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Novel Titanium Alkylidenes and their Application in the Synthesis of Indoles and Quinolines

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Calum Macleod

Department of Chemistry
University of Glasgow
Glasgow G12 8QQ

February 2003

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VARIABLE PRINT QUALITY
Dedicated to my family

(for everything)
Acknowledgements

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And finally the “non-chemists”. A huge thanks to all my friends, including friends from my undergraduate days and those in Glasgow Island FC (even the team mascot), for their constant support and friendship – you know who you are!
Initially, we attempted to synthesise β-heterosubstituted vinylboronates by employing boronate-containing titanium alkylidene reagents, but our approach was unsuccessful.

We synthesised functionalised titanium alkylidenes from thioacetals i and we then employed them to convert resin-bound esters ii into immobilised enol ethers iii. Cleavage from the resin in mild acid with concomitant cyclisation yielded indoles iv. This chameleon catch strategy ensures the high purity of indole products. This is a novel synthesis of indoles, but also represents a traceless solid-phase indole synthesis as no trace of the former site of attachment to the solid-support remains in the indole products.

Similarly, we used titanium alkylidenes, prepared from thioacetals v, to convert resin-bound esters ii into the corresponding enol ethers, which were cleaved from the resin in mild acid to yield ketones vi. Boc deprotection and cyclisation to give indoles vii, was then achieved in acid.

Titanium alkylidenes, prepared from thioacetals viii, converted resin-bound esters ii into the corresponding enol ethers, which were cleaved from the resin in acid to yield ketones ix. Cyclisation and oxidation to yield quinolines x was achieved employing manganese dioxide in dichloromethane (DCM).
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Abbreviations

Å  angstrom
Ac  acetyl
AIBN  2,2'-azobisisobutyronitrile
aq.  aqueous
atm  atmosphere (pressure)
bmim  1-butyl-3-methylimidazolium tetrafluoroborate
Bn  benzyl
Boc  tert-butyl carbamate
n-Bu  normal butyl
t-Bu/ tert-Bu  tertiary butyl
b.p.  boiling point
bs  broad singlet (NMR spectroscopy)
°C  degrees centigrade
cal  calories
cat.  catalyst
Cl  chemical ionisation
cm  centimetre
cod  cis,cis-1,5-cyclooctadiene
conc.  concentrated
Cp  cyclopentadienyl anion
Cp*  pentamethylcyclopentadienyl anion
Cy  cyclohexyl
d  doublet (NMR spectroscopy)
dba  dibenzylideneacetone
DBU  1,8-diazabicyclo[2.2.2]octane
DCC  1,3-dicyclohexylcarbodiimide
DCE  dichloroethane
DCM  dichloromethane
DIC  1,3-diisopropylcarbodiimide
DIPEA  N,N-diisopropylethylendiamine
DMAP  4-Ν,Ν-dimethylanilino pyridine
DMF  dimethylformamide
DMFDMA  dimethylformamide dimethyl acetal
DMPU  1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dppe  1,2-bis(diphenylphosphino)ethane
dppf  1,2-bis(diphenylphosphino)ferrocene
d.r.  diastereomeric ratio
EI  electron impact
eq.  equivalent(s)
FAB  fast atom bombardment
h  hour(s)
h  Planck constant
HMDS  1,1,1,3,3,3-hexamethyldisilazane
HPLC  high pressure liquid chromatography
HMP  hydroxymethylphenoxy
Hz  hertz
IDO  indoleamine 2,3-dioxygenase
IR  infrared
J  joules
K_B  Boltzmann constant
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>kC</td>
<td>rate of rotation</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Ln</td>
<td>ligand</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>MAS</td>
<td>magic angle spinning</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>MLT</td>
<td>melatonin</td>
</tr>
<tr>
<td>MT</td>
<td>methoxytryptamine</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>min(s)</td>
<td>minute(s)</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidone</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhH</td>
<td>benzene</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluene sulphonate</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectroscopy)</td>
</tr>
<tr>
<td>qn</td>
<td>quintet (NMR spectroscopy)</td>
</tr>
<tr>
<td>R</td>
<td>gas constant</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SEM</td>
<td>trimethylsilylethoxymethyl</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>SPS</td>
<td>solid-phase synthesis</td>
</tr>
<tr>
<td>STABASE</td>
<td>base stable</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>Tc</td>
<td>temperature of coalescence</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TfO</td>
<td>triflate (trifluoromethanesulfonate)</td>
</tr>
<tr>
<td>TFP</td>
<td>trifurylphosphine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethlenediamine</td>
</tr>
<tr>
<td>TMG</td>
<td>tetramethylguanidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl (para-toluensulphonyl)</td>
</tr>
</tbody>
</table>
Chapter 1 - Background

Initially, we aimed to develop a novel, connective, synthesis of β-hetero-substituted alkenylboronic esters. They are useful intermediates for many transformations, including cross-coupling reactions (section 1.3) and to date can only be made by the hydroboration of 1-ethoxy-1-alkynes. Our strategy involved generating titanium alkylidenes 1 from thioacetals 2 under Takeda conditions, which could then alkylidenate a range of esters or thioesters 3, to give β-hetero-substituted alkenylboronates 4 (Scheme 1). Takeda alkylidation, would allow tetra-substituted β-hetero-substituted alkenylboronic esters, with the hetero atom cis to the boronic ester, inaccessible by hydroboration/thioboration.

Recent work within the group has seen the development of a novel synthesis of Benzo[b]furans, carried out on solid phase (section 8.1).\(^1\) I aimed to investigate the scope of this methodology, and then extend it to the synthesis of nitrogen containing heterocycles. The proposed synthesis employs titanium benzylidenes 5 containing a suitably protected ortho-aniline, which would convert resin-bound 6 esters into enol ethers 7 (Scheme 2). Concomitant deprotection, cleavage from resin, and cyclisation under mild acid conditions, would then yield indoles 8. Substrates, should be prepared from readily available precursors, so as to maximise the diversity of the synthesis. The choice of protecting group is critical, as it should be easily formed, stable to the reaction conditions, acid labile, and by-products formed upon its removal should be volatile, thus avoiding contamination of the heterocyclic products.
Chapter 2 - Alkylidenation Reactions

2.1 The Wittig and related reactions

Wittig olefination

The Wittig reaction is one of the most effective and general methods for the conversion of carbonyl compounds into alkenes and it has become the standard by which all subsequent methodology is judged. The reaction involves the addition of an aldehyde or ketone to a phosphonium ylide, producing the corresponding alkene and phosphine oxide as a by-product (Scheme 3).

\[
\begin{align*}
R^3P=\overset{X}{\rightleftharpoons} & \quad R^2\text{CHO} \\
\text{Scheme 3} & \quad R^2\overset{X}{\rightleftharpoons} \quad R^3P=O \\
\end{align*}
\]

The Wittig reaction is synthetically useful as it proceeds with defined positional selectivity, often with chemoselectivity, and the stereochemistry of the alkene can be controlled as generally a stabilised ylide will produce an \(E\) alkene and an unstabilised ylide will produce a \(Z\) alkene. Mechanistic studies have shown that the reaction of aldehyde with non-stabilised triphenylphosphorous ylid proceeds via observable (by NMR) 1,2 oxaphosphetanes, which then eliminate to give alkene. Two steps of the Wittig reaction are thought to be responsible for the stereochemical outcome. Firstly, the initial formation and therefore, the ratio of the cis- and trans-oxaphosphetanes obtained. Secondly, the ability of these intermediates to further equilibrate by reversal to reactants obtained. Elimination of phosphine oxide occurs, stereospecifically, in a \(syn\) manner.
Maryanoff has reported examples where the initial ratios of oxaphosphetanes 15 and 16 (observed by NMR spectroscopy), do not correspond to the final $E:Z$ ratios formed in alkenes products. He proposes this is caused by decomposition of oxaphosphetanes to the reactants (cis oxaphosphetanes were more likely to fragment), followed by recombination, and has termed this phenomenon "stereochemical drift". Vedejs and coworkers have reported that salt-free (soluble lithium salts are known to enhance equilibration) Wittig reactions of unbranched aliphatic aldehydes, occur with less than 2% equilibration. He suggests that in this case the reaction is under kinetic control, and has proposed a theory, which suggests that non-stabilised ylides add in an early transition state, giving a high ratio of cis- to trans-oxaphosphetanes. Stabilised ylides, as a result of a later transition state, give more of the trans isomer. Both cases being under kinetic control and equilibration occurring only in special circumstances.

Horner and Wadsworth and Emmons used the anions of phosphine oxide 18 and diethyl phosphonate 19 (Figure 1) respectively, to alkenate carbonyls [the Horner-Wadsworth-Emmons (HWE) reaction]. These reagents are more nucleophilic than the corresponding phosphonium ylides. Therefore, they are more reactive towards carbonyls and the HWE reaction has proven to be effective with hindered ketones that are unreactive in the classical Wittig reaction. Also, the reaction by-products are water soluble, and by altering the bulk on the phosphonate moiety either the $E$- or the $Z$-alkene can be prepared.

![Figure 1](image-url)
Peterson olefination

Alternatives to the Wittig reaction include the Peterson olefination\textsuperscript{10} which utilises an $\alpha$-silyl-substituted alkyl anion $20$. These reagents convert carbonyl compounds to $\beta$-silylcarbinols $21$, which in turn can undergo acid catalysed elimination or can be treated with base, resulting in intramolecular alkoxide attack on silicon and then elimination of the silanolate, to give the alkene $22$ (Scheme 5). Peterson alkenation has the advantage that the by-product (hexamethyldisiloxane) is volatile and thus easier to remove than the phosphine oxides produced in the Wittig reaction. The reagent is more basic and less sterically hindered than the phosphorous ylide and so more reactive. However, when alkenation is not simply methylenation, the anion can be more difficult to prepare (limited to alkyllithium addition to vinyl silanes or transmetalation of silanes with $\alpha$-halogens). Also, selectivity in the stereochemistry of elimination, requires separation of the $\beta$-silylcarbinols $21$, to ensure control of alkene geometry.\textsuperscript{3}

\[
\begin{align*}
R^1_3Si & \quad \text{Li} \quad + \quad R^2 \quad \overset{\text{BASE}}{\longrightarrow} \quad \overset{\text{ACID}}{\longrightarrow} \quad R^2 \quad 22
\end{align*}
\]

Scheme 5
Julia Olefination

Marc Julia introduced the use of sulfur-stabilised carbanions in alkenations\(^ {11, 12}\). In this reaction a metalated sulfone derivative \(23\) is added to a carbonyl compound \(24\), followed by functionalisation [quench with an electrophile (E)] and reductive elimination (usually with sodium amalgam) to give the alkene \(25\) (Scheme 6). As well as giving excellent yields of the alkene, the reaction gives high \(E\)-selectivity for di-substituted alkenes as demonstrated by Kocienski and Lythgoe.\(^ {3}\) It is hypothesised that this aspect of the reaction is due to anion \(26\) adopting the lower energy \(trans\) conformation before loss of the leaving group (OR).\(^ {3}\) More recently a one-pot procedure was introduced by Sylvestre Julia.\(^ {13}\)

\[\text{Ph}_2\text{S}^\text{M}\text{R}_1\text{R}_2 + \text{Ph}_2\text{S}^\text{R}_3\text{R}_4 \rightarrow \text{Ph}_2\text{S}^\text{HO}\text{R}_1\text{R}_2\text{R}_3 \rightarrow \text{EX} \]

\[\text{Ph}_2\text{S}^\text{EO}\text{R}_1\text{R}_2\text{R}_3 \rightarrow \text{Na}(\text{Mg}) \rightarrow \text{EX} \]

\(E = \text{Electrophile}\)

A disadvantage of the Julia, Wittig and related reactions is that the basic reagents employed can deprotonate alpha to enolisable carbonyl groups, leading to side products.\(^ {3}\) Other problems with the Wittig reaction include the lack of reactivity with respect to sterically hindered carbonyls, and their inability to convert carboxylic acid derivatives into alkenes. These problems have been addressed through the use of transition metal alkylidene chemistry and in particular titanium-based reagents.\(^ {14}\) This area has been recently reviewed.\(^ {15}\)
2.2 Titanium alkylidenes (Schrock carbenes) and 1,1-bimetallics

Tebbe reagent

The Tebbe reagent 27 is commercially available as a 0.50 mol dm\(^{-3}\) solution in toluene, and is prepared from titanocene dichloride and 2 eq. of trimethylaluminium in toluene (Scheme 7).\(^{16,17}\) When treated with a Lewis base such as pyridine or THF, this titanium-aluminium metallacycle 27 forms a highly reactive titanocene alkylidene 28. This methylenates a range of carbonyl compounds 29, including carboxylic and carbonic acid derivatives,\(^{18}\) to give alkenes 30. Titanocene methyldene 28 is a typical Schrock carbene being an electron-deficient (16e) complex of an early transition metal in high formal oxidation state [Ti(IV)].\(^{19}\) Schrock carbenes are nucleophilic at carbon and electrophilic at titanium, with their reactivity, and hence nucleophilicity towards carbonyl groups, being dominated by their high energy HOMOs.\(^{19}\)

\[
\text{Cp}_2\text{TiCl}_2 + 2\text{AlMe}_3 \rightarrow \text{Cp}_2\text{Ti} = \text{CH}_2 + \text{CH}_4 + \text{Me}_2\text{AlCl}
\]

Scheme 7

Tebbe methylenation of aldehydes and ketones in the presence of esters or amides is straightforward and the selective methylenation of aldehyde 31 can be achieved in Lewis basic THF (Scheme 8).\(^{20}\)
There are many recent examples of the methylenation of esters and lactones, by the Tebbe reagent, to give enol ethers.\textsuperscript{15} Regioselective Tebbe methylenation of esters and lactones are possible in the presence of more sterically hindered esters.\textsuperscript{21, 22} Methylenation of $\alpha,\beta$-unsaturated esters giving higher yields with the Tebbe reagent than with the Petasis reagent (discussed below), have been reported.\textsuperscript{23} Methylenation of thioesters to give vinyl sulfides is much rarer,\textsuperscript{15} with the only recent example\textsuperscript{24} being the conversion of thiolactone 32 into the corresponding alkenyl sulfide 33 in low yield (Scheme 9). Methylenation of tertiary amides\textsuperscript{25} and carbonates\textsuperscript{26} give enamines and ketene acetals, respectively.

![Scheme 9](image)

Carbonyls with good leaving groups undergo reactions other than methylenation when treated with the Tebbe reagent. Titanium enolates 34 [presumably formed \textit{via} oxatitanacyclobutanes 35] are the products formed in the reaction of acid chlorides with Tebbe reagent 27, in the presence of a Lewis base (Scheme 10)\textsuperscript{27, 28} Anhydrides and imides react in a similar way to acid chlorides, when subjected to the Tebbe reagent.\textsuperscript{29} This is in contrast to the Petasis reagent described below.

![Scheme 10](image)
The Tebbe reagent in Lewis basic solvents also catalyses alkene metathesis, but metathesis is usually slower than methylenation of carbonyl groups. Alkenes including dienes and terminal alkenes react with the Tebbe reagent slower than the Tebbe reagent reacts with carbonyl groups. Therefore, lactone 36 gave enol ether 37 in moderate yield when treated with the Tebbe reagent (Scheme 11). However, lactone 36 is both methylenated and methylated giving enol ether 38 when exposed to a vast excess of Tebbe reagent, presumably via titanacyclobutane 39 (Scheme 11).

The Tebbe reagent has also been employed in the methylenation of resin-bound esters to give the corresponding enol ethers (Section 4.2.5).

Tebbe methylenation has been accomplished in the presence of a wide range of functional groups, with alkyl and aryl halides, ethers, silyl ethers, acetals, selenoglycosides and thioglycosides, unprotected indoles, carbamates including NHBoc, and also sulfonamides, reportedly surviving the reaction conditions.

The main advantage of the Tebbe reagent over other titanium reagents used in alkenations is that the reactive titanium methylidene 28, is generated, and can be reacted, at low temperature. Its disadvantages include its sensitivity to both moisture and air, and its Lewis acidic character. More importantly, it is limited to methylenation and employing triethylaluminium does not give ethylidenation. Pine et al. have published the definitive procedure for the preparation of the Tebbe reagent.
Grubbs reagents

Grubbs later reported that Titanacycles 40 and 41 can be prepared by the reaction of the Tebbe reagent 27 with the corresponding terminal alkenes in the presence of a Lewis base.\(^{16,26}\) These complexes are more air stable than the Tebbe reagent 27 and when these complexes are heated titanocene methylidene 28 is formed (Scheme 12). Intramolecular versions of this reaction are known.\(^{35,36}\)

![Scheme 12](image-url)
Petasis reagents

Dimethyltitanocene 42 is non-pyrophoric, relatively stable to both air and water, and is prepared by adding methyl lithium37 or methylmagnesium chloride38 to titanocene dichloride. Hughes et. al. have published the definitive procedure for the preparation of dimethyltitanocene.38, 39 Petasis reported that this compound methylenates carbonyl compounds when heated to 60-75 °C in THF or toluene.37, 40 The reaction is presumed to proceed via formation of titanocene methylidene 28, which is formed by α-elimination, which in turn can then react with the carbonyl moiety (Scheme 13).41 There is evidence for the proposal41 that titanocene methylidene 28 is the active species.15 Reactions are zero order in carbonyl and first order in dimethyltitanocene, with ethyl acetate and methyl benzoate methylidenedated at similar rates, which confirms that only dimethyltitanocene is involved in the rate determining step. Also, reactions of Cp2Ti(CD3)2 with esters produce substantial kinetic isotope effects of 9-10. Moreover, no scrambling of isotopic labels from ester substrates is observed.15 Finally, dimethyltitanocene has been shown to catalyse alkene metathesis including the ring-opening metathesis polymerisation of norbornene, in which titanocene methylidene 28 is thought to be the active species.42

\[
\begin{align*}
\text{Cp}_2\text{TiMe}_2 & \xrightarrow{\text{THF or PhMe}} \text{Heat} \xrightarrow{\text{H}} \left[ \text{Cp}_2\text{Ti} = \text{CH}_2 \right] + \text{CH}_4 \\
\end{align*}
\]

Scheme 13

As with the Tebbe reagent, aldehydes and ketones can be selectively methylenated in the presence of less electrophilic carbonyl groups including esters, amides and carbamates.43, 44 Dimethyltitanocene will methylenate esters (including silyl esters)40 and lactones,40 and by careful choice of conditions, it is possible to methylenate the less sterically hindered of two esters45, 46 using the Petasis reagent. Petasis methylenation of 2-alkynoate esters and α,β-unsaturated esters are also successful.40 Highly strained β-lactones 43 undergo Petasis methylenation in 20-86% yield with excellent chemoselectivity (Scheme 14).47, 48 However, Tebbe methylenation is unsuccessful for the same transformation, probably due to the greater Lewis acidity of the Tebbe reagent.

\[
\begin{align*}
\text{R'} & \text{R} & \text{R} & \text{O} & \xrightarrow{\text{Cp}_2\text{TiMe}_2 42} \text{PhMe} & \xrightarrow{\text{75 °C, 5-10 h}} \text{R'} & \text{R} & \text{O} & \xrightarrow{\text{20-88%}} \\
\end{align*}
\]

Scheme 14
Thioesters, selenoesters, and acylsilanes are effective substrates for Petasis methylenation, as are carbonates (Scheme 15).40

![Scheme 15](image)

Titanocene methylidene 28, generated under Petasis conditions, gives methylenation of amides and lactams (but not carbamates) although more slowly than for the methylenation of other carbonyls.40 The resulting, highly polar, enamines are often difficult to purify, and are reacted further without prior purification.40 Herdeis and Heller avoided these problems in their route to pipecolic acid derivatives. Petasis methylenation of \textit{N}-methoxycarbonyl-protected lactam 44 gave carbamate 45 via selective methylenation of the amide-like carbonyl group (Scheme 16).49 The methoxycarbonyl group presumably not only protects but also activates the lactam towards methylenation.15

![Scheme 16](image)

In a later paper, Tehrani and De Kimpe reported the methylenation of \(\beta\)-lactams and \(\alpha\)-lactams but the resulting strained enamines were difficult to purify.50 However, Martínez and Howell used an excess of dimethyltitanocene to synthesise 2-methyleneacetidines in good isolated yields, and with excellent chemoselectivity, when the reactions were quenched upon consumption of \(\beta\)-lactams.51 Methylenation of the strained \(\beta\)-lactam 46 gave 2-methyleneacetidine 47 in high yield, without affecting the acetate ester or the Boc group (Scheme 17).

![Scheme 17](image)
Selective mono- or bismethylenation of acid anhydrides or cyclic thioanhydrides by the Petasis reagent, is successful. The selective mono- and bis-methylenation of imide by the Petasis method of generating titanocene methylidene, allows the preparation of a range of dialkyltitanocenes which can alkylidenate carbonyls in the same way to give a mixture of the cis- and trans- alkenes (Scheme 19). Where R² is hydrogen (aldehydes) or R² is the smallest substituent (ketones), trans-alkenes are normally formed preferentially, albeit with poor selectivity. Any selectivity can be explained by minimisation of steric interactions in the reaction intermediates. Titanium alkylidenes, generated by α-elimination, are thought to be the active alkylidenating species. However, as β-elimination is generally faster than α-elimination, dialkyltitanocenes with hydrogen atoms (β to the titanium atom) will readily undergo β-elimination and are unlikely to form effective alkylidenating agents.

Dibenzyltitanocene is easily prepared from benzylmagnesium chloride and titanocene dichloride, and when heated with aldehydes and ketones, gives the corresponding di- and tri-substituted alkenes respectively, as mixtures of isomers. Dibenzyltitanocene also converts esters into Z and E enol ethers (Scheme 20). Unless R¹ is small (R¹ = H or Me), the products are formed with good Z-selectivity. The Z-selectivity is explained by considering the relative steric interactions in formation of
oxatitanacyclobutane intermediates 57 and 58 (Scheme 20). Large $R^1$ will disfavour formation of intermediate 58. Although large $R^2$ will disfavour formation of intermediate 57, in this model, Z-enol ethers 55 are favoured because the oxygen atom acts as a spacer, favouring the formation intermediate 57. However, some isomerization can be observed if acid-washed glassware is used, or if reactions are spiked with trace amounts of acid, (presumably via protonation of the enol ether).

