), 3.53 (1H, dd, J 4.6 & 11.5 Hz, HCH-O), 2.50 (1H, ddd, J 6.6 & 9.3 & 16.0 Hz, H-4α), 2.06-2.15 (1H, m, H-4β), 0.93 (9H, s, (CH₃)₃), 0.00 (6H, d, J 3.6 Hz, 2 × (CH₃)); δC(100 MHz; CDCl₃) 174.9 (s) (C=O), 133.8 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 78.0 (s) (C-5), 64.3 (s) (CH₂), 45.9 (s) (CH), 31.4 (s) (CH₂), 26.7 (s) (CH₃), 19.1 (s) (C); m/z (APCI) 339.0 [(M + H)+, 100%].

(3R,5S) & (3S,5S)-5-(trityloxymethyl)-3-phenylsulfanyldihydro(3H)furan-2-one (189)—This was prepared by the General Method using diisopropylamine (3.96 ml, 28.2 mmol, n-butyllithium (2.5 M in hexanes) (11.3 ml, 28.24 mmol), the lactone 188 (5.0 g, 14.12 mmol),

142
phenyl disulfide (3.08 g, 14.12 mmol), DMPU (1.71 ml, 14.12 mmol) to give the crude product (6.40 g) as an orange oil. The product was purified by column chromatography (ethyl acetate:hexane 1:3) to give the two diastereoisomers (4.34 g, 66%) in a 7:3 ratio. The two diastereoisomers were not able to be separated by column chromatography.

3-Bromo-4-nitrophenol\textsuperscript{159} (200)—In a 3 necked (500 ml) round bottom flask fitted with a condenser and nitrogen bubbler was added sodium nitrate (22.6 g, 266 mmol), sulphuric acid (31.4 g) and water (60 ml). \(m\)-Bromophenol (25.0 g, 144.5 mmol) in ethanol (20 ml) was slowly added keeping the temperature below 25 °C. After stirring at room temperature for two hours, the mixture was diluted with water (150 ml). The product was then extracted with ether (3 x 100 ml). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and the solvent removed on a rotary evaporator to give the crude product (29.71 g) as an orange solid. The crude product was then purified by column chromatography Rf 0.20 (silica, ethyl acetate:hexane; 1:3) to give the pure product (19.3 g, 61%) as white needles. M.p. 129-131 °C (lit. 131 °C\textsuperscript{159}; \(\nu\text{max} (\text{nujol, NaCl plates/ cm}^-1) 2926 (s), 1556 (s), 1460 (s), 1376 (m), 1297 (m), 1194 (m); \(\delta\text{H}(400 \text{MHz; CDCl}_3) 7.93 (1H, d, J 8.8 \text{Hz, H-5}), 7.17 (1H, d, J 2.4 \text{Hz, H-2}), 6.88 (1H, dd, J 2.4 & 8.8 \text{Hz, H-6}); \(\delta\text{C}(100 \text{MHz; CDCl}_3) 163.7 (s) (C, Ar), 143.2 (s) (C, Ar), 129.7 (s) (CH, Ar), 122.7 (s) (CH, Ar), 117.6 (s) (C, Ar), 116.4 (s) (CH, Ar); \text{m/z (APCI) 218.0 [(M + H)}^+, 50%), 220.0 (50%)

3-Bromo-4-nitroanisole\textsuperscript{161} (201)—3-Bromo-4-nitrophenol (200) (10.0 g, 45.66 mmol) was dissolved in acetone (75 ml) and treated with potassium carbonate (12.63 g, 90 mmol) at 40 °C for 10 minutes. The resulting suspension was then cooled to 0 °C. Methyl iodide (5.63 ml, 90 mmol) was added dropwise. The solution was stirred at 40 °C for 3 hours. The solvent was removed on a rotary evaporator and dichloromethane (50 ml) was added to the residue. The insoluble material was filtered off and the solvent removed on a rotary evaporator to leave the product (9.1 g, 86%) as yellow needles. M.p. 44-46 °C (lit. 44-45 °C\textsuperscript{161}; \(\nu\text{max} (\text{nujol, NaCl}
Diethyl 2-allyl-2-(2,4-dinitrophenyl)malonate (213)—In a two necked round bottom flask fitted with a condenser and nitrogen bubbler was added sodium hydride (60% dispersion in oil (0.11 g, 2.75 mmol) followed by dry THF (5 ml). The flask was then cooled to 0 °C. Diethyl allyl malonate (0.50 ml, 2.54 mmol) in dry THF (5 ml) was then added dropwise. The reaction mixture was stirred at 0 °C for 20 minutes. 2,4-Dinitrofluorobenzene (0.47 g, 2.54 mmol) was then added dropwise to the reaction mixture. The solution was stirred at 0 °C for a further 30 minutes. The solution was then allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was then poured into an ice/HCl solution (1M) and then extracted with dichloromethane (3 x 25 ml). The organic solution was then washed with water (3 x 25 ml) and then dried over Na$_2$SO$_4$. The solvent was then removed on a rotary evaporator to give the crude product (0.84 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.33 (silica, ethyl acetate:hexane; 1:3) to give the pure product (0.77 g, 83%) as a clear oil. $\nu_{\text{max}}$ (neat, NaCl plates/ cm$^{-1}$) 3098 (s), 1554 (s), 2982 (s), 1733 (s), 1639 (w), 1606 (m), 1539 (s), 1466 (s), 1351 (s), 1202 (s), 1028 (s); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 8.78 (1H, d, $J$ 2.4 Hz, H-3'), 8.34 (1H, dd, $J$ 2.4 & 8.8 Hz, H-5'), 7.53 (1H, d, $J$ 8.8 Hz, H-6'), 5.60-5.70 (1H, m, H$_2$C=CH-), 4.97-5.02 (2H, m, H$_2$C=), 4.08-4.20 (4H, m, CH$_2$-0), 3.25 (2H, d, $J$ 7.2 Hz, CH$_2$-C-Ar), 1.16 (6H, t, $J$ 7.2 Hz, CH$_3$-CH$_2$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 168.1 (s) (C=O), 150.0 (s) (C, Ar), 147.2 (s) (C, Ar), 139.1 (s) (C, Ar), 133.1 (s) (CH), 132.5 (s) (CH), 126.8 (s) (CH), 121.2 (s) (CH), 120.6 (s) (CH$_2$), 63.5 (s) (C, quaternary), 62.8 (s) (CH$_2$), 40.1 (s) (CH$_2$), 14.4 (s) (CH$_3$); $m/z$ (APCI) 367.0 [(M + H)$^+$, 100%]. (Found: (M + H)$^+$ (APCI), 367.1068. C$_{16}$H$_{18}$N$_2$O$_8$ requires (M + H)$^+$ 367.1063).
**Dihydro-3-carbomethoxy(3H)furan-2-one** (215)—To a solution of diisopropylamine (3.65 ml, 26.0 mmol) and dry THF (10 ml) was added at 0 °C n-butyllithium (2.5 M in hexanes) (10.42 ml, 26.0 mmol). The solution was stirred at 0 °C for 10 minutes before being cooled to -78 °C. γ-Butyrolactone (1.0 ml, 13.0 mmol) was added dropwise to the stirred solution. The solution was stirred for a further 20 minutes at -78 °C before dimethyl carbonate (6.57 ml, 78.0 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. Saturated NH₄Cl (5 ml) was then added slowly to the solution. The product was then extracted with ether (3 × 50 ml). The combined extracts were dried over Na₂SO₄ and the solvent removed on a rotary evaporator to give the crude product (2.06 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.38 (silica, ethyl acetate:hexane; 1:1) to give the pure product (1.36 g, 73%) as a clear oil. νₘₐₓ (neat, NaCl plates/cm⁻¹) 3098 (s), 1740 (s), 1538 (s), 1465 (s), 1351 (s), 1028 (s); δ₁H(400 MHz; CDCl₃) 4.24 (1H, dt, J 5.2 & 8.4 Hz, H-5α), 4.13 (1H, dt, J 5.2 & 8.8 Hz, H-5β), 3.57 (3H, s, O-CH₃), 3.43 (1H, t, J 8.4 Hz, H-3), 2.30-2.45 (2H, m, H-4); δ₁C(100 MHz; CDCl₃) 172.0 (s) (C=O), 167.7 (s) (C=O), 66.6 (s) (CH₂), 51.9 (s) (CH₃), 44.8 (s) (CH), 25.5 (s) (CH₂); m/z (APCI) 145.0 [(M + H)⁺, 100%].

**Dihydro-3-(2'-4'-Dinitrophenyl)-3-carbomethoxy(3H)furan-2-one** (216)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (167 mg, 4.16 mmol), dihydro-3-carbomethoxy(3H)furan-2-one (215) (0.50 g, 3.47 mmol) and 2,4-dinitrofluorobenzene (0.65 g, 3.47 mmol) to give the crude product (1.11 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.19 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.93 g, 86%) as an orange oil. νₘₐₓ (neat, NaCl plates/cm⁻¹) 3028 (s), 1733 (s), 1539 (s), 1465 (s), 1348 (s); δ₁H(400 MHz; CDCl₃) 8.86 (1H, d, J 2.4
Dihydro-3-(2'-4'-dinitrophenyl)-3-carbomethoxy-5-methyl(3H)furan-2-one (223)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.38 g, 9.49 mmol), 5-methyldihydro-3-carbomethoxy(3H)furan-2-one (221) (1.50 g, 9.49 mmol) and 2,4-dinitrofluorobenzene (1.76 g, 9.49 mmol) to give the crude product (2.76 g) as an orange oil (only the trans product was observed). The crude product was then purified by column chromatography Rf 0.20 (silica, hexane:ethyl acetate; 3:1) to give the pure product (2.44 g, 80%) as a yellow crystalline solid. M.p. 120-121 °C; \( \nu_{\text{max}} \) (nujol, NaCl plates/ cm\(^{-1}\)) 2922 (s), 2853 (s), 1668 (s), 1538 (m), 1462 (s), 1376 (s), 1158 (w); \( \delta_{\text{t}} \) (400 MHz; CDCl\(_3\)) 8.99 (1H, d, \( J = 2.4 \) Hz, H-3'), 8.51 (1H, dd, \( J = 2.4 \) & 8.6 Hz, H-5'), 7.63 (1H, d, \( J = 8.6 \) Hz, H-6'), 4.54 (1H, ddd, \( J = 5.6 \) & 8.0 & 14.0 Hz); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 172.3 (s) (C=O), 167.4 (s) (C=O), 148.4 (s) (C, Ar), 148.1 (s) (C, Ar), 138.7 (s) (C, Ar), 131.7 (s) (CH, Ar), 128.5 (s) (CH, Ar), 122.4 (s) (CH, Ar), 76.1 (s) (O-CH\(_3\)), 63.5 (s) (C, quaternary), 54.3 (s) (CH), 43.6 (s) (CH\(_2\)), 20.6 (CH\(_3\)); m/z (APCI) 325.0 [(M + H\(^+\), 100%]. (Found: (M + H\(^+\)) (APCI), 325.0591 C\(_{13}\)H\(_{12}\)N\(_2\)O\(_8\) requires (M + H\(^+\)) 325.0594).
(S)-5-Carboethoxypyrrolidin-2-one (231)—To a stirred suspension of L-pyroglutamic acid (230) (52.0 g, 403 mmol) in dry toluene (260 ml) was added ethanol (50 ml) and sulphuric acid (1 ml). The reaction vessel was fitted with a Dean-Stark apparatus and the mixture was heated under reflux with azeotropic removal of water for six hours. After cooling the reaction mixture was diluted with chloroform (250 ml) and then treated with potassium carbonate (20.0 g, 145 mmol). After effervescence ceased the reaction mixture was filtered through celite and concentrated in vacuo to afford the product (63.3 g, 100%) as a white crystalline solid. M.p. 53-54 °C (lit. 54-55 °C); $\nu_{\text{max}}$ (neat, NaCl plates/ cm$^{-1}$) 2985 (s), 1700 (s), 1404 (s), 1377 (s), 1203 (s), 1111 (m), 1021 (s), 918 (m); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 4.14 (1H, dd, $J = 4.9$ & $8.7$ Hz, H-5), 4.07 (2H, q, $J = 7.1$ Hz, O-CH$_3$), 2.20-2.38 (3H, m, H-3 & H-4a), 2.02-2.06 (1H, m, H-4β), 1.14 (3H, t, $J = 7.1$ Hz, CH$_3$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 179.3 (s) (C=O), 172.6 (s) (C=O), 61.7 (s) (CH), 56.0 (s) (CH$_2$), 29.7 (s) (CH$_2$), 25.0 (s) (CH$_3$), 14.3 (s) (CH$_2$); $m/z$ (APCI) 158.0 [(M + H)$^+$, 100%].

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\text{NH} \quad \xrightarrow{\text{NaBH}_4} \quad \text{NH} \quad \text{OH}
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(S)-5-Hydroxymethyl pyrrolidin-2-one (232)—The ester 231 (5.0 g, 31.85 mmol) dissolved in ethanol (30 ml) was treated at 0 °C with sodium borohydride (1.25 g, 33.0 mmol) portionwise over 10 minutes. The reaction mixture was slowly allowed to warm to room temperature and stirred for a further 90 minutes. The reaction was then cooled to 0 °C hydrochloric acid (2 ml) was cautiously added to quench the reaction mixture. Filtration of the precipitated salts through celite and concentration of the resultant liquor afforded the crude product (4.6 g) as a colourless oil. The crude product was then purified by column chromatography Rf 0.20 (silica, hexane:ethyl acetate; 2:1) to give the pure product (2.97 g, 81%) as a white solid. M.p. 85-87 °C (lit. 86-87 °C); $\nu_{\text{max}}$ (neat, NaCl plates/ cm$^{-1}$) 2926 (s), 1680 (s), 1460 (s), 1377 (s), 1081 (w), 1017 (w), 722 (m); $\delta_{\text{H}}$(400 MHz; CDCl$_3$), 7.54 (1H, s, O-H), 4.89 (1H, s, NH), 3.70-3.74 (1H, m, H-5), 3.65 (1H, dd, $J = 3.7$ & 11.6 Hz, HCH-O), 3.48 (1H, dd, $J = 4.7$ & 11.6 Hz, HCH-O), 2.25-2.34 (1H, m, H-4), 2.08-2.12 (1H, m, H-3α), 1.70-1.74 (1H, m, H-3β); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 179.8 (s) (C=O), 65.8 (s) (CH$_2$), 56.8 (s) (CH), 30.5 (s) (CH$_2$), 22.8 (s) (CH$_2$); $m/z$ (APCI) 116.0 [(M+H)$^+$, 100%].
(S)-5-Trityloxymethyl pyrrolidin-2-one$^{168}$ (233)—To a solution of the alcohol 232 (2.37 g, 20.61 mmol) in dichloromethane (50 ml) was added triethylamine (5.60 ml, 40.0 mmol) and triphenylchloromethane (7.75 g, 28 mmol) and the reaction mixture was stirred at room temperature for 20 hours. Water (30 ml) was then added and the product was extracted with dichloromethane (3 × 50 ml). The combined extracts were dried over Na$_2$SO$_4$ and the solvent removed on a rotary evaporator to give the crude product (9.1 g) as an orange powder. The crude product was then purified by column chromatography Rf 0.43 (silica, hexane:ethyl acetate; 1:3) to give the pure product (4.81 g, 65%) as a white powder. \[\alpha\]$_D$ $^{+}$28.4° (c 1.71 in ethanol) (lit. $^{+}$28.9° c 1.71 in ethanol)$^{168}$; M.p. 164-166 °C (lit. 165.5-166 °C)$^{168}$; $\nu_{max}$ (nujol on NaCl plates/cm$^{-1}$) 2922 (s), 1668 (s) (C=O), 1462 (s), 1377 (s); $\delta_{H}$ (400 MHz; CDCl$_3$) 7.27-7.44 (15H, m, Ph), 3.84-3.94 (1H, m, H-5), 3.22 (1H, dd, $J$ 4.0 & 9.3 Hz, HCH-O), 3.02 (1H, dd, $J$ 8.3 & 9.3 Hz, HCH-O), 2.33 (2H, t, $J$ 8.1 Hz, H-3), 2.12-2.21 (1H, m, H-5α), 1.63-1.74 (1H, m, H-5β); $\delta_{C}$ (100 MHz; CDCl$_3$) 178.5 (s) (C=O), 144.0 (s) (C, Ar), 129.0 (s) (2 × CH, Ar), 128.3 (s) (2 × CH, Ar), 127.6 (s) (CH, Ar) 87.2 (s) (C-Ph), 67.5 (s) (CH$_2$), 54.5 (s) (CH), 30.1 (s) (CH$_2$), 23.7 (s) (CH$_2$); m/z (APCI) 358.0 [(M+H)$^+$, 100%].