![Scheme 20](image)

Reaction with amides gives enamines, in modest yield (45-48%) and good E-selectivity ($E:Z = 71:29$ to $>99:1$) and the stereoselectivity can be explained using a similar argument to that presented for Z-selectivity in enol ether formation above.  

Bis(3-fluorobenzyl)titanocene and bis(3-chlorobenzyl)titanocene 59 also benzylideneate carbonyl compounds more readily and with greater selectivity than the parent complex 53. Therefore, lactone 60 is converted into enol ether 61 in quantitative yield with total Z-selectivity (Scheme 21).  

![Scheme 21](image)
Bis(trimethylsilylmethyl)titanocene \([\text{Cp}_2 \text{Ti}(\text{CH}_2 \text{TMS})_2]\) 62 and tris(trimethylsilylmethyl)titanium complex \([\text{CpTi}(\text{CH}_2 \text{TMS})_3]\) 63 can be prepared from titanocene dichloride using two or three equivalents of trimethylsilylmethyl lithium, respectively.\(^{56}\) An improved procedure for the synthesis of complex 63 involves consecutive addition of trimethylsilylmethylmagnesium bromide and trimethylsilylmethyl lithium.\(^{57}\) Both will alkylidenate esters, but complex 62 requires a higher temperature (110 °C in ethylene glycol diethyl ether) presumably due to its higher thermal stability, and also gives lower yields.\(^{56}\) Also, Z-selectivities are slightly lower than observed in the corresponding benzylidenations discussed above. Again, acid chlorides do not give alkylidenation products but give \(\alpha\)-trimethylsilylketones when treated with either complex 62 or 63.\(^{56}\) Esters, thioesters and amides derived from trifluoroacetate have been alkylidenated with complex 63, though the thioester gave a very poor yield and no stereoselectivity.\(^{58}\)

A better trimethylsilylmethylenating agent is titanacyclobutene 64, formed in near quantitative yield by the thermolysis of complex 62 in the presence of bis(trimethylsilyl)ethyne (Scheme 22).\(^{57}\) Esters are alkylidenated in high yield using 1.5 eq. of complex 64 at only 25-60 °C. Thioester 65 is converted into vinyl sulfide 66 in excellent yield, though the \(Z:E\) stereoselectivity was only 2.2:1.

![Scheme 22](image-url)
Bis(cyclopropyl)titanocene $67$ is easily prepared from titanocene dichloride and cyclopropyllithium, which is generated from cyclopropyl bromide and lithium metal.$^{59}$ Although thermally unstable at room temperature, bis(cyclopropyl)titanocene can be stored at -20 °C for several months. Esters, including formate esters and lactones [lactone $68$ gives enol ether $69$ in good yield (Scheme 23)], are cyclopropylidenated with 2.5 eq. of complex $67$.\(^\text{59}\)

![Scheme 23](image)

Bis(alkenyl)titanocenes $70$ can be synthesised from titanocene dichloride with two equivalents of an alkenyl magnesium bromide. Bis(vinyllic)titanocenes $70$ undergo thermal $\alpha$-elimination to give the corresponding vinylidenes $71$, which react with aldehydes and ketones to form allenes. Bis(vinyllic)titanocene $70$ ($R^1, R^2 = H$) converted ketone $72$ into allene $73$ in good yield, without affecting the ester carbonyl moiety (Scheme 24). However, alkenylidenation was unsuccessful with esters and lactones, presumably due to facile product decomposition.$^{60}$

![Scheme 24](image)
Petasis alkylidenation has been accomplished in the presence of alkenes, alkyl and aryl halides, ethers, silyl ethers, acetics, amines and carbamates. Hydroxyl groups are best protected, but Petasis methylenation has been carried out in the presence of free hydroxyls employing an excess of the reagent.\textsuperscript{15}

Advantages of the Petasis alkylidenation, include the stability to both air and moisture of dialkyltitanocenes 42 and 53, the absence of Lewis acids from the reaction, and the ease of purification following reaction (titanium impurities can often be precipitated from reaction mixtures). A range of dialkyltitanocenes can be prepared but only dimethyltitanocene 42 has proved popular.\textsuperscript{15} The disadvantages of Petasis reagents include, the high temperature (65 °C) required for α-elimination, several equivalents of the reagent are often necessary for complete reaction, and reactive organometallics are required for their synthesis. Furthermore, alkylidenations with titanium alkylidenes containing alkyl groups with β-hydrogens (with respect to titanium) are not possible. Petasis has published a full review on his work with these titanocene reagents.\textsuperscript{61}
Takeda reagents

Takeda et al have demonstrated that thioacetals can be reduced by low valent titanium(II) complex Cp₂Ti[P(OEt)₃]₂ 74 to give titanium reagents that will alkylidene a wide variety of carbonyl derivatives. Takeda has reviewed his work on the desulfurisation of thioacetals and applications including alkylideneation reactions.⁶²

Titanium complex 74 is generated by the reduction of titanocene dichloride with magnesium in the presence of 2 eq. of triethylphosphite and 4 Å Molecular sieves, in dry THF (Scheme 25).⁶³ Thioacetals 75 are added to the low valent titanium reagent 74 presumably generating titanium alkylidenes 76, perhaps via geminal bimetallic species 77. Both 1,3-dithianes and diphenyldithioacetals may be used,⁶³ but the latter are more reactive.⁶² Alkylidenes 76 alkenate carbonyls 78 to give alkenes 79. Methylenation is ineffective under Takeda conditions but allylic, benzylic or alkyl thioacetals are suitable substrates for generating alkylidenating reagents.

![Scheme 25](image)

The reaction proceeds smoothly with aldehydes and ketones, however, the E-selectivity obtained in products is poor, e.g. the E:Z ratio of alkenes 80 is only 56:44 (Scheme 26).⁶²

![Scheme 26](image)
Esters\(^6^3\) and thioesters\(^6^4\) are effectively alkylidenated. In the case of esters, alkylidenation proceeds with high Z-selectivity.\(^6^3\) The Z-selectivity can be explained using the same arguments as presented for Petasis benzylidenation and indeed the selectivity is slightly higher in Takeda benzylidenations. The titanium alkylidene derived from dithiane 81, converts methyl benzoate into dienes 82 (Scheme 27).\(^6^3\) In the case of thioesters, alkylidenation proceeds with substrate-dependant variation in Z-selectivity. When thioacetal 83 is treated with low valent titanium complex 74 and then with thioester 84 in refluxing THF, vinyl sulfides 85 are produced with high Z-selectivity (Scheme 27).\(^6^4\)

![Scheme 27](image)

Titanium cyclobutylidene complex 86, generated from 1,1-bis(phenylthio)cyclobutane 87, alkylidenates ketones, esters and thioesters to give alkylidene cyclobutanes 88 in high yields (Scheme 28).\(^6^5\)

![Scheme 28](image)
The titanium alkylidene generated from methoxybis[(phenylthio)methane] 89 converts aldehydes and ketones into enol ethers.\textsuperscript{66} Esters and thioesters yield β-(alkoxy)vinyl ethers and β-(alkylthio)vinyl ethers, respectively, and ester 90 gave vinyl ethers 91 in good yield but poor stereoselectivity (Scheme 29).\textsuperscript{66} In a similar way, triphenyl thiothio-orthoformate 92 converts aldehydes and ketones into vinyl sulphides.\textsuperscript{66} Esters and thioesters, similarly yield β-(alkoxy)vinylsulfides and β-(alkylthio)vinyl sulfaides, respectively, with modest \(E\)-selectivity, exemplified by thioester 93 and triphenyl thiothio-orthoformate 92 giving β-(propylthio)vinyl sulfide 94 in good yield and moderate \(E\)-selectivity (Scheme 29).\textsuperscript{66}

\begin{align*}
\text{Scheme 29}
\end{align*}

Allylsilanes can be prepared by Takeda alkylidenation of aldehydes, ketones, esters, lactones, or thioesters using β-trialkylsilylthioacetals as substrates.\textsuperscript{67} Allylsilanes are formed from aldehydes and ketones with moderate \(E\)-selectivity. \(γ\)-(Alkylthio)allylsilanes are formed with moderate \(Z\)-selectivity, seemingly unaffected by the bulk of the \(S\)-alkyl group in the thioester substrates. \(γ\)-(Alkoxy)allylsilanes are formed from ester substrates, with better \(Z\)-selectivity in most cases, and a branch \(α\) to the ester carbonyl group leads to complete stereoselectivity as exemplified by formation of \(γ\)-(ethoxy)allylsilane 95 from ester 96 (Scheme 30).\textsuperscript{67} The alkene configuration was not determined but it is assumed to be \(Z\)-selective.\textsuperscript{15}

\begin{align*}
\text{Scheme 30}
\end{align*}
Intramolecular alkylidenations are also possible. Treatment of \( S-[3,3\text{-bis(phenylthio)propyl}]\text{thioalkanoates} \) with 4 eq of low-valent titanium complex 74 in THF produced 5-substituted 2,3-dihydrothiophenes. Improved yields were obtained when there was a branch \( \alpha \) to the carbonyl group as in thioester 97 (Scheme 31). Isomerisation to the exocyclic alkenes was initially observed but by carrying out both the reaction and work-up in the dark this was suppressed. Indeed, the product vinyl sulfide 98 isomerises in light to give an equilibrium mixture (80% \( \text{exo} \)) of alkenes.

\[
\begin{align*}
\text{PhS} & \quad \text{SPh} \\
\text{O} & \quad \text{Cp}_2\text{Ti[P(OEt)]_2} 74 \\
\text{97} & \quad \text{98} 65\% \\
& >99\% \text{ endo isomer}
\end{align*}
\]

Scheme 31

Titanium alkylidenes generated from \( \omega,\omega\text{-bis(phenylthio)alkyl esters} \) (e.g. 99) undergo oligomerisation as well as cyclisation. The best yield obtained was for cyclic enol ether 100 and this was only 32% (Scheme 32). However, the reaction provides a useful route to \( \omega\text{-hydroxy ketones} \) (e.g. 101), and by carrying out the alkylidenation reaction under reflux in THF, and then hydrolysing the resulting crude cyclic enol ether (e.g. 100) \textit{in situ}, yields are improved considerably.

\[
\begin{align*}
\text{PhS} & \quad \text{SPh} \\
\text{O} & \quad \text{Cp}_2\text{Ti[P(OEt)]_2} 74 \\
\text{99} & \quad \text{100} 32\% \\
\text{i. } \text{Cp}_2\text{Ti[P(OEt)]_2} 74 & \quad \text{ii. } \text{H}_3\text{O}^+ \\
& \quad \text{101} 67\%
\end{align*}
\]

Scheme 32
Intramolecular alkylidenation is more effective when the oxygen atom of the product enol ether is exocyclic and 5-, 6-, 7- and 9-membered rings have been made in this way, with thioacetal 102 giving cyclic E-enol ether 103 in 70% yield (Scheme 33).\(^7^0\) Again, some isomerisation of the alkene products was observed in some cases but was suppressed by carrying out the reactions at lower temperatures. Reactions were carried out under high dilution conditions, on 0.50 mmol scale, and attempts at scale-up resulted in lower yields being obtained.

\[
\text{Scheme 33}
\]

The generation of titanium alkylidenes from thioketals is generally problematic due to competing formation of vinyl sulfides.\(^7^1\) However, the use of more easily reduced gem dichlorides, allows the conversion of carbonyl compounds into tetra-substituted olefins. Takeda's group have recently reported a convenient synthesis of gem dihalides (e.g. 104), via oxidation of hydrazones (e.g. 105, Scheme 34), produced by treatment of carbonyls with hydrazine hydrate.\(^7^2\) Aldehydes and ketones are converted into tri- and tetra-substituted alkenes respectively, and esters and lactones into trisubstituted enol ethers (e.g. 106, Scheme 34).\(^7^1\) The reaction is effective even if all of the substituents are acyclic. This is the first practical procedure for the preparation of trisubstituted enol ethers and \(E:Z\) ratios range from 60:40 to 90:10.\(^7^1\) However, Takeda's procedure is unsuccessful for the formation of benzylic dihalides as vinyl halides are the main products formed, and there remains no reported method for the production of titanium benzylidenes with an alpha substituent.\(^1^5\)

\[
\text{Scheme 34}
\]
Under Takeda conditions, titanium alkylidenes are thought to be the active species as they have been shown to catalyse alkene metathesis. The titanocene(II)-promoted formation of titanium alkylidenes from thioacetals, and subsequent metathesis reaction of these alkylidenes with terminal trialkyl(allyl)silanes, stereoselectively forms the corresponding Z-γ-substituted allylsilanes. Ring-closing alkene metathesis of thioacetals containing an alkene moiety proceeds smoothly upon treatment with 3-4 eq. of low-valent titanocene at rt, and then heating under reflux in THF. Loss of the terminal alkene allowed the synthesis of 5-, 6-, and 7-membered cycloalkenes in good yields. Similarly the 7- and 8-membered unsaturated cyclic ethers and cyclic amines were also prepared. Employing 4 eq. of low-valent titanocene complex, initially at rt and then heating under reflux in THF, converted thioacetal into cyclic amine in good yield (Scheme 35). Generally, the titanocene promoted ring-closing metathesis (RCM) reactions are done under high dilution to suppress the intermolecular reactions. More recently (Z)-Alk-2-ene-1,5-diols have been prepared stereoselectively via the titanocene promoted RCM of trialkyl silyl ethers containing both a thioacetal and terminal alkene moiety, followed by oxidative cleavage of the resulting cyclic silyl ethers.

![Scheme 35](image)

Titanium alkylidenes, formed under Takeda conditions from thioacetals, add to alkynes to give the corresponding titanacyclobutenes, which then undergo β-hydride elimination and subsequent reductive elimination to give the corresponding dienes in good yields and high stereoselectivity (Scheme 36).
Titanium alkylidenes, formed under Takeda conditions, add to nitriles and then undergo a β-hydride elimination to give vinylimido complexes 111. These can then be hydrolysed directly to give ketones 112, or in-situ addition of an alkyl halide followed by hydrolysis gives monoalkylated ketones 113 (Scheme 37).80

Titanium allylidenes, formed from β,γ-unsaturated thioacetals 114, can cyclopropanate alkenes to give the corresponding vinylcyclopropanes 115 (Scheme 38), which probably proceeds via the reductive elimination of a titanacyclobutane intermediate.81 Similarly, γ-cyclopropyl allylsilanes are prepared from 2,4-bis(phenylthio)but-3-enylsilanes, upon treatment with low-valent titanium complex 74 and then a terminal alkene.82 Titanium allylidenes can also be alkylated with tertiary alkyl chlorides before quenching.83

Scheme 37

Scheme 38
Titanium propargyldienes, formed from 1,1-bis(phenylthio)-2-alkynes 116, can also
cyclopropanate terminal alkenes to give the corresponding alkynylcyclopropanes 117
(Scheme 39), which presumably proceeds via the reductive elimination of the
titanacyclobutane intermediate. In order to obtain good yields excess triethyl phosphite is
required.84

![Scheme 39](image)

Previous to our work, functional group tolerance within titanium alkylidenes generated
under Takeda conditions and within carboxylic and carbonic acid derivatives treated with
such reagents, was not fully explored. A full discussion is given later in the results and
discussion section.

The key advantage of Takeda alkylidenation, is the easy access to a range of alkylidenating
agents produced from thioacetals that are easily made from carbonyl compounds. The
reaction is not limited to methylenation or benzylidenation and the preparation of a wide
range of alkylidene reagents is theoretically possible. The mildness of the reaction
conditions (with both formation and often reaction of the titanium alkylidene being
conducted at rt) and the lack of Lewis acidic conditions, are also attractive. The main
disadvantage is the requirement for excess titanocene (at least 3 eq.) and triethylphosphite
(at least 6 eq.), which often makes product purification problematic.
Takai has reported a simple and general method for the alkylidenation of carbonyls 118 to give alkenes 119, using a reagent prepared in a reaction mixture containing a 1,1-dibromoalkane, zinc, titanium(IV) chloride and \( N,N,N',N'\)-tetramethylenediamine (TMEDA) in THF (Scheme 40). Takai reagents are prepared by addition of 4 eq. titanium(IV) chloride in dichloromethane to THF, followed by 8 eq. TMEDA, which turns the suspension from yellow to orange/brown. Addition of 9 eq. of zinc then leads to a dark blue/green suspension. Upon addition of 1 eq. of the ester and 2.2 eq. of a dibromoalkane, the reaction mixture turns dark brown or black, and is then quenched with aqueous potassium carbonate giving the alkene 119. Trace amounts of lead(II) salts are reportedly vital for successful reaction, and so a small quantity of lead(II) chloride is generally added, though lead is often a contaminant of commercial zinc powder. Although, the commercially available DCM solution of titanium(IV) chloride can be used, optimal yields are obtained with freshly prepared solutions from high quality titanium(IV) chloride, and also employing a DCM-THF mixed solvent system. However, reactions in only THF are also successful. The definitive procedure for the preparation of this reagent has been published.

The reaction mechanism is not yet fully understood. In the absence of lead, zinc is known to rapidly insert into diiodomethane giving carbenoid 120, but second insertion is slow to give geminal dizinc 121 (Scheme 41). It is known that lead(II) chloride accelerates the conversion of diiodomethane into geminal dizinc 121, and so would seem to catalyse the conversion of zinc carbenoid 120 into geminal dizinc 121. Takai proposed that transmetalation from zinc to lead gives rise to lead carbenoid 122, which is further reduced by zinc to give lead-zinc compound 123. He suggested that since the Pb-C bond has greater covalent character, lead carbenoid 122 is more easily reduced than the corresponding zinc carbenoid 120. He proposed that transmetalation from lead to zinc then gives geminal dizinc 121. However, titanium complexes must be involved in the reduction of the dibromoalkanes used in Takai alkylidenation of esters, as the rate of conversion of...
dibromomethane into a geminal dizinc (even with catalytic lead) in the absence of titanium salts is too slow to account for the alkylidenation reaction times.  

\[
\begin{align*}
\text{CH}_2\text{I}_2 & \overset{\text{Zn, THF}}{\rightarrow} \text{ICH}_2\text{Zn} \\
& \overset{\text{Zn}}{\rightarrow} \text{CH}_2(\text{ZnI})_2 \\
\end{align*}
\]

\[X = \text{Cl, I}\]

\[
\begin{align*}
\text{Zn} & \quad \text{THF} \\
\text{Zn} & \quad \text{CH}_2(\text{ZnI})_2 \\
\end{align*}
\]

\[120 \quad 121\]

\[
\begin{align*}
\text{ZnX}_2 & \quad \text{Fast} \\
\text{PbX}_2 & \quad \text{Fast} \\
\end{align*}
\]

\[122 \quad 123\]

\[
\begin{align*}
\text{Zn} & \quad \text{Fast} \\
\end{align*}
\]

\[124 \quad 125 \quad 126\]

\text{Scheme 41}

It is also evident that low valent titanium complexes are generated prior to the addition of dibromoalkanes, but the identity of these low valent titanium complexes has not yet been established. Blue titanium(III) complex 124 can be obtained from titanium(IV) chloride in DCM-THF by treating it with 2 eq. TMEDA, and only 1.1 eq. of zinc (half the stoichiometry used in the generation of the alkylidenating agent) and 6 mol% lead(II) chloride (Scheme 42). Also, when \(\text{TiCl}_3(\text{THF})_3\) is reduced in THF with excess lithium in the presence of 6 eq. TMEDA, violet titanium(II) complex 125 is formed slowly (2 d) via the brown mixed valence titanium(II)/titanium(III) species 126 (Scheme 42). Complex 125 dissolves in THF to give a golden yellow solution, but is oxidised easily back to the mixed valence titanium(II)/titanium(III) species 126. A mixture of titanium species 124, 125 and 126 would account for the greenish blue colour formed under Takai conditions in THF.

\[
\begin{align*}
\text{TiCl}_4 & \overset{\text{i. DCM-THF}}{\rightarrow} \\
& \overset{\text{ii. TMEDA (2 eq.)}}{\rightarrow} \\
& \overset{\text{iii. Zn (1.1 eq.), PbCl}_2 (6 \text{ mol} \%)}{\rightarrow} \\
\end{align*}
\]

\[124\]

\[
\begin{align*}
\text{TiCl}_3(\text{THF})_3 & \overset{\text{i. THF}}{\rightarrow} \\
& \overset{\text{ii. TMEDA (6 eq.)}}{\rightarrow} \\
& \overset{\text{iii. Li}}{\rightarrow} \\
\end{align*}
\]

\[126 \quad 125\]

\text{Scheme 42}
Takai proposed that in the presence of titanium(IV) salts, geminal dizinc 121 transmetallates to give a titanium-containing geminal dimetallic 127 or a titanium methylidene 128, one of which is the active species (Scheme 43).86 We propose that the Takai reaction [and related reactions employing Ti(II) salts], requires oxidative addition to a titanium(II) intermediate, which is involved in the formation of at least one of the carbon-metal bonds to give a titanium(IV)-containing geminal dimetallic 127 [or less likely a titanium(IV) alkylidene 128], as the active species.

\[
\text{CH}_2\text{(ZnI)}_2 \xrightarrow{\text{TiCl}_4} \begin{cases} \text{X}_n\text{MCH}_2\text{TiX}_n & \text{(127)} \\ \text{H}_2\text{C=::TiX}_n & \text{(128)} \end{cases} \quad \text{M = Ti or Zn}
\]

Scheme 43

There are numerous examples of the methylenation of aldehydes and ketones (when Lewis acid mediators are used) employing geminal dizinc and related reagents.93, 94, 95 Matsubara and co-workers have demonstrated that pre-formed bis(iodozincio)methane 121 methylenates aldehydes effectively. When 2 eq. of 121 is used in conjunction with titanium(IV) chloride, ketones are effectively methylenated, although poor yields are observed with the use of 1 eq. of 121. This suggests that 1 eq. of 121 reduces titanium(IV) chloride to titanium(II) chloride which mediates the olefination reaction.96 They later, demonstrated that a reagent derived from pre-formed bis(iodozincio)methane 121, TMEDA, and titanium(II) chloride in THF, can carry out the methylenation of esters (Scheme 44).97 The reagent requires 2 eq. of titanium(II) chloride and 4 eq. of TMEDA, with respect to geminal dizinc 121, for optimal results. They also state that NMR studies on the \(\text{CH}\) coupling constants in the active species formed from titanium(II) chloride suggests that the carbon atom has \(\text{sp}^3\) character. A different colour (reddish brown) results from this reagent than that of the Takai reagent (brown or black), and it also methylenates esters more effectively than the Takai reagent.97

\[
\begin{array}{c}
\text{R}^2\text{OR}^3 \xrightarrow{\text{CH}_2\text{(ZnI)}_2, \text{TiCl}_2, \text{TMEDA, THF}} \text{CH}_2\text{OR}^3 \\
\text{46-90%}
\end{array}
\]

Scheme 44
Takai reports no examples of the alkylidenation of aldehydes and only one example of the reaction of a ketone. In this example, ketone 129 was converted into a mixture of alkenes 130 in good yield (Scheme 45).

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 \\
\text{C}_5\text{H}_{11}\text{CHBr}_2, \text{Zn} & \\
\text{TiCl}_4, \text{TMEDA} & \\
\text{THF} & \\
\text{Ph} & \quad \text{CH}_3 \\
\text{C}_5\text{H}_{11} & \\
129 & \quad 78\% \text{ Z:E 45:55} \\
130 & \\
\end{align*}
\]

Scheme 45

Takai reagents alkylidenate esters 131 effectively, generally giving enol ethers 132 in yields over 70% (Scheme 46). All reactions are Z-selective and stereoselectivities are generally over 89%. The reaction is not very sensitive to the bulk of R\(^3\) (although bulky R\(^3\) can reduce yields), but bulky R\(^2\) reduces the stereoselectivity and a branch in R\(^1\) α to the carbonyl group ensures total Z-selectivity. The stereoselectivity can be explained using the same arguments as presented for Petasis benzylidenation and Takeda alkylidenation, where stereoselectivity is a result of limiting any steric interactions in the formation of intermediates (possibly oxatitanacyclobutanes). Takai and co-workers reported that methylenation gave poor yields, and in general Takai alkylidenations are more reliable and generally higher yielding than the corresponding methylenation. Takai claims this is due to the increased nucleophilicity provided on account of electron-donation from the alkyl groups in the active species. Silyl esters are also effectively alkylidenated to give the corresponding silyl enol ethers, with Z-selectivities generally similar to those for alkyl esters, but stereoselectivities being reduced when the bulk of substituents on silicon is increased. Lactones produce mixtures of the desired enol ethers and hydroxy ketones, the former presumably being a result of enol ether hydrolysis. Alkylidenation is also successful with diiodoalkanes, but the yields are lower than with the corresponding dibromides.

\[
\begin{align*}
\text{R}^1\text{CH}_2\text{OR}^2 & + \quad \text{R}^3\text{CHBr}_2 \\
\text{TiCl}_4, \text{TMEDA} & \\
\text{THF} & \\
\text{Zn, rt} & \\
\text{Zn, rt} & \\
\text{R}^1\text{OR}^2 & \quad \text{R}^3 \\
\end{align*}
\]

Scheme 46
Takai alkylidenation of thioesters 133 gives Z-alkenyl sulfides 134 (Scheme 47). The Z-selectivity is lower than for alkylidenation of esters, but total Z-selectivity is obtained when both R¹ and R² are branched. S-phenyl thioesters gave lower yields and slightly lower Z-selectivity. However, α,β-unsaturated thioesters do not give conjugated vinyl sulfides although 1,3-dithian-2-ones are converted into the corresponding ketene dithioacetals in good yield.

$$\begin{align*}
\text{R}^1\text{C}^=\text{SMe} + \text{R}^2\text{CHBr}_2 & \xrightarrow{\text{TiCl}_4, \text{TMEDA, THF, Zn, rt}} \text{R}^1\text{Z}^=\text{SMe}\ \\
\text{Scheme 47} & \text{134 75-97% } Z:E \ 73:27 - 100:0 
\end{align*}$$

Tertiary amides 135 give enamines 136 in good yields, and with >96% E-selectivity, when R¹ = Ph or primary alkyl (Scheme 48). However, when R¹ = cyclohexyl, stereoselectivity is lost. A mixture of regioisomers is obtained from straight chain amides 135 (R¹ = primary alkyl), presumably due to isomerisation of the initially formed enamine via an iminium ion intermediate.

$$\begin{align*}
\text{R}^1\text{C}^=\text{N} & \xrightarrow{\text{TiCl}_4, \text{TMEDA, Zn, THF, R}^2\text{CHBr}_2, \text{rt}} \text{R}^1\text{Z}^=\text{N} \\
\text{Scheme 48} & \text{136 70-87% } Z:E \ 53:47 - >99:1 
\end{align*}$$

The synthesis of β-hetero-substituted vinylsilanes via Takai trimethylsilylmethylenation of esters has been achieved using (dibromomethyl)trimethylsilane as the 1,1-dibromide. The reactions are slower (3-5 h) than other alkylidenations, and 3.3 eq. rather than 2.2 eq. of dibromide is needed to obtain good yields. Enol ethers are formed with >86% Z-stereoselectivity, and a branch α to the carbonyl group again ensures virtually complete Z-selectivity. Ester 137 gives essentially only Z-enol ether 138 (Scheme 49). Trimethylsilylmethylenation of thioesters is less Z-selective, and yields are slightly lower than the corresponding reaction with esters.
Aromatic esters can be cyclopropanated with an excess of Takai reagent. Methylenation of methyl azulene carboxylates 139 and 140 proceeds smoothly under standard Takai conditions, but when an excess of the reagent is used, cyclopropyl ethers 141 and 142 are produced in good yield (Scheme 50).\(^\text{100}\) Methyl benzoate undergoes the same reaction, albeit in modest yield, but methyl phenylacetate does not. Enol ethers are not cyclopropanated under these conditions. This indicates that a titanium-containing intermediate derived from the ester reacts with excess reagent.\(^\text{15}\)

There have been recent reports of Takai reagents giving the products of alkene metathesis.\(^\text{101}\) However, the researchers proposed that a titanium alkylidene is generated from an allylic group (see Grubbs reagents) present in the substrate, which then alkylidenates the carbonyl group intramolecularly.\(^\text{15}\)

The advantage of Takai alkylidenation is that it is a mild one-pot procedure that allows the alkylidenation of a range of carboxylic acid and carbonic acid derivatives, often with very high stereoselectivity. Takai alkylidenation tolerates many functional groups, in the ester substrates, including aryl and vinyl halides, alkenes, ethers, silyl ethers and acetals.\(^\text{15}\) Its main disadvantage is that it requires a source of 1,1-dihaloalkanes, which can be difficult to prepare.
Boronic esters are useful synthetic intermediates as they undergo palladium-catalysed cross-coupling reactions.\textsuperscript{102} They couple with aryl, alkynyl, and vinyl halides providing a general technique for carbon-carbon bond formation (Scheme 51).\textsuperscript{102} The reaction is compatible with a wide range of functional groups due to the mild reaction conditions employed. Many other organometallic reagents are equally successful but organoboronates have advantages in that they are thermally stable, inert to water and oxygen, and the boron-containing side products are non-toxic.\textsuperscript{102}

\[
R^1-X + R^2-B(OR)_2 \xrightarrow{\text{Pd[O] Cat.}} R^1-R^2
\]

Scheme 51

\(\beta\)-(Alkoxy-substituted alkenyl)boronic esters are also useful intermediates but can only be made by the hydroboration of alkynes. \(\beta\)-(Ethoxy)alkenylboronic ester 143, with the hydrogen atom \textit{cis} to the boron atom, was prepared from 1-ethoxy-1-alkyne 144 and was then used in a subsequent cross coupling reaction (Scheme 52).\textsuperscript{103}

\[
\begin{align*}
\text{EtO} & \quad 144 + H-B- \quad \xrightarrow{\text{EtO-} \quad 143} \quad \xrightarrow{i. \text{Pd(PPh}_3\text{)}_4, \quad \text{NaOH, THF}} \\
\text{EtO-} & \quad 144 + \quad \xrightarrow{\text{ii. 2M HCl}} \\
& \quad \xrightarrow{\text{1. Pd(PPh}_3\text{)}_4, \quad \text{NaOH, THF}} \\
& \quad \xrightarrow{\text{ii. 2M HCl}} \quad \xrightarrow{\text{40\%}} \\
\end{align*}
\]

Scheme 52

Similarly, \(\beta\)-(alkylthio)alkenylboronic esters 145 have been synthesised both regioselectively and stereoselectively using palladium- or nickel-catalysed hydroboration (Scheme 53).\textsuperscript{104} Thioboration allows the synthesis of related (Z)-vinylboranes but has not yet been applied to the synthesis of boronic esters.\textsuperscript{105}

\[
R^1 S- \quad 145 + H-B- \xrightarrow{\text{NiCl}_2(dppe) \quad \text{or} \quad \text{PdCl}_2(dpfp)} \xrightarrow{\text{or}} R^2-B-145
\]

Scheme 53
Dienylboronate 146 has also been used in diastereoselective Diels-Alder reactions, quantitatively yielding endo functionalised cyclohexane 147, which could then be further reacted with aldehydes as shown (Scheme 54). The dienylboronates were prepared by the hydroboration of terminal eneynes.\textsuperscript{106}

\begin{equation}
\begin{aligned}
\text{B(OR)}_2 & \rightarrow \text{B(OR)}_2 \\
\text{Me} & \text{Me} \\
\text{B(OR)}_2 & = \text{B} \\
\text{O} & \text{O} \\
146 & \rightarrow \\
\end{aligned}
\end{equation}

\begin{multicols}{2}
\text{PhMe, 80 °C} & \rightarrow \\
\text{(RO)}_2 & \text{B} \\
\text{H} & \text{H} \\
\text{Me} & \text{Me} \\
\text{Ph} & \text{Ph} \\
\text{NPh} & \text{NPh} \\
\text{147} & \text{100%} \\
\text{(endo only)} & \\
\end{multicols}

\begin{equation}
\begin{aligned}
\text{RCHO} & \rightarrow \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{149} & \text{d.r > 99:1} \\
\end{aligned}
\end{equation}

\textbf{Scheme 54}

Alkenylboronic esters are also useful substrates for diastereoselective reduction, allowing the control of stereochemistry at up to three adjacent centres, in both cyclic and acyclic systems. Z-Alkenylboronic ester 148 was reduced diastereoselectively, giving alkylboronate 149, which could then be either oxidised or aminated as shown (Scheme 55).\textsuperscript{107}

\begin{equation}
\begin{aligned}
\text{Ph} & \text{Me} \\
\text{O} & \text{O} \\
\text{148} & \rightarrow \\
\text{Ph} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{Ph} & \text{Ph} \\
\text{H}_2, \text{Pd/C} & \rightarrow \\
\text{MeOH} & \\
\text{149 d.r > 99:1} & \\
\end{aligned}
\end{equation}

\begin{equation}
\begin{aligned}
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{Ph} & \text{Ph} \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{2M NaOH,} \\
\text{H}_2\text{O}_2, \text{THF} & \rightarrow \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{77% d.r > 99:1} & \\
\text{i. BCl}_3, \text{DCM} & \rightarrow \\
\text{Me} & \text{Me} \\
\text{Me} & \text{Me} \\
\text{Ph} & \text{Ph} \\
\text{NHBn} & \text{NHBn} \\
\text{66% d.r > 99:1} & \\
\text{ii. BnN}_3, \text{DCM} & \\
\end{aligned}
\end{equation}

\textbf{Scheme 55}
Chapter 4 - Solid-Phase Chemistry

4.1 Background

The pioneer in the field of solid-phase chemistry was Merrifield, who in 1963 described the use of solid-support in peptide synthesis. Since that time the use of solid phase synthesis (SPS) has grown to encompass the synthesis of small organic molecules and many different organic reactions have been carried out on solid-phase.

One of the main attractions of SPS to the organic chemist is the ease of product isolation. Assuming that complete conversion from resin-bound starting material to product occurs, purification merely requires the washing away of reagents and side products, thus avoiding the need for costly chromatography. Indeed, most SPS reactions can be driven to completion by use of excess reagents, despite reducing the atom-economy of the transformations. However, it must be noted that not all reactions can be moved seamlessly from solution to solid-phase and it often requires time to develop optimal conditions for solid-phase procedures. In addition, the introduction of two extra steps in linking compounds to and cleaving compounds from the resin must be taken into account, and these procedures are often not trivial. In these steps the choice of linker (the moiety which attaches the molecule to the resin) can be of vital importance.
4.2 Linkers

4.2.1 Introduction

The criteria used when assessing which type of linker to employ in a solid-phase reaction should be much the same as when making a choice of protecting group. Indeed a linker could be described as a bifunctional protecting group, in that it is attached to the molecule being synthesised through a bond labile to the cleavage conditions and attached to the resin through a more stable bond (Figure 2).\textsuperscript{113}

![Protecting Group-/Functional Group-Molecule](#)

\[\downarrow\text{Deprotection}\]

*Functional Group-Molecule*

*Polymer-Spacer-Linker-/Functional Group-Molecule*

\[\downarrow\text{Cleavage}\]

*Functional Group-Molecule*

Figure 2

An ideal linker would be cheap; its attachment to the starting material would be facile and high yielding; it would withstand all the synthetic steps in the synthesis; most importantly it must be possible to cleave the final product from the resin under conditions that do not destroy it. The cleavage step can be problematic, particularly with traditional peptide linkers, which tend to require harsh conditions for cleavage (e.g. HF). Despite this, peptide linkers have found a role in the SPS of small molecules. However, a new generation of traceless linkers, not based on the traditional protecting group strategy, are becoming increasingly common (see section 4.2.3).\textsuperscript{110,113}

I will begin with a discussion of common acid labile linkers, and will then explain what is meant by “traceless”, “safety catch” and “chameleon catch” linkers, and finally “cyclative termination”. These are the strategies most relevant to my work. However, it should be noted that there are numerous SPS strategies and linker types, and they have been fully reviewed elsewhere.\textsuperscript{113} The SPS synthesis of indoles and quinolines will be discussed in detail in chapters 5 and 6, respectively.
4.2.2 Acid-Labile linkers

Merrifield gave his name to the original linker used in peptide synthesis.\textsuperscript{108} Merrifield resin 150 comprises cross-linked polystyrene functionalised with a chloromethyl group (Figure 3). Carboxylic acids are attached by reacting the resin with the caesium carboxylates and cleavage of the resin-bound ester occurs when the resin is treated with HF. In 1973 Wang reported a second major class of ester linker 151 (Figure 3).\textsuperscript{114} This linker comprises an activated benzyl alcohol design and is also known as HMP (hydroxymethylphenoxy resin). It is more acid labile than the corresponding Merrifield linker, due to the increased stability of the resulting benzylic cation, and so cleavage can occur under milder conditions (50% TFA in DCM).\textsuperscript{115} A linker that is even more sensitive to acid was reported by Mergler \textit{et al.} in 1988. The SASRIN (Super Acid Sensitive Resin) resin 152 resembles Wang resin but has an additional methoxy substituent, and successful cleavage can occur with only 0.5-1% TFA in DCM (Figure 3).\textsuperscript{116}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Figure 3}
\end{figure}
4.2.3 Traceless linkers

Cleavage of a product from a conventional linker generally leaves functionality (e.g. a carboxylic acid, amide or alcohol) at the former site of attachment to the solid support. Such extraneous functionality may affect structure-activity relationships in drug-like molecules. Consequently traceless linkers, where there is no apparent sign of the original site of attachment, have been developed. Many traceless strategies have been reported and reviewed extensively and only a brief discussion of the more general strategies will be discussed herein.\textsuperscript{117, 118, 119} The initial definition of “traceless” referred to the introduction of a hydrogen atom at the former linkage site. However, since reports of syntheses of various functional groups at the former site of attachment have been reported to occur in a “traceless” fashion, the definition was extended to include examples where the former attachment site bears no resemblance to the linkage site before cleavage (such a definition is so broad as to include most cleavage reactions). A more recent definition describes tracelessness as being the result of overall reduction of functionality at the site of attachment upon cleavage from the support.\textsuperscript{118} We will use a loose “no apparent sign of the original site of attachment” definition of tracelessness.

Ellman was a pioneer in this field with the development of aryl silicon linkers. The original linker was cleaved under strongly acidic conditions (HF), forming a new carbon-hydrogen bond at the site of attachment.\textsuperscript{120} More recently, silicon linkers that are cleaved under milder conditions have been reported, with one example being utilised in the synthesis of tricyclic compounds 153 (Scheme 56).\textsuperscript{117}
Selenium has proved a useful element for traceless solid-phase synthesis, due to the susceptibility of alkenyl selenides to homolysis. However, seleno-polystyrene resin-bound 154 can undergo oxidative cleavage generating alkene 155, as well as radical cleavage to give alkane 156 (Scheme 57).

Numerous examples of traceless cleavage employing nitrogen linkers have been reported, where cleavage is facilitated by nitrogen quaternization followed by elimination. Rees and co-workers reported the traceless synthesis of tertiary amines 157, employing the Michael addition of secondary amines 158 onto the regeneratable Michael (REM) linker 159 (Section 11.3), followed by quaternization and Hofmann elimination (Scheme 58).

Many other traceless cleavage strategies rely on release from the resin upon aromatization.
4.2.4 Safety-catch linkers

Safety-catch linkers that rely on a two-step cleavage process are often more general traceless linkers. A stable linker used throughout a synthesis in a relatively stable form is then activated, ensuring that the following cleavage step occurs under mild conditions. Wagner and co-worker's cleavage of benzylsulfonium salts 160, formed by S-alkylation, under palladium cross-coupling conditions to give biphenylmethyl derivatives 161 (Scheme 59), illustrates this methodology.\textsuperscript{123}

\begin{equation}
\text{O-CH}_{2}-\text{CH}_{2}-\text{SH} \xrightarrow{\text{Br}^+ \text{Ar}^-} \text{S}^+ \text{Ar}^-\text{R} \xrightarrow{\text{Et}_3\text{NOBF}_4, \text{DCM}} \text{S}^+ \text{Ar}^-\text{R}
\end{equation}

Scheme 59

\begin{equation}
\text{S}^+ \text{Ar}^-\text{R} + \text{ArB(OH)}_2 \xrightarrow{\text{Pd(dppf)Cl}_2, \text{K}_2\text{CO}_3, \text{THF}} \text{S}^+ \text{Ar}^-\text{R}
\end{equation}

\textbf{Scheme 59}
4.2.5 Chameleon-Catch linkers

Chameleon-catches are linkers which can be switched to another linker type during the synthesis.\textsuperscript{124} The original linker can be cleavable but is converted into a more labile linker (often this involves converting an acid cleavable linker into a more acid labile linker). This strategy ensures high purity in products cleaved from the resin, but can also increases diversity by introducing further functionality during the linker switch. Barrett and co-workers used the Tebbe reagent 27 (Section 2.2) to methylenate resin-bound esters 162 yielding dienes 163, which underwent Diels-Alder cycloadditions followed by cleavage from resin in mild acid to give the corresponding cyclohexanone derivatives 164 (Scheme 60).\textsuperscript{124} Resin-bound enol ethers 165 formed in the same fashion, underwent [3 + 2] cycloadditions with ethyl chlorooximidoacetate 166, allowing concomitant aromatization/cleavage in mild acid to give isoxazoles 167 (Scheme 60).\textsuperscript{125}

![Scheme 60](image-url)
4.2.6 Cyclative cleavage

Cyclative cleavage is when cyclisation induces cleavage from the resin. The key advantage of cyclative cleavage is that only cyclised compounds are released from resin, which ensures the high purity of the products. There are numerous examples of cyclative cleavage, including the cyclisation of internal nucleophiles such as alcohols, amines, anilines, ureas, thioureas, and guanidines onto carboxylic acid derivatives that form the link to the resin. A recent example, involves cyclisation of resin-bound guanidine 168 to give quinazoline 169 (Scheme 61).

\[
\begin{align*}
\text{Scheme 61}
\end{align*}
\]

There are also numerous examples of cyclative cleavage by ruthenium-catalysed ring closing metathesis (RCM). RCM cyclative cleavage of substrates 170 gives lactams 171 (Scheme 62).

\[
\begin{align*}
\text{Scheme 62}
\end{align*}
\]

Other cyclative cleavage strategies include reactions of stabilised phosphorus (Section 5.3) and sulfur ylides, which proceed in a traceless fashion.
4.3 Product characterisation/Automation tools

Infra Red (IR) Spectroscopy

Although not useful for quantitative analysis, IR spectroscopy proves a non-destructive method for the qualitative analysis of certain functional groups on solid phase. Dried polystyrene resin can be used to prepare KBr discs that provide adequate spectra. The more recent Golden Gate IR technology, means that the resin can be analysed with no further manipulation.

Nuclear Magnetic Resonance (NMR) Spectroscopy

Gel phase NMR spectra can be obtained but suffer from significant line broadening due to chemical-shift anisotropy and dipolar coupling. For this reason, only nuclei with a strong chemical shift dispersion such as $^{13}$C, $^{15}$N, $^{19}$F and $^{31}$P give useful spectra, while $^1$H NMR spectra remain poorly resolved. However the development of magic angle spinning (MAS) NMR has addressed this problem. This technique was developed particularly for resin-bound compounds. Well-resolved spectra including high quality $^1$H NMR spectra can be produced.

Use of IRORI 'kans'

IRORI 'kans' are polypropylene reaction vessels, often described as 'plastic tea bags', as the resin remains within the reactor while the reaction mixture can flow in and out through the plastic mesh. A number of sizes of kan exist; the 'macrokan' used by our group is the largest and holds approximately 0.3 mmol of resin-bound material. Advantages of the IRORI technology include the 'split and mix' strategy, where different resin-bound products can be formed in one pot by adding reagents to a flask containing a mixture of kans, each containing different resin-bound substrates. Thus, kans are used in industry in a combinatorial fashion, where a radio-labelled tag is present in each kan, therefore allowing product identification at each stage, and so suitable for automation. Also, kans can be useful in heterogeneous reactions (such as the Takeda reaction, which uses powdered molecular sieves and generates insoluble titanium salts), where by using loose resin, it can be difficult to separate the resin from the heterogeneous reagent.
5.1 Activity

The indole nucleus is present in numerous natural products, including the indole alkaloids, which have been extensively reviewed.\textsuperscript{130, 131} So numerous are biologically active indole containing compounds that only very recent studies, with particular emphasis on 2-substituted indoles, will be discussed herein.