(S)-l-Methyl-5-trityloxymethylpyrrolidin-2-one (234)—5-Trityloxymethyl pyrrolidin-2-one (233) (1.5 g, 4.2 mmol) in dry THF (5 ml) was added dropwise at 0 °C to a suspension of sodium hydride (60% dispersion in oil) (0.50 g, 12.6 mmol). The mixture was then stirred at 0 °C for 20 minutes. Methyl iodide (1.26 ml, 20.3 mmol) was slowly added and the mixture was stirred overnight at room temperature. The mixture was filtered through a celite plug and which was washed several times with THF. The filtrate and the washings were pooled together and evaporated to dryness. The residue was partitioned between chloroform (50 ml) and water (50 ml). The water layer was washed with chloroform (3 × 25 ml). The combined extracts were pooled together and dried over MgSO$_4$. The solvent was removed on a rotary evaporator.
to give the crude product (2.3 g) as a yellow oil. The crude product was then purified by
column chromatography Rf 0.43 (silica, hexane:ethyl acetate; 1:3) to give the pure product
(0.97 g, 62%) as a yellow oil. $\nu_{\text{max}}$ (nujol on NaCl plates/cm$^{-1}$) 2936 (s), 2235 (w), 1963 (w), 1681 (s), 1449 (s); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 7.27 (6H, app. d, $J$ 7.3 Hz, Ph), 7.15 (6H, app. t, $J$ 7.3 Hz, Ph), 7.10 (3H, app. t, $J$ 7.3 Hz, Ph), 3.59 (1H, dd, $J$ 3.6 & 10.0 Hz, HCH-O), 2.99 (1H, dd, $J$ 4.5 & 10.0 Hz, HCH-O), 2.61 (3H, s, N-CH$_3$), 2.33-2.43 (1H, m, H-3$\alpha$), 2.11-2.22 (1H, m, H-3$\beta$), 1.86-1.97 (1H, m, H-4$\alpha$), 1.64-1.72 (1H, m, H-4$\beta$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 175.8 (s) (C=O), 144.0 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 127.8 (s) (CH, Ar) 87.3 (s) (C-Ph), 64.5 (s) (CH$_2$), 60.4 (s) (CH), 30.7 (s) (CH$_2$), 28.8 (s) (CH$_3$), 22.0 (s) (CH$_2$); m/z (APCI) 372.0 [(M+H)$^+$, 100%].

(S)-1-Boc-5-trityloxymethylpyrrolidin-2-one$^{29}$ (234a)—To a solution of 5-Trityloxymethyl
pyrrolidin-2-one (238) (1.5 g, 4.20 mmol) in acetonitrile (50 ml) at 0 °C was added DMAP (52
mg, 0.42 mmol) and di-tert-butyl dicarbonate (1.83 g, 8.4 mmol) with stirring. The reaction
was allowed to slowly warm to room temperature and stirred overnight. The solvent was then
removed on a rotary evaporator to give the crude product (2.56 g) as a brown solid. The crude
product was then purified by column chromatography Rf 0.12 (silica, hexane:ethyl acetate;
3:1) to give the pure product (1.24 g, 65%) as a white solid. M.p. 107-108 °C (lit. 108 °C)$^{230}$;
$\nu_{\text{max}}$ (nujol on NaCl plates/cm$^{-1}$) 2928 (s), 1685 (s), 1449 (s) 1376 (s); $\delta_{\text{H}}$(400 MHz; CDCl$_3$)
7.30 (6H, app. d, $J$ 7.6 Hz, Ph), 7.13 (6H, app. t, $J$ 7.6 Hz, Ph), 7.06 (3H, app. t, $J$ 7.6 Hz, Ph),
4.13-4.16 (1H, m, H-5), 3.41 (1H, dd, $J$ 4.3 & 13.7 Hz, HCH-O), 2.87 (1H, dd, $J$ 2.5 & 9.4 Hz,
HCH-O), 2.67-2.74 (1H, m, H-3$\alpha$), 2.27-2.34 (1H, m, H-3$\beta$), 1.91-1.98 (1H, m, H-4$\alpha$), 1.78-
1.83 (1H, m, H-4$\beta$), 1.34 (9H, s, (CH$_3$)$_3$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 175.7 (s) (C=O), 150.1 (s) (C,
Ar), 144.0 (s) (2 × CH, Ar), 129.0 (s) (2 × CH, Ar), 128.4 (s) (CH, Ar) 127.3 (s) (C-Ar), 87.3
(s) (C-Ph), 83.1 (s) (C), 64.6 (s) (CH), 58.0 (s) (CH$_2$), 32.7 (s) (CH$_2$), 28.3 (s) (3 × CH$_3$), 21.8
(s) (CH$_2$); m/z (APCI) 458.0 [(M+H)$^+$, 100%].
(5S,3R)-3-Phenylsulfanyl-1-methyl-5-trityloxymethylpyrrolidin-2-one (235)—To a solution of diisopropylamine (0.38 ml, 2.70 mmol) in dry THF (5 ml) was added at 0 °C n-butyllithium (2.5 M in hexanes) (1.08 ml, 2.31 mmol). The solution was stirred at 0 °C for 20 minutes before cooling to -78 °C. 1-Methyl-5-trityloxymethyl pyrrolidin-2-one (234) (0.50 g, 1.35 mmol) dissolved in dry THF (5 ml) was added dropwise to the solution which was then stirred at -78 °C for 35 minutes. Phenyl disulfide (0.30 g, 1.35 mmol) and DMPU (1.08 ml, 1.35 mmol) in dry THF (5 ml) was added dropwise to the reaction mixture. The solution was then stirred for a further 35 minutes at -78 °C and then allowed to warm to room temperature. The reaction mixture was then poured into water (20 ml) and extracted with ether (3 × 20 ml). The combined extracts were washed successively with 10% NaOH (25 ml), Water (25 ml), 10% HCl (25 ml) and water (25 ml) and then dried over Na2SO4. The solvent was removed on the rotary evaporator to give the crude product (0.80 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.43 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.36 g, 55%) as a yellow oil. v_max (neat, NaCl plates/cm^-1) 2929 (s), 1689 (s); δ_H(400 MHz; CDCl3) 7.41-7.49 (2H, m, Ph), 7.17-7.31 (18H, m, Ph), 4.00 (1H, t, J 8.3 Hz, H-3), 3.27-3.30 (1H, m, H-5), 3.22 (1H, dd, J 3.3 & 10.2 Hz, HCH-O), 3.02 (1H, dd, J 3.9 & 10.2 Hz, HCH-O), 2.65 (3H, s, CH3), 2.24-2.28 (1H, m, H-4α), 2.01-2.10 (1H, m, H-4β); δ_C(100 MHz; CDCl3) 172.7 (s) (C=O), 143.4 (s) (C, Ar), 133.6 (s) (C, Ar), 132.6 (s) (CH, Ar), 128.9 (s) (2 × CH, Ar) 128.6 (s) (2 × CH-Ar), 128.0 (s) (CH, Ar), 127.9 (s) (2 × CH, Ar), 127.7 (s) (CH, Ar), 127.3 (s) (2 × CH, Ar), 87.0 (s) (C), 63.1 (s) (CH2), 58.1 (s) (CH), 47.5 (s) (CH), 30.5 (s) (CH2), 28.8 (s) (CH); m/z (APCI) 480.0 [(M+H)^+], 100%. (Found: (M + H)^+ (APCI), 480.1924 C31H29NO2S requires (M + H)^+ 480.1919).

5-Phenyl-pyrrolidin-2-one (238)—In a 500 ml round bottom flask was added magnesium turnings (4.75 g, 200 mmol) followed by dry ether (100 ml). Bromobenzene (7.9 g, 51.4 mmol) was slowly added to the flask over a period of 30 minutes. The reaction mixture was
then cooled to 0 °C. Succinimide (5.0 g, 50.4 mmol) dissolved in dichloromethane (200 ml) was then added to the solution which was then allowed to warm to room temperature and stirred for 18 hours. Sodium cyanoborohydride (3.8 g, 60.55 mmol) was added to the solution followed by slow addition of a 6 M HCl solution to keep the pH 3-4. After stirring for 30 minutes the solution was neutralised with 10% NaOH and extracted with dichloromethane (3 × 100 ml). The solvent was removed on a rotary evaporator to give the crude product (9.14 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.42 (ethyl acetate) to give the pure product (4.95 g, 61%) as a white solid. M.p. 105-107 °C (lit. 107 °C)\(^{169}\); \(\nu_{\text{max}}\) (nujol on NaCl plates/cm\(^{-1}\)) 3451 (s), 2938 (s), 1663 (s), 1458 (s), 1395 (s), 1351 (s); \(\delta_{\text{H}}\)(400 MHz; CDCl\(_3\)) 7.21-7.41 (5H, m, Ph), 6.72 (1H, s, N-H), 4.76 (1H, t, J 7.1 Hz, H-5), 2.31-2.72 (3H, m, H-3 & H-4a), 1.92-1.97 (1H, m, H-4 \(\beta\)), \(\delta_{\text{C}}\)(100 MHz; CDCl\(_3\)) 178.9 (s) (C=O), 142.5 (s) (C, Ar), 128.9 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 125.6 (s) (2 × CH, Ar) 58.2 (s) (CH), 31.3 (s) (CH\(_2\)), 30.4 (s) (CH\(_2\)); \(m/z\) (APCI) 162.0 [(M+H)+, 100%].

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \\
\text{1. NaH} & \quad \downarrow \\
\text{2. CH}_3\text{I} & \quad \text{N} \\
\text{Ph} & \quad \\
\end{align*}
\]

1-Methyl-5-phenyl-pyrrolidin-2-one\(^{170}\) (239)—To a suspension of sodium hydride (60% dispersion in oil) (0.37 g, 9.32 mmol) in dry THF (10 ml) was added dropwise at 0 °C a solution of 5-phenyl-2-pyrrolidinone (238) (1.5 g, 9.32 mmol) in dry THF (5 ml). The mixture was stirred at 0 °C for 10 minutes before being allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was then cooled to 0 °C and iodomethane (0.58 ml, 9.32 mmol) was added dropwise to the reaction mixture which was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured onto ice/HCl (1 M solution) and extracted with dichloromethane (3 × 50 ml). The combined extracts were then washed with water (3 × 50 ml) and dried over MgSO\(_4\). The solvent was then removed on a rotary evaporator to give the crude product (1.45 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.34 (silica, hexane:ethyl acetate; 3:1) to give the pure product (1.51 g, 92%) as a yellow oil. \(\nu_{\text{max}}\) (neat, NaCl plates/cm\(^{-1}\)) 1692 (s), 1377 (m), 1134 (s); \(\delta_{\text{H}}\)(400 MHz; CDCl\(_3\)) 7.06-7.54 (5H, m, Ph), 4.52 (1H, dt, J 2.1 & 6.5, H-5), 2.66 (3H, s, N-CH\(_3\)), 1.48-2.94 (4H, m, H-3 & H-4); \(\delta_{\text{C}}\)(100 MHz; CDCl\(_3\)) 176.0 (s) (C=O), 141.5 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 128.5 (s) (CH, Ar), 151
126.7 (s) (2 x CH, Ar) 65.0 (s) (CH), 30.6 (s) (CH₂), 28.8 (s) (CH₃), 28.6 (s) (CH₂); \( m/z \) (APCI) 176.0 [(M+H)+, 100%].

1-Methyl-5-phenyl-3-phenylsulfanylpyrrolidin-2-one (240)—This was prepared by the General Method using diisopropylamine (1.52 ml, 10.8 mmol) \( n \)-butyllithium (2.5 M in hexanes) (4.32 ml, 9.24 mmol), 1-methyl-5-phenyl-pyrroldin-2-one (239) (0.94g, 5.40 mmol), DMPU (4.32 ml, 5.4 mmol) and phenyl disulfide (1.2 g, 5.4 mmol) to give the crude product as a yellow oil (0.31 g). The crude product was then purified by column chromatography \( R_f \) 0.31 (hexane: ethyl acetate 3:1) to give a mixture of diastereoisomers (0.56 g, 37%) that could not be separated by column chromatography.

**General Method for the VNS-S\(_{NAr}\) Process**

Sodium hydride (60% dispersion in oil) (20.3 mmol) was added to anhydrous DMF (5 ml) and the mixture flushed with nitrogen and cooled to 0 °C. The VNS nucleophile (8.13 mmol) and the nitroarene (8.13 mmol) were dissolved in anhydrous DMF (5 ml) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature. The reaction mixture was then cooled to -50 °C using \( \text{CO}_2 \)/methanol cooling bath. The electrophile (8.13 mmol) in anhydrous DMF (2 ml) was then added and the resulting mixture was allowed to warm to room temperature and stirred for a further two hours. The reaction mixture was poured onto ice/hydrochloric acid (50 ml, 1 M solution) and extracted with dichloromethane (3 x 30 ml). The combined organic extracts were washed well with distilled water (5 x 50 ml), saturated aqueous sodium bicarbonate solution (3 x 50 ml), dried (magnesium sulfate) and the solvent removed under reduced pressure to give the crude product.
Ethyl 2-(4'-nitrophenyl)-2-(2''-nitro-4''-trifluoromethylphenyl)propionate (257a)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), ethyl 2-chloropropionate (1.11 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 4-fluoro-3-nitrobenzotrifluoride (1.14 ml, 8.13 mmol) to give the crude product (3.09 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.21 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.42 g, 73%) as a yellow crystalline powder. M.p. 114-115.5 °C; (Found C, 52.40; H, 3.72; N 6.82. C_{18}H_{15}F_{3}N_{2}O_{6} requires C, 52.43; H, 3.67; N, 6.79%); νmax (nujol on NaCl plates/cm⁻¹) 2924 (s), 1708 (s) (C=O), 1626 (m), 1604 (m), 1571 (m), 1518 (m), 1462 (s), 1349 (s), 1129 (s), 905 (m), 857 (s), 796 (m), 729 (s), 706 (m); δH (400 MHz; CDCl₃) 8.20-8.23 (3H, m, H-3' & H-5' & H-3''), 7.72 (1H, d, J 8.4 Hz, H-5''), 7.67 (2H, d, J 9.0 Hz, H-2' & H-6'), 7.06 (1H, d, J 8.4 Hz, H-6''), 4.13-4.16 (1H, m, HCH), 4.01-4.08 (1H, m, HCH), 2.25 (3H, s, CH₃), 1.18 (3H, t, J 7.1 Hz, CH₂CH₃); δC (100 MHz; CDCl₃) 170.8 (s) (C=O), 149.2 (s) (C, Ar), 148.6 (s) (C, Ar), 147.4 (s) (C, Ar), 143.3 (s) (C, Ar), 132.5 (s) (CH, Ar), 130.8 (q) (C-CF₃, J 34.3 Hz), 129.2 (s) (2 × CH, Ar) 124.0 (s) (2 × CH, Ar), 122.6 (s) (CH, Ar), 122.6 (q) (CF₃, J 271.1 Hz), 62.4 (s) (CH₂), 56.0 (s) (C, quaternary), 25.6 (s) (C-CH₃), 13.6 (CH₂CH₃); m/z (APCI) 413.1 [(M+H)+, 100%] 412.5 (49); (Found (ES+): (M + NH₄)+ 430.1224 C_{18}H_{15}N₂O₆F₃ requires (M + NH₄)+ 430.1226).

Ethyl 2-(2',4'-dinitrophenyl)-2-(4''-nitrophenyl)propionate (257b)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), ethyl 2-chloropropionate (1.11 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 2,4-dinitrofluorobenzene (1.02 ml, 8.13 mmol) to give the crude product (2.85 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.17 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.41 g, 77%) as a brown oil. νmax (liquid film on NaCl plates/cm⁻¹) 2984 (m), 1738 (s) (C=O), 1604 (s), 1521 (s), 1349 (s), 909 (m), 835 (m), 650 (m); δH (400 MHz; CDCl₃) 8.80 (1H, d, J 2.4 Hz, H-3'), 8.30 (1H, dd, J 2.4 & 8.7 Hz, H-5'), 8.22 (2H, d, J 9.0 Hz, H-3'' & H-5''), 7.68 (2H, d, J 9.0 Hz, H-2'' & H-6''), 7.16 (1H, d, J 8.7 Hz, H-6'), 4.15-4.22 (1H, m, O-HCH-CH₃), 4.01-4.09 (1H, m, O-HCH-CH₃), 2.26
(3H, s, CH₃), 1.18 (3H, t, J 7.2 Hz, CH₃-CH₂); δC (100 MHz; CDCl₃) 170.5 (s) (C=O), 149.4 (s) (C, Ar), 148.0 (s) (C, Ar), 147.6 (s) (C, Ar), 146.7 (s) (C, Ar), 146.0 (s) (C, Ar), 132.9 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 120.9 (s) (CH, Ar), 62.6 (s) (CH₂), 56.2 (s) (C, quaternary), 25.6 (s) (CH₃), 13.7 (s) (CH₃-CH₂); m/z (APCI) 389.9 [(M+H)+, 100%], 345.1 (36); (Found (APCI) (M + H)+, 390.0943 C₁₇H₁₅N₃O₈ requires (M + H)+ 390.0937).