Many inflammatory and neurodegenerative diseases are thought to be caused by the aberrant metabolism of the amino acid L-tryptophan 172 (Figure 4).\textsuperscript{132} Indoleamine 2,3-dioxygenase (IDO) is known to be the first enzyme involved in the degradation of tryptophan in certain cells.\textsuperscript{133} A recent enantioselective synthesis of L-isotryptophan 173, and its D-enantiomer have been reported with a view to determining the IDO activity of L-tryptophan analogues.\textsuperscript{132} Racemic isotryptophan has also been reported to show some bacteriostatic activity.\textsuperscript{134}

![Figure 4](image)

*Figure 4*

Melatonin (N-acetyl-5-methoxytryptamine, MLT, 174, Figure 5) influences a variety of functions in animals, and although its exact role in humans remains unclear, it is thought possible clinical implications may include the treatment of circadian-rhythm-based sleep disorders, and protection of the cardiovascular system by reducing the risk of atherosclerosis and hypertension.\textsuperscript{135, 136} Most functions in humans are associated with the action of MLT on the high-affinity, G-protein, membrane methoxytryptamine receptors MT\textsubscript{1} and MT\textsubscript{2}.\textsuperscript{136} Derivatives with 2-alkyl amine, 4-methoxy and N-aryl substituents, show higher affinity for the MT\textsubscript{1} receptor than MLT 174, with indole 175 (Figure 5) exhibiting submicromolar activity as a partial agonist for MT\textsubscript{1}.\textsuperscript{135} Interestingly, a related study found that indole 176 (Figure 5) showed similar affinity as MLT to the MT\textsubscript{1} receptor but much lower affinity for the MT\textsubscript{2} receptor.\textsuperscript{136} Therefore 2-substituted analogues of naturally occurring indoles, may exhibit greater selectivity for certain receptors.
The neurotransmitter serotonin (5-hydroxytryptamine 177, Figure 6) is a secondary metabolite of tryptophan 172. A number of different classes of serotonin receptors (5-HT₁ - 5-HT₇) have been identified. One of the more recently identified populations are the 5-HT₆ receptors, which are found primarily in the central nervous system. Although their exact clinical significance is still unknown, a number of antipsychotic agents and antidepressants bind with high affinity at 5-HT₆ receptors and 5-HT₆ ligands are thought to be involved in various disorders including anxiety, memory deficiency, mood dependant behaviour and motor related function.¹³⁷ A recent study identified indole 178 (Figure 6) as the most selective 5-HT₆ agonist reported to date with other 2-substituted analogues acting as antagonists.¹³⁷ A related study found that indole 179 (Figure 6) also showed high affinity for the same receptor.¹³⁸

Recent independent studies identified a range of ligands as potent and selective Factor Xa (a pivotal enzyme in blood coagulation) inhibitors. 2-Substituted indole 180 was identified as a subnanomolar inhibitor,¹³⁹ whereas indoles 181 and 182 showed nanomolar activity and high selectivity¹⁴⁰ for Factor Xa (Figure 7). Such compounds could potentially lead to the development of safer and more effective antithrombotic agents.
Nonsteroidal anti-inflammatory drugs (NSAIDs) target cyclooxygenases, but show undesirable gastric side effects. Potent selective cyclooxygenase-2 inhibitors have recently been reported, with indole 183 (Figure 8) identified as a lead candidate for a potentially effective NSAID without the usual side effects.141

![Figure 8](image)

Bacterial enoyl-ACP reductase (FabI) catalyses the final step in each cycle of bacterial fatty acid biosynthesis and so is an attractive target for the development of new antibacterial agents. A recent study identified indole 184 (Figure 9) as a low micromolar inhibitor of FabI. It caused inhibition of fatty acid biosynthesis and so can be considered a valid antibacterial target.142

![Figure 9](image)

Both natural and synthetic bisindoles have recently been investigated, and members of the indolocarbazole family are known to exhibit nanomolar topoisomerase inhibitory action.143, 144 Amongst the indolopyrrolocarbazoles currently in clinical trials is NCS 655649 185 and carbazole 186 was also shown to be strongly cytotoxic towards four tumour cell lines (Figure 10).144

![Figure 10](image)
5.2 Indole Synthesis

The synthesis of the indole nucleus has been an object of research for over a century.\textsuperscript{145} As a result, numerous strategies for the construction of indole derivatives have been reported and extensively reviewed,\textsuperscript{146} and so only those employing classical $N$-C\textsubscript{2} indole ring constructions (formation of the indole nucleus is attained \textit{via} formation of a bond between the indole nitrogen and C\textsubscript{2} of the indole ring) and/or very recent examples will be discussed here. However, methodologies for the synthesis of the indole skeleton on solid-phase (Section 5.3) will be covered comprehensively.

The Reissert synthesis of indoles, relies on the acidity of the methyl protons \textit{ortho} to a nitro substituent on an aromatic ring. The resulting anion from 2-nitrotoluidine undergoes condensation with oxalate to give anion 187, which in turn undergoes a reductive cyclisation/dehydration to yield indole 188 (Scheme 63).\textsuperscript{147}

\begin{center}
\textbf{Scheme 63}
\end{center}

\begin{equation*}
\begin{aligned}
\text{NO}_2 & \xrightarrow{(\text{CO}_2\text{Et})_2, \text{KOEt}} \text{NO}_2 \\
\text{EtOH-Et}_2\text{O} & \xrightarrow{187 \ 76\%} \text{H}_2, \text{Pt} \text{AcOH} \xrightarrow{188 \ 65\%}
\end{aligned}
\end{equation*}

Similarly, the Leimgruber-Batcho synthesis involves the condensation of 2-nitrotoluidines with dimethylformamide dimethyl acetal (DMFDMA), with reductive cyclisation of the resulting enamine giving an indole.\textsuperscript{148} The DMFDMA reagent supposedly generates \textit{in situ} MeOCH=$N^+Me_2$, and methoxide ion which deprotonates a toluide proton, and the resulting anion reacts with the electrophilic MeOCH=$N^+Me_2$ component. A useful extension of this methodology involves acylating the intermediate enamine, which ultimately allows substitution at the indole C-2 position. Trisubstituted enamine 189 was prepared and underwent reductive cyclisation to yield indole 190 (Scheme 64).\textsuperscript{149}

\begin{center}
\textbf{Scheme 64}
\end{center}

\begin{equation*}
\begin{aligned}
\text{Br} & \text{NO}_2 \xrightarrow{i. \text{Me}_2\text{NCH(OMe)}_2, \text{piperidine, DMF}} \text{O} \xrightarrow{l. \text{dioxane,}} \text{H}_2\text{O reflux} \xrightarrow{190 \ 63\%}
\end{aligned}
\end{equation*}
The Sugasawa indole synthesis utilises the cyclisation of ortho-chloroacetyl arylamines (e.g. 191), which are prepared from unprotected anilines via a regioselective Friedel-Crafts acylation (Scheme 65).\(^{150}\) Cyclisation onto the ortho-chloroacetyl moiety, followed by reduction of the ketone to the alcohol, with subsequent dehydration gives the indole nucleus.

\[
\text{Scheme 65}
\]

The cyclisation of nitrenes, generated by the triethyl phosphite deoxygenation of ortho-nitrostyrenes or ortho-nitrostilbenes, is termed the Cadogan-Sundberg synthesis.\(^{146}\) A further variation of this deoxygenation method employs CO and Se, which the authors propose forms carbonyl selenide (COSe), as the deoxygenating species (Scheme 66).\(^{151}\) Other variations of this deoxygenation method are possible, including the thermolysis of ortho-azidostyrenes.\(^{146}\)

\[
\text{Scheme 66}
\]

Heating β,β-difluorostyrenes 192 containing ortho-tosylamino groups with sodium hydride in DMF promotes a normally disfavoured 5-endo-trig cyclisation, yielding 2-fluoroindoles 193 (Scheme 67).\(^{152}\)

\[
\text{Scheme 67}
\]
The Watanabe indole synthesis involves the metal-catalysed oxidative cyclisations of anilines with glycols or ethanolamines. Intramolecular versions of this reaction on ortho-aminophenethyl alcohols, are known, with a recent example employing [Cp*IrCl₂]₂ as catalyst, giving a range of indoles (Scheme 68). Remarkably, the catalyst also worked for ortho-nitropheneethyl alcohol when propan-2-ol was used as the solvent giving indole (Scheme 68). Propan-2-ol presumably acts as a hydride source enabling reduction of the nitro group. Both nitro reduction and alcohol oxidation are catalysed in one pot by 5 mol % of [Cp*IrCl₂].

![Scheme 68](image)

Intramolecular Heck reactions have been employed for the cyclisations of ortho-allyl substituted anilines yielding indoles, representing an N-C₂ indole formation as shown (Scheme 69). Heck reactions have also been used for the C₃-benzene ring indole (formation of the indole nucleus is attained via formation of a bond between the benzene ring and C₃ of the indole) forming reaction, which has been demonstrated on solid-phase and is discussed in section 5.3.

![Scheme 69](image)

Perhaps the most common method for indole synthesis involves Pd-catalysed Sonagashira cross-coupling reactions of ortho-halo anilines with alkynes. The ortho-ethynylanilines can then be cyclised to the indole, using a variety of reagents, including Cu(I) salts, Pd(II) species, NaAuCl₄·H₂O catalyst, alkoxides, and tetrabutylammonium fluoride. Restrictions include the requirement for N-protection and cyclisation onto alkynes with electron-withdrawing groups often fail. A more recent method overcomes these restrictions, employing Cu(II) salts [Cu(OAc)₂ or Cu(OTf)₂ are optimal]. This has also been applied to tandem cyclisations, via the intramolecular displacement of a tosylate group, yielding 2,3-fused indole (Scheme 70).
Recently, the Sonagashira cross-coupling has been applied to indole synthesis employing triflates rather than ortho-halo anilines. A range of triflates were synthesised from commercially available 2-aminophenols, allowing increased structural diversity in the cyclisation substrates. Triflates underwent Pd(0)-Cu(I) coupling with terminal alkynes, employing triethylamine as base and n-Bu₄NI as a necessary additive (Scheme 71). It was proposed that iodide acts by replacing the triflate anion in the square-planar Pd(II) complex, or by forming a new pentacoordinated anionic palladium species, making the following transmetalation occur easily. Cyclisation to indoles was accomplished with t-BuOK in N-methyl-2-pyrollidinone (NMP).

The intramolecular Pd-coupling of ortho-halo anilines with alkynes, with subsequent annulation to the indole in one operation has been termed the Larock indole synthesis. The method is very common and has also been applied to the synthesis of indoles on solid-phase and it is discussed further in section 5.3.

Similarly, vinyl triflates react with ortho-aminophenylacetylene in a palladium-catalysed reaction giving a range of 2-substituted indoles. More recently (2-alkynyl)phenylisocyanates have been shown to couple with allyl carbonates, employing a Pd-Cu bimetallic catalyst to afford indoles (Scheme 72). The best copper additive was CuI, which may act as a Lewis acid and coordinate to the alkyne, activating it to promote insertion into a π-allyl palladium intermediate. However an alternative mechanism involving activation of the nitrogen nucleophile by copper, with alkyne activation a result of coordination to the π-allyl palladium species, cannot be ruled out.
A very recent, related indole construction, employs a reductive annulation of aromatic nitroso compounds 202 with alkynes (Scheme 73). The unstable, highly polar intermediate, was tentatively assigned as the N-hydoxy indole 203, which was then converted into indole 204 by hydrogenolysis. Complete regioselectivity was observed with terminal alkynes giving substituents at the indole 3-position. Disubstituted alkynes with one conjugating group gave 2,3-substituted indoles with the conjugating group at the indole 3-position. The transformation could also be carried out in one pot in the presence of [Cp*Ru(CO)]2 and carbon monoxide but yields were lower. This transformation has the advantage that no functionality is required ortho to the nitro moiety in substrate 202.

Intramolecular alkylidenations of amides or imides have also been used to generate indoles. Such alkylidenations include Wittig reactions of benzyltriphenylphosphonium salts, with an example having been carried out on solid-phase (section 5.3). A more recent example involved treating (2-aminobenzyl)triphenylphosphonium bromides 205 with acid anhydrides in the presence of base (Scheme 74). Presumably (2-diacylaminobenzyl)triphenylphosphonium bromides 206 were the active intermediates undergoing cyclisation under basic conditions. Acid chlorides could be used, when 2,6-lutidine was employed as base but the yields were lower.
A related C1-C2 (formation of the indole nucleus is attained via formation of a bond between C1 and C2 of the indole ring) synthetic strategy relied on the synthesis of N-H insertion product 207, from 2-aminobenzophenone 208 and α-diazo phosphonates 209, with subsequent cyclisation in base to give indole 210 in high yield (Scheme 75). This methodology was also employed in the synthesis of benzothiophenes and isocoumarins.

![Scheme 75](image)

A recent report described the cyclisation of an amine onto an intramolecular enol ether, under acidic conditions. Treatment of amidine-protected diiodoamidine 211 with i-PrMgCl, transmetalation with CuCN·2LiCl, and allylation with 2-methoxyallyl bromide, gave enol ether 212. Grignard formation with i-PrMgCl from aryl iodide 212, transmetalation to give the corresponding arylcuprate, followed by allylation and then cyclisation in acid, gave indole 213 in high yield (Scheme 76).

![Scheme 76](image)
5.3 Solid-Phase Indole Synthesis

Due to the huge range of biological activity exhibited by compounds containing the indole skeleton, the search for new and/or improved methodologies for their synthesis continues. In particular, the adaptation of syntheses (both modern and classical) to solid-phase (S-P) is important for drug discovery through automated high speed parallel syntheses. Numerous useful approaches to the construction of the indole core on solid phase have been reported.

The Fischer indole synthesis has been adapted to solid phase. A polystyrene-bound ketone 214 reacted with phenylhydrazine hydrochloride, under Lewis acid conditions to give hydrazone 215 which cyclised in situ (Scheme 77). Nucleophilic cleavage from the resin with MeOH in triethylamine gave the 2-phenyl indole 216. However, the synthesis is not traceless, leaving an ester at the site where the resin was attached, and the yields and purity were variable. Employing different hydrazine hydrochlorides, allows the only point of diversity, although poor results were obtained when electron-deficient hydrazine hydrochlorides were used. Yang used a similar approach for the synthesis of a library of somatostatin agonists.

\[
\text{PhNHNNH}_2, \text{HCl, ZnCl, AcOH, 70 °C}
\]
\[
\text{9:1 MeOH:Et}_3\text{N, 50 °C}
\]

\(\text{O = Polystyrene}\)

Scheme 77

A recent concise solid-phase synthesis of N-hydroxy indoles involving tin chloride reduction of aromatic nitro compounds and subsequent dehydration of ortho-ketones has been reported. A Wang resin-bound ester was employed as the linker, and upon cleavage, an extraneous carboxyl group remained at the indole 6-position.
The Nenitzescu indole synthesis has been applied to solid-phase with the synthesis of 5-hydroxyindole-3-carboxamides 217 (Scheme 78). Argopore®-Rink-NH-Fmoc resin 218 was deprotected and then treated with diketene to introduce the dicarbonyl species giving resin-bound acetoacetamide 219. Treatment with a primary amine, in the presence of trimethylorthoformate as dehydrating agent, gave resin-bound enamionamides 220. Subsequent treatment with benzoquinones at room temperature for 1-2 days gave the resin-bound indoles 221 which were then cleaved in acid. A wide range of primary amines were employed but many resulted in low yields. Indoles produced in this way have a primary amide at the site where the resin was attached, so the method is not traceless. Complete regioselectivity was observed, with monosubstituted benzoquinones giving substitution at C-6 of the indole and 2,5-disubstituted benzoquinones giving 4,7-disubstituted indoles, although 2,3-disubstituted and 2,6-disubstituted benzoquinones were unsuccessful.

Scheme 78
A recent palladium-catalysed tandem C,N-arylation of resin-bound enamines has been reported. In a one pot procedure, resin-bound N-acetyl dehydroalanine 222 and 1,2-dibromo aniline undergo a Heck coupling followed by an amination reaction to give the corresponding resin-bound indole (Scheme 79). Cleavage from the resin by transesterification, yielded indolecarboxylate 223 in good yield, upon aqueous work-up and column chromatography. The ester moiety marks the site of resin-attachment.

\[
\begin{align*}
&\text{O}^{\text{N}}\text{NH}^+ \\
\text{O}^{\text{N}}\text{H} &\text{Ac} \\
\text{222} &\text{1 eq.} \\
\text{Br} &\text{1 eq.} \\
\text{Br} &\text{2 eq.}
\end{align*}
\]

\[\text{OH} \xrightarrow{\text{H}_2\text{N}} \text{224} \xrightarrow{\text{DIC, THF}} \text{NH}_2 \xrightarrow{(i-\text{Pr})_2\text{NEt, DMF}} \text{225} \xrightarrow{\text{i. Pd(PPh_3)_2Cl}_2, \text{Bu}_4\text{NCl, Et}_3\text{N, DMF-H}_2\text{O (9:1), 70} \, ^\circ\text{C, 24 h}} \text{CONH}_2 \]

Scheme 79

Palladium-catalysed cyclisation of α-anilino-α,β-unsaturated resin-bound esters containing a halogen ortho to the aniline to give polymer-bound 2-indolecarboxylates, has been reported recently. Similarly, Heck-type cyclisations of resin-bound N-allyl-substituted ortho-haloanilines for the construction of the indole nucleus have been reported. Zhang et. al. utilised Rink amide resin 224, which was coupled with γ-bromocrotonic acid, aminated with a range of ortho-iodoanilines, and then alkylated with benzyl bromides to give resin-bound cyclisation precursors 225 (Scheme 80). A 5-exo-trig Heck cyclisation, followed by resin-cleavage gave indoles 226 in high yields and reasonable purity. Again, a 3-methylcarboxamide group is left at the former site of attachment to solid-support.
The most common method for the solid-phase synthesis of indoles involves the palladium-catalysed heteroannulation of internal alkynes, which in turn are prepared from ortho-haloanilines. A synthesis of 6-indole carboxylic acids utilised Tentagel-S® resin-bound esters containing an ortho-iodo N-acetoxy-anilines and coupling/cyclisation with a terminal alkyne. Trisubstituted 6-indole carboxylic acids were prepared using a similar approach employing Wang resin-bound esters containing ortho-iodoanilines. Zhang reported a similar approach, employing Rink amide AM® resin-bound amides containing ortho-iodoanilines to give 5-carboxamide indoles (Scheme 81). 2,3-Disubstituted indoles had the more sterically demanding group at the 2-position, due to insertion of the intermediate arylpalladium species into the less hindered end of the alkyne. Using the same linker but employing an N-(butyn-1-yl)acetamide as the alkyne under microwave assistance, allowed the synthesis of 5-carboxamido-N-acetyltryptamine.

![Scheme 81](image)

All the methods discussed above, involve cleavage strategies which leave polar substituents at the site where the resin was attached, and so are of limited use in the synthesis of libraries for drug discovery, as such groups are known to affect structure-activity relationships.
Therefore traceless solid-phase methodologies are required for the synthesis of indoles, where the former site of resin-attachment is not apparent in the final cleaved product. A number of such traceless indole syntheses have appeared, employing the heteroannulation of internal alkynes, coupled to ortho-haloanilines which are immobilised via an N-aniline linker. The first approach involved loading 2-idoaniline onto Ellman’s THP resin 229 with pyridinium tosylate (PPTS) to give aminal linked aryl iodide 230 (Scheme 82). Palladium-catalysed cross-coupling/cyclisation with alkynes in the presence of tetramethylguanidine (TMG) base gave resin-bound indoles 231. Unfortunately, the coupling reaction must be repeated in order to drive it to completion. Coupling is generally regioselective with bulky substituents ending up at the 2-position of the indole. Problems arise when the opposite regiochemistry is required, and yields are reduced when alkynes with sterically demanding substituents are used. Cleavage from the resin gave 2,3-disubstituted indoles 232 or 3-substituted indoles 233 upon protodesilylation, although details of purity were not given.

![Scheme 82](image)

Gmeiner has reported a similar linkage strategy, which was used to immobilise 5-cyano indoles. Upon further functionalisation by a Mannich reaction on resin, and by resin-cleavage a range of highly selective Dopamine D4 receptor partial agonists were synthesised.
Zhang reported a similar linkage strategy, employing an N-sulfonyl linker, which can be cleaved using tetrabutylammonium fluoride in a traceless fashion. 2-Substituted indoles and 3-substituted 2-arylindoles were prepared in this way, via successive palladium-catalysed reactions. The same linker was employed in a recent synthesis of 2,3,5-trisubstituted indoles. 4-Bromo-2-idoaniline was loaded onto the commercially available PS-TsCl (polystyrene sulfonyl chloride) resin giving resin-bound aniline (Scheme 83). A selective coupling reaction of a range of terminal alkynes with the 2-iodo moiety of was carried out in the presence of the 4-bromo group, followed by intramolecular cyclisation to give resin-bound indoles. Subsequent acylation at the 3-position employing aluminium trichloride gave 3-acyl indoles. Further functionalisation at the 5-position, via either a Sonagashira coupling with terminal alkynes, or a Suzuki coupling with aryl boronic acids were successful. Cleavage from the resin was then achieved with base, and acidification gave the corresponding indoles. By carrying out the cleavage in the presence of methyl iodide, N-methyl indoles were prepared. Other alkylations were unsuccessful. The methodology is restricted to aryl, acyl and alkynyl substituents at the 2-, 3-, and 5-positions, respectively. Also, it does not allow substitution at either the 4-, 6-, or 7-positions and gives only N-methylation. Despite these limitations, it is amongst the most diversity-based, traceless, solid-phase, indole synthesis reported to date, and as it employs IRORI technology it seems ideal for automation. Schultz recently utilised the same linkage strategy for preparing N,N-dimethyltryptamines on solid-phase, although the indole nucleus was not formed on resin.

Scheme 83
An intramolecular Wittig reaction, of a polymer-bound phosphonium salt, has been applied to traceless solid-phase indole synthesis.\textsuperscript{128} Phosphonium salt 239 was easily prepared from resin-bound triphenylphosphine 240 (Scheme 84). Reduction of the nitro group, followed by regeneration of the bromine counter ion, gave polymer-bound aniline 241. Acylation gave amide 242, which underwent an intramolecular Wittig reaction, under strictly anhydrous conditions, generating indole 243. The phosphine oxide by-products stay attached to the resin, so the method is traceless and also ensures high purity in the final products. However, only one indole was made in this way.

\[
\begin{align*}
\text{Ph} & \quad \text{PPh}_2 \quad \text{Br} \\
\rightarrow & \quad \text{DMF, 70°C, 48 h} \\
& \rightarrow \quad \text{Ph} & \quad \text{PPh}_2 \quad \text{Br} \\
i & \quad \text{Na}_2\text{S}_2\text{O}_4, \text{EtOH, reflux, 90 mins} \\
& \rightarrow \quad \text{HBr, MeOH, dioxane} \\
\text{Cl} & \quad \text{O} & \quad \text{Me} \\
\rightarrow & \quad \text{Pyridine, DCM, 2 h} \\
\text{O} & \quad \text{Me} & \quad \text{O} \\
i & \quad \text{PhMe, DMF, distill} \\
& \rightarrow \quad \text{KO}^+\text{Bu}, \text{DMF, reflux, 45 mins} \\
& \rightarrow \quad \text{Ph}, \text{OMe} \\
\end{align*}
\]

\(\text{Scheme 84}\)

More recently, a modified Madelung synthesis of indoles has been carried out on solid-phase.\textsuperscript{184} Aniline 244 was loaded onto Bal-resin 245, and the resulting imine was reduced to give secondary amine 246 (Scheme 85). Acylation was followed by an intramolecular cyclisation-dehydration step to give the resin-bound indole 247, which was cleaved from the resin under strongly acidic conditions to give the 3-cyano indoles 248.

\[
\begin{align*}
\text{O} & \quad \text{Me} \\
\rightarrow & \quad \text{KO}^+\text{Bu (2 eq.), DMF, reflux, 2 h} \\
& \rightarrow \quad \text{95:5 TFA:Et}_3\text{SiH, rt, 30 mins} \\
\text{CN} & \quad \text{R} \\
\rightarrow & \quad \text{HPLC UV 254 nm} \\
\end{align*}
\]

\(\text{Scheme 85}\)
Chapter 6 - Quinolines

6.1 Activity

The quinoline nucleus plays an important role as an intermediate for the design of many pharmacologically active compounds. An example being chloroquine 249 (Figure 11), which has been by far the most successful antimalarial, being cheap, highly efficacious, and of relatively low toxicity. However, due to the advance of multidrug resistance, chloroquine and other available drugs are becoming less and less effective. Therefore, the search for successful alternatives, including analogues of current drugs, continues. A recent study found that having a moderately lipophilic group at the 7-position, was optimal against a chloroquine resistant strain of \textit{Plasmodium falciparum}.\textsuperscript{186} Another study found that some short chain alkyl amine derivatives [e.g. 250 (Figure 11)] were more potent than chloroquine, against the same strain of \textit{Plasmodium falciparum}.\textsuperscript{187}

![Figure 11](image)

A range of 2-phenyl-4-diaminoquinolines 251 (Figure 12) have shown potent immunostimulant activity in a mouse protection assay.\textsuperscript{188}

![Figure 12](image)

Quinoline 252 (Figure 13), one of a range of quinoline alkaloids isolated from the bark of \textit{Galipea officinalis}, showed activity against a range of strains of mycobacterium tuberculosis.\textsuperscript{189}

![Figure 13](image)
6.2 Quinoline Synthesis

There are numerous examples of syntheses of the quinoline nucleus. Indeed so many only the most general of the classical approaches and a variety of very recent methods will be discussed here.

The Combes synthesis involves the condensation of a 1,3-dicarbonyl compound (e.g. 253) with an arylamine (e.g. 254) to give the β-amino-enone (e.g. 255). Cyclisation by electrophilic substitution in acid on β-amino-enone 255, followed by dehydration affords quinoline 256 (Scheme 86).190

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{NH}_2 & \quad 254 \\
\text{MeO} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]  

\[
\begin{align*}
& \quad \text{heat} \\
& \quad \text{MeO} \\
& \quad \text{MeO} \\
& \quad \text{MeO} \\
& \quad \text{MeO} \\
& \quad \text{MeO} \\
\end{align*}
\]  

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]  

\[
\begin{align*}
& \quad \text{conc. } \text{H}_2\text{SO}_4 \\
& \quad 95 ^\circ \text{C} \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

Scheme 86

The Skraup quinoline synthesis utilises an arylamine (e.g. 257) and an α,β-unsaturated carbonyl compound (e.g. 258) in the presence of an oxidising agent (Scheme 87).191 The conjugate addition product (e.g. 259) cyclises to the dihydroquinoline, which is oxidised in situ to give the quinoline (Scheme 87). When using meta-substituted aryl amines, electron-donating and halide substituents give mainly 7-substituted quinolines, whereas electron-withdrawing substituents give predominantly the 5-substituted quinolines.

\[
\begin{align*}
& \quad \text{EtOH} \\
& \quad \text{ZnCl}_2, \text{FeCl}_3 \\
& \quad \text{reflux} \\
\text{EtOH} & \quad \text{EtOH} \\
\text{EtOH} & \quad \text{EtOH} \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{[O]} \\
\text{EtOH} & \quad \text{EtOH} \\
\text{EtOH} & \quad \text{EtOH} \\
\end{align*}
\]

Scheme 87

The analogous Doebner-Miller reaction employs α,β-unsaturated aldehydes although aldehyde polymerisation is commonly a problem. It was recently reported that utilising a bi-phasic system, yields improved considerably and the reaction proceeded smoothly in the absence of oxidants (Scheme 88).192

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{NHR}^2 & \quad \text{CHO} \\
\text{R}^2 = \text{Ac} \text{ or } \text{H} \\
\text{PhMe, 6 M HCl} & \quad \text{reflux} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

Scheme 88
The Friedländer synthesis involves the condensation of ortho-acylarylamines (e.g. 260) with a ketone (e.g. 261) or an aldehyde (containing an α-methylene group), to give quinolines (Scheme 89). The condensation can be carried out employing acid or base catalysis and the orientation of the condensation depends on the regioselectivity in formation of the enol or enolate, respectively.\textsuperscript{193}

\[
\begin{align*}
\text{Ph} & \quad \text{aq. KOH} & \quad \text{KOH} \\
\text{N}^{\text{Et}} & \quad \text{EtOH} & \quad \text{EtOH} \\
\text{71\%} & \quad \text{0 \textdegree C} & \quad \text{0 \textdegree C}
\end{align*}
\]

Scheme 89

A recent, ruthenium-catalysed modified Friedländer reaction of 2-aminobenzyl alcohol with ketones 262 has been reported.\textsuperscript{194} Methyl ketones with one enolisable substituent gave 2-substituted quinolines 263 (Scheme 90) although cyclic ketones were also converted to the corresponding 2,3-fused quinolines. The reaction is thought to proceed via oxidation of the alcohol to the aldehyde, followed by cross aldol reaction with the ketone.\textsuperscript{194} The resulting α,β-unsaturated ketone is then proposed to be hydrogenated to the product by a dihydron ruthenium (RuH\textsubscript{2}), generated by the initial oxidation of the starting alcohol. Another recent variation employs the microwave-assisted, one pot reaction of amines and aldehydes forming enamines, which then react with 2-azidobenzophenones affording 2-aminoquinolines.\textsuperscript{195}

\[
\begin{align*}
\text{R} & \quad \text{RuCl\textsubscript{2}(=CHPh)(PCy\textsubscript{3})\textsubscript{2}} \\
\text{1 eq.} & \quad \text{[1 mol \%]} \\
\text{Dioxane, KOH (1 eq.)} & \quad \text{80 \textdegree C}
\end{align*}
\]

Scheme 90

Recently, cyclisation of Baylis-Hillman adducts (of 2-nitrobenzaldehydes) 264 have been applied to quinoline synthesis (Scheme 91). Formation of 3-acetoxymethyl-2-alkylquinolines 265 occurred under reflux with Fe/AcOH, and could then be converted into the corresponding 3-hydroxymethyl-2-alkylquinolines 266 by hydrolysis.\textsuperscript{196}

\[
\begin{align*}
\text{R}^1, \text{R}^2 \text{H, R}^3 \text{Me} & \quad \text{K}_2\text{CO}_3 \\
\text{MeOH, rt} & \quad \text{MeOH, rt}
\end{align*}
\]

Scheme 91

60
Baylis-Hillman acetates (from benzaldehydes) 267 have also been employed in quinoline synthesis (Scheme 92). Adducts 267 undergo rearrangement to tosylamide derivatives 268, and in the presence of iodobenzene diacetate and iodine were converted into a mixture of N-tosyl dihydroquinolines 269 and quinolines 270. The mixture containing dihydroquinolines 269, could then be quantitatively converted into quinolines 270 via the elimination of p-toluenesulphinic acid. The cyclisation reaction is thought to proceed via an N-tosylamidyl radical, which cyclises to give an aryl stabilised C-centred radical, followed by oxidation to the dihydroquinolines 269.197

\[
\text{Scheme 92}
\]

Reductive cyclisation of nitroarenes with trialkylamines, catalysed by ruthenium complexes, yielding quinolines, has been reported recently.194 RuCl$_2$(PPh$_3$)$_3$ was shown to be the optimal catalyst, for the reduction of nitrobenzene with tributylamine employing SnCl$_2$·2H$_2$O as reductant, to give 3-ethyl-2-propylquinoline (Scheme 93).194 Similarly, a range of nitroarenes reacted with other trialkylamines, to give the corresponding quinolines. The mechanism for this remarkable transformation is not yet entirely clear.

\[
\text{Scheme 93}
\]
A recent quinoline synthesis involves the palladium-catalysed hydroarylation of alkynes, with aryl iodides, in the room temperature ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [(bmim)BF$_4$]. A range of Pd(0) catalysts were tested but the [(E,E,E)-1,6,11-tris(p-toluenesulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene]Pd(0) complex [Pd(0)L] proved to be optimal. A range of aryl iodides, were coupled with 3,3-di-I-phenyl-1-propyne 271 under the conditions shown, to give a range of quinolines as a mixture of isomers 272 and 273 (Scheme 94).

Rh(I) complexes were recently reported to catalyse the coupling cyclisation of N-aryl trifluoroacetimidoyl chlorides 274 with symmetrical alkynes 275 to afford 2-trifluoromethylated quinolines 276 (Scheme 95). A combination of [RhCl(cod)$_2$] and either of the Ph$_2$P(CH$_2$)$_2$PPh$_2$ (dppe) 277 or P(2-furyl)$_3$ (TFP) 278 phosphine ligands, with triethylamine in toluene under reflux were successful (Scheme 95). Using unsymmetrical alkynes results in quinolines being formed regioselectively, and bulky substituents are placed at the quinoline 4-position but electron-withdrawing groups at the 3-position. Terminal alkynes give 4-substituted quinolines, or 3-substituted quinolines when the substituent is electron-withdrawing.
N-Allyl-N-protected-ortho-aminostyrenes 279 have recently been shown to undergo ene­ene metathesis to give 1,2-dihydroquinolines 280, which are then converted into quinoline 281 quantitatively by silica gel chromatography and air oxidation (Scheme 96).\textsuperscript{200} Although Grubbs' first generation catalyst was successful with the Boc protecting group (PG), it gave lower yields of metathesis product, and also failed when utilising acetyl as PG. However, Grubbs' second generation catalyst 282, gave excellent yields.\textsuperscript{200}

![Scheme 96](image)

Symmetrical zirconacyclopentadienes 282 couple with 2-bromo-3-iodopyridine 283 in the presence of CuCl and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), to afford quinolines 284 in moderate to good yields (Scheme 97).\textsuperscript{201} Unsymmetrical zirconacyclopentadienes gave mixtures of regioisomers. This methodology was also employed for the synthesis of isoquinolines and anthracenes.\textsuperscript{201}

![Scheme 97](image)

To our knowledge, there are no reported syntheses of quinolines on solid-phase to date.
Chapter 7 - Synthesis of Alkenylboronates

7.1 Synthesis and Takeda reactions of boronic esters

As discussed in section 1.1, we aimed to synthesise thioacetals 2, which under Takeda conditions would alkylidenate a range of esters or thioesters 3 to give β-hetero-substituted alkenylboronates 4 (Scheme 98).

\[
\begin{align*}
\text{RS}_2\text{BO} & \quad \xrightarrow{\text{i. } \text{Cp}_2\text{Ti}[\text{P(OEt)}_3]_2} \quad \text{R}^1\text{BO}\text{XR}_3 \\
\text{RS}_2\text{R}^1 & \quad \xrightarrow{\text{ii. } \text{O}_3\text{XR}_3, \text{THF}} \quad \text{X = O, S}
\end{align*}
\]

Scheme 98

Before attempting the synthesis/reactions of thioacetals 2, it was necessary to repeat a standard Takeda alkylidenation in order to establish conditions that would be successful in my hands. Therefore, thioacetal 285 was synthesised by a literature procedure\textsuperscript{202} and was used to convert cyclohexanone into alkene 286 in reasonable yield (Scheme 99). Cyclohexanone was chosen initially, as it is more electrophilic than an ester or thioester and gives a more stable product. It is also symmetrical so there is no issue of geometrical isomers. The moderate yield is most likely a result of the difficulty in isolation of, as opposed to the conversion to, alkene 286.

\[
\begin{align*}
&\text{Cp}_2\text{TiCl}_2 \\
&\xrightarrow{\text{Mg, 4 Å MS, P(OEt)}_3, \text{THF}} \\
&\text{PhSH, BF}_3\text{OEt}_2 \quad \xrightarrow{\text{PhMe-AcOH}} \\
&\text{PhH} \quad \xrightarrow{\text{i. } \text{Cp}_2\text{Ti}[\text{P(OEt)}_3]_2} \quad \text{285 85%} \\
&\text{PhSPh} \quad \xrightarrow{\text{ii. O}_3\text{Ph}} \quad \text{286 57%}
\end{align*}
\]

Scheme 99

We then turned our attention to the synthesis of boronates 287 and 288 from bis(phenylthio)methane and 1,3-dithiane, respectively (Scheme 100). A literature procedure was employed,\textsuperscript{203} and boronic esters 287\textsuperscript{203} and 288 were obtained in moderate yields and purity upon distillation/low temperature crystallisation. However, thioacetals 287 and 288 failed to yield alkenylboronate 289, when employed separately under standard Takeda reactions (Scheme 100). The crude \textsuperscript{1}H NMR spectrum upon work-up, filtration
through celite, and removal of triethyl phosphite by Kugelrohr distillation, showed no evidence of signals corresponding to either an alkene proton or the methyl groups of the pinacol moiety. It should be noted that hydrolysis of the boronic ester during work-up of the Takeda reaction, to generate the corresponding boronic acid cannot be ruled out. However, significant amounts of cyclohexanone were observed in the crude $^1$H NMR spectrum [$\delta$ 2.64 (4H, t, $J$ 5.8, $CH_2$CO)], suggesting that the Takeda reaction was not very successful.

![Scheme 100](image)

In order to overcome the problems associated with product isolation, we attempted to alkyldenate Wang resin-bound ester 290 (Section 8.2), with the titanium alkylidene derived from thioacetal 287. However, a complex mixture was obtained after the Takeda reaction, washing of the resin, and subjecting to standard acid conditions for cleavage from the resin. We concluded that the reaction was not very successful as the $^1$H NMR spectrum confirmed that this mixture contained mostly dihydrocinnamic acid and triethyl phosphite with some other impurities. The presence of ketone 291, or the corresponding boronic acid, in this mixture cannot be ruled out, but the mass recovery for the reaction was very low.

![Scheme 101](image)

The failure of thioacetals 287 and 288 in the above Takeda reactions may not be surprising as the Takeda procedure is not particularly useful for methylenation (see section 2.2). Boronates 287 and 288 may suffer similar problems to methylene thioacetals in either the formation or the reactivity of the resulting titanium carbene. Therefore, we attempted to synthesise the corresponding thioacetals with a substituent $\alpha$ to the boron atom.
7.2 Lithiation/Alkylation of thioacetals

7.2.1 Generation and reactivity of bis(phenylthio)phenylmethyllithium

Initially, we attempted to synthesise boronate 292 from thioacetal 285 (Scheme 102), following Mendoza and Mattesson’s procedure, as above. We hoped that benzylic thioacetal 292 would be more susceptible to reduction to give a titanium alkylidene, and so would allow the synthesis of α-phenyl-β-hetero-vinylboronates 293 (Scheme 102).

\[
\begin{align*}
\text{PhS} \quad & \text{Ph} \\
\text{PhS} \quad & \text{Ph} \\
\text{285} & \\
\text{i. } \text{^7BuLi, THF} & \rightarrow \quad \text{PhS} \quad & \text{PhS} \quad & \text{Ph} \\
\text{ii. } \text{B(OMe)}_3 & \rightarrow \quad \text{PhS} \quad & \text{B} \quad & \text{O} \\
\text{iii. } 2\text{M HCl} & \quad \rightarrow \quad \text{PhS} \quad & \text{PhS} \quad & \text{Ph} \\
\text{iv. pinacol} & \quad \rightarrow \quad \text{PhS} \quad & \text{PhS} \quad & \text{Ph} \\
\end{align*}
\]

Scheme 102

In order to synthesise boronic ester 292, we needed to generate bis(phenylthio)phenylmethyllithium, and then react it with a boron electrophile (Scheme 103).

\[
\begin{align*}
\text{PhS} \quad & \text{Ph} \\
\text{PhS} \quad & \text{Ph} \\
\text{285} & \\
\text{i. Base, THF} & \rightarrow \quad \text{PhS} \quad & \text{PhS} \quad & \text{Ph} \\
\text{ii. E} & \rightarrow \quad \text{PhS} \quad & \text{PhS} \quad & \text{Ph} \\
\end{align*}
\]

Scheme 103

Following Mendoza and Mattesson’s procedure (Method A, Table 1), we found that considerable carbon-sulfur bond cleavage occurred, confirmed by the detection of 1-(phenylthio)phenylmethane and 1-(phenylthio)butane in the crude \( ^1 \text{H} \) NMR spectrum (see experimental). Starting material (SM) was always isolated and an almost identical result was obtained with the use of \( N, N, N', N' \)-tetramethylethylenediamine (TMEDA)-butyllithium complex under similar conditions (Method B). Using the less nucleophilic base, lithium di-isopropylamide [(LDA), Method C], only starting material was recovered. Employing LDA but quenching with \( \text{D}_2\text{O} \) gave 40% conversion to the deuterated product (Method D). Slight variations of temperature and reaction times gave similar results. Finally, the generation of the more “naked” potassium ion, by means of the “superbasic Schlosser’s base” (Method E) also proved unsuccessful.
<table>
<thead>
<tr>
<th>METHOD</th>
<th>BASE</th>
<th>ELECTROPHILE (E)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>n-BuLi</td>
<td>B(OMe)₃</td>
<td>SM + C-S cleavage (38%)</td>
</tr>
<tr>
<td>B</td>
<td>n-BuLi-TMEDA</td>
<td>B(OMe)₃</td>
<td>SM + C-S cleavage (40%)</td>
</tr>
<tr>
<td>C</td>
<td>LDA</td>
<td>B(OMe)₃</td>
<td>SM</td>
</tr>
<tr>
<td>D</td>
<td>LDA</td>
<td>D₂O</td>
<td>40% conversion</td>
</tr>
<tr>
<td>E</td>
<td>KO'Bu- n-BuLi</td>
<td>B(OMe)₃</td>
<td>SM</td>
</tr>
</tbody>
</table>

Deprotonation and alkylation of diphenyldithioacetals is difficult. This is particularly the case for bis(phenylthio)phenylmethane 285 due to steric hindrance and the presence of the extra anion stabilising phenyl group.²⁰⁶,²⁰⁸ Lithiation generally results in a yellow/orange anion which reacts with benzoyl chloride but not aldehydes and ketones.²⁰⁶ Attack of butyl anion on a sulfur atom in thioacetal 285 to yield anion 294 could explain the formation of both the observed side products (Scheme 104).

\[
\begin{align*}
\text{Bu} & \quad \text{PhS} & \quad \text{PhS} \\
285 & \quad \text{Ph} & \quad \text{PhS} \\
\text{Bu} & \quad \text{PhS} & \quad \text{PhS} \\
\text{BuSPh} & + & \quad \text{PhS} & \quad \text{Ph} \\
\text{quench} & & & \quad \text{PhS} & \quad \text{Ph} \\
\end{align*}
\]

Scheme 104

Interestingly, a recent report by Yu and Jin²⁰⁹ stated that a 1,1-bis(phenylthio)alkylpotassium undergoes rearrangement when it is treated with alkyl halides, but the anion reacts in high yield with D₂O. They propose that elimination of phenylthiolate to form a carbene is accelerated by addition of certain electrophiles.²⁰⁹ In the case of bis(phenylthio)phenylmethylthium 295, elimination of phenylthiolate could form carbene 296, which could further react and/or be quenched in the work-up (Scheme 105). This suggests that the problems could arise both in the preparation of the carbanion, and in reacting the carbanion with electrophiles (E).

\[
\begin{align*}
\text{PhS} & \quad \text{Ph} & \quad \text{PhS} \\
295 & \quad \text{Li} & \quad \text{PhS} \\
\text{quench} & & & \quad \text{PhS} & \quad \text{Ph} \\
\text{Decomposition Products} \\
\end{align*}
\]

Scheme 105
7.2.2 Generation and reactivity of 2-Lithio-2-phenyl-1,3-dithiane

We reasoned that dithianes would be less susceptible to nucleophilic attack at sulfur. Therefore, 2-phenyl-1,3-dithiane 297 was synthesized from benzaldehyde as before, and then I attempted to generate 2-lithio-2-phenyl-1,3-dithiane and react it, initially with boron electrophiles, and later with a range of other electrophiles to probe the reactivity of the lithium salt (Scheme 106).