Ethyl 2-(2'-cyano-4'-nitrophenyl)-2-(4''-nitrophenyl)propionate (257c)—This was prepared by the General Method, but cooling to 0 °C instead of −50 °C using sodium hydride (60% dispersion in oil) (0.25 g, 6.09 mmol), ethyl 2-chloropropionate (0.52 ml, 4.07 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2-fluoro-5-nitrobenzonitrile (0.34 g, 2.03 mmol) to give the crude product (1.08 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.18 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.66 g, 88%) as a yellow crystalline powder. M.p. 115-117 °C; νmax (nujol on NaCl plates/ cm⁻¹) 2954 (s), 2853 (s), 1715(s), 1606 (m), 1527 (s), 1463 (s), 1377 (m), 1355 (s), 1257 (m), 1217 (m), 1089 (m), 1046 (m), 906 (w), 864 (m), 736 (m); δH (400 MHz; CDCl₃) 8.56 (1H, d, J 1.9 Hz, H-3'), 8.33 (1H, dd, J 1.9 & 8.8 Hz, H-5'), 8.28 (2H, d, J 8.6 Hz, H-3'' & 5''), 7.63 (2H, d, J 8.6 Hz, H-2'' & 6''), 7.21 (1H, d, J 8.8 Hz, H-6'), 4.31-4.41 (1H, m, HCH-CH₃), 4.23-4.29 (1H, m, HCH-CH₃), 2.17 (3H, s, CH₃), 1.28 (3H, t, J 7.1 Hz, CH₃-CH₂); δC (100 MHz; CDCl₃) 171.4 (s) (C=O), 154.0 (s) (C, Ar), 147.7 (s) (C, Ar), 146.8 (s) (C, Ar), 146.5 (s) (C, Ar), 129.9 (s) (CH, Ar), 126.5 (s) (CH, Ar), 129.1 (s) (2 × CH, Ar), 127.2 (s) (CH, Ar), 124.0 (s) (2 × CH, Ar), 115.8 (s) (CN or C-CN), 114.5 (s) (CN or C-CN), 63.1 (s) (CH₂), 56.9 (s) (C, quaternary), 25.3 (s) (CH₃), 13.8 (s) (CH₃-CH₂); m/z (APCI) 369.8 [(M+H)+, 100%], 341.8 (18), 295.8 (42); (Found (ES+) (M + NH₄)+, 387.1306 C₁₈H₁₅N₃O₆ requires (M + NH₄)+ 387.1305.)
Ethyl 2-(4'-nitrophenyl)-2-(4''-nitro-2''-trifluoromethylphenyl)propionate (257d)—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride (60% dispersion in oil) (0.25 g, 6.09 mmol), ethyl 2-chloropropionate (0.52 ml, 4.07 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.43 g, 2.03 mmol) to give the crude product (1.20 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.26 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.75 g, 89%) as a yellow crystalline powder. M.p. 117-118.2 °C; (Found C, 51.74; H, 3.67; N, 6.79%); \( \nu_{\text{max}} \) (nujol on NaCl plates/cm\(^{-1}\)) 1737 (s) (C=O), 1591 (m), 1527 (s), 1462 (s), 1349 (m), 1309 (m), 1117 (w), 910 (w), 857 (w), 737 (w); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 8.58 (1H, d, J 2.4 Hz, H-3''), 8.32 (1H, dd, J 2.4 & 8.9 Hz, H-5''), 8.20 (2H, d, J 8.9 Hz, H-3' & H-5''), 7.64 (2H, d, J 8.9 Hz, H-2' & H-6''), 7.41 (1H, d, J 8.9 Hz, H-6''), 4.23-4.29 (1H, m, HCH-CH\(_3\)), 4.11-4.20 (1H, m, HCH-CH\(_3\)), 2.10 (3H, s, CH\(_3\)), 1.19 (3H, t, J 7.1 Hz, CH\(_3\)-CH\(_2\)); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 172.1 (s) (C=O), 149.4 (s) (C, Ar), 148.3 (s) (C, Ar), 147.1 (s) (C, Ar), 146.8 (s) (C, Ar), 131.2 (s) (CH, Ar), 130.9 (q) (C-CF\(_3\), J 32.6 Hz), 128.8 (s) (2 × CH, Ar), 126.1 (s) (CH, Ar), 124.4 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 122.7 (q) (CF\(_3\), J 273 Hz), 62.4 (s) (CH\(_2\)), 56.2 (s) (C, quaternary), 28.4 (s) (CH\(_3\)), 13.7 (s) (CH\(_3\)-CH\(_2\)); \( m/z \) (APCI) 369.8 [(M+H)+, 100%], 341.8 (17.5), 295.8 (42); \( m/z \) (APCI) 412.9 [(M+H)+, 100%], 370.1 (65), 364.9 (14); (Found (APCI) (M + H)+, 413.0960. C\(_{18}\)H\(_{13}\)F\(_3\)N\(_2\)O\(_6\) requires (M + H)+ 413.0953).

Methyl 2-(4'-nitrophenyl)-2-(2''-nitro-4''-trifluoromethylphenyl)propionate (257e)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), methyl 2-chloropropionate (1.0 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol)
and 4-fluoro-3-nitrobenzotrifluoride (1.14 ml, 2.03 mmol) to give the crude product (3.59 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.30 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.21 g, 69%) as a yellow crystalline solid. M.p. 125.5-127.5 °C; \( \nu_{max} \) (nujol on NaCl plates/cm\(^{-1}\)) 2925 (s), 1974 (w), 1722 (s), 1626 (m), 1572 (m), 1518 (s), 1464 (s), 1321 (s), 1136 (s) 1048 (m), 1013 (w), 974 (m), 899 (m), 882 (m); \( \delta_{H} \) (400 MHz; CDCl\(_3\)) 8.19-8.23 (3H, m, H-3' & H-5' & H-3''), 7.72 (1H, d, \( J = 8.3 \) Hz, H-5''), 7.68 (2H, d, \( J = 8.9 \) Hz, H-2' & H-5'), 7.09 (1H, d, \( J = 8.3 \) Hz, H-6''), 3.66 (3H, s, O-CH\(_3\)), 2.25 (3H, s, CH\(_3\)); \( \delta_{C} \) (400 MHz; CDCl\(_3\)) 171.5 (s) (C=O), 149.3 (s) (C, Ar), 148.3 (s) (C, Ar), 147.5 (s) (C, Ar), 143.2 (s) (C, Ar), 132.3 (s) (CH, Ar), 131.0 (q) (C-CF\(_3\), \( J = 34.5 \) Hz), 129.3 (s) (2 \times CH, Ar), 129.3 (s) (CH, Ar), 123.7 (s) (2 \times CH, Ar), 122.8 (s) (C, Ar), 122.3 (q) (CF\(_3\), \( J = 271.1 \) Hz), 55.9 (s) (C, quaternary), 52.9 (s) (H\(_3\)C-O-), 25.8 (s) (CH\(_3\)); m/z (EI) 398.1 [(M\(^+\), 100%)] (Found (EI) M\(^+\) 398.0723 C\(_{17}\)H\(_{13}\)F\(_3\)N\(_2\)O\(_6\) requires M\(^+\) 398.0720).

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\text{Methyl 2-(2',4'-dinitrophenyl)-2-(4''-nitrophenyl)propionate (257f)} - \text{This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.10 mmol), methyl 2-chloropropionate (0.25 g, 2.03 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2,4-dinitrofluorobenzene (0.26 ml, 2.03 mmol) to give the crude product (0.79 g) as a brown oil. The crude product was then purified by column chromatography, Rf 0.45 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.53 g, 71%) as a yellow crystalline solid. M.p. 153-155 °C; \( \nu_{max} \) (nujol on NaCl plates/cm\(^{-1}\)) 2925 (s), 1731 (s), 1600 (s), 1463 (s), 1349 (s), 1204 (m), 1125 (w), 1093 (m), 1046 (w), 1012 (w), 981 (m), 919 (m), 900 (w), 869 (w), 834 (m), 737 (m); \( \delta_{H} \) (400 MHz; CDCl\(_3\)) 8.80 (1H, d, \( J = 2.4 \) Hz, H-3'), 8.30 (1H, dd, \( J = 2.4 \) & 8.8 Hz, H-5''), 8.23 (2H, d, \( J = 9.0 \) Hz, H-3'' & H-5''), 7.66 (2H, d, \( J = 9.0 \) Hz, H-2'' & H-6''), 7.14 (1H, d, \( J = 8.8 \) Hz, H-6'), 3.72 (3H, s, O-CH\(_3\)), 2.26 (3H, s, CH\(_3\)); \( \delta_{C} \) (100 MHz; CDCl\(_3\)) 171.1 (s) (C=O), 149.4 (s) (C, Ar), 147.8 (s) (C, Ar), 147.7 (s) (C, Ar), 146.7 (s) (C, Ar), 145.8 (s) (C, Ar), 132.8 (s) (CH, Ar), 129.3 (s) (2 \times CH, Ar), 126.8 (s) (CH, Ar), 123.9 (s) (CH, Ar), 120.9 (s) (CH, Ar), 56.1 (s) (C, quaternary), 53.1 (s) (O-CH\(_3\)), 25.7 (s) (CH\(_3\)); m/z (APCI) 375.9}
Methyl 2-(2'-cyano-4'-nitrophenyl)-2-(4''-nitrophenyl)propionate (257g)—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride (60% dispersion in oil) (0.25 g, 6.09 mmol), methyl 2-chloropropionate (0.47 ml, 4.07 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2-fluoro-5-nitrobenzonitrile (0.34 g, 2.04 mmol) to give the crude product (1.0 g) as a brown oil. The crude product was then purified by column chromatography, Rf 0.19 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.62 g, 86%) as a yellow crystalline solid. M.p. 163-164.4 °C; (Found C, 58.04; H, 3.85; N 11.93. C_{18}H_{15}F_{3}N_{2}O_{6} requires C, 57.47; H, 3.69; N, 11.82%; ν_{max} (nujol on NaCl plates/ cm⁻¹) 2922 (s), 2852 (s), 2225 (w), 1724 (s), 1607 (m), 1520. (s), 1464 (s), 1377 (w) 1356 (s), 1299 (s), 1256 (m), 1217 (m), 1088 (m), 1046 (m), 905 (m), 836 (m), 736 (m); δ_{H} (400 MHz; CDCl₃) 8.57 (1H, d, J 2.4 Hz, H-3'), 8.32 (1H, dd, J 2.4 & 8.8 Hz, H-5'), 8.30 (2H, d, J 8.9 Hz, H-3'' & H-5''), 7.63 (2H, d, J 8.9 Hz, H-2'' & H-6''), 7.18 (1H, d, J 8.8 Hz, H-6'), 3.86 (3H, s, O-CH₃), 2.26 (3H, s, CH₃); δ_{C} (100 MHz; CDCl₃) 171.9 (s) (C=O), 153.9 (s) (C, Ar), 147.7 (s) (C, Ar), 146.6 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.6 (s) (CH, Ar), 129.1 (s) (2 × CH, Ar), 127.2 (s) (CH, Ar), 124.1 (s) (2 × CH, Ar), 115.7 (s) (CN or C-CN), 114.4 (s) (CN or C-CN), 56.9 (s) (C, quaternary), 53.7 (s) (O-CH₃), 25.3 (s) (CH₃); m/z (APCI) 355.9 [(M+H)^{+}, 100%], 335.7 (10), 295.9 (12); (Found (ES^-) (M + NH₄)^{+}, 373.1147, C_{17}H_{13}N_{2}O_{6} requires (M + NH₄)^{+} 373.1148).

Methyl 2-(4'-nitrophenyl)-2-(4''-nitro-2''-trifluoromethyl)phenylpropionate (257h)—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride
(60% dispersion in oil) (0.25 g, 6.09 mmol), methyl 2-chloropropionate (0.47 ml, 4.07 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.45 ml, 2.04 mmol) to give the crude product (1.27 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.24 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.70 g, 86%) as a yellow crystalline solid. M.p. 135.5-137.5 °C; (Found C, 51.43; H, 3.27; N 6.92. C_{18}H_{15}F_{3}N_{2}O_{6} requires C, 51.27; H, 3.29; N, 7.03%); \( \nu_{\text{max}} \) (nujol on NaCl plates/cm\(^{-1}\)) 2922 (s), 2918 (w), 2870 (w), 1742 (m), 1594 (m), 1512 (s), 1461 (s), 1377 (s), 1170 (m), 1124 (m), 1071 (w), 920 (w), 854 (m); \( \delta_{H} \) (400 MHz; CDCl\(_3\)) 8.59 (1H, d, \( J \) 2.4 Hz, H-3”), 8.34 (1H, dd, \( J 2.4 \) & \( 8.9 \) Hz, H-5”), 7.64 (2H, d, \( J 9.0 \) Hz, H-2’ & H-6’), 7.44 (1H, d, \( J 8.9 \) Hz, H-6”), 3.74 (3H, s, O-CH\(_3\)); 5C (100 MHz; CDCl\(_3\)) \( 173.0 \) (s) (C=O), 149.6 (s) (C, Ar), 148.6 (s) (C, Ar), 147.6 (s) (C, Ar), 147.3 (s) 131.6 (s) (CH, Ar), 131.2 (q) (C-CF\(_3\), \( J 32.1 \) Hz), 130.3 (s) (CH, Ar), 129.1 (s) (2 \( \times \) CH, Ar), 126.5 (s) (CH, Ar), 124.8 (s) (C, Ar), 124.0 (s) (2 \( \times \) CH, Ar)123.6 (q) (CF\(_3\), \( J 273.5 \) Hz), 123.0 (C, Ar), 56.5 (s) (C, quaternary), 53.5 (s) (O-CH\(_3\)), 28.8 (s) (CH\(_3\)); m/z (APCI) 399.0 [(M+H)\(^+\), 100%]; (Found (Cl) (M + NH\(_4\))\(^+\), 416.1067, C\(_{17}\)H\(_{13}\)N\(_3\)O\(_6\) requires (M + NH\(_4\))\(^+\) 416.1069).

\[
\begin{align*}
\text{NO}_2 & \quad \text{Cl} \quad \text{CO}_2\text{Me} \\
\text{NO}_2 & \quad \text{F} \\
\text{NO}_2 & \quad \text{F} \\
\text{F_3C} & \quad \text{NO}_2 \\
\text{F_3C} & \quad \text{NO}_2 \\
\text{CO}_2\text{Me} & \\
\end{align*}
\]

1) NaH, DMF
2) \( \beta \)-Naphthalene

\textit{Methyl 2-(4’-nitrophenyl)-2-(2”-nitro-4”-trifluoromethyl)butanoate} (257i)—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.19 g, 4.60 mmol), methyl 2-chlorobutanoate (0.25 g, 1.83 mmol), nitrobenzene (0.19 ml, 1.83 mmol) and 4-fluoro-3-nitrobenzotrifluoride (0.26 ml, 1.83 mmol) to give the crude product (0.78 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.45 g, 60%) as a yellow oil. \( \nu_{\text{max}} \) (liquid film on NaCl plates/cm\(^{-1}\)) 3090 (m), 2955 (s), 1739 (s), 1629 (s), 1606 (m), 1538 (s), 1462 (m), 1327 (s), 1127 (s) 1014 (s), 903 (s), 883 (w), 851 (s), 798 (m), 752 (m); \( \delta_{H} \) (400 MHz; CDCl\(_3\)) 8.21 (1H, d, \( J 1.3 \) Hz, H-3”), 8.16 (2H, d, \( J 9.0 \) Hz, H-3’ & H-5”), 7.85 (1H, dd, \( J 1.3 \) & \( 8.4 \) Hz, H-5”), 7.63 (2H, d, \( J 9.0 \) Hz, H-2’ & H-6’), 7.46 (1H, d, \( J 8.4 \) Hz, H-6”), 3.65 (3H, s, O-CH\(_3\)), 2.74-2.83 (1H, m, HCH-CH\(_3\)), 2.64-2.72 (1H, m, HCH-CH\(_3\)), 0.90 (3H, t, \( J 7.4 \) Hz, CH\(_3\)); \( \delta_{C} \) (100 MHz; CDCl\(_3\)) 171.0 (s) (C=O), 150.0 (s) (C, Ar), 147.4 (s) (C, Ar), 147.0 (s) (C, Ar), 140.1 (s) (C, Ar), 132.6 (s) 131.1 (q) (C-CF\(_3\), J
34.7 Hz), 129.6 (s) (2 × CH, Ar), 128.6 (s) (CH, Ar), 123.4 (s) (2 × CH, Ar), 123.1 (s) (CH, Ar), 59.5 (s) (C, quaternary), 52.7 (s) (O-CH₃), 30.6 (s) (CH₂), 9.7 (s) (CH₃); m/z (APCI) [(M + H)⁺, 100%], (Found: (M + NH₄)⁺ (ES⁺): 430.1221 C₁₈H₁₅F₃N₂O₆ requires (M + NH₄)⁺ 430.1226).

**Methyl 2-(2′,4′-dinitrophenyl)-2-(4″-nitrophenyl)butanoate (257j)**—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), methyl 2-chlorobutanoate (0.50 g, 3.66 mmol), nitrobenzene (0.19 ml, 1.83 mmol) and 2,4-dinitrofluorobenzene (0.23 ml, 1.90 mmol) to give the crude product (0.85 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.12 (silica, 3:1, hexane:ethyl acetate; v/v) to give the pure product (0.57 g, 80%) as a yellow crystalline solid. M.p. 59.1-61.7 °C; νmax (nujol on NaCl plates/ cm⁻¹) 2922 (s), 1738 (s), 1462 (s), 1376 (m); δH (400 MHz; CDCl₃) 8.78 (1H, d, J 2.4 Hz, H-3′), 8.45 (1H, dd, J 2.4 & 8.9 Hz, H-5′), 8.16 (2H, d, J 9.0 Hz, H-3″ & H-5″), 7.64 (2H, d, J 9.0 Hz, H-2″ & H-6″), 7.59 (1H, d, J 8.9 Hz, H-6′), 3.66 (3H, s, O-CH₃), 2.79-2.89 (1H, m, HCH), 2.67-2.77 (1H, m, HCH), 0.92 (3H, t, J 7.4 Hz, CH₃-CH₂); δC (100 MHz; CDCl₃) 170.7 (s) (C=O), 150.1 (s) (C, Ar), 147.1 (s) (C, Ar), 146.9 (s) (C, Ar), 142.9 (s) (C, Ar), 133.1 (s) (CH, Ar), 129.7 (s) (2 × CH, Ar), 126.3 (s) (CH, Ar), 123.5 (s) (2 × CH, Ar), 121.2 (s) (CH, Ar), 59.7 (s) (C, quaternary), 52.8 (s) (O-CH₃), 30.8 (s) (CH₂), 9.7 (s) (CH₃); m/z (APCI) [(M + H)⁺, 100%], (Found: (M + NH₄)⁺ (ES⁺): 407.1198 C₁₇H₁₅N₃O₆ requires (M + NH₄)⁺ 407.1203).