![Scheme 106](image)

Lithiation of 2-phenyl-1,3-dithiane 297 by a standard procedure (see experimental), and quenching with trimethylborate (Method A, Table 2) gave considerable amounts of starting material and approximately 40% conversion to an unknown undesired product(s). Quenching with D₂O (Method B, Table 2) gave similar results, but quenching with benzaldehyde (Method C, Table 2) gave complete conversion to benzoin thioacetal 298 [(Figure 14), see experimental]. The use of LDA (Method D, Table 2) and Schlosser’s base²⁰⁷ (Method E, Table 2) were also unsuccessful. Replacing trimethylborate with the more reactive boron trichloride, by adding a solution of the anion in THF via cannula to the boron trichloride solution, gave a mixture of starting material and considerably more of the unknown by-product(s) (Method F, Table 2).

**Table 2**

<table>
<thead>
<tr>
<th>METHOD</th>
<th>BASE</th>
<th>ELECTROPHILE (E)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>n-BuLi</td>
<td>B(OMe)₃</td>
<td>SM + side product(s) (40%)</td>
</tr>
<tr>
<td>B</td>
<td>n-BuLi</td>
<td>D₂O</td>
<td>SM + side product(s) (50%)</td>
</tr>
<tr>
<td>C</td>
<td>n-BuLi</td>
<td>Benzaldehyde</td>
<td>complete conversion</td>
</tr>
<tr>
<td>D</td>
<td>LDA</td>
<td>D₂O</td>
<td>SM</td>
</tr>
<tr>
<td>E</td>
<td>KO⁻Bu n-BuLi</td>
<td>B(OMe)₃</td>
<td>SM</td>
</tr>
<tr>
<td>F</td>
<td>n-BuLi</td>
<td>BCl₃, DCM</td>
<td>SM + side product(s) (75%)</td>
</tr>
</tbody>
</table>

![Figure 14](image)
Lithiation and alkylation of dithianes is common, but in the case of 2-phenyl-1,3-dithiane 297, the phenyl group stabilises the anion and so reduces its reactivity. Lithiation and alkylation of dithiane 297 has been reported and the generation of a carbanion and successful reaction with benzaldehyde is consistent with this. The failure to react with D$_2$O remains unexplained (quenching with MeOD may have given better results). The formation of undesired by-products in some runs, may occur by attack of a butyl anion at sulfur, and/or by generation and reaction of a carbene (as for thioacetal 285, scheme 105). However, the lack of self-consistency in Table 2 makes any explanation tentative.

7.2.3 Generation and reactivity of 2-Lithio-2-(1-styryl)-1,3-dithiane

Allylic thioacetals would be expected to be easily reduced by low-valent titanium complex 74 to give titanium allylidenes. Therefore, 2-(1-styryl)-1,3-dithiane$^{212}$ 299 was synthesised from cinnamaldehyde according to the literature procedure (Scheme 107). I then attempted to generate of 2-lithio-2-(1-styryl)-1,3-dithiane and react it with a range of electrophiles, including boronates, to probe the reactivity of the lithium salt (Scheme 107).

Scheme 107

Although the lithiated adduct of thioacetal 299 can react α or γ to the sulfur atoms, hard electrophiles react at the α-position. Consequently, we expected boron electrophiles to react at the α-position. Lithiation under the standard conditions (see experimental) gave the dark orange anion. Although deuteration (Method A, Table 3) was successful giving a mixture of 2-deutero-2-(1-styryl)-1,3-dithiane 300 (Figure 15) and SM 299 (80% conversion by $^1$H NMR spectroscopy, see experimental), the anion failed to react in the desired way with any boron electrophiles (Methods B, C and D Table 3). Indeed, employing B(OiPr)$_3$ led to a significant amount of side product(s), but the $^1$H NMR spectrum was complex and difficult to interpret.

Table 3

<table>
<thead>
<tr>
<th>METHOD</th>
<th>BASE</th>
<th>ELECTROPHILE (E)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>n-BuLi</td>
<td>D$_2$O</td>
<td>80% conversion</td>
</tr>
<tr>
<td>B</td>
<td>n-BuLi</td>
<td>B(OiPr)$_3$</td>
<td>SM + side product(s) (25%)</td>
</tr>
<tr>
<td>C</td>
<td>n-BuLi</td>
<td>B(OMe)$_3$</td>
<td>SM</td>
</tr>
<tr>
<td>D</td>
<td>KO$i^+$Bu- n-BuLi</td>
<td>B(OMe)$_3$</td>
<td>SM</td>
</tr>
</tbody>
</table>
The formation of undesired by-products may be due to the carbene formation as proposed for thioacetals 285 and 297.

Conclusions

It would appear that thioacetals 287 and 288 are not sufficiently reactive under Takeda reaction conditions. Moreover, 2-lithium salts of thioacetals 285, 297 and 299 seem difficult to generate, are unreactive with boron electrophiles, and are prone to decomposition. The employment of thioacetals with a simple alkyl group may allow the generation of suitably reactive carbanions, which would then react with boronates. However, due to the difficulties we had in preparing suitable substrates for novel Takeda reactions, we decided that this route to vinylboronates was not general enough to merit more time being invested on it.
Chapter 8 – Synthesis of N-Boc Indoles

8.1 Background

As discussed in section 1.1, recent work within the group has seen the development of a novel benzo[b]furan synthesis on solid phase. Thioacetals 301, containing an ortho-protected phenol, alkylidenate Wang-resin-bound esters 302 (Scheme 108) under Takeda conditions as discussed in section 2.2. The resulting resin-bound enol ethers 303 can be cleaved from the resin to give ketones 304. Alternatively, removal of the TBS protecting group followed by cleavage from the resin, allows concomitant cyclisation to give the 2-substituted benzo[b]furans 305. The resin was contained in IRORI macroKans, which can be described as porous polypropylene, tubular, reactor vessels.

Scheme 108

As discussed in Section 1.1, we aimed to extend this methodology to the synthesis of nitrogen-containing heterocycles, and in particular to indoles. Thioacetals 306, with a suitably protected ortho-aniline moiety should be prepared from readily available precursors. The titanium alkylidenes of thioacetals 306 should alkylidenate resin-bound esters 302 yielding enol ethers 307 (Scheme 109). The protecting group should be easily formed, stable to the reaction conditions, preferably acid labile, and by-products formed upon its removal should be volatile. Should these requirements be met, then cleavage from the resin and concomitant cyclisation should allow isolation of the indole in high purity upon solvent removal.

Scheme 109
8.2 Synthesis of resin-bound esters

Esters were formed on Wang and Merrifield resins using standard methods. The difference in reactivity of these two resins under acid conditions has been discussed earlier (see section 4.2.2).

The formation of Wang resin-bound ester 290 was achieved by reacting Wang resin (swollen) in THF with dihydrocinammic acid employing 1,3-diisopropylcarbodiimide (DIC) as coupling agent with a catalytic amount of 4-dimethylaminopyridine (DMAP) (Scheme 110). DIC was employed instead of the more commonly used 1,3-dicyclohexylcarbodiimide (DCC) due to the greater solubility of its by-product in organic solvents.

![Scheme 110](image)

Treating Merrifield resin (swollen) in DMF with 5 eq. of caesium carboxylates 308 at 60-70 °C yielded Merrifield resin-bound esters 309 (Scheme 111). The caesium salt has a larger cation than the equivalent lithium or sodium salt. This results in a greater dissociation between the ion pair, particularly when using a polar solvent such as DMF. The resulting naked carboxylate anions give a higher rate of ester formation than that achieved with other metal counterions.²¹⁵

![Scheme 111](image)

For both Merrifield and Wang resin-bound esters, IRORI macroKans were employed (see Section 4.3) with 3-12 kans used per reaction.
8.3 Initial Studies

8.3.1 Use of 2-Aminophenones

As 2-aminophenones are readily available, we envisioned that thioacetalization, followed by base stable (STABASE) or silyloxyethoxy methyl (SEM) amine protection, would provide us with suitable substrates for Takeda alkyldenation. Both SEM and STABASE protecting groups can be removed in mild acid conditions, and are standard amine protecting groups.216

Initially, we formed thioacetal 310 from 2-aminoacetophenone, but purification by chromatography led to decomposition of the thioacetal to give the 2-aminoacetophenone (the \( ^1 \)H NMR spectrum showed identical signals to that of a spectrum of 2-aminoacetophenone) and 1,3-propanedithiol (Scheme 112). Crystallisation was also unsuccessful. However, thioacetal 311 was synthesised in good yield (Scheme 112). Attempts to protect aniline 311 as the SEM 312 and STABASE 313 analogues were unsuccessful (Scheme 112). In the case of SEM, the use of \( \text{K}_2\text{CO}_3 \) as base, only yielded a complex mixture of compounds that was uninterpretable by \( ^1 \)H NMR spectroscopy although considerable amounts of starting material 311 and SEMCI could be identified. Adaptation of a literature procedure employing \( \text{NaH} \) as base,217, 218 gave similar results. The attempted STABASE procedure\(^ {219} \) gave mixtures that contained mostly unreacted starting material (from the \( ^1 \)H NMR spectrum), but TLC analysis confirmed the presence of at least four products.

\[
\begin{align*}
\text{ Benzaldoxime} & \quad \text{BF}_3\cdot\text{OEt}_2, \quad \text{PhMe-AcOH} \\
& \quad \text{i. n-BuLi, THF} \\
& \quad \text{ii. SEMCI, DMF} \\
\text{311} & \quad \text{i. \text{K}_2\text{CO}_3 \text{ or NaH} } \\
& \quad \text{ii. SEMCI, DMF} \\
\text{312} & \quad \text{313}
\end{align*}
\]

Scheme 112

Although a common protecting group for \( N \)-heterocycles, SEM is rarely used for anilines. Both the SEM and STABASE protections may well have suffered from severe steric hindrance caused by the bulky substituent ortho to the amino group.
As dithianes are easier to prepare from 2-aminobenzophenones than the corresponding, bis(phenylthio) thioketals, we decided to test the reactivity of dithianes 314 and 315 under Takeda conditions (Scheme 113). Employing thioacetal 314 would help establish optimum conditions for desulfurising dithianes, and the use of thioketal 315 would determine if 3-substituted heterocycles could be accessed by this methodology. Thioacetal 314 was prepared by a literature procedure, and thioketal 315 was prepared by adapting Barton's procedure, and then both were protected as tert-butyldimethylsilyl ethers (Scheme 113). Thioacetal 316, under Takeda conditions, converted Wang resin-bound ester 290 into the corresponding enol ether 317. Cleavage from the resin then generated the ketone 318 in good yield and high purity. Thioacetal 319, under the same standard conditions, gave only hydrocinamic acid with minute quantities of another compound that may have been the desired ketone 320, observed by \(^1\)H NMR spectroscopy.

![Scheme 113](image-url)

These results confirmed that dithianes could be employed. However, benzylic thioketals fail to generate effective alkylidenating reagents under Takeda conditions, in agreement with Takeda's reports (see section 2.2).
8.3.2 Introduction of Formyl group ortho to a protected aniline

Our next approach was to introduce the ortho-aldehyde moiety in the presence of a protected aniline. The aldehyde could then be converted into a thioacetal. It was important to demonstrate that a protected aniline ortho to the thioacetal could survive the Takeda reaction conditions, allowing both formation and reaction of the titanium alkylidene.

2-Bromo-\(N,N\)-dibenzylaniline 321 was prepared (Scheme 114), in the hope of inducing lithium-halogen exchange and quenching the resulting anion with \(N,N\)-dimethylformamide (DMF). Although anion 322 presumably was formed employing \(n\)-BuLi, intramolecular deprotonation then occurred, yielding a more stable benzylic anion 323, which then reacted with butyl bromide to give aniline 324. Indeed, the reaction would require an extra equivalent of \(n\)-BuLi to prevent butylation but formylation would presumably still occur at the benzylic position.

\[
\begin{align*}
\text{Br} & \quad \text{N} \quad \text{Br} \\
\text{Br} & \quad \text{N} \quad \text{Br} \\
N(Bn)_2 & \quad N(Bn)_2 \\
\end{align*}
\]

Scheme 114

Next we hoped to carry out a Vilsmeier-Haack reaction\(^\text{221}\) on \(N,N\)-dibenzyl-p-toluidine 325, readily prepared from \(p\)-toluidine (Scheme 115), using the methyl moiety as a blocking group. However, the main products observed in the crude \(^1\text{H}\) NMR spectrum were 2,4-dimethylaniline [2.21 ppm (3H, s, \(\text{CH}_3\)), 2.23 ppm (3H, s, \(\text{CH}_3\)), 3.47 ppm (2H, s, \(\text{NH}_2\))] and considerable amounts of benzaldehyde [10.0 ppm (1H, s, \(\text{CHO}\))].

\[
\begin{align*}
\text{NH}_2 & \quad \text{BnBr, NMP} \\
\text{NH}_2 & \quad \text{BnBr, NMP} \\
N(Bn)_2 & \quad N(Bn)_2 \\
\end{align*}
\]

Scheme 115
Finally, we carried out the Vilsmeier-Haack reaction\textsuperscript{221} on \(N,N\)-dimethyl-p-toluidine which gave aldehyde 326 in moderate yield after chromatography (Scheme 116). Thioacetal 327 was prepared from aldehyde 326 in moderate yield after chromatography, and then subjected to the standard solid phase Takeda reaction sequence, employing Merrifield resin-bound ester 309a'. To our satisfaction ketone 328 was obtained in moderate yield and very high purity. Although the \(N,N\)-dimethyl moiety did not allow deprotection to give the aniline and so consequent cyclisation to the indole, its use confirmed that a protected aniline \textit{ortho} to the thioacetal could survive the Takeda reaction.

\[
\begin{array}{c}
\text{POCl}_3, \text{DMF} \quad 80 \, ^\circ\text{C} \\
\text{O} \quad \text{NMe}_2 \quad \text{326} \, 58\% \\
\text{i. Cp}_2\text{Ti}[[\text{P(OEt)}_3]_2] \quad 74 \\
\text{4 eq.} \\
\text{ii. O} \quad \text{O} \quad \text{Ph} \\
\text{0.2 eq. 309a'} \\
\end{array}
\]

\[
\begin{array}{c}
\text{HS} \quad \text{SH} \quad \text{BF}_3\text{-OEt}_2, \quad \text{327} \, 58\% \\
\text{1% TFA/DCM} \\
\text{328} \, 53\% \\
\text{(Yield from 309a')} \\
\end{array}
\]

Scheme 116
8.4 Use of 2-Nitrobenzaldehydes

We then planned to investigate routes to suitable thioacetals from 2-nitrobenzaldehydes, as 2-aminobenzaldehydes self-condense. 2-Nitrobenzaldehyde was converted into thioacetals 329 and 330 (Scheme 117). Thioacetal 330 was then reduced with sodium borohydride and Pd/C$^{222}$ to give aniline 331. The reduction of nitro compound 329 was unsuccessful, as elimination of the thioacetal occurred yielding 2-nitrobenzaldehyde (aldehyde singlet at 9.10 ppm observed in the crude $^1$H NMR spectrum), amongst a complex mixture of other compounds. SEM protection of aniline 331, employing $n$-butyllithium as base, yielded a complex mixture of compounds with considerable amounts of starting material 331 and SEMCl still present in the $^1$H NMR spectrum (Scheme 117).

![Scheme 117](image)

Thioacetals 330 and 331 were subjected to the standard solid-phase Takeda reaction sequence (Scheme 118). We hoped that the titanium complex 74, would reduce both the nitro and thioacetal moieties in thioacetal 330, and allow alkylidenation of Wang resin-bound ester 290. However, after subjecting the resin to the standard cleavage conditions, only hydrocinnamic acid and cyclopentadienyl titanium by-products (singlets at 6.49 ppm) were observed in the $^1$H NMR spectrum. Similarly, thioacetal 331 failed to form an effective alkylidenating reagent, as there was no evidence of indole 332 observed in the crude $^1$H NMR spectrum after reacting with Merrifield resin-bound ester 309a'.

![Scheme 118](image)
Due to the difficulties we had in protecting aniline 331 we decided to employ Boc protection. Despite containing a carbonyl moiety we hoped that the electron-rich nature of the carbamate carbonyl, combined with steric hindrance from the tert-butyl group, would render the carbonyl group(s) inert to alkylidenation.

Aniline 331 was synthesised as before (Scheme 117) but on scale up, azoxy dimer 333 was also formed, which we isolated by chromatography and recrystallisation (Scheme 119). A crystal structure of dimer 333 was obtained (appendix 2). Diazine-N-oxides are common intermediates/by-products in nitro reductions.\textsuperscript{223} It should be noted than when dimer 333 was re-exposed to the reduction conditions, aniline 331 was not isolated. Aniline 331 was converted into imide 334 with 2.2 eq. Boc anhydride and sodium hexamethyldisilazide (NaHMDS) as base, and also to carbamate 335a by heating with 1.1 eq. Boc anhydride in THF (Scheme 119).

\begin{equation}
\begin{array}{c}
\text{NaBH}_4 \quad \text{Pd/C} \\
\text{THF} \\
\downarrow \\
\text{329} \\
\end{array} \quad \downarrow \quad \downarrow \quad \downarrow \\
\begin{array}{c}
\text{331} \\
\text{2.2 eq. NaHMDS} \\
\text{2.2 eq. (Boc)$_2$O} \\
\text{THF, reflux} \\
\end{array} \quad \downarrow \quad \downarrow \\
\begin{array}{c}
\text{334 78\%} \\
\text{335a 86\%} \\
\end{array}
\end{equation}

\textbf{Scheme 119}

Thioacetals 334 and 335a were both, in turn, subjected to the standard solid-phase Takeda reaction sequence employing Merifield resin-bound ester 309a'. When employing imide 334 there was little evidence of indole 336aa' (in the $^1$H NMR spectrum) upon subjecting the resin to the standard cleavage conditions (Scheme 120). It was concluded that failure was due to intramolecular nucleophilic attack on one of the imide carbonyls.

\begin{equation}
\begin{array}{c}
\text{i. Cp}_2\text{Ti[P(OEt)$_3$]}_2 \quad 74 \\
\text{4 eq.} \\
\downarrow \\
\text{334} \\
\end{array} \quad \downarrow \quad \downarrow \\
\begin{array}{c}
\text{309a'} \\
\text{1\% TFA/DCM} \\
\end{array} \\
\end{equation}

\textbf{Scheme 120}
When employing carbamate 335a, although the mass recovery of crude material was low (13%), indole 336aa' was obtained in poor yield after column chromatography (Scheme 121). The low yield is probably the result of intramolecular deprotonation of the carbamate N-H by benzylic titanium intermediates.

![Scheme 121](image)

When imide 334 was treated with 2.7 eq. of low-valent titanium complex 74 and then quenched in 2 mol dm$^{-3}$ HCl, toluidines 337 and 338 were isolated along with thiol 339 (Scheme 122). These were present in a 1:1:9 ratio in the $^1$H NMR spectrum of the crude mixture, but mass recovery was poor. Toluidine 337 was presumably formed by quenching the resultant titanium alkylidene derived from thioacetal 334. Toluidine 338 could have been formed in the same way with Boc deprotection occurring during the acid quench.

![Scheme 122](image)

Thiol 339 was difficult to isolate and on silica gel, appeared to oxidise to the corresponding disulfide, which was not isolated. The formation of thiol 339, could be explained by titanium insertion into one C-S bond, followed by acyl migration to the benzylic position, and subsequent quench in acid (Scheme 123). The imide nitrogen lone pair in intermediate 340 is cross-conjugated, making the carbonyls more electrophilic than simple carbamates and hence susceptible to intramolecular nucleophilic attack by the organotitanium moiety in 340. Furthermore, the crystal structure$^{214}$ of imide 334 (Figure 16) suggests that one of the carbonyl moieties in intermediate 340 would be in an ideal orientation to undergo nucleophilic attack. Titanium-mediated intramolecular nucleophilic acyl substitution reactions have been used to synthesise cyclopropanols, lactones and other cyclic compounds.$^{225}$ Related zirconium-mediated acyl migrations from carbamate groups have been employed recently in the synthesis of $\gamma$-aminobutyric acid derivatives.$^{226}$
When carbamate 335a was treated with 2.7 eq. of low-valent titanium complex 74 under similar conditions, toluidine 338 and thiol 341 were formed in the ratio shown (Scheme 124). Insertion of titanium into one C-S bond [as for imide 334 (Scheme 123)], followed by intramolecular deprotonation of the carbamate N-H and subsequent quench in acid, could explain the formation of thiol 341. The nitrogen anion would be stabilised by conjugation with both the carbonyl group and the aromatic ring. Furthermore, in the crystal structure of carbamate 335a (Figure 17) the N-H bond is orientated towards the benzylic carbon atom. A conformation with the N-H and N-Boc bonds coplanar with the aromatic ring must be energetically accessible in solution, as C4 and C6 of the dithiane are equivalent in the $^{13}$C NMR spectrum.
We hoped that a salt generated by deprotonating carbamate 335a, would be stable to the formation of the titanium carbene, and would allow complete reaction with the resin-bound ester. However, we encountered severe solubility problems in THF, when trying to form the sodium (NaHMDS) and lithium (LDA) salts of carbamate 335a (see section 9.1).

8.5 Use of N-TMS-N-Boc Protection in N-Boc indole synthesis

The use of an N-silylated N-Boc species as protecting group has only recently been reported by Voyer, although it was not employed for the protection of anilines. However, N-silylation followed by thermolysis is a well-established method of generating isocyanates.