**Methyl 2-(4″-nitrophenyl)-2-(4″-nitro-2″-trifluoromethylphenyl)butanoate (257k)**—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride (60%
dispersion in oil) (0.18 g, 4.50 mmol), methyl 2-chlorobutanoate (0.25 g 1.83 mmol), nitrobenzene (0.19 ml, 1.83 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.38 g, 1.83 mmol) to give the crude product (0.72 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.23 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.52 g, 69%) as a yellow crystalline solid. M.p. 119-121 °C; νmax (nujol on NaCl plates/cm⁻¹) 2966 (s), 1737 (s), 1618 (m), 1591 (m), 1529 (m), 1376 (s), 1173 (m), 1122 (m), 1051 (m), 998 (m), 909 (m), 854 (m), 740 (m); δH (400 MHz; CDCl₃) 8.50 (1H, d, J 2.5 Hz, H-3'”), 8.38 (1H, dd, J 2.5 & 8.8 Hz, H-5”), 8.06 (2H, d, J 9.0 Hz, H-3’ & H-5’), 7.73 (1H, d, J 8.8 Hz, H-6”), 7.57 (2H, d, J 9.0 Hz, H-2’ & H-6’), 3.62 (3H, s, O-CH₃), 2.53-2.62 (1H, m, HCH), 2.28-2.37 (1H, m, HCH), 0.84 (3H, t, J 7.3 Hz, CH₂CH₃); δC (100 MHz; CDCl₃) 171.9 (s) (C=O), 149.0 (s) (C, Ar), 147.3 (s) (C, Ar), 147.1 (s) (C, Ar), 147.0 (s) (C, Ar), 131.8 (q) (C-CF₃ J 32 Hz), 131.2 (s) (CH, Ar), 129.4 (s) (2 × CH, Ar), 126.4 (s) (CH, Ar), 124.9 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 59.4 (s) (C, quaternary), 53.0 (s) (O-CH₃), 34.8 (s) (CH₂), 10.2 (s) (CH₃CH₂); m/z (APCI) 412.9 [(M+H)+, 100%], (Found: (M + NH₄)+ (Ammonia Cl) 430.1228, C₁₈H₁₅F₃N₂O₆ requires (M + NH₄)+ 430.1226).

**General Method for VNS-Sₐ Ar with KOr-Bu**—In a three necked round bottomed flask fitted with a condenser and nitrogen bubbler was added potassium tert-butoxide (7.2 mmol) followed by anhydrous DMF (5 ml). Nitrobenzene (2.39 mmol) the VNS nucleophile (4.8 mmol) dissolved in anhydrous DMF (2 ml) were added at -40 °C. The reaction mixture was stirred for 30 minutes allowing the temperature to warm to -20 °C. The reaction mixture was then checked by LC. The electrophile (3.59 mmol) was then added dropwise to the reaction mixture. The solution was then allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was then poured onto ice/HCl (1M solution) and then extracted with dichloromethane (3 × 50 ml). The organic solution was then washed with water (3 × 50 ml) and then dried over Na₂SO₄. The solvent was removed to give the crude product.
Ethyl 2-(2',4'-dinitrophenyl)-2-(4''-nitrophenyl)propionate (257b)—This was prepared by the method above using potassium tert-butoxide (0.80 g, 7.2 mmol), ethyl 2-chloropropionate (0.61 ml, 4.8 mmol), nitrobenzene (0.25 ml, 2.39 mmol) and 2,4-dinitrofluorobenzene (0.45 ml, 3.59 mmol) to give the crude product as an orange oil (2.02 g). The crude product was then purified by column chromatography Rf 0.17 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.53 g, 57%) as an orange oil. $\nu_{\text{max}}$ (liquid film on NaCl plates/cm$^{-1}$) 2984 (m), 1738 (s) (C=O), 1604 (s), 1521 (s), 1349 (s), 909 (m), 835 (m), 650 (m); $\delta_H$ (400 MHz; CDCl$_3$) 8.80 (1H, d, $J$ 2.4 Hz, H-3'); 8.30 (1H, dd, $J$ 2.4 & 8.7 Hz, H-5'); 8.22 (2H, d, $J$ 9.0 Hz, H-3'' & H-5''); 7.68 (2H, d, $J$ 9.0 Hz, H-2'' & H-6''), 7.16 (1H, d, $J$ 8.7 Hz, H-6'), 4.15-4.22 (1H, m, O-HCH-CH$_3$), 4.01-4.09 (1H, m, O-HCH-CH$_3$), 2.26 (3H, s, CH$_3$), 1.18 (3H, t, $J$ 7.2 Hz, CH$_3$-CH$_2$); $\delta_C$ (100 MHz; CDCl$_3$) 170.5 (s) (C=O), 149.4 (s) (C, Ar), 148.0 (s) (C, Ar), 147.6 (s) (C, Ar), 146.7 (s) (C, Ar), 146.0 (s) (C, Ar), 132.9 (s) (CH, Ar), 129.3 (s) (2 x CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 x CH, Ar), 120.9 (s) (CH, Ar), 62.6 (s) (CH$_2$), 56.2 (s) (C, quaternary), 25.6 (s) (CH$_3$), 13.7 (s) (CH$_3$-CH$_2$); m/z (APCI) 389.9 [(M+H)$^+$, 100%], 345.1 (36); (Found (APCI) (M + H)$^+$ 390.0943. C$_{17}$H$_{13}$N$_3$O$_8$ requires (M + H)$^+$ 390.0937).

Ethyl 2-(4'-nitrophenyl)-2-(4''-nitro-2''-trifluoromethylphenyl)propionate (257d)—This was prepared by the General Method using potassium tert-butoxide (0.80 g, 7.2 mmol), ethyl 2-chloropropionate (0.61 ml, 4.8 mmol), nitrobenzene (0.25 ml, 2.39 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.44 ml, 3.1 mmol) to give the crude product (1.10 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.26 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.68 g, 69%) as a yellow crystalline powder. M.p. 117-118.2 °C; (Found C, 51.74; H, 3.64; N 6.83. C$_{18}$H$_{13}$F$_3$N$_2$O$_6$ requires C, 52.43; H, 3.67; N, 6.79%); $\nu_{\text{max}}$ (nujol on NaCl plates/cm$^{-1}$) 1737 (s) (C=O), 1591 (m), 1527 (s), 1462 (s), 1349 (m), 1309 (m), 1117 (w), 910 (w), 857 (w), 737 (w); $\delta_H$ (400 MHz; CDCl$_3$) 8.58 (1H, d, $J$ 2.4 Hz, H-3''), 8.32 (1H, dd, $J$ 2.4 & 8.9 Hz, H-5''), 8.20 (2H, d, $J$ 8.9 Hz, H-3' & H-5''), 7.64 (2H, d, $J$ 8.9 Hz, H-2' & H-6''), 7.41 (1H, d, $J$ 8.9 Hz, H-6''), 4.23-4.29 (1H, m, HCH-CH$_3$), 4.11-4.20 (1H, m, HCH-CH$_3$), 2.10 (3H, s, CH$_3$), 1.19 (3H, t, $J$ 7.1 Hz, CH$_3$-CH$_2$); $\delta_C$ (100 MHz; CDCl$_3$) 172.1 (s) (C=O), 149.4 (s) (C, Ar), 148.3 (s) (C, Ar), 147.1 (s) (C, Ar), 13.7 (s) (CH$_3$-CH$_2$); m/z (APCI) 389.9 [(M+H)$^+$, 100%], 345.1 (36); (Found (APCI) (M + H)$^+$ 390.0943. C$_{17}$H$_{13}$N$_3$O$_8$ requires (M + H)$^+$ 390.0937).
146.8 (s) (C, Ar), 131.2 (s) (CH, Ar), 130.9 (q) (C-CF₃, J 32.6 Hz), 128.8 (s) (2 x CH, Ar), 126.1 (s) (CH, Ar), 124.4 (s) (CH, Ar), 123.6 (s) (2 x CH, Ar), 122.7 (q) (CF₃, J 273 Hz), 62.4 (s) (CH₂), 56.2 (s) (C, quaternary), 28.4 (s) (CH₃), 13.7 (s) (CH₃-CH₂); m/z (APCI) 369.8 [(M+H)+, 100%], 341.8 (17.5), 295.8 (42); m/z (APCI) 412.9 [(M+H)+, 100%], 370.1 (65), 364.9 (14); (Found (APCI) (M + H)+ 413.0960. C₁₇H₁₅N₅O₈ requires (M + H)+ 413.0953).

Ethyl 2-(2′,4′-dinitrophenyl)-2-(4″-nitrophenyl)propionate (257b)—This was prepared by the General Method used in the previous compound using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), ethyl 2-chloropropionate (1.11 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 2,4-dinitrochlorobenzene (1.64 g, 8.13 mmol) to give the crude product (2.85 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.17 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (2.16 g, 69%) as a brown oil. ν̇max (liquid film on NaCl plates/ cm⁻¹) 2984 (m), 1738 (s) (C=O), 1604 (s), 1521 (s), 1349 (s), 909 (m), 835 (m), 650 (m); δ H (400 MHz; CDCl₃) 8.80 (1H, d, J 2.4 Hz, H-3'), 8.30 (1H, dd, J 2.4 & 8.7 Hz, H-5'), 8.22 (2H, d, J 9.0 Hz, H-3" & H-5"'), 7.68 (2H, d, J 9.0 Hz, H-2" & H-6"'), 7.16 (1H, d, J 8.7 Hz, H-6'), 4.15-4.22 (1H, m, O-HCH-CH₃), 4.01-4.09 (1H, m, O-HCH-CH₃), 2.26 (3H, s, CH₃), 1.18 (3H, t, J 7.2 Hz, CH₃-CH₂); δ C (100 MHz; CDCl₃) 170.5 (s) (C=O), 149.4 (s) (C, Ar), 148.0 (s) (C, Ar), 147.6 (s) (C, Ar), 146.7 (s) (C, Ar), 146.0 (s) (C, Ar), 132.9 (s) (CH, Ar), 129.3 (s) (2 x CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 x CH, Ar), 120.9 (s) (CH, Ar), 62.6 (s) (CH₂), 56.2 (s) (C, quaternary), 25.6 (s) (CH₃), 13.7 (s) (CH₃-CH₂); m/z (APCI) 389.9 [(M+H)+, 100%], 345.1 (36); (Found (APCI) (M + H)+ 390.0943. C₁₇H₁₅N₅O₈ requires (M + H)+ 390.0937).
**Ethyl 2-(4'-cyano-2'-nitro)-2-(4''-nitrophenyl)propionate (2571)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.68 g, 17.01 mmol), ethyl 2-chloropropionate (1.24 ml, 9.72 mmol), nitrobenzene (0.5 ml, 4.86 mmol) and 4-chloro-3-nitrobenzonitrile (0.89 g, 4.86 mmol) to give the crude product (4.02 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.12 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (1.29 g, 72%) as a brown crystalline solid. M.p. 129-131 °C (nujol NaCl plates/cm-1) 2919 (s), 2234 (w), 1721 (s), (C=O), 1603 (w) 1464 (s), 1347 (s), 1265 (m); δH (400 MHz; CDCl3) 8.17 (1H, d, J 1.8 Hz, H-3′), 8.15 (2H, d, J 9.0 Hz, H-3′ & H-5″), 7.66 (1H, dd, J 1.7 & 8.2 Hz, H-5′), 7.58 (2H, d, J 9.0 Hz, H-2″ & H-6″), 6.97 (1H, d, J 8.7 Hz, H-6′), 4.10 (1H, dq, J 3.7 & 7.2 Hz, HCH-CH3), 1.11 (3H, t, J 7.2 Hz, CH3CH2); δC (100 MHz; CDCl3) 171.0 (s) (C=O), 149.8 (s) (C, Ar), 148.5 (s) (C, Ar), 147.9 (s) (C, Ar), 144.8 (s) (C, Ar), 136.0 (s) (CH, Ar), 133.0 (s) (CH, Ar), 129.7 (s) (2 × CH, Ar), 129.4 (s) (CH, Ar), 124.2 (s) (2 × CH, Ar), 116.5 (s) (C, Ar), 113.2 (s) (C, Ar), 62.0 (s) (CH2), 56.5 (s) (C, quaternary), 25.9 (s) (CH2), 14.1 (s) (CH2-CH2); m/z (APCI) 370.1 [(M+H)+, 100%]; (Found (APCI) (M + NH4)+, 387.1308 C17H15N3O8 requires (M + NH4)+ 387.1305).

![Reaction Scheme]

**Ethyl 2,2-bis(4'-nitrophenyl)propionate**—This was prepared by the General Method, cooling to 0 °C instead of -50 °C using sodium hydride (60% dispersion in oil) (1.3 g, 32.54 mmol), ethyl 2-chloro-propionate (2.07 ml, 16.26 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 4-fluoronitrobenzene (0.86 ml, 8.13 mmol) to give the crude product (3.68 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.24 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (2.07 g, 74%) as an orange oil; vmax (nujol on NaCl plates/cm-1) 3081 (w), 2989 (s), 2457 (w), 1928 (w), 1721 (s), 1596 (s), 1530 (s), 1463 (s) 1342 (s), 1248 (s), 1094 (s), 1014 (s), 858 (m); δH (400 MHz; CDCl3) 8.10 (4H, d, J 8.9 Hz, H-3′ & H-5″), 7.33 (4H, d, J 8.9 Hz, H-2″ & H-6″), 4.19 (2H, q, J 7.1 Hz, CH2), 1.93 (3H, s, CH3), 1.16 (3H, t, J 7.1 Hz, CH2CH3), δC (100 MHz; CDCl3) 173.2 (s) (C=O), 150.9 (s) (C, Ar), 147.3 (s) (C, Ar), 129.4 (s) (4 × CH, Ar), 123.9 (s) (4 × CH, Ar), 62.8 (s) (CH2), 57.2
Isopropyl 2-(4’-nitrophenyl)-2-(2”-nitro-4”-trifluoromethylphenyl)propionate (268)—In a 100 ml round bottom flask was added potassium tert-butoxide (0.75 g, 6.64 mmol) and DMF (5 ml). The mixture was flushed with nitrogen and cooled to −50 °C in a CO2/methanol cooling bath. Nitrobenzene (0.34 ml, 3.32 mmol) and isopropyl 2-chloropropionate (0.50 g, 3.32 mmol) dissolved in anhydrous DMF (5 ml) was added dropwise to the reaction mixture. The bright purple solution was stirred at −50 °C for 10 minutes and then slowly warmed to −20 °C before cooling back to −50 °C. 4-Fluoro-3-nitrobenzotrifluoride (0.47 ml, 3.32 mmol) was added dropwise to the reaction mixture, which was then slowly warmed to room temperature. The reaction mixture was stirred at room temperature for 2 hours and then poured onto a ice/HCl (1M) solution. The product was extracted with dichloromethane (3 × 30 ml), then washed with water (3 × 30 ml), sodium bicarbonate (30 ml) and dried over sodium sulfate. The drying agent was filtered and the solvent removed on a rotary evaporator to give an orange oil (1.7 g). The crude product was then purified by column chromatography Rf 0.25 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.86 g, 61%) as a yellow crystalline powder. M.p. 284-286 °C vmax (nujol NaCl plates/ cm−1 ) 2922 (s), 1705 (s), 1630 (w) 1454 (s), 1376 (m), 1318 (m); δH (400 MHz; CDCl3 ) 8.13-8.16 (3H, m, H-3’ & H-3’ & H-5’), 7.64 (1H, dd, J 1.7 & 8.5 Hz, H-5”), 7.60 (2H, d, J 9.0 Hz, H-2’ & H-6’), 7.0 (1H, d, J 8.5 Hz, H-6”), 4.88 (1H, sept, J 6.3 Hz, CH-(CH3)2), 2.16 (3H, s, CH3), 1.09 (3H, d, J 6.3 Hz, CH3-CH-CH3), 1.03 (3H, d, J 6.3 Hz, CH3-CH-CH3); δC (100 MHz; CDCl3 ) 170.6 (s) (C=O), 149.6 (s) (C, Ar), 149.0 (s) (C, Ar), 147.8 (s) (C, Ar), 143.7 (s) (C, Ar), 132.8 (s) (CH, Ar), 130.9 (q) (J 34.3 Hz) (C-CF3), 129.3 (s) (2 × CH, Ar), 129.2 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 122.9 (s) (CH, Ar), 122.6 (q) (J 271.2 Hz) (CF3), 70.7 (s) (C-O), 56.2 (s) (C, quaternary), 25.5 (s) (CH3), 21.4 (s) (CH3), 21.1 (s) (CH3); m/z (APCI) 427 [(M+H)+, 100%], 316 (8); (Found (ES+) (M + NH4)+ 444.1383. C19H17N2O6F3 requires (M + NH4)+ 444.1377).
tert-Butyl 2-(2',4'-dinitrophenyl)-2-(4'-nitrophenyl)propionate (271)—This was prepared by the General Method using potassium tert-butoxide (0.85 g, 7.6 mmol), tert-butyl 2-chloropropionate (0.50 g, 3.04 mmol), nitrobenzene (0.31 ml, 3.04 mmol), 2,4-dinitrofluorobenzene (0.57 ml, 4.56 mmol) and anhydrous DMF (10 ml) to give the crude product as an orange oil (2.51 g). The crude product was then purified by column chromatography Rf 0.29 (silica, 7:3. hexane:acetone; v/v) to give the product as an orange oil (1.0 g). To remove the excess 2,4-dinitrofluorobenzene still present the product was dissolved in ethyl acetate (5 ml) and added to a plastic filter syringe containing poly(styrene-co-divinylbenzene)amino methylated (0.75 g). The column was fitted with a cap and shaken vigorously for 24 hours. The filtrate was then collected and the solvent removed on a rotary evaporator to give the pure product as an orange oil (0.88 g, 69%). \( \nu_{\text{max}} \) (oil, NaCl plates/cm) \( ^{-1} \) 2918 (s), 1731 (s), 1603 (s), 1524 (s), 1463 (s), 1375 (s); \( \delta_H \) (400 MHz; CDCl\(_3\)) 8.72 (1H, d, \( J \) 2.4 Hz, H-3'), 8.20 (1H, dd, \( J \) 2.4 & 8.6 Hz, H-5'), 8.16 (2H, d, \( J \) 9.0 Hz, H-3'' & H-5''), 7.58 (2H, d, \( J \) 9.0 Hz, H-2'' & H-6''), 7.04 (1H, d, \( J \) 8.6 Hz, H-6'), 2.16 (3H, s, CH\(_3\)), 1.25 (9H, s, (CH\(_3\))\(_3\)); \( \delta_C \) (100 MHz; CDCl\(_3\)) 169.4 (s) (C=O), 149.9 (s) (C, Ar), 148.9 (s) (C, Ar), 147.9 (s) (C, Ar), 146.9 (s) (C, Ar), 146.6 (s) (C, Ar), 133.4 (s) (CH,Ar), 129.6 (s) (2 \( \times \) CH, Ar), 127.0 (s) (CH, Ar), 124.0 (s) (2 \( \times \) CH, Ar), 121.2 (s) (CH, Ar), 84.7 (s) (C-0), 57.5 (s) (C,quaternary), 27.8 (s) ((CH\(_3\))\(_3\)), 25.9 (s) (CH\(_3\)); \( m/z \) (ES+) 435.2 [(M+NH\(_4^+\)), 100%]; (Found (ES+) (M + NH\(_4^+\)) 435.1505. C\(_{19}\)H\(_{19}\)N\(_3\)O\(_8\) requires (M + NH\(_4^+\)) 435.1510.
**Phenyl (5'-chloro-2'-nitrophenyl)(4''-trifluoromethyl-2''-nitrophenyl)methyl sulfone (276a)**—This was prepared by the General Method, cooling to 0 °C instead of -50 °C using sodium hydride (60% dispersion in oil) (0.26 g, 6.55 mmol), chloromethyl phenyl sulfone (0.42 g, 2.22 mmol), p-chloronitrobenzene (0.50 g, 2.62 mmol) and 4-fluoro-3-nitrobenzotrifluoride (0.38 ml, 2.64 mmol) to give the crude product (1.12 g) as a yellow oil. The crude product was then purified by column chromatography, Rf 0.38 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.98 g, 75%) as a yellow crystalline solid. M.p. 178-179.8 °C; \( \nu_{\text{max}} \) (nujol on NaCl plates/cm\(^{-1}\)) 2922 (s), 1627 (w), 1602 (w), 784 (w), 720 (w); \( \delta_H \) (400 MHz; CDCl\(_3\)) 8.53 (1H, d, \( J_{8.3} \) Hz, H-3'), 8.30 (1H, d, \( J_{2.2} \) Hz, H-3''), 8.23 (1H, d, \( J_{1.3} \) Hz, H-6'), 8.02 (1H, dd, \( J_{1.3} \) & \( J_{8.3} \) Hz, H-4'), 7.93 (1H, d, \( J_{8.8} \) Hz, H-6''), 7.69 (2H, d, \( J_{7.6} \) Hz, -SO\(_2\)-Ph), 7.64 (1H, t, \( J_{7.6} \) Hz, -SO\(_2\)-Ph), 7.55 (1H, dd, \( J_{2.2} \) & \( J_{8.8} \) Hz, H-5''), 7.48 (2H, t, \( J_{7.6} \) Hz, -SO\(_2\)-Ph), 7.40 (1H, s, CH); \( \delta_C \) (100 MHz; CDCl\(_3\)) 149.8 (s) (C, Ar), 147.8 (s) (C, Ar), 140.1 (s) (C, Ar), 136.8 (s) (C, Ar), 135.1 (s) (CH, Ar), 132.7 (q) (C-CF\(_3\), \( J_{32} \) Hz), 132.6 (s) (CH, Ar), 131.6 (s) (CH, Ar), 130.6 (s) (CH, Ar), 129.9 (s), (CH, Ar), 129.8 (s), (C, Ar), 129.5 (s) (2 x CH, Ar), 129.1 (s) (2 x CH, Ar), 127.8, (s) (C, Ar), 127.3 (s) (CH, Ar), 123.1 (s) (CH, Ar), 122.06 (q) (CF\(_3\), \( J_{271} \) Hz), 121.0 (s) (CH, Ar), 61.3 (s) (CH); \( m/z \) (APCI) 501.1 [M+H]+, 100%, 500.4 (57), 360.9 (26), 358.7 (81) (Found (ES+) (M + H)+ 501.0136. \( C_{20}H_{12}ClF_3N_2O_6S \) requires (M + H)+ 501.0135).

![Chemical structure of Phenyl (5'-chloro-2'-nitrophenyl)(4''-trifluoromethyl-2''-nitrophenyl)methyl sulfone (276a)](attachment)

**Phenyl (5'-chloro-2'-nitrophenyl)(2'',4''-dinitrophenyl)methyl sulfone (276b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), chloromethyl phenyl sulfone (0.42 g, 2.22 mmol), p-chloronitrobenzene (0.35 g, 2.22 mmol) and 2,4-dinitrofluorobenzene (0.28 ml, 2.62 mmol) to give the crude product (1.20 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.41 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.78 g, 74%) as a yellow crystalline solid. M.p. 178.1-179.7 °C; (Found C, 47.74; H, 2.57; N 8.71. \( C_{18}H_{13}F_3N_2O_6 \) requires C, 47.76; H, 2.53; N, 8.79%; \( \nu_{\text{max}} \) (nujol on NaCl plates/cm\(^{-1}\)) 2925 (s), 2360 (w), 166.
Phenyl (5'-chloro-2'-nitrophenyl)(2''-nitrile-4''-nitrophenyl)methyl sulfone (276c)—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), chloromethyl phenyl sulfone (0.50 g, 2.62 mmol), p-chloronitrobenzene (0.42 g, 2.62 mmol) and 2-fluoro-5-benzonitrile (0.44 g, 2.64 mmol) to give the crude product (1.20 g) as an orange solid. The crude product was then purified by column chromatography, Rf 0.18 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.78 g, 74%) as a yellow crystalline solid. M.p. 196-198 °C; (Found C, 52.49; H, 2.64; N, 9.23%; v_max (nujol on NaCl plates/cm⁻¹) 2933 (s), 1608.0 (w), 1533.8 (m), 1460.0 (m), 1342.9 (m), 1152.7 (m); δH (400 MHz; CDCl₃) 8.53 (1H, dd, J 2.4 Hz & 8.8 Hz, H-5''), 8.47 (1H, d, J 2.4 Hz, H-3''), 8.29 (1H, d, J 8.8 Hz, H-4''), 8.02 (1H, d, J 8.8 Hz, H-6'''), 7.71 (3H, m, -SO₂-Ph), 7.60 (1H, dd, J 2.2 Hz & 8.8 Hz, H-3''), 7.54 (1H, t, J 7.8 Hz, -SO₂Ph), 6.90 (1H, s, H₃C-SO₂-Ph); δC (100 MHz; CDCl₃) 147.7 (s) (C, Ar), 147.3 (s) (C, Ar), 140.8 (s) (C, Ar), 140.6 (s) (C, Ar), 136.1 (s) (C, Ar), 135.5 (s) (CH, Ar), 131.9 (s) (CH, Ar), 131.1 (s) (CH, Ar), 130.9 (s) (CH, Ar), 129.8 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 127.6 (s) (CH, Ar), 127.5 (s) (C, Ar), 127.4 (s) (CH, Ar), 117.1 (s) (CN or C, Ar), 114.4 (s) (CN or C, Ar), 65.6 (s) (CH); m/z (APCI) 458.0 [(M+H)⁺, 100 %]; (Found: (M+NH₄)⁺, 457.0491. C₂₀H₁₂ClN₅O₆S requires (M+NH₄)⁺ 475.0479).
Phenyl (5'-chloro-2'-nitrophenyl)(2''-trifluoromethyl-4''-nitrophenyl)methyl sulfone (276d)—This was prepared by the General Method, cooling to 0 °C instead of −50 °C using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), chloromethyl phenyl sulfone (0.42 g, 2.22 mmol), p-chloronitrobenzene (0.35 g, 2.22 mmol) and 2-fluoro-5-benzotrifluoride (0.54 g, 2.64 mmol) to give the crude product (1.48 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.41 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.98 g, 75%) as a yellow crystalline solid. M.p. 178.2-180.0 °C; (Found C, 48.12; H, 2.39; N 5.60. C_{18}H_{15}F_{3}N_{2}O_{6} requires C, 47.96; H, 2.41; N, 5.59%); \nu_{\text{max}} \ (\text{nujol on NaCl plates/cm}^{-1}) \ 2925 \ (s), \ 2360 \ (w), \ 1734 \ (w), \ 1618 \ (w), \ 1597 \ (m), \ 1532 \ (m), \ 1466 \ (s), \ 1376 \ (s), \ 1309 \ (s), \ 1154 \ (s), \ 1084 \ (w), \ 1051 \ (m), \ 917 \ (m), \ 842 \ (m), \ 757 \ (w), \ 728 \ (m); \delta_{\text{H}} \ (400 \text{MHz; CDCl}_3) \ 9.10 \ (1\text{H, d, } J = 8.8 \text{ Hz, H-3'}), \ 8.65 \ (1\text{H, dd, } J = 2.3 \text{ & } 8.8 \text{ Hz, H-5'}), \ 8.50 \ (1\text{H, d, } J = 2.2 \text{ Hz, H-3''}), \ 8.10 \ (1\text{H, d, } J = 8.7 \text{ Hz, H-4'}), \ 7.75 \ (2\text{H, d, } J = 8.1 \text{ Hz, PhSO}_2), \ 7.62-7.65 \ (3\text{H, m, H-6' & PhSO}_2 \text{ & CH}), \ 7.57 \ (1\text{H, dd, } J = 2.1 \text{ & } 8.7 \text{ Hz, H-6''}), \ 7.49 \ (2\text{H, t, } J = 8.1 \text{ Hz, PhSO}_2); \delta_{\text{C}} \ (100 \text{MHz; CDCl}_3), \ 148.4 \ (s, \text{ C, Ar}), \ 148.1 \ (s, \text{ C, Ar}), \ 140.4 \ (s, \text{ C, Ar}), \ 137.0 \ (s, \text{ C, Ar}), \ 137.0 \ (s, \text{ C, Ar}), \ 135.4 \ (s, \text{ CH, Ar}), \ 133.6 \ (s, \text{ CH, Ar}), \ 132.4 \ (q, \text{ C-CF}_3, J = 32 \text{ Hz}), \ 131.8 \ (s, \text{ CH, Ar}), \ 131.0 \ (s, \text{ CH, Ar}), \ 129.9 \ (s, 2 \times \text{ CH, Ar}), \ 129.3 \ (s, 2 \times \text{ CH, Ar}), \ 128.3 \ (s, \text{ CH, Ar}), \ 127.3 \ (s, \text{ CH, Ar}), \ 126.6 \ (s, \text{ C, Ar}), \ 122.8 \ (q, \text{ CH, Ar, } J = 6.1 \text{ Hz}), \ 122.6 \ (q, \text{ CF}_3, J = 266 \text{ Hz}), \ 61.5 \ (s, \text{ CH}; m/z \ (\text{APCI}) \ 501.0 \ [(M + H)^{+}, \text{ 100%}]; \text{ (Found (ES+): (M + NH}_4)^{+}, \ 518.0393, C_{20}H_{12}ClF_3N_2O_6 \text{ requires (M + NH}_4)^{+} \ 518.0400).
Phenyl (5'-trifluoromethyl-2'-nitrophenyl)(2''-trifluoromethyl-4''-nitrophenyl)methyl sulfone (276e)—This was prepared by the General Method, cooling to 0 °C instead of -50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluorotoluene (0.25 g, 1.31 mmol) and 4-fluoro-3-benzotrichloride (0.19 ml, 1.35 mmol) to give the crude product (0.80 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.38 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.57 g, 81%) as a yellow crystalline solid. M.p. 158-159.8 °C; ν max (nujol on NaCl plates/cm⁻¹) 2925 (s), 2852 (s), 1628 (w), 1538 (s), 1462 (s), 1375 (w), 1330 (s), 1248 (w), 1184 (m), 1155 (m), 1131 (m), 1094 (m), 935 (w), 854 (m), 727 (m); δH (400 MHz; CDCl3) 8.63 (1H, s, H-3'), 8.25 (1H, d, J 8.4 Hz, H-3'), 8.24 (1H, s, H-6'), 8.04 (2H, d, J 8.6 Hz, H-4' & H-5'), 7.86 (1H, d, J 8.5 Hz, H-6'), 7.68 (2H, d, J 7.8 Hz, PhSO2), 7.64 (1H, t, J 7.5 Hz, PhSO2), 7.48 (2H, t, J 7.8 Hz, PhSO2), 7.38 (1H, s, CH); δC (100 MHz; CDCl3) 151.7 (s) (C, Ar), 149.9 (s) (C, Ar), 136.6 (s) (C, Ar), 135.2 (s) (CH, Ar), 134.9 (q) (C-CF3, J 34 Hz), 132.9 (q) (C-CF3, J 34 Hz), 132.4 (s) (CH, Ar), 130.0 (s) (CH, Ar), 129.6 (s) (2 × CH, Ar), 129.5 (s) (C, Ar), 128.6 (2 × CH, Ar), 128.6, (s) (CH, Ar), 127.7 (s) (CH, Ar), 126.9 (s) (C, Ar), 126.4 (s) (CH, Ar), 123.2 (s) (CH, Ar), 122.5 (q) (CF3, J 72 Hz), 122.3 (q) (CF3, J 72 Hz), 61.2 (s) (CH); m/z (APCI) 535.2 [(M+H)⁺, 100%], 534.5 (65); Found (ES⁺): (M + NH₄)⁺, 552.0663. C21H12F₆N₂O₆ requires (M + NH₄)⁺ 552.0664.

Phenyl (5'-trifluoromethyl-2'-nitrophenyl)(2''-4''-dinitrophenyl)methyl sulfone (276f)—This was prepared by the General Method, cooling to 0 °C instead of -50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluorotoluene (0.25 g, 1.31 mmol) and 2,4-dinitrofluorobenzene (0.17 ml, 1.31 mmol) to give the crude product (0.68 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.41 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.53 g, 79%) as a yellow crystalline solid. M.p. 215.1-217.3 °C; (Found C, 46.67; H, 2.39; N 8.25. C₁₈H₁₅F₂N₂O₆ requires C, 46.98; H, 2.37; N, 8.20%; ν max (nujol on NaCl plates/cm⁻¹) 2918 (s), 2852 (s), 1604 (s), 1539 (s), 1465 (s), 1400 (s), 1180 (m), 1154 (m), 1128 (m), 1094 (m), 935 (w), 854 (m), 727 (m); δH (400 MHz; CDCl3) 8.63 (1H, s, H-3'), 8.46 (1H, d, J 8.4 Hz, H-3'), 8.25 (1H, d, J 8.4 Hz, H-3'), 8.04 (2H, d, J 8.6 Hz, H-4' & H-5'), 7.86 (1H, d, J 8.5 Hz, H-6'), 7.68 (2H, d, J 7.8 Hz, PhSO2), 7.64 (1H, t, J 7.5 Hz, PhSO2), 7.48 (2H, t, J 7.8 Hz, PhSO2), 7.38 (1H, s, CH); δC (100 MHz; CDCl3) 151.7 (s) (C, Ar), 149.9 (s) (C, Ar), 136.6 (s) (C, Ar), 135.2 (s) (CH, Ar), 134.9 (q) (C-CF3, J 34 Hz), 132.9 (q) (C-CF3, J 34 Hz), 132.4 (s) (CH, Ar), 130.0 (s) (CH, Ar), 129.6 (s) (2 × CH, Ar), 129.5 (s) (C, Ar), 128.6 (2 × CH, Ar), 128.6, (s) (CH, Ar), 127.7 (s) (CH, Ar), 126.9 (s) (C, Ar), 126.4 (s) (CH, Ar), 123.2 (s) (CH, Ar), 122.5 (q) (CF3, J 72 Hz), 122.3 (q) (CF3, J 72 Hz), 61.2 (s) (CH); m/z (APCI) 535.2 [(M+H)⁺, 100%], 534.5 (65); Found (ES⁺): (M + NH₄)⁺, 552.0663. C₂₁H₁₂F₆N₂O₆ requires (M + NH₄)⁺ 552.0664.
**Phenyl (5′-trifluoromethyl-2′-nitrophenyl)(2″-4″-dinitrophenyl)methyl sulfone (276g)—** This was prepared by the General Method, cooling to 0 °C instead of -50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluorotoluene (0.25 g, 1.31 mmol) and 2-fluoro-5-nitrobenzonitrile (0.22 g, 1.32 mmol) to give the crude product (1.03 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.26 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.51 g, 78%) as a yellow crystalline solid. M.p. 197.9-200 °C; (Found C, 51.41; H, 2.42; N 8.55. C_{32}H_{21}F_{6}N_{6}O_{8}S requires C, 51.33; H, 2.46; N, 8.55%) ν_{max} (nujol on NaCl plates/cm\(^{-1}\)) 2924 (s), 1610 (w), 1581 (w), 1542 (s), 1464 (s), 1356 (m), 1334 (m), 1253 (w), 1177 (m), 1129 (m), 1092 (m), 976 (w), 932 (m), 858 (s), 788 (m), 730 (m); δ_{H} (400 MHz; CDCl\(_3\)) 8.84 (1H, d, J 2.4 Hz, H-3″), 8.65 (1H, s, H-6′), 8.6 (1H, dd, J 2.4 & 8.7 Hz, H-5″), 8.48 (1H, d, J 8.8 Hz, H-6″), 8.06 (1H, d, J 8.4 Hz, H-4′), 7.88 (1H, d, J 8.5 Hz, H-3″), 7.65-7.71 (3H, m, PhSO\(_2\)), 7.50 (2H, t, J 7.8 Hz, PhSO\(_2\)), 7.40 (1H, s, CH); δ_{C} (100 MHz; CDCl\(_3\)) 151.7 (s) (C, Ar), 150.0 (s) (C, Ar), 148.0 (s) (C, Ar), 136.5 (s) (C, Ar), 135.3 (s) (C, Ar), 133.0 (s) (CH, Ar), 132.0 (s) (C, Ar), 129.7 (s) (2 × CH, Ar), 129.0 (s) (2 × CH, Ar), 128.50 (s) (CH, Ar), 127.9 (s) (CH, Ar), 127.4, (s) (CH, Ar), 126.6 (s) (C, Ar), 126.5 (s) (CH, Ar), 121.3 (s) (CH, Ar), 61.29 (s) (HC=SO\(_2\)Ph); m/z (APCI) 512.0 [(M + H)+, 100%], 511.4 (75); Found (ES+): (M + NH\(_4\))\(^{+}\), 529.0636, C\(_{20}\)H\(_{12}\)F\(_{6}\)N\(_{3}\)O\(_{8}\)S requires (M + NFLt)\(^{+}\) 529.0641.
C, Ar), 61.3 (s) (HC-SO₂Ph); m/z (APCI) 491.9 [(M + H)+, 100 %], 349.5 (85); (Found (M + NH₄)+, 509.0748, C₂₁H₁₂F₃N₃O₆S requires (M + NH₄)+ 509.0743).