In order to prevent intramolecular proton-transfer under Takeda conditions, carbamate 335a was deprotonated and silylated to give N-silylated species 342a in high yield (Scheme 125). Due to the insoluble nature of salts derived from carbamate 335a, we used an in situ quench by adding LDA to a mixture of the carbamate and TMSCl in THF. N-silylated carbamate 342a is unstable, mostly decomposing to carbamate 335a, when stored under argon overnight. This made full characterisation difficult. However, the $^{13}$C NMR spectrum (at 52 C to allow rapid equilibration of the carbamate geometrical isomers) of N-silylated carbamate 342a was obtained. As expected, C4 and C6 of the dithiane ring were found to be non-equivalent showing that rotation about the aryl-nitrogen bond is slow on an NMR timescale. N-silylated carbamate 342a was then subjected to our standard solid-phase reaction sequence employing resin-bound ester 309a' (Scheme 125). Resin-wash with solvents including methanol, presumably ensures N-desilylation to yield enol ether 343, which when treated with 1% TFA, gave N-Boc indole 336aa' in good yield and high purity after removal of the solvent (see appendix 1 for $^1$H NMR spectra).

\[
\begin{align*}
\text{(Scheme 125)} \\
\text{335a} & \xrightarrow{i. \text{TMSCl, THF}} \text{342a} \quad \text{86\%} \\
& \xrightarrow{ii. \text{LDA, THF-hex, -78°C to rt}} \text{342a} \\
& \xrightarrow{iii. \text{wash resin}} \text{336aa'} \quad \text{69\%} \\
\end{align*}
\]
It should be noted that this is the first reported example of a carbonyl moiety surviving within a titanium alkylidene reagent.\textsuperscript{15}

With this result in hand we set about preparing a range of thioacetal substrates to further examine the functional group tolerance of the Takeda alkylidenation. Readily available 2-nitrobenzaldehydes 344 were converted into thioacetals 329a-d (Scheme 126). An improved procedure for the reduction of nitro groups, employing iron/ammonium chloride\textsuperscript{229} as reducing agent, prohibited the formation of diazine-N-oxides and yielded anilines 331a-d. Boc protection as before\textsuperscript{230} yielded carbamates 335, except in the case of the unstable electron-rich aniline 331c, which always gave a mixture of mono- and di-protected anilines. Consequently, nitro compound 329c was reduced, converted to the corresponding imide, and mono-deprotected\textsuperscript{231} without purifying the intermediates. Phenol 335d was converted into TMS ether 335e employing TMSCl in pyridine. N-Silylation of carbamates 335a-c and 335e as above, gave unstable N-silylated carbamates 342a-c and 342e.

\begin{align*}
\text{R} & \text{H} \\
\text{334} & \text{HS} \quad \text{SH} \\
& \text{BF}_3 \cdot \text{OEt}_2 \\
& \text{PhMe} \\
\rightarrow \quad \text{Fe-NH}_4 \text{Cl} \\
& \text{EtOH-H}_2 \text{O} \\
\rightarrow \quad \text{NH}_2 \\
\text{329a-d} & \text{77-86\%} \\
\text{331a-d} & \text{71-87\%}
\end{align*}

Scheme 126

\(N\)-silylated carbamates 342a-c and 342e were then subjected to our standard solid-phase reaction sequence employing resin-bound esters 309 (Scheme 127). Upon washing the resin and resin-cleavage, \(N\)-Boc indoles 336 were obtained in good yield and high purity, with the exception of the \(N\)-Boc-7-methoxyindoles 336b. \(N\)-Boc-7-methoxyindole 336ba' was contaminated with trace amounts of the deprotected indole, and \(N\)-Boc-7-methoxyindoles 336bb' and 336bc' underwent significant spontaneous Boc deprotection under the resin-cleavage conditions, and so were fully deprotected\textsuperscript{232} by treating with 20%
TFA in dichloromethane for 1 h. N-H indoles 332ba' and 332bb' were isolated in high purity (appendix 1) following solvent removal, but the deprotection conditions led to substantial decomposition in the case of 2-methylindole 332bc'. It should also be noted that indoles 336d were fully O-TMS deprotected under the resin-cleavage conditions.

Scheme 127

The yields obtained for N-Boc indoles and N-H indoles are based on the loading of the Merrifield resin used to prepare Merrifield resin-bound esters 309 (yields, Figure 18).

Later, we investigated using fewer equivalents of the titanium carbene, and found that 3 equivalents of thioacetal 342a converted resin-bound ester 309a' into indole 336aa' without significant loss of yield (Scheme 128) under the standard reaction sequence.

Scheme 128
8.6 Deprotection of N-Boc indoles

Next we attempted the deprotection of N-Boc indoles prepared above. Initially, we followed the procedure used for indoles 332b employing TFA in DCM\(^{232}\) and found in some cases significant indole decomposition/oxidation occurred. Indoles 336ab', 336ea' and 336ee' gave pure products 332ab', 332ea' and 332ec', with or without column chromatography (Scheme 129). However, in the deprotection of 336aa', 336ac' and 336eb' complex mixtures of products were obtained, with the crude \(^1\)H NMR spectra being difficult to interpret (Scheme 129). Due to the small scale of these reactions, further purification of such impure indoles was not attempted.

Indoles 332da' and 332dc' were each dissolved in d-4 MeOH in an attempt to obtain their \(^{13}\)C NMR spectra. Indole 332dc' underwent complete conversion in the NMR tube to indole 345dc' within 20 mins (Scheme 130). This was confirmed by the disappearance of the relevant proton signals [\(\delta 4.44 (1\text{H}, \text{s, OH}), 6.10 (1\text{H}, \text{s, H-3}), 7.72 (1\text{H}, \text{s, NH})\)] of indole 332dc' in the \(^1\)H NMR spectrum. Indole 332da', after 2 h in d-4 MeOH, underwent partial deuteration at the 3-position as confirmed by the disappearance of the signal [\(\delta 6.16 (1\text{H, d, J} 1.4, \text{H-3})\)] in the \(^1\)H NMR spectrum (Scheme 130). However, even, after heating in d-4 MeOH or allowing the sample to stand for two months, complete deuteration at this position was not observed, and so full characterisation of indole 345da' was not possible.
Next, we attempted the nucleophilic deprotection of N-Boc indole 336cb', employing NaOMe in MeOH (Scheme 131). However, after work-up of the reaction, only unreacted starting material was recovered.

![Scheme 131](image)

We then attempted a literature procedure for N-Boc deprotection, employing TBAF and heating under reflux in THF. N-Boc indole 336cb' was converted into indole 332cb' (Scheme 132), purified by tritration from chloroform, and a $^1$H NMR spectrum was obtained. However, in an attempt to acquire a $^{13}$C NMR spectrum in CDCl$_3$, significant decomposition to an unknown compound was observed and so full characterisation of the highly electron-rich indole 332cb' was not possible. These results confirm how reactive 2-substituted indoles are at the 3-position, particularly when they are electron-rich.

![Scheme 132](image)

The authors report two possible mechanisms for the TBAF deprotection. Fluoride could act as a nucleophile, attacking the carbamate carbonyl, eliminating the amine as a leaving group (Mechanism A, Figure 19). Alternatively, E2 elimination could eliminate the amine as shown (Mechanism B, Figure 19). In both cases, CO$_2$ would be produced, and the HF formed would be neutralised by the released amine.

![Figure 19](image)
8.7 Use of chloro-substituted thioacetals

We felt it was important to investigate the stability of an aryl halide bond within the titanium alkylidene reagent. 5-Chloro-2-nitrobenzaldehyde 334f is commercially available but is contaminated with 15% of the 4-chloro isomer. The mixture was converted into the corresponding thioacetals and after recrystallisation gave thioacetal 329f contaminated with 7% of the 4-chloro isomer (Scheme 133). Nitro reduction as above, yielded pure aniline 331f after two recrystallisations. Boc protection as before gave carbamate 335f, and this was followed by N-silylation to yield N-silylated carbamate 342f.

\[ \text{Cl} - \text{C} = \text{N} - \text{NO}_2 \quad 334f \quad 85\% \text{ this isomer} \]

\[ \text{HS} - \overset{\text{BF}_3\overset{\text{OEt}_2}{\text{S}}}{} \quad \text{Cl} - \text{C} = \text{N} - \text{NO}_2 \quad 329f \quad 77\% \text{ reflux} \]

\[ \text{Fe} - \text{NH}_4\text{Cl} \quad \text{EtOH-H}_2\text{O} \quad \text{reflux} \quad \text{NH}_2 \quad 331f \quad 51\% \]

\[ \text{Cl} - \text{C} = \text{N} - \text{HBOc} \quad 335f \quad 89\% \]

\[ \text{Cl} - \text{C} = \text{N} - \text{CH}_2\text{SiMe}_3\text{OBu}^f \quad 342f \quad 88\% \]

Scheme 133

N-silylated carbamate 342f was subjected to our standard solid-phase reaction sequence employing resin-bound esters 309a-c (Scheme 134). In each case, following cleavage from the resin, a 2:1 mixture of indoles 336a and 336f were obtained in poor yield. Presumably this is the result of titanium insertion into the C-Cl bond under the conditions used to generate the titanium alkylidene.

\[ \text{Cl} - \text{C} = \text{N} - \text{CH}_2\text{SiMe}_3\text{OBu}^f \quad 342f \]

\[ \text{Cp}_2\text{Ti[P(OEt)]}_2 \text{Cl}_2 \quad 74 \quad 4 \text{ eq.} \]

\[ \text{O} \quad R^2 \quad \text{Boc} \quad \text{R} = (\text{CH}_2)_2\text{Ph}, 21\% 336aa' : 336fa' (2:1) \]

\[ \text{O} \quad R^2 \quad \text{Boc} \quad \text{R} = \text{Ph}, 14\% 336ab' : 336fb' (2:1) \]

\[ \text{O} \quad R^2 \quad \text{Boc} \quad \text{R} = \text{CH}_3, 14\% 336ac' : 336fc' (2:1) \]

Scheme 134
Further attempts to generate an alkylidenating reagent from thioacetal 342f (Scheme 135), without affecting the aryl chloride moiety by employing fewer equivalents of low-valent titanium complex 74 were relatively unsuccessful (Table 4). The use of 2 equivalents of low-valent titanium complex 74 did prevent C-Cl reduction but gave indole 336fa' in only 14% yield. Reverse addition (Table 4), i.e. adding a THF solution of low-valent titanium complex 74 to thioacetal 342f in an attempt to keep the thioacetal in excess, also proved unsuccessful.

Thus, it can be concluded that there is poor chemoselectivity for the Takeda reduction of a benzylic thioacetal in the presence of an aryl chloride.

Scheme 135

Table 4

<table>
<thead>
<tr>
<th>74(A) &amp; 342f(B) order of add.</th>
<th>equivalents of 74 (x)</th>
<th>ratio of a: f obtained</th>
<th>yield of 336aa' &amp; 336fa'</th>
</tr>
</thead>
<tbody>
<tr>
<td>B added to A</td>
<td>4</td>
<td>1: 2</td>
<td>21%</td>
</tr>
<tr>
<td>A added to B</td>
<td>4</td>
<td>1: 3</td>
<td>12%</td>
</tr>
<tr>
<td>B added to A</td>
<td>3</td>
<td>7: 1</td>
<td>16%</td>
</tr>
<tr>
<td>B added to A</td>
<td>2</td>
<td>1: 0</td>
<td>14%</td>
</tr>
</tbody>
</table>
Chapter 9 – Synthesis of N-Alkyl Indoles

9.1 Use of N-alkyl-N-Boc carbamates

Next, we aimed to test if the N-alkyl-N-Boc moiety survived the Takeda reaction conditions, and if so, utilise this amine protection in the synthesis of N-alkyl indoles. Carbamate 335a was deprotonated with LDA in THF, concentrated in vacuo, before dissolving in DCM (as the lithium salt was insoluble in THF as described above), and then methylated by adding MeI. N-Methyl carbamate 346 was then subjected to our standard solid-phase reaction sequence employing resin-bound ester 309a' (Scheme 136). Washing of the resin and treatment with 1% TFA gave ketone 347aa' (see section 9.3) in good yield and high purity (see appendix 1 for 1H NMR spectra). Clearly, the N-Boc group is not very susceptible to benzylidenation.

We required an improved procedure for carbamate alkylation and found that adding NaH to a mixture of carbamate 335 and alkyl halide in DMF resulted in excellent conversion to N-alkyl carbamates 346a-d (Scheme 137). No chromatography was required, and tertiary carbamates 346a-d were simply purified by recrystallisation. Carbamate 346a was then subjected to our standard solid-phase reaction sequence employing resin-bound esters 309a-d'. The resulting ketones were not isolated but instead further treated with TFA (10% in DCM), and upon aqueous work-up yielded indoles 348a in excellent purity without need for further purification. Similarly, N-benzyl carbamate 346b and N-prenyl carbamate 346c gave indoles 348b and 348c, respectively. However, N-allyl carbamate 346d failed to generate an effective alkylidenating reagent, and complex mixtures of products were observed by 1H NMR spectroscopy. The failure of N-allyl carbamate 346d is not surprising as Takeda and co-workers have shown that titanium alkylidenes generated from thioacetals bearing terminal or disubstituted alkenes undergo metathesis reactions (see section 2.2).74, 75, 77
The N-alkyl indoles 348 that were prepared are shown in Figure 20, and the yields shown are based on the loading of Merrifield resin used to prepare esters 309. The yields are moderate to good, suggesting that in some instances some intramolecular alkylidenation of the carbamate carbonyl may occur. However, the purity obtained in all cases was excellent.

The success of N-alkyl carbamates under the Takeda reaction conditions may at first seem surprising. However, it is evident from the crystal structures214 of carbamates 346a (Figure 21) and 346c (Figure 22) that the carbonyl group of tertiary carbamates 346a and 346c will be less electrophilic than that of secondary carbamate 335a as the nitrogen lone pair is less conjugated to the aromatic ring. The degree of conjugation is determined by the torsion angle C1'-C2'-N1-C1" (or C3'-C2'-N1-C1"). The C1'-C2'-N1-C1" torsion angles in the crystal structures of tertiary carbamates 346a and 346c are 78.71(16)° and 77.30(16)° respectively, as compared to 36.3(3)° for C3'-C2'-N1-C2" in secondary carbamate 335a. Indeed, in solution there is restricted rotation about the Ar-N bonds of all the tertiary carbamates 342 and 346 making C4 and C6 (CH2S) of the dithiane moiety non-equivalent in the 13C NMR spectra, with two signals appearing in the chemical shift range of 31-33 ppm. Furthermore, the benzylic hydrogen atoms of carbamate 346b and the allylic hydrogen atoms of carbamates 346c and 346d are inequivalent in the 1H NMR spectra of these compounds, confirming that they are diastereotopic. Interestingly, each crystal of
dithiane 346a is homochiral (though of course the material as a whole is racemic), while carbamate 346c produces racemic crystals. Presumably, the lower electrophilicity of tertiary carbamates 346a-c compared to both secondary carbamate 335a and imide 334, combined with the absence of an acidic proton in close proximity to the benzylic carbon atom, must account for their stability to the Schrock carbene.

As in the N-Boc indole series, we investigated using fewer equivalents of the titanium carbene, and found that 3 equivalents of thioacetal 346a converted resin-bound ester 309a' into indole 348aa' in almost identical yield (Scheme 138), under the standard reaction sequence (see appendix 1 for 1H NMR spectra of indole 348aa').

Although in theory only two equivalents of titanium(II) complex 74 should be needed to generate titanium alkylidenes from thioacetals, we found that using fewer than 4 equivalents of titanocene dichloride with respect to the thioacetals gave very poor yields of indoles. Thus, the optimum ratio of reagents for the benzylidenation reaction appears to be 12 eq. titanocene dichloride: 3 equivalents of thioacetal: 1 equivalent of resin-bound ester.
9.2 Use of O-Benzyl and O-Methyl carbamates

Next we investigated the stability of carbamates other than the tert-butyl carbamate under Takeda conditions. N-Methyl carbamate 349 was synthesised from aniline 331 in two steps (Scheme 139). O-Methyl carbamate 350 was prepared in high yield employing methyl chloroformate. Deprotonation using LDA and quenching the anion with MeI then gave N-methyl carbamate 349. No solubility problems were encountered with the lithium salt of carbamate 350 (unlike the Boc analogue - section 9.1) and a 9:1 mixture of product: starting material was observed by $^1$H NMR spectroscopy, purified by recrystallisation.

\[
\begin{align*}
\text{Scheme 139} \\
\begin{align*}
\text{N-Methyl carbamate 351 was synthesised in a similar fashion. O-Benzyl carbamate 352} \\
\text{was synthesised employing benzyl chloroformate,}^{235} \text{but was not isolated as it decomposed} \\
\text{on silica gel during chromatography (Scheme 140). Alkylation by adding NaH to a mixture} \\
\text{of carbamate 352 and MeI in DMF yielded N-methyl carbamate 351, purified by} \\
\text{chromatography.}
\end{align*}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 140}
\end{align*}
\]
In solution there is restricted rotation about the Ar-N bonds of tertiary carbamates 349 and 351 making C4 and C6 (CH₂S) of the dithiane moiety non-equivalent in the $^{13}$C NMR spectra, as with the tertiary tert-butyl carbamates. Furthermore, the benzylic hydrogen atoms of carbamate 351 are inequivalent in its $^1$H NMR spectrum, confirming that they are diastereotopic. Thus, the carbonyl groups of these tertiary carbamates would be electronically less electrophilic than secondary carbamate 335a and imide 334. Despite these observations, O-methyl carbamate 349 and O-benzyl carbamate 351 failed to give the corresponding ketone products when subjected to the standard solid-phase Takeda/cleavage sequence of reactions. Thus, steric hindrance must contribute to the lack of reactivity of the N-Boc group towards the Schrock carbene.
The $^1$H NMR spectrum of ketone 347 is more complicated than would normally be expected and so we took its $^1$H NMR spectrum over a range of temperatures (Figure 23).

![Diagram of Rotamers and Geometrical Isomers of Ketone 347](Image)

- **At 253 K**
  - 2 AB systems
  - 2 $\text{NMe}$
  - 2 $\text{tBu}$

- **At 273 K**
  - 1 AB system
  - 1 $\text{NMe}$
  - 2 $\text{tBu}$

- **At 333 K**
  - 1 AB system
  - 1 $\text{NMe}$
  - 1 $\text{tBu}$

**Figure 23**
We believe that as the Ar-N(Me)Boc moiety is non-planar (resulting in diastereotopicity), restricted rotation around the C2'-N1, Cl-C1' and N1-C1'' bonds in ketone 347 (Figure 24) could be responsible for the complexity in the $^1$H NMR spectrum at certain temperatures.

Restricted rotation around the C2'-N1 bond would result in the Ar-N(Me)Boc moiety being non-planar. This would cause H$^A$ and H$^B$ to be diastereotopic and give ketone 347 as a pair of enantiomers (Figure 25).

Similarly, restricted rotation around the C1-C1' bond would also cause diastereotopicity and give ketone 347 as a pair of enantiomers (Figure 26).
The combination of restricted rotation around the C2'-N1 and C1-C1' bonds would give rise to diastereomers. Restricted rotation around the C2'-N1 (causing diastereotopicity) and C1-C1' bonds would prevent interconversion (via a higher energy intermediate) of the two diastereomers (Figure 27). This phenomenon would result in doubling of signals in the 1H NMR spectrum.

Restricted rotation around the N1-C1'' bond (an electronic effect as having nitrogen coplanar with the carbonyl group allows conjugation) would lead to the presence of two geometrical isomers, also causing doubling of signals in the 1H NMR spectrum (Figure 28). However, this interconversion alone cannot lead to diastereotopicity.

Therefore, if there is restricted rotation around all three C2'-N1, C1-C1' and N1-C1'' bonds, ketone 347 will exist as two diastereomers of each geometrical isomer (Figure 29). As a result there will be up to four signals for each inequivalent proton and an AB system will also be observed in the 1H NMR spectrum.
Nuclei involved in a given exchange process, can at higher temperatures, experience an 'average environment' as the process becomes rapid. In NMR spectroscopy, two separate signals (corresponding to nuclei being distinct as a result of this exchange process) move towards the mean as this 'averaging' process increases. Two distinct signals in an NMR spectrum can therefore coalesce to give one signal at the mid-point of the two original signals, upon reaching the coalescence temperature, $T_C$. Additionally, a given exchange process can cause extra complexity to more than one signal in the NMR spectrum and the order which they begin to coalesce depends on the separation (Hz) of these signals with the closest achieving coalescence first.

Before further considering the phenomenon of coalescence, some relevant rate theory expressions must first be introduced. The Eyring equation for simple transformations, including certain bond rotations, can be written:

$$k = K K_B T / h \exp (-\Delta G^\ddagger / RT)$$

In this expression, $k$ is the rate constant, $K_B$ is the Boltzmann constant, $h$ is the Planck constant, $R$ is the gas constant, $T$ is the temperature, and $\Delta G^\ddagger$ is the free energy of activation. Moreover, $K$ is also constant, and provided the transition state can easily transfer energy to the surroundings, then $K$ is near unity.

For first order cases of mutual exchange, the Gutowsky equation states that the rate of rotation, $k_C$, at the temperature of coalescence, $T_C$, where $\Delta \nu$ is the measured difference in frequency (Hz) of the NMR signals which are approaching coalescence, is given by

$$k_C = \pi (\Delta \nu) / \sqrt{2}$$

If $k_C$ is substituted for $k$ in the Eyring equation, natural log is converted into log_{10}, and then the values for $K_B$, $h$, and $R$ are included, then the equation simplifies to

$$\Delta G^\ddagger (\text{cal}) = 4.57 T_C (10.32 + \log_{10} T_C - \log_{10} k_C) \text{ or}$$

$$\Delta G^\ddagger (J) = 2.303 \times 8.314 T_C (10.32 + \log_{10} T_C - \log_{10} k_C)$$

and despite the difficulty in identifying the exact coalescence point $T_C$, the Eyring equation in these forms can be used to calculate approximate energy barriers for a process. Also, $\Delta \nu$ can be used for any coalescing signals, which are a result of that particular process.
At 253 K there may be restricted rotation around the C2'-N1, C1-C1' and N1-C1" bonds in ketone 347 which would result in a mixture of two diastereomers of each geometrical isomer (Figure 29). The ¹H NMR spectrum is complex, and although up to four signals for each inequivalent proton and an AB system could be observed, we actually observe two t-Bu singlets, two NMe singlets and two AB systems (Figure 23a).

At 273 K the ¹H NMR spectrum contains two t-Bu singlets, one NMe singlet, and one AB system (Figure 23b). This may suggest that diastereomers are no longer present because there is rapid rotation on the NMR timescale about the C1-C1' bond at 273 K. The AB system remains as there is still restricted rotation about the C2'-N1 bond. Thus, there remains one compound as a mixture of geometric isomers (Figure 30) due to restricted rotation about the N1-C1" bond. For this situation we would expect to see up to two signals for each inequivalent proton and AB system, but actually we only observe two signals for the Boc group.