**Phenyl (5'-trifluoro-2'-nitrophenyI)(2''-trifluoromethyl-4''-nitrophenyI)methyl sulfone (276h)**—This was prepared by the General Method, cooling to 0 °C instead of -50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-a,a,a-trifluorotoluene (0.25 g, 1.31 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.28 g, 1.34 mmol) to give the crude product (1.16 g) as an orange solid.

The crude product was then purified by column chromatography, Rf 0.42 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.55 g, 78%) as a yellow crystalline solid. M.p. 190-192 °C; (Found C, 47.17; H, 2.26; N 5.34. C₂₁H₁₂F₆N₂O₆S requires C, 47.2; H, 2.26; N, 5.24% νmax (nujol on NaCl plates/cm⁻¹) 2924 (s), 1621 (m), 1596 (m), 1537 (s), 1462 (s), 1329 (s), 1127 (s), 919 (s), 854 (s), 797 (w), 784 (w); δH (400 MHz; CDCl₃) 9.00 (1H, d, J 8.7 Hz, H-5'), 8.57 (1H, dd, J 2.3 & 8.7 Hz, H-6'), 8.43 (1H, d, J 2.3 Hz, H-3'), 8.17 (1H, d, J 8.5 Hz, H-3'), 7.85 (1H, s, H-6'), 7.80 (1H, d, J 8.5 Hz, H-4'), 7.66 (2H, t, J 7.7 Hz, PhSO₂), 7.56 (1H, t, J 7.7 Hz, PhSO₂), 7.49 (1H, s, CH), 7.41 (2H, t, J 7.7 Hz, PhSO₂); δC (100 MHz; CDCl₃), 149.8 (s) (C, Ar), 147.8 (s) (C, Ar), 140.1 (s) (C, Ar), 136.8 (s) (C, Ar), 135.1 (s) (C, Ar), 132.9 (s) (CH, Ar), 131.6 (s) (CH, Ar), 130.6 (s) (CH, Ar), 129.9 (s) (CH, Ar), 129.5 (s) (CH, Ar), 129.1 (s) (CH, Ar), 127.8 (s) (C, Ar), 127.3 (s) (CH, Ar), 123.1 (s) (CH, Ar), 121.0 (s) (C, Ar), 61.3 (s) (HC-SO₂Ph); m/z (APCI) 535.4 [(M+H)+, 100%]), 511.4 (75), 370.9 (25).

**General Methods for the Formation of Oxindoles**

**Method A**

In a Multi-Parr reaction vessel the ester (0.51 mmol) was added followed by 5% Pd/C (25 mg) (Johnson Mattey type 58 paste) (47.5% H₂O), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The mixture was stirred, purged with nitrogen (5 times) and then hydrogen (5 times) and left under hydrogen (50 psi). Continual checking by LC led to complete conversion of the starting material after 16 hours. The product was then filtered through a celite plug and then the solvent removed on a rotary evaporator to give the crude product.
Method B

In a 2-necked round bottom flask fitted with a condenser and nitrogen bubbler was added tin(II) chloride dihydrate (25.7 mmol), the ester (2.57 mmol), ethanol (40 ml), ethyl acetate (10 ml) and conc. HCl (3 drops). The solution was heated under reflux for 36 hours and then cooled to room temperature. The solution was reduced on a rotary evaporator to give a pale yellow oil. Ethyl acetate (50 ml) was added followed by sodium hydrogen carbonate (50 ml). The product was extracted with ethyl acetate (3 x 25 ml) and then washed with water (50 ml) and saturated sodium chloride (50 ml). The solution was then dried over magnesium sulfate and reduced on a rotary evaporator to give the crude product.

\[
\begin{align*}
\text{Method A: } & H_2, \text{Pd/C} \\
\text{Method B: } & \text{SnCl}_2(\text{H}_2\text{O})_2 \\
\text{EtOH/EtOAc} \\
\text{HCl}
\end{align*}
\]

3-Methyl-3-(4'-aminophenyl)-6-aminooxindole (292a) Method A:—This was performed by the General Method using the ester 257b (200 mg, 0.51 mmol), 5% Pd/C (25 mg), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The product was left in the vessel for 16 hours, checking by LC until complete conversion had occurred. The crude product (115 mg) was obtained as an orange crystalline solid after being filtered through celite. The crude product was then washed with chloroform on a filter, dried and collected leaving a slightly brown crystalline solid (70 mg, 54%).

Method B:—This was prepared by the General Method using the ester 257b (1.0 g, 2.57 mmol), tin(II) chloride dihydrate (5.81 g, 25.7 mmol), ethanol (40 ml), ethyl acetate (10 ml) and conc. hydrochloric acid (3 drops) and heating under reflux for 36 hours, to give the crude product as a brown crystalline solid (0.82 g). The crude product was then washed with chloroform on a filter, dried and collected leaving a slightly brown crystalline solid (0.46 g, 71%). M.p. 149-151 °C; ν\text{max} (nujol NaCl plates/ cm\(^{-1}\)) 3350 (wk, br) (O-H), 1698 (s) (C=O); δ\text{H} (400 MHz; MeOD) 7.05 (2H, d, J 8.6 Hz, H-2' & H-6'), 6.87 (1H, d, J 8.0 Hz, H-4), 6.70 (2H, d, J 8.6 Hz, H-3' & H-5'), 6.56 (1H, d, J 2.0 Hz, H-7), 6.46 (1H, dd, J 2.0 & 8.0 Hz, H-5'); 1.66 (3H, s, CH\(_3\)); δ\text{C} (100 MHz; MeOD) 178.3 (s) (C=O), 150.6 (s) (C, Ar), 146.7 (s) (C, Ar), 144.0 (s) (C, Ar), 132.9 (s) (C, Ar), 128.9 (s) (2 x CH, Ar), 125.7 (s) (CH, Ar), 123.0 (s)
Method A: H₂, Pd/C
EtOAc

Method B: SnCl₂(H₂O)₂
EtOH/EtOAc
HCl

1-Hydroxy-3-methyl-3-(4'-aminophenyl)-6-trifluoromethyloxindole (292b) Method A:—This was prepared by the General Method using the ester 257a (100 mg, 0.24 mmol), 5% Pd/C (25 mg), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The product was left in the vessel for 17 hours, checking by LC until complete conversion had occurred. The crude product (130 mg) was obtained as a brown crystalline solid after being filtered through celite. This was then washed with chloroform to leave a white crystalline solid (60 mg, 77%).

Method B:—This was prepared by the General Method using the ester 257a (0.35 g, 0.85 mmol), tin(II) chloride dihydrate (1.95 g, 8.5 mmol), ethanol (9 ml), ethyl acetate (3 ml) and conc. hydrochloric acid (3 drops). The reaction mixture was heated under reflux for 24 hours, and then worked up as before to give a brown crystalline solid (0.31 g). This solid was then washed with chloroform as before to leave a white crystalline solid (0.23 g, 76%). M.p. 219-221 °C; ν max (nujol NaCl plates/ cm⁻¹) 3420 (Br, s) (N-OH), 1666 (s) (C=O) (s); δ H (400 MHz; MeOD) 7.44 (1H, d, J 3.6 Hz, H-7), 7.34-7.38 (2H, m, H-4 & H-5), 7.01 (2H, d, J 8.8 Hz, H-2' & H-6'), 6.68 (2H, d, J 8.8 Hz, H-3' & H-5'), 1.76 (3H, s, CH₃); δ C (100 MHz; MeOD) 175.6 (s) (C=O), 147.1 (s) (C, Ar), 142.3 (s) (C, Ar), 136.7 (s) (C, Ar), 130.2 (q, J 32 Hz), (C-CF₃) 128.0 (s) (C, Ar), 126.8 (s) (2 × CH, Ar), 124.1 (s) (CH, Ar), 119.9 (s) (CH, Ar), 115.1 (s) (2 × CH, Ar), 103.8 (s) (CH, Ar), 50.4 (s) (C, q), 21.5 (s) (CH₃); m/z (ES⁺) 323.1 [(M+H)⁺, 100%], (Found (ES⁺) (M + NH₄)⁺ 340.1266; (M + NH₄)⁺ 340.1266.)
**1-Hydroxy-3-methyl-3-(4′-aminophenyl)-6-cyanooxindole (292c)**

Method A: This was prepared by the General Method using the ester 2571 (200 mg, 0.54 mmol), 5% Pd/C (25 mg), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The product was left in the vessel for 20 hours, checking by LC until complete conversion had occurred. The crude product (124 mg) was obtained as a yellow crystalline solid after being filtered through celite. This was then washed with chloroform to leave a white crystalline solid (104 mg, 69%).

Method B: This was prepared by the General Method using the ester 2571 (1.0 g, 2.71 mmol), tin(II) chloride dihydrate (6.12 g, 27.1 mmol), ethanol (40 ml), ethyl acetate (10 ml) and conc. hydrochloric acid (3 drops). The reaction mixture was heated under reflux for 36 hours, and then worked up as before to give a brown crystalline solid (0.80 g). This solid was then washed with chloroform as before to leave a white crystalline solid (0.60 g, 79%). M.p. 254-256 °C \( \nu_{\text{max}} \) (nujol NaCl plates/ cm\(^{-1} \)) 3350 (wk, br) (O-H), 1712 (s) (C=O); \( \delta_{\text{H}} \) (400 MHz; DMSO) 11.10 (1H, s, O-H), 7.54 (1H, dd, \( J \) 1.6 & 7.6 Hz, H-5), 7.40-7.42 (2H, m, H-4 & H-7), 6.86 (2H, d, \( J \) 8.4 Hz, H-2' & H-6'), 6.49 (2H, d, \( J \) 8.4 Hz, H-3' & H-5'), 1.63 (3H, s, CH\(_3\)); \( \delta_{\text{C}} \) (100 MHz; DMSO) 174.2 (s) (C=O), 148.5 (s) (C, Ar), 142.9 (s) (C, Ar), 138.0 (s) (C, Ar), 127.8 (s) (CH, Ar), 127.2 (s) (2 × CH, Ar), 126.2 (s) (C, Ar), 125.1 (s) (CH, Ar), 119.1 (s) (C, Ar), 114.1 (s) (2 × CH, Ar), 110.9 (s) (CN), 109.9 (s) (CH, Ar), 50.1 (s) (C, quaternary), 22.4 (s) (CH\(_3\)); \( m/z \) (ES+) 280.2 [(M+H)+, 100%], Found (ES+) (M + NH\(_4\))\(^+\) 297.1348. C\(_{16}\)H\(_{13}\)N\(_3\)O\(_2\) requires (M + NH\(_4\))\(^+\) 297.1346.

Chloromethyl phenyl sulfone\(^{321}\) (322)—Sodium benzenesulfinate dihydrate (15 g, 75 mmol) and bromochloromethane (11.63 g, 90 mmol) in DMSO (40 ml) was heated at 100 °C for 4 hours. The mixture was cooled, poured into water and extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with water (3 × 100 ml) and dried over magnesium sulfate. The solvent was removed to leave an orange crystalline solid (14.6 g). Recrystallisation from carbon tetrachloride provided white crystals of the sulfone (10.25 g, 72 %). M.p. 52-54 °C (lit. M.p. 52-53 °C\(^{321}\), \( \nu_{\text{max}} \) (nujol on NaCl plates/cm\(^{-1} \)) 3055 (s), 3016 (s), 2942 (s), 1584 (m), 1444 (m), 1376 (w), 1322 (s), 1309 (s), 1240 (s), 1161 (s), 1140 (s), 1079 (s), 1015 (m), 866 (m); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 7.96 (2H, dd, \( J \) 1.1 & 7.9 Hz, ortho CH), 7.73 (1H, dd, \( J \) 1.1 & 7.9 Hz, para CH), 7.61 (2H, t, \( J \) 7.9 Hz, meta CH), 4.55 (2H, s, CH\(_2\)); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 135.5 (s) (C, Ar), 134.7 (s) (2 × CH, Ar), 129.3 (s) (CH, Ar), 129.2 (s) (2 × CH, Ar), 58.4 (s) (CH\(_2\)); \( m/z \) (APCI) 191.2 [(M+H)+, 100%].
Methyl 2-chlorobutanoate\(^{190}\) (259)—Chlorobutyric acid (10.59 g, 8.17 mmol) and methanol (100 ml) were added to a 250 ml 2-necked round bottomed flask fitted with a condenser and nitrogen bubbler. Sulfuric acid (0.5 ml) was added and the mixture was heated under reflux for 3 hours. The mixture was then cooled and most of the methanol was removed on a rotary evaporator. The product was then extracted with ether (3 × 50 ml), dried followed by removal of the ether on a rotary evaporator to give the product as a clear oil (7.77 g, 70%). \( \nu_{\text{max}} \) (liquid film on NaCl plates/ cm\(^{-1}\)) \( 2995 \) (m), \( 2975 \) (m, br), \( 2955 \) (w), \( 2886 \) (w), \( 1750 \) (s) (C=O), \( 1460 \) (w), \( 1440 \) (w), \( 1380 \) (m), \( 1355 \) (m), \( 1170 \) (w); \( \delta_{\text{H}} \) (400 MHz; CDC\(_3\)) \( 3.68 \) (3H, t, \( J \) 7.0 Hz, OCH\(_3\)), \( 4.20 \) (1H, t, \( J \) 7.0 Hz, CH-Cl), \( 1.92 \) (2H, quintet, \( J \) 7.0 Hz, CH\(_2\)), \( 1.00 \) (3H, t, \( J \) 7.0 Hz, CH\(_3\)); \( \delta_{\text{C}} \) (100 MHz; CDC\(_3\)) \( 169.6 \) (s) (C=O), \( 58.7 \) (s) (C-O), \( 52.5 \) (s) (C-Cl), \( 28.7 \) (s) (CH\(_2\)), \( 10.5 \) (s) (CH\(_3\)); \( m/z \) (APCI) 138 [(M (\(^{37}\)Cl)+ H)+, 33%), 136 [(M (\(^{35}\)Cl) + H)+, 100%].

Isopropyl 2-chloropropionate\(^{232}\) (267)—This was achieved using the General Method above as a yellow oil (69%). \( \nu_{\text{max}} \) (liquid film on NaCl plates/ cm\(^{-1}\)) \( 3478 \) (wk, br), 2984 (m), 2936 (w), 2360 (w), 1744 (s) (C=O), 1452 (m), 1379 (m), 1326 (m), 1278 (m), 1248 (m); \( \delta_{\text{H}} \) (400 MHz; CDC\(_3\)) \( 5.0 \) (1H, septet, \( J \) 6.2 Hz, H\(_3\)C-CH-CH\(_3\)), \( 4.33 \) (1H, q, \( J \) 6.8 Hz, CH-Cl), \( 1.67 \) (3H, d, \( J \) 6.8 Hz, CH\(_3\)), \( 1.27 \) (6H, dd, \( J \) 6.2 & 2.1 Hz, 2 × CH\(_3\)); \( \delta_{\text{C}} \) (100 MHz; CDC\(_3\)) \( 170.1 \) (s) (C=O), \( 70.1 \) (s) (C-O), \( 53.2 \) (s) (C-Cl), \( 21.8 \) (s) (2 × CH\(_3\)); \( m/z \) (APCI) 152 [(M (\(^{37}\)Cl)+ H)+, 33%], 150 [(M (\(^{35}\)Cl) + H)+, 100%]

t-Butyl 2-chloropropionate\(^{193}\) (269)—To a solution of 2-chloropropionyl chloride (10 ml, 108.5 mmol) and tert-butanol (28.0 g, 0.35 mol) in toluene (100 ml) was added dropwise over an hour a triethylamine (15.8 ml, 115 mmol) at room temperature. The solution was then stirred for 20 minutes before heated to 90 °C for 6 hours. Water (50 ml) was added after cooling. The organic layer was separated and washed successively with water (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml). The organic layer was then dried over
magnesium sulfate. Removal of the solvent on a rotary evaporator gave a clear oil (53%). $v_{\text{max}}$ (liquid film on NaCl plates/cm$^{-1}$) 2981 (s), 2936 (m), 1739 (s) (C=O), 1480 (w), 1454 (m), 1252 (m), 1157 (s), 1074 (m), 993 (m), 846 (m); $\delta_H$ (400 MHz; CDCl$_3$) 4.22 (1H, q, J 7.0 Hz, Cl-CH), 1.58 (3H, d, J 7.0 Hz, CH$_3$), 1.42 (9H, s, 3 × CH$_3$); $\delta_C$ (100 MHz; CDCl$_3$) 169.6 (s) (C=O), 82.8 (s) (C-O), 54.1 (s) (C-Cl), 28.2 (s) (3 × CH$_3$), 21.9 (s) (CH$_3$); m/z (APCI) 166.0 [(M $^{37}$Cl + H)$^+$, 33%], 164 [(M $^{35}$Cl + H)$^+$, 100%].

**General Procedure for esterification of nitrophenylacetic/propionic acids**—The acid (55.24 mmol) in ethanol (100 ml) and sulfuric acid (1 ml) was heated under reflux for 3 hours. Most of the ethanol was then removed on a rotary evaporator. Ether (50 ml) and sodium bicarbonate (sat. aq. 50 ml) was added and the organic product was extracted with ether (3 × 50 ml). The solvent was then dried over Na$_2$SO$_4$ and then removed on a rotary evaporator to give the pure product

![Diagram](image)

**Ethyl 4-nitrophenylacetate**($^{233}$ (311)—This was prepared by the General Method using 4-nitrophenylacetic acid (10 g, 51.28 mmol), ethanol (100 ml) and sulfuric acid (1 ml) to give the pure product as a yellow crystalline solid (11.24 g, 97%). M.p. 65-67 °C (65-66 °C)$^{233}$, $v_{\text{max}}$ (nujol on NaCl plates/cm$^{-1}$) 1725 (s), 1601 (m), 1465 (s), 1375 (s); $\delta_H$(400 MHz, CDCl$_3$) $\delta$ 8.20 (2H, d, J 8.8 Hz, H-3 & H-5), 7.46 (2H, d, J 8.8 Hz, H-2 & H-6), 4.18 (2H, q, J 7.2 Hz, CH$_2$), 3.73 (2H, s, CH$_2$), 1.27 (3H, t, J 7.2 Hz, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 171.9 (s) (C=O), 148.7 (s) (C, Ar), 141.9 (s) (C, Ar), 131.5 (s) (2 × CH, Ar), 124.8 (s) (2 × CH, Ar), 57.1 (s) (CH$_2$), 41.3 (s) (CH$_2$), 14.8 (s) (CH$_3$); m/z (APCI) 210.0 [(M + H)$^+$, 100%].
Ethyl 2-(4'-nitrophenyl)propionate86 (313)—This was prepared by the General Method using 2-(4'-nitrophenyl)propionic acid (169) (10 g, 51.28 mmol), ethanol (100 ml) and sulfuric acid (1 ml) to give the product (10.38 g, 91%) as a yellow oil (%). \( \nu_{\text{max}} \) (liq. film on NaCl plates/cm\(^{-1}\)) 1736 (s) (C=O), 1601 (m), 1521 (s), 1478 (s), 1210 (s), \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 8.19 (2H, d, \( J \) 8.8 Hz, H-3 & H-5), 7.50 (2H, d, \( J \) 8.8 Hz, H-2 & H-6), 4.09-4.21 (2H, m, CH\(_2\)), 3.84 (1H, q, \( J \) 7.2 Hz, CH\(_3\)), 1.55 (3H, d, \( J \) 7.2 Hz, CH\(_3\)), 1.24 (3H, q, \( J \) 7.4 Hz, CH\(_3\)); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)), 174.1 (s) (C=O), 147.7 (s) (C, Ar), 146.3 (s) (C, Ar), 129.3 (s) (2 \( \times \) CH, Ar), 124.5 (s) (2 \( \times \) CH, Ar), 57.3 (s) (O-CH\(_2\)), 41.9 (s) (CH), 19.8 (s) (CH\(_3\)), 14.9 (s) (CH\(_3\)). m/z (APCI) 224.0 [(M + H\(^+\)), 100 %].

Methyl 4-nitrophenylacetate234 (167)—This was prepared by the General Method using 4-nitrophenyl acetic acid (166) (10 g, 55.24 mmol), methanol (100 ml) and sulfuric acid (1 ml) to give the pure product as a yellow crystalline solid (10.3 g, 95%). M.p. 53-55 °C (53-54 °C); \( \nu_{\text{max}} \) (nujol on NaCl plates/cm\(^{-1}\)) 1724 (s), 1600 (m), 1464 (s), 1377 (s) 1347 (m), 1108 (w), 1014 (w), 854 (w); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) \( \delta \) 8.20 (2H, d, \( J \) 8.7 Hz, H-3 & H-5), 7.46 (2H, d, \( J \) 8.7 Hz, H-2 & H-6), 3.75 (3H, s, OCH\(_3\)), 3.70 (3H, s, CH\(_2\)); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 172.1 (s) (C=O), 148.9 (s) (C, Ar), 141.7 (s) (C, Ar), 131.5 (s) (2 \( \times \) CH, Ar), 124.7 (s) (2 \( \times \) CH, Ar), 53.0 (s) (O-CH\(_3\)), 41.2 (s) (CH\(_2\)); m/z (APCI) 196.0[(M + H\(^+\)), 100%], 89.2 (8), 61.3 (7.4), 60.5 (16.7).

Methyl 2-(4'-nitrophenyl)propionate235 (164)—This was prepared by the General Method using 2-(4'-nitrophenyl)propionic acid (163) (10 g, 51.28 mmol), methanol (100 ml) and sulfuric acid (1 ml) to give the pure product as a yellow oil (9.57 g, 90%). \( \nu_{\text{max}} \) (liq. film on
NaCl plates/cm$^{-1}$) 1738 (s) (C=O), 1606 (m), 1522 (s), 859 (s), $\delta_H$(400 MHz, CDCl$_3$) 8.17 (2H, d, $J$ 8.7 Hz, H-3 & H-5), 7.4 (2H, d, $J$ 8.7 Hz, H-2 & H-6), 3.84 (1H, q, $J$ 7.2 Hz, CH$_3$), 3.55 (3H, s, OCH$_3$), 1.40 (3H, d, $J$ 7.2 Hz, CH$_3$), $\delta_C$(100 MHz, CDCl$_3$) 174.2 (s) (C=O), 147.9 (s) (C, Ar), 146.5 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 124.6 (s) (2 × CH, Ar), 53.9 (s) (OCH$_3$), 45.1 (s) (-C=O), 19.8 (s) (CH$_3$). m/z (APCI) 209.9 [(M+H)$^+$, 100 %], 192.9 (7), 177.9 (14), 163.9 (3), 150.9 (6), 149.9 (13).

![Chemical Structure](image)

**Isopropyl 2-nitrophenylacetate**$^{236}$ (315)—This was prepared by the General Method using 2-nitrophenylacetic acid (8.0 g, 44.2 mmol), IPA (100 ml) and sulfuric acid (1 ml) to give the pure product as a pale yellow oil (7.90 g, 80%). $\nu_{\text{max}}$ (liq. film on NaCl plates/cm$^{-1}$) 3444 (w), 3070 (w), 2981 (m), 2936 (m), 2878 (w), 2363 (w), 1949 (w), 1729 (m), 1580 (m), 1526 (s), 1467 (m), 1414 (m), 1348 (s), 1222 (s), 1105 (s), 1047 (w), 957 (s); $\delta_H$(400 MHz, CDCl$_3$) 8.11 (1H, d, $J$ 8.5 Hz, H-3), 7.60 (1H, t, $J$ 8.5 Hz, H-5), 7.47 (1H, t, $J$ 8.5 Hz, H-4), 7.36 (1H, d, $J$ 8.5 Hz, H-6), 5.04 (1H, septet, $J$ 6.4 Hz, HC(CH$_3$)$_2$), 3.99 (2H, s, CH$_2$), 1.24 (6H, d, $J$ 6.4 Hz, 2 × CH$_3$), $\delta_C$(100 MHz, CDCl$_3$) 169.9 (s) (C=O), 149.2 (s) (C, Ar), 133.9 (s) (CH, Ar), 133.7 (s) (CH, Ar), 130.4 (s) (C, Ar), 128.9 (s) (CH, Ar), 125.6 (s) (CH, Ar), 69.3 (s) (CH) 40.6 (s) (CH$_2$), 22.1 (s) (2 × CH$_3$); m/z (APCI) 224.1 [(M+H)$^+$, 100%].

![Chemical Structure](image)

**Ethyl 3-nitrophenylacetate**$^{237}$ (326)—This was prepared by the General Method using 3-nitrophenylacetic acid (325) (5 g, 27.7 mmol), ethanol (50 ml) and sulfuric acid (0.5 ml) to give the pure product as a pale yellow oil (4.04 g, 70%). $\nu_{\text{max}}$ (liq. film on NaCl plates/cm$^{-1}$) 3091 (w), 2983 (m), 2938 (w), 2360 (w), 1737 (s) (C=O), 1619 (w), 1583 (w), 1531 (s), 1480 (w), 1445 (w), 1417 (w), 1352 (s), 1253 (m), 1227 (m), 1162 (s), 1098 (m), 1030 (s); $\delta_H$(400 MHz, CDCl$_3$) 8.17 (1H, s, H-2), 8.14 (1H, d, $J$ 8.4 Hz, H-6), 7.64 (1H, d, $J$ 8.4 Hz, H-4), 7.52 (1H, t, $J$ 8.4 Hz, H-5), 4.19 (2H, q, $J$ 7.2 Hz, O-CH$_2$), 3.74 (2H, s, Ar-CH$_2$), 1.28 (3H, t, $J$ 7.2 Hz, CH$_3$), $\delta_C$(100 MHz, CDCl$_3$) 170.8 (s) (C=O), 148.6 (s) (C, Ar), 136.4 (s) (C, Ar), 136.1 (s)
tert-Butyl 2-nitrophenylacetate—Potassium tert-butoxide (0.6 g, 6.1 mmol) was dissolved in anhydrous THF (5 ml) under nitrogen, then cooled to -70 °C (bath temp). Nitrobenezene (0.25 ml, 2.43 mmol) and tert-butyl chloroacetate (0.35 ml, 2.43 mmol) dissolved in THF (2 ml) were slowly added to the basic solution. The solution was then stirred while slowly warming to around -20 °C for an hour. The reaction was then quenched with HCl (1M) (2 ml), then allowed to warm to room temperature. The product was then extracted with dichloromethane (3 x 20 ml), washed with water (3 x 20 ml), sodium bicarbonate (sat. aq. 20 ml) and dried over Na2SO4. The solvent was then removed on a rotary evaporator to give an orange oil (0.75 g). The crude product was then purified by column chromatography Rf 0.21 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.27 g, 47%) as a yellow oil.

General Method for cross-coupling nitrophenylacetates with aryl halides—In a 100 ml two-necked round bottom flask fitted with a condenser which was attached to a schlenk line, under a flow of nitrogen was added the base (2.39 mmol), and solvent (3 ml). The flask was cooled to 0 °C in an ice bath and the ester (2.39 mmol) dissolved in solvent (2 ml) was then added dropwise to the basic solution. The solution was allowed to warm to room temperature and a mixture of palladium acetate (5 mol %), the ligand (10 mol %) and electrophile (2.39 mmol) dissolved in solvent were added to the bright purple solution. The mixture was heated in an oil bath while monitoring the reaction progress by HPLC. The mixture was then cooled to room temperature where ethyl acetate (20 ml) was added and the mixture was filtered through a silica gel plug to remove the palladium. The filtrate was collected and the solvent was removed on a rotary evaporator to give the crude product.
Ethyl 2-(4'-nitrophenyl)-2-phenylacetate (312)—This was prepared by the General Method using potassium tert-butoxide (268 mg, 2.39 mmol), 1,4-dioxane (8 ml), ethyl 4-nitrophenylacetate (311) (0.50 g, 2.39 mmol), palladium acetate (26.8 mg, 0.12 mmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (114) (94.5 mg, 0.24 mmol) and bromobenzene (0.26 ml, 2.39 mmol). The mixture was heated in an oil bath (110 °C) (bath temp) for 2 hours while monitoring the reaction progress by HPLC to give the crude product as a brown oil (0.76 g). The crude product was then purified by column chromatography R_f 0.3 (silica, 3:1 hexane:ethyl acetate; v/v) to give the pure product (0.61 g, 90%) as a yellow oil.

\[ \text{Ethyl 2-(4'-nitrophenyl)-2-phenylacetate (312)} \]

\[ \text{Ethyl 2-(4'-nitrophenyl)-2-(4''-methoxyphenyl)acetate (324a)} \]—This was prepared by the General Method using 4-bromoanisole (0.30 ml, 2.39 mmol) instead of bromobenzene to give the pure product as a pale yellow oil after chromatography R_f 0.5 (silica, 1:1 hexane:ethyl acetate; v/v) (0.35 g, 47%). \( \nu_{\text{max}} \) (liq. film on NaCl plates/cm\(^{-1}\)) 3051 (w), 3049 (m), 1901 (w), 1735 (s) (C=O), 1549 (m), 1416 (m), 1361 (s), 1209 (m); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 8.16 (2H, d, \( J = 8.6 \) Hz, H-3' & H-5'), 7.50 (2H, d, \( J = 8.6 \) Hz, H-2' & H-6'), 7.28-7.37 (5H, m, Ph), 5.10 (1H, s, CH-Ph), 4.24 (2H, q, \( J = 7.0 \) Hz, CH\(_2\)), 1.26 (3H, t, \( J = 7.0 \) Hz, CH\(_3\)); \( m/z \) (APCI) 286.0 [(M+H\(^{+}\), 100%]; (Found (EI+): M\(^+\) 285.1014. C\(_{16}\)H\(_{15}\)NO\(_4\) requires M\(^+\) 285.1001).

Ethyl 2-(4'-nitrophenyl)-2-(4''-methoxyphenyl)acetate (324a)—This was prepared by the General Method using 4-bromoanisole (0.30 ml, 2.39 mmol) instead of bromobenzene to give the pure product as a pale yellow oil after chromatography R_f 0.5 (silica, 1:1 hexane:ethyl acetate; v/v) (0.35 g, 47%). \( \nu_{\text{max}} \) (liq. film on NaCl plates/cm\(^{-1}\)) 3051 (w), 3049 (m), 1901 (w), 1735 (s) (C=O), 1549 (m), 1416 (m), 1361 (s), 1209 (m); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 8.16 (2H, d, \( J = 8.6 \) Hz, H-3' & H-5'), 7.50 (2H, d, \( J = 8.6 \) Hz, H-2' & H-6'), 7.28-7.37 (5H, m, Ph), 5.10 (1H, s, CH-Ph), 4.24 (2H, q, \( J = 7.0 \) Hz, CH\(_2\)), 1.26 (3H, t, \( J = 7.0 \) Hz, CH\(_3\)); \( m/z \) (APCI) 286.0 [(M+H\(^{+}\), 100%]; (Found (EI+): M\(^+\) 285.1014. C\(_{16}\)H\(_{15}\)NO\(_4\) requires M\(^+\) 285.1001).
8.8 Hz, H-3' & H-5'), 7.48 (2H, d, J 8.8 Hz, H-2' & H-6'), 7.23 (2H, d, J 8.2 Hz, H-2" & H-6"), 6.88 (2H, d, J 8.2 Hz, H-3" & H-5'"), 5.05 (1H, s, CH), 4.24 (2H, q, J 6.8 Hz, CH₂), 1.26 (3H, t, J 6.8 Hz, CH₃); δc (100 MHz, CDCl₃) 171.7 (s) (C=O), 149.1 (s) (C, Ar), 148.2 (s) (C, Ar), 131.1 (s) (2 x CH, Ar), 129.6 (s) (C, Ar), 128.3 (s) (2 x CH, Ar), 123.9 (s) (2 x CH, Ar), 119.1 (s) (C, Ar), 109.1 (s) (2 x CH, Ar), 79.7 (s) (CH), 63.9 (s) (CH₂), 56.7 (s) (O-CH₃), 14.7 (s) (CH₃); m/z (APCI) 316.3 [(M+H)+, 100%]; (Found (EI+): M⁺ 315.1110. C₁₇H₁₇NO₅ requires M⁺ 315.1107).

**Ethyl 2-(4'-nitrophenyl)-2-(3''-trifluoromethylphenyl)acetate (324b)**—This was prepared by the General Method using 3-bromonitrobenzotrifluoride (0.34 ml, 2.39 mmol) instead of bromobenzene to give the pure product as a pale yellow oil after chromatography Rf 0.5 (silica, 3:1. hexane:ethyl acetate; v/v) (0.55 g, 65%). νmax (liq. film on NaCl plates/cm⁻¹) 3049 (w), 2981 (s), 1733 (s) (C=O), 1608 (s), 1521 (s), 1487 (m), 1350 (s), 1196 (s), 1160 (s), 1028 (s); δh(400 MHz, CDCl₃) 8.21 (2H, d, J 8.8 Hz, H-3' & H-5'), 7.57-7.60 (2H, m, H-Ar), 7.48-7.51 (5H, m, H-Ar), 5.15 (1H, s, CH), 4.26 (2H, q, J 7.2 Hz, CH₂), 1.28 (3H, t, J 7.2 Hz, CH₃); δc (100 MHz, CDCl₃) 171.8 (s) (C=O), 145.4 (s) (C, Ar), 138.6 (s) (C, Ar), 132.3 (s) (C, Ar), 130.8 (q) (C-CF₃, J 34.2 Hz) 129.9 (s) (2 x CH, Ar), 129.8 (s) (CH, Ar), 125.7 (s) (CH, Ar), 125.2 (s) (CH, Ar), 124.4 (s) (2 x CH, Ar), 123.9 (s) (CH, Ar), 122.7 (q) (CF₃, J 271 Hz), 62.4 (s) (CH₂), 56.8 (s) (O-CH₃), 14.4 (s) (CH₃); m/z (APCI) 354.1 [(M+H)+, 100%]; (Found (EI+): M⁺ 353.0863. C₁₇H₁₄NO₄F₃ requires M⁺ 353.0875).
Ethyl 2-(4’-nitrophenyl)-2-(3”-cyanophenyl)acetate (324c)—This was prepared by the General Method using 3-iodobenzonitrile (0.55 g, 2.39 mmol) instead of bromobenzene and DMF as the solvent to give the pure product as a pale yellow oil after chromatography Rf 0.3 (silica, 1:1. hexane:ethyl acetate; v/v) (0.55 g, 74%). νmax (liq. film on NaCl plates/cm⁻¹) 3057 (w), 3049 (w), 1941 (w), 1729 (s) (C=O), 1611 (m), 1594 (w), 1517 (s), 1479 (s), 1345 (s); δH(400 MHz, CDCl₃) 8.23 (2H, d, J 8.9 Hz, H-3’ & H-5’), 7.76 (1H, s, H-2”), 7.62-7.70 (4H, m, H-2’, H-6’, H-4” & H-6”), 7.50 (1H, t, J 8.2 Hz, H-5”), 4.50 (1H, s, CH-Ar), 4.40 (2H, q, J 7.8 Hz, CH₂), 1.32 (3H, t, J 7.8 Hz, CH₃); δC(100 MHz, CDCl₃) 172.6 (s) (C=O), 148.2 (s) (C, Ar), 148.1 (s) (C, Ar), 142.9 (s) (C, Ar), 132.6 (s) (CH, Ar) 132.0 (s) (CH, Ar), 131.1 (s) (CH, Ar), 129.8 (s) (CH, Ar), 128.6 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 118.8 (s) (C, Ar), 113.1 (s) (CN), 80.1 (s) (CH), 64.6 (s) (CH₂), 14.4 (s) (CH₃); m/z (APCI) 311.1 [(M+H)+, 100%]; (Found (EI+): M⁺ 310.0956. C₁₇H₁₄N₂O₄ requires M⁺ 310.0954).

Ethyl 2-(3’-nitrophenyl)-2-phenyacetate (327)—This was prepared by the General Method using ethyl 3-nitrophenylacetate (326) (0.50 g, 2.39 mmol) instead of ethyl 4-nitrophenylacetate (316) and DMF as the solvent to give the pure product as a pale yellow oil after chromatography Rf 0.3 (silica, 3:1. hexane:ethyl acetate; v/v) (0.47 g, 69%). νmax (liq. film on NaCl plates/cm⁻¹) 2924 (s), 1770 (s) (C=O), 1681 (s), 1604 (m), 1537 (m), 1401 (s), 1354 (m), 1107 (m); δH(400 MHz, CDCl₃) 8.21 (1H, s, H-2’), 8.12 (1H, d, J 8.3 Hz, H-4’), 7.67 (1H, d, J 8.3 Hz, H-6’), 7.48 (1H, t, J 8.3 Hz, H-5’), 7.28-7.36 (5H, m, Ph), 5.11 (1H, s, CH-Ar), 4.24 (2H, q, J 7.4 Hz, CH₂), 1.26 (3H, t, J 7.4 Hz, CH₃); δC(100 MHz, CDCl₃) 171.9 (s) (C=O), 148.7 (s) (C, Ar), 141.3 (s) (C, Ar), 137.8 (s) (C, Ar), 135.3 (s) (CH, Ar) 129.9 (s) (CH, Ar), 129.4 (s) (2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 124.1 (s) (CH, Ar), 122.8 (s) (CH, Ar), 62.2 (s) (CH), 57.0 (s) (CH₂), 14.5 (s) (CH₃); m/z (APCI) 286.3 [(M+H)+, 100%]; (Found (ES+): (M + NH₄)⁺, 303.1342. C₁₆H₁₉N₂O₄ requires (M + NH₄)⁺ 303.1345).
N-(2'-Chlorophenyl)-N-methyl-2-(2"-nitrophenyl)acetamide (332)—This was prepared according to the general method developed by Jones. In a 2-necked round bottom flask fitted with a condenser connected to a Schlenk line was added, under nitrogen, 2-nitrophenylacetic acid (1.0 g, 5.52 mmol), dichloromethane (10 ml) and carbonyldiimidazole (0.96 g, 5.52 mmol). The mixture was heated under reflux for 1 hour. 2-Chloro-N-methylaniline (0.68 ml, 5.52 mmol) was then added dropwise to the reaction mixture after cooling. The mixture was then heated under reflux for 1 hour. After checking the progress of the reaction by HPLC the mixture was left to stir at room temperature for 24 hours. The mixture was then diluted with ethyl acetate then washed with 1M HCl (20 ml), water (20 ml) and brine (20 ml). The solution was then dried over MgSO₄ and the solvent removed on a rotary evaporator to give an orange oil (2.18 g). The crude product was then purified by column chromatography R_f 0.10 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.69 g, 49%) as a white crystalline powder. M.p. 154-156 °C. Found C, 59.17; H, 4.26; N 9.45. C₁₅H₁₃N₂O₃Cl requires C, 59.12; H, 4.30; N, 9.19%; ν_max (nujol on NaCl plates/cm⁻¹) 3058 (w), 2991 (s), 1691 (s) (C=O), 1613 (m), 1518 (s), 1479 (s), 1360 (s); δ_H(400 MHz, CDCl₃) 8.07 (1H, app. d, J 8.1 Hz, H-3'), 7.53-7.57 (3H, m, H-Ar), 7.38-7.42 (3H, m, H-Ar), 7.29 (1H, app. d, J 8.4 Hz, H-6'), 3.97 (1H, d, J 16.6 Hz, HCH), 3.45 (1H, d, J 16.6 Hz, HCH), 3.25 (3H, s, CH₃), δ_C(100 MHz; CDCl₃) 169.5 (s) (C=O), 149.3 (s) (C, Ar), 141.1 (s) (C, Ar), 134.0 (s) (CH, Ar), 133.7 (s) (CH, Ar), 133.5 (s) (C, Ar), 131.5 (s) (C, Ar), 131.2 (s) (CH, Ar) 130.7 (s) (CH, Ar), 130.3 (s) (CH, Ar), 129.1 (s) (CH, Ar), 128.5 (s) (CH, Ar), 125.5 (s) (CH, Ar), 39.9 (s) (CH₃), 36.8 (s) (CH₂); m/z (APCI) 305.4 [(M+H)^{+}, 100%]; 307.1 (34%); (Found (ES^+): (M + H)^{+}, 305.0686. C₁₅H₁₄N₂O₃Cl requires (M + H)^{+} 305.0693).
**3-(2'-Nitrophenyl)oxindole (333)**—This was prepared by the General Method using \(N\)-(2'-chlorophenyl)-\(N\)-methyl-2-(2''-nitrophenyl)acetamide (332) (187 mg, 0.58 mmol) instead of ethyl 4-nitrophenylacetate and tricyclohexyphosphine (8.2 mg, 0.058 mmol) instead of 2-dicyclohexylphosphino-2'-(\(N\),\(N\)-dimethylamino)biphenyl with no bromobenzene present and 1,4-dioxane (4 ml) in total to give the pure product as a white crystalline solid after chromatography \(R_f\) 0.3 (silica, 1:1 hexane:ethyl acetate; \(v/v\)) (104 mg, 67%). M.p. 145-157 \(^\circ\)C. (Found C, 67.41; H, 4.45; N 10.32. \(\text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O}_{3}\) requires C, 67.16; H, 4.51; N, 10.44%); \(\nu_{\text{max}}\) (nujol on NaCl plates/cm\(^{-1}\)) 3057 (w), 2990 (s), 2910 (m), 2869 (m), 1689 (s) (C=O), 1645 (m), 1609 (s), 1517 (s), 1495 (s), 1375 (s), 1209 (m), 1173 (m); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 8.09 (1H, d, \(J\) 8.3 Hz, H-3'), 7.52-7.57 (3H, m, H-Ar), 7.40-7.45 (3H, m, H-Ar), 7.27 (1H, d, \(J\) 8.3 Hz, H-Ar), 5.19 (1H, s, CH), 3.22 (3H, s, CH\(_3\)), \(\delta_{\text{C}}\) (100 MHz; CDCl\(_3\)) 169.9 (s) (C=O), 149.2 (s) (C, Ar), 141.2 (s) (C, Ar), 133.7 (s) (CH, Ar), 133.5 (s) (CH, Ar), 133.2 (s) (C, Ar), 131.0 (s) (C, Ar), 130.7 (s) (CH, Ar) 130.4 (s) (CH, Ar), 129.7 (CH, Ar), 128.4 (s) (CH, Ar), 128.0 (s) (CH, Ar), 124.9 (s) (CH, Ar), 99.7 (s) (CH), 38.7 (s) (CH\(_3\)); \(m/z\) (APCI) 269.1 [(M+H)]\(^+\), 100%; (Found (ES+): (M + H\(^+\)) 269.0927. \(\text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O}_{3}\) requires (M + H\(^+\)) 269.0927).
References
References

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Appendix
Table 1. Crystal data and structure refinement for 02LAWRENCE2.

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<th>Property</th>
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</tr>
<tr>
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<td>R1 = 0.0887, wR2 = 0.1451</td>
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Table 3. Bond lengths [Å] and angles [°] for 02LAWRENCE2.

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<th>Length</th>
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<th>Length</th>
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Table 1. Crystal data and structure refinement for Lawrencel.

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<td><strong>R indices (all data)</strong></td>
<td>R1 = 0.0589, wR2 = 0.1142</td>
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<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>0.303 and -0.277 e.A^-3</td>
</tr>
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Table 3. Bond lengths [\(\text{Å}\)] and angles [deg] for Lawrencel.

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<th>Bond</th>
<th>Length [(\text{Å})]</th>
<th>Bond</th>
<th>Length [(\text{Å})]</th>
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Synthesis of Diaryl Acetates and Oxindoles via a Sequential $\text{VNS}_\text{Ar}-\text{SNAr}$ Three-Component Coupling Reaction

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ABSTRACT

The VNS and $\text{SNAr}$ reactions combine to form an efficient three-component one-pot route to diarylmethanes. The products of selected diaryl acetates provide modular 3-aryloxindole derivatives.

The vicarious nucleophilic substitution (VNS$\text{Ar}$) of hydrogen in aromatic systems provides a direct and efficient route to functionalized aromatics. The reaction, pioneered by Mako­
sza and co-workers,1 is most often encountered with nitro­
renes, as illustrated in Scheme 1. In contrast to conventional
nucleophilic aromatic substitution reactions, a good nucleo­
fugal group is not required. We have shown that the anion
2 produced by addition of the nucleophile 1 to nitrobenzene,
and elimination of HX from the $\alpha$-adduct, can react with a
range of electrophiles.2 This aspect of VNS chemistry
provides a powerful process in which simple precursors can
be elaborated in a three-component coupling reaction.

We have shown that 2 exhibits reactivity similar to that
of the malonate ion. This is not too surprising given that
other properties such as acidity are similar. For example the
pK$\alpha$ (DMSO) of ethyl $p$-nitrophenylacetate is 15.1,3 while
that of diethyl malonate is 16.4.4 Malonate is an excellent
nucleophile for many $\text{SNAr}$ reactions,5 and some examples6
of the use of nitrophenylacetates in the $\text{SNAr}$ reaction have
been reported. We were therefore hopeful that the anion 2,
derived from the VNS reaction, would react in the $\text{SNAr}$
reaction.

Scheme 1. One-Pot VNS—Electrophilic Quench Process$^a$

$^a$LG = leaving group (e.g., Cl or PhS); EWG = electron-
withdrawing group.
Diarylmethanes are extremely useful synthetic intermediates, and the diarylmethyl motif is found in many pharmacologically important agents. A versatile route to this important scaffold incorporating several points of diversity is potentially useful. The diarylmethyl group is also embedded within many important drugs, e.g., 3-arylindole derivatives. Makosza and Katritzky have described the synthesis of diarylmethanes via VNS reaction of nucleophiles of type I in which the electron-withdrawing group comprises one of the aryl groups. The new method described below is ideally suited for the synthesis of functionalized diarylmethanes in which only one of the aryl groups is introduced in the VNS reaction.

We now report that the anion 2 can be arylated by the reaction with substituted ortho-haloniitroarenes. The process not only is efficient but also uniquely combines two different sequential modes of aromatic nucleophilic substitution.

Reaction of ethyl 2-chloropropanoate (4a) with nitrobenzene in the presence of NaH gave the usual dark blue-colored solution of the intermediate anion 2 (Scheme 1). Addition of 2,4-dinitrofluorobenzene (5a) in DMF resulted in rapid decolorization of the solution. The desired diarylmethane 3a was isolated in 77% yield (Scheme 2). The 1H NMR spectrum clearly indicated the presence of both 1,4-disubstituted and 1,2,4-trisubstituted aryl group. This is consistent with the expected para-selective VNS reaction followed by SAr process.

To explore the scope of the reaction, a number of simple esters 4a–c were combined with nitrobenzene and different SAr electrophiles 5a–d under the reaction conditions described above. The results show in Table 1 clearly indicate that the process is general and efficient. The efficiency of the SAr process is high, as the yields are close to that expected for the protonation of the anion 2. The use of activated arynes 5a–d allows the SAr reaction to proceed conveniently at ambient temperature, avoiding the need for heating.

Table 1. Yields of Product Diarylmethyl Sulphones 8a–h

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>yield (%)</th>
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<tr>
<td>a</td>
<td>Cl</td>
<td>NO2</td>
<td>NO2</td>
</tr>
<tr>
<td>b</td>
<td>Cl</td>
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<td>CF3</td>
</tr>
<tr>
<td>c</td>
<td>Cl</td>
<td>CN</td>
<td>NO2</td>
</tr>
<tr>
<td>d</td>
<td>Cl</td>
<td>CF3</td>
<td>NO2</td>
</tr>
<tr>
<td>e</td>
<td>CF3</td>
<td>NO2</td>
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</tr>
<tr>
<td>g</td>
<td>CF3</td>
<td>NO2</td>
<td>NO2</td>
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<tr>
<td>h</td>
<td>CF3</td>
<td>NO2</td>
<td>CF3</td>
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</table>
heating. This can be problematic for NaH in DMF when the reaction is performed on a large scale.\(^\text{13}\) We have therefore shown that the process has potential for scale-up by using tert-BuOK as the base. In these cases, the VNS reaction between nitrobenzene (1 equiv) and 4a (2 equiv) was performed with tert-BuOK (3 equiv) while carefully maintaining the temperature between \(-40\) and \(-50\) °C. The solution of the post-VNS anion was warmed to \(-20\) °C before addition of 5a or 5d to give 3a and 3d in 57 and 69% yields, respectively.

The process is not limited to the use of fluoronitroarenes (Scheme 3). 2,4-Dinitrochloronitrobenzene (5e) was used in place of 2,4-dinitrofluorobenzene (5a) to give 3a from 4a in 69% yield. Similarly, the VNS-S\textsubscript{Ar}Ar reaction of 4-chloro-3-nitrobenzonitrile (5f) and 4a gives the nitrile 3n (Scheme 3). The use of the less activated 4-fluoronitrobenzene (Scheme 3) is still sufficiently reactive to engage ion the VNS-\text{SN Ar} reaction to give 3p in 74% yield.

Branched esters behave well in the reaction. The isopropyl ester 4d gave ester 3q when aryl fluoride 5b was used as the electrophile. The tert-butyl ester 3r was obtained in the same way from the VNS nucleophile 4e. In the synthesis of 3r, we were unable to separate the product from unreacted 5a by chromatography. The unreacted aryl fluoride was scavenged using dimethylamino-functionalized polystyrene. Simply shaking the mixture of 5b and 3r with the resin in EtOAc cleanly removed the aryl fluoride, leaving the product ester pure.

The VNS-\text{SN Ar} reaction was used for the synthesis of diarylmethyl sulfones, to provide examples of the process with ortho selectivity. Reaction of chloromethyl phenyl sulfone (6) with p-chloronitrobenzene (7a) and 5a gave the sulfone 8a (Scheme 4). Other examples (Table 1) indicate that the arylation of the ortho-nitrobenzyl sulfonyl anion is not problematic.

The synthetic utility of the method is illustrated in Scheme 5, by the synthesis of oxindole derivatives. This class of heterocycle is an important synthetic building block and also includes members with important biological activity.\(^\text{14,24}\) Those products 3 possessing an ortho nitro group (R\textsuperscript{3} = NO\textsubscript{2}), are converted into their corresponding 3,3-disubstituted oxindole, by hydrogenation (method a), or Sn(II)-mediated reduction (method b). The presence of other nitro groups that are also reduced under these conditions provides additional points for further functionalization and incorporation of extra diversity. The ester 3a cleanly gave the oxindole.

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9a by both methods. However, reduction of both 3b and 3c gave the 1-hydroxyoxindoles 9b and 9c.\textsuperscript{15} It seems that the presence of the electron-withdrawing group impedes reduction of the intermediate hydroxylamine such that cyclization to form the indole occurs faster. The formation of 9a from 3a involves first reduction of the less hindered nitro group at position 4.

In conclusion, we have shown that the intriguing one-pot VNS\textsubscript{N}-S\textsubscript{Ar} combination of two types of nucleophilic substitution reaction provides an excellent synthesis of diaryl acetate derivatives.


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Supporting Information Available: General experimental procedures and characterization data and \textsuperscript{1}H and \textsuperscript{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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