![Figure 30]

At 333 K the ¹H NMR spectrum contains one t-Bu group, one NMe singlet, and one broadened AB system (Figure 23c). This suggests that there is still restricted rotation about the C2'-N1 bond, but broad singlets are observed as the temperature is close to the coalescence temperature. No geometric isomers remain as there is now free rotation about the N1-C1" bond. Therefore, the ¹H NMR spectrum (Figure 23c) contains one signal for each inequivalent proton, but an AB system, as expected.

![Figure 31]
The order in which restriction of rotation around the C2'-N1, N1-C1", and C1-C1' bonds are overcome upon raising the temperature, cannot be definitively stated. Either restriction of rotation around the C1-C1' or C2'-N1 bonds must be overcome last as ketone 347 still contains an AB system at 333 K. However, the $^1$H NMR spectra of tertiary carbamates 346a and 346c prove that $H^A$ and $H^B$ are diastereotopic (Chapter 9.1) as a result of restricted rotation around their analogous C2'-N1 bonds. Also, the crystal structures of carbamates 346a and 346c show that the C1'-C2'-N1-C1 torsion angles are 78.71(16)$^\circ$ and 77.30(16)$^\circ$ respectively (Chapter 9.1), suggesting that there is a substantial energy barrier to coplanarity of the Boc and aryl groups in these compounds. Therefore, we propose that there is a similar energy barrier for rotation around the C2'-N1 bond in ketone 347 and so this is the last barrier to be overcome. At 273 K the $^1$H NMR spectrum contains two $t$-Bu groups, suggesting that the restriction on rotation around the N1-C1" bond is overcome second upon raising the temperature.

If we approximate 273 K as $T_c$ and take $\Delta \nu = 10.42$ (obtained from fine doublet splitting of the AB system in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a value of 59.54 KJmol$^{-1}$ for the free energy barrier to rotation around the C1-C1' bond. This energy barrier seems very high for the rotation depicted in Figure 27, and so we conclude that another explanation cannot be ruled out.

Therefore, if there is only restricted rotation around the C2'-N1 and N1-C1" bonds at low temperature, and not around the C1'-C2 bond, ketone 347 will exist as atropisomers (and so containing diastereotopic protons) and as a pair of geometrical isomers (Figure 32). As a result up to two signals for each inequivalent proton and AB system could be observed in the $^1$H NMR spectrum.

![Figure 32](image)

At 253 K if there is restricted rotation around the C2'-N1 and N1-C1" bonds ketone 347 could contain diastereotopic protons and exist as a pair of geometrical isomers (Figure 32). The $^1$H NMR spectrum is complex and we observe two $t$-Bu singlets, two NMe singlets.
and two AB systems (Figure 23a), which is correct for having two signals for each inequivalent proton and AB system.

At 273 K the $^1$H NMR spectrum contains two broad $t$-Bu singlets, one NMe singlet, and one broadened AB system (Figure 23b). We have passed the coalescence temperature for the NMe signals and the signals for one of the diastereotopic AB hydrogens have coalesced; the other now being close to its coalescence temperature. At 273 K we are approaching, but have not passed, the coalescence temperature for the Boc groups resulting from restricted rotation about the N1-C1" bond. It should be noted at this temperature that the presence of the AB system and the two Boc groups must be a result of two different processes since the AB system integrates exactly as 1:1 although the two Boc signals quite clearly do not.

At 333 K the $^1$H NMR spectrum contains one broad $t$-Bu singlet, one NMe singlet, and one broadened AB system (Figure 23c). This suggests that there is now rapid rotation on the NMR timescale about the N1-C1" bond. However, the AB system resulting from restricted rotation about the C2'-N1 bond has not yet coalesced, although broad singlets are observed as the temperature is close to the coalescence temperature.

If we approximate 273 K as $T_c$ and take $\Delta \nu = 10.42$ (obtained from fine doublet splitting of the AB system in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a value of 59.54 KJmol$^{-1}$ for the free energy barrier to rotation around the N1-C1" bond. If we approximate 333 K as $T_c$ and take $\Delta \nu = 73.77$ (obtained from the difference in frequency of the two Boc singlets in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a value of 67.67 KJmol$^{-1}$ for the free energy barrier to rotation around the N1-C1" bond. This value is too high as the coalescence temperature for the Boc signals is below 333 K. Therefore, for the rotation around the N1-C1" bond $\Delta G^\# \leq 59.54$ KJmol$^{-1}$. Similarly, if we approximate 333 K as $T_c$ and take $\Delta \nu = 68.39$ (obtained from doublet splitting of the AB system in the NMR spectrum in Figure 23a) in the simplified Erying equation above, we obtain a minimum value of 67.97 KJmol$^{-1}$ for the free energy $\Delta G^\#$ barrier to rotation around the C2'-N1 bond. This value can only be taken as a minimum as the coalescence point has not yet been reached at 333 K. The minimum value is only approximate but seems appropriate as the C-N barrier to rotation in CH$_3$CON(CH$_3$)$_2$ is around 80 KJmol$^{-1}$.

Therefore, we conclude that both explanations are possible and so we cannot definitively state (based on the information we have) which sequence of events is occurring.
Release of \(N\)-Boc indoles 336 could either involve cyclative termination (Scheme 141), or postcleavage cyclisation (Scheme 142) of a ketone 353, that is released by one of the mechanisms below. In the cyclative cleavage pathway (Scheme 141), protonation of enol ethers 354 to give oxonium ions 355 is followed by intramolecular addition. An elimination reaction then gives \(N\)-Boc indoles 336. Release of ketones 353 (Scheme 142) from the resin (as in synthesis of \(N\)-alkyl indoles) must involve protonation as above to give enol ether 356, followed by nucleophilic attack by an external nucleophile (TFA anion or water). This nucleophilic attack could either proceed via acetal hydrolysis (arrows a), or \(S_N1\) substitution (arrow b) or \(S_N2\) substitution (arrows b and c) to yield ketone 353. In the case of \(N\)-Boc indoles, any ketones 353 formed by this mechanism, would most probably undergo \(N\)-desilylation before release from the resin, given that \(N\)-Si cleavage is facile (as discussed earlier).

**Cyclative termination Pathway**

\[
\begin{align*}
354 \quad X &= H \text{ or } \text{TMS} \\
355 \\
336 \quad \text{Boc}
\end{align*}
\]

Scheme 141
The solid-phase synthesis of ketones 353 shows that cyclative termination is not necessary for release. However, introducing a spacer group between the benzylic polystyrene moiety and the ester/enol ether oxygen moiety may ensure cyclative termination by preventing $S_{N1}$ and $S_{N2}$ cleavage (although if pathway a is responsible for cleavage, it cannot be avoided).
11.1 Towards 2,3-fused

We then investigated carrying out Diels-Alder reactions on dienol ethers 357, attainable by carrying out Takeda reactions on resin-bound acrylic acid derivatives 358 (Scheme 143). The resulting enol ether 359 would allow cleavage and cyclisation to yield the corresponding 2,3-fused indoles.

![Scheme 143](image)

Treating N-silyl carbamate 342a with low-valent titanium complex 74 and then ester 309d' gave the corresponding enol ether 360. We cleaved dienol ether 360 under the usual resin-cleavage conditions and obtained the corresponding N-Boc indole 336ad' in high yield (Scheme 144). Dienol ether 360 was treated with N-methylmaleimide under literature solid-phase Diels-Alder\textsuperscript{124} conditions, and then the standard resin-cleavage conditions (Scheme 144); this yielded only pure indole 336ad' (60-65% yield) with no sign of the 2,3-fused indole 361 by \textsuperscript{1}H NMR spectroscopy.

![Scheme 144](image)
Presumably, the steric hindrance due to the geminal dimethyl moiety at the dieneol ether terminus in 360 renders such substrates unsuitable for Diels-Alder cycloadditions.

It was decided to employ a simpler system to attempt solid-phase Diels-Alder reactions. We tried, in turn, to alkylidenate commercially available Merrifield REM resin 361 and the resin-bound ester 362 (derived from trans-methyl acrylic acid) with the titanium carbene derived from thioacetal 285. It was hoped that the reduction in steric hindrance at the dienol ether terminus would allow successful cycloaddition to occur. However, after standard resin-cleavage conditions, ketones 363 and 364 were generated in low purity (Scheme 145). The $^1$H NMR spectra in each case, showed complex mixtures of products were obtained, but significantly, large singlets ($\delta$ 6.59, 6.61 and 6.65 ppm) corresponding to cyclopentadienyl (Cp) ligands were observed. This suggests that side reactions, such as 1,4-additions of nucleophilic titanium alkylidenes (and/or of intermediates formed in their preparation) or alkene metathesis reactions (see section 2.2) on acrylate derivatives 361 and 362, contributed to the low purity of ketones 363 and 364.

Scheme 145
11.2 Towards Bis-indoles

We then envisaged carrying out two alkylidenations on resin-bound oxalate esters 365 to generate resin-bound bis-enol ethers 366, which could then undergo cleavage from resin and cyclisation to yield symmetrical bis-indoles 367 (Scheme 146).

Resin bound oxalate 368 was synthesised by adding methyl oxalyl chloride to Wang resin. Resin-bound oxalate 369 was synthesised, by adding oxalyl chloride to Wang resin and quenching the intermediate with ethanol. In both cases, two ester stretches were observed in the Infrared (Golden Gate) spectrum (Scheme 147), confirming product formation.
Standard alkylidenation reactions were carried out in turn, on resin bound oxalates 368 and 369, employing 6 equivalents of thioacetal and 24 equivalents of low-valent titanium complex 74, which corresponds to our proposed optimal number of equivalents for both ester groups (Scheme 148). Both resins were subjected to cleavage conditions, employing 5% TFA in DCM, and the solvent was then removed. In each case we found that the $^1$H NMR spectrum (obtained in d-6 acetone as the mixture was insoluble in CDCl$_3$) confirmed that there was little evidence of aromatic signals corresponding to the desired product 370, with large singlets (δ 6.30-6.70 ppm) corresponding to cyclopentadienyl (Cp) ligands observed.

As little or no aromatic containing product was cleaved from the resin, it suggests that formation of the enol ether from the resin's benzylic ester does not occur. A number of explanations for such a failure are possible. We tentatively propose that co-ordination of a titanium intermediate to either a resin-bound oxalate (such as intermediate 371, Figure 32) or to a resin-bound enol ether (such as intermediate 372, Figure 32), could promote premature cleavage from the resin. Also, steric hindrance introduced after alkylidenation at the terminal ester could prevent the second alkylidenation and encourage Michael addition to an intermediate such as 373 (Figure 33). Finally, reduction of the 1,2-dicarbonyl moiety in esters 368 or 369 by the low-valent titanium complex 74 cannot be ruled out.
11.3 Towards iso-Serotonin Derivatives

We hoped to develop a convenient route to iso-serotonin derivatives employing REM\textsuperscript{122} resin. Treating REM resin with a range of dialkylamines would generate resin-bound β-amino esters 374,\textsuperscript{122} which we hoped to alkylidenate using benzylidene reagents 375, and then transform the corresponding enol ethers into indoles 376 (Scheme 149) by the same methods as used for the conventional indoles (Chapters 8 and 9). Although natural indoles are almost always 3-substituted, 2-substituted indoles are currently of interest (section 5.1). A large range of amines could in theory be tolerated, as well as a wide degree of functionality around the indole ring, allowing an attractive, diversity-based synthesis of serotonin analogues.

![Scheme 149](image)

Initial studies were carried out using GSK “in-house” REM resin 377, which had not been fully characterised. The exact method of preparation of resin 377 is unknown, but it was thought to have been derived from Merrifield resin (1.70 mmol g\textsuperscript{-1} loading) which would result in a loading of 1.64 mmol g\textsuperscript{-1} for resin 377. Resin 377 was treated with morpholine in DMF to yield resin-bound β-amino ester 378, which in turn was used in a range of Takeda reactions employing the titanium alkylidene derived from thioacetal 285 (Scheme 150).

![Scheme 150](image)
The 12-20 eq. of titanocene 74 (assuming complete conversion of \( \text{Cp}_2\text{TiCl}_2 \) to complex 74) and 3-5 eq. of thioacetal 285 used in our standard Takeda reactions (methods A and B) failed to generate ketone 379 in good purity from ester 378, upon cleavage from the resin (Scheme 150). The yields obtained were low to moderate and ketone 379 was contaminated with \( \text{CpTi} \) containing impurities in both cases. We decided to further reduce the excess of reagents used in the Takeda reaction. Employing 6 eq. low-valent titanium complex 74 and 2 eq. of thioacetal 285 (method C), with resin-bound ester 378 yielded ketone 379 in high purity but in greater than 100% yield, confirming that REM resin 377 was not prepared from 1.70 mmol g\(^{-1}\) Merrifield resin (Scheme 150). However, this demonstrated that thioacetal 285 could be effectively reduced using just 3 eq. of low-valent titanium complex 74 to form the titanium carbene. It also suggests that alkylidenation of \( \beta \)-amino ester 378 gives cleaner products if less low-valent titanium complex 74 is employed.

Employing thioacetal 346a and resin-bound ester 378, our standard conditions (A, scheme 151) yielded ketone 380 in poor yield and very low purity. We then investigated reducing thioacetal 346a with 3 eq. of low-valent titanium complex 74 (B, scheme 151) but after resin-cleavage ketone 380 was not observed by \(^1\)H NMR.

Employing 6 eq. of low-valent titanium complex 74 and 2 eq. of thioacetal 285, the standard Merrifield resin-bound ester 309a', upon cleavage from the resin, yielded ketone 381 in high yield and excellent purity (Scheme 152). This confirms that 1 eq. of thioacetal 285 requires only 3 eq. of low-valent titanium complex 74 for effective reduction. The lower yield obtained than with ester 378 may simply be explained by poorer loading of ester 309a' compared to ester 378.
Due to the uncertainty in the nature of resin 377, and therefore β-amino ester 378, we decided to use commercially available Merrifield-REM resin 382. Resin 382 was treated with morpholine to give β-amino ester 383, which was subjected to a range of alkylidenation reactions. Our standard reaction conditions (A, Scheme 153) yielded ketone 379 in poor yield and low purity (CpTi impurities). Employing 10% TFA in DCM as the cleavage conditions improved yields but products were still contaminated with CpTi impurities. Employing 6 eq. of low-valent titanium complex 74 and 2 eq. of thioacetal 285 (B, Scheme 153), gave very low yields (<10%) and CpTi impurities were also observed. We also washed the resin with TMEDA, after subjecting it to Takeda conditions (B, Scheme 153), in the hope that the co-ordinating solvent could remove Ti containing impurities. However, we were unsuccessful with the same by-products being obtained.

Scheme 153

Employing thioacetal 346a and resin-bound ester 383, our standard conditions (Scheme 154) yielded ketone 380 in poor yield and very low purity, even when employing 10% TFA in DCM as the cleavage conditions.

Scheme 154
Next we prepared Wang REM resin 384 by coupling acrylic acid to Wang resin (using the standard coupling procedure used for ester 290, see section 8.2), which was then treated with morpholine to yield β-amino ester 385 (Scheme 155). 2 eq. of thioacetal 285 was reduced employing 6 eq. of low-valent titanium complex 74, and the resulting Ti carbene solution was added to ester 385 (Scheme 155). Upon resin-wash and cleavage from the resin (both methods), ketone 379 was obtained in high yields and good purity with tiny amounts of CpTi impurities being observed by $^1$H NMR. Employing ester 385, 2 eq. of thioacetal 297 failed to be effectively reduced by 6 eq. low-valent titanium complex 74, as ketone 379 was not cleaved from the resin with aromatic signals not observed in the $^1$H NMR spectrum.

Employing thioacetal 346a and resin-bound ester 385, our standard conditions (scheme 156) failed to yield ketone 380 upon resin-cleavage. Only the corresponding carboxylic acid 386 was observed in the $^1$H NMR spectrum of the crude material following cleavage from resin (this is a result of unreacted ester 385 being cleaved from the resin by the TFA solution).

Scheme 155

Scheme 156
It was important to establish if the problems experienced were not simply due to the oxygen atom in the morpholine moiety (perhaps providing an extra co-ordination point for titanium intermediates). Thus piperidene was added to Wang REM resin 384 to yield resin-bound β-amino ester 387. Thioacetal 342a was reduced using the standard conditions, and the mixture was added to ester 387, which upon resin-cleavage yielded a crude mixture of products containing mostly indole 389, but it also contained impurities including CpTi containing compounds and at least one other aromatic compound (Scheme 157).

Next we investigated using thioacetal 390\textsuperscript{214} (obtained from another member of the group). Co-ordination of the ortho protected nitrogen moiety to a titanium intermediate could not be ruled out, and so the protected oxygen moiety could behave differently. We checked if the bis(thiophenyl) thioacetal moiety could be reduced with 3 eq. of low-valent titanium 74 (A, Scheme 158). After subjecting ester 387 to the low-valent titanium carbene mixture, and then washing the resin and cleaving from the resin, only carboxylic acid 391 was isolated with no sign of the desired benzofuran 392 observed by \textsuperscript{1}H NMR. Using our standard, optimal set of conditions (B, Scheme 158), similar results were obtained along with large amounts of CpTi containing impurities. If, indeed co-ordination of the ortho-nitrogen atom is the problem, then the same could be occurring in the oxygen series.

Next we investigated using thioacetal 390\textsuperscript{214} (obtained from another member of the group). Co-ordination of the ortho protected nitrogen moiety to a titanium intermediate could not be ruled out, and so the protected oxygen moiety could behave differently. We checked if the bis(thiophenyl) thioacetal moiety could be reduced with 3 eq. of low-valent titanium 74 (A, Scheme 158). After subjecting ester 387 to the low-valent titanium carbene mixture, and then washing the resin and cleaving from the resin, only carboxylic acid 391 was isolated with no sign of the desired benzofuran 392 observed by \textsuperscript{1}H NMR. Using our standard, optimal set of conditions (B, Scheme 158), similar results were obtained along with large amounts of CpTi containing impurities. If, indeed co-ordination of the ortho-nitrogen atom is the problem, then the same could be occurring in the oxygen series.

Next we investigated using thioacetal 390\textsuperscript{214} (obtained from another member of the group). Co-ordination of the ortho protected nitrogen moiety to a titanium intermediate could not be ruled out, and so the protected oxygen moiety could behave differently. We checked if the bis(thiophenyl) thioacetal moiety could be reduced with 3 eq. of low-valent titanium 74 (A, Scheme 158). After subjecting ester 387 to the low-valent titanium carbene mixture, and then washing the resin and cleaving from the resin, only carboxylic acid 391 was isolated with no sign of the desired benzofuran 392 observed by \textsuperscript{1}H NMR. Using our standard, optimal set of conditions (B, Scheme 158), similar results were obtained along with large amounts of CpTi containing impurities. If, indeed co-ordination of the ortho-nitrogen atom is the problem, then the same could be occurring in the oxygen series.
Next we prepared Merrifield REM resin 393 by reacting acrylic acid with Merrifield resin by a standard procedure.\textsuperscript{122} This was treated with morpholine to yield $\beta$-amino ester 394 (Scheme 159). Employing thioacetal 346a and resin-bound ester 394, our standard conditions (A, Scheme 159) failed to yield ketone 380 upon cleavage from the resin. Lowering the number of equivalents (B, Scheme 159) was also unsuccessful. In both cases mostly CpTi signals were observed in the crude $^1$H NMR spectrum.

![Scheme 159](image)

Finally we employed thioacetal 346b and resin-bound ester 394, under standard conditions (scheme 160). Upon cleavage from the resin, ketone 395 was the main product, but signals in the $^1$H NMR spectrum were broad and difficult to interpret. The crude material was subjected to the standard deprotection cyclisation conditions, and yielded a mixture of compounds. This mixture contained mostly the desired indole 396 and was purified by chromatography and a $^1$H NMR spectrum was obtained. Purification was difficult due to the small amounts of material obtained, and indole 396 was not obtained completely pure, and so was not fully characterised.

![Scheme 160](image)
The failure to effectively alkylidenate resin-bound β-amino esters with titanium benzyldienes containing a heteroatom in ortho position remains unexplained. However, thioacetal 285, which is more easily reduced (with 3 eq. of low-valent titanium complex 74), cleanly reacted with β-amino esters under Takeda conditions. PhS thioacetals are known to be more easily reduced than 1,3-dithianes but the failure to effectively reduce thioacetal 390 (with 3 eq. of low-valent titanium complex 74) suggests that the ortho heteroatom is significant. This could be explained, by its presence slowing down titanium alkylidene formation at the more electron-rich benzylic position, hence resulting in a larger excess of low-valent titanium 74 being required for successful reduction. Excess titanium intermediates present could then interact with any unreacted β-amino ester.

However, the two most successful attempts [formation of indoles 389 (Scheme 157) and 396 (Scheme 160)] utilised titanium alkylidenes with the largest degree of steric hindrance around the ortho nitrogen heteroatom. If the nitrogen lone pair is out of the plane (therefore not in conjugation with the aromatic ring), the less electron-rich benzylic thioacetals may be more easily reduced with low-valent titanium complex 74. However, to achieve clean reaction with β-amino esters, PhS thioacetals may be required.

It should also be noted that the nature of resin 377 still remains unclear.
Chapter- 12 Synthesis of Quinolines

12.1 Strategy

We envisaged using thioacetals 397 to generate titanium alkylidenes that would allow the synthesis of quinolines using our methodology. Merrifield resin-bound esters 309 would be converted into the corresponding enol ethers, which after cleavage from resin would yield ketones 398 (Scheme 161). A Boc-deprotection/cyclisation/oxidation series of reactions (preferably in one pot) would then yield quinolines 399.

\[ \text{i. } \text{Cp}_2\text{Ti[P(OEt)}_3\text{]}_2 \text{ 74 4 eq.} \]
\[ \text{ii. } \text{Deprotect Cyclise Oxidise} \]
\[ \text{iii. } 1\% \text{TFA/ DCM} \]

Scheme 161

12.2 Synthesis of Thioacetal Substrates

Our first strategy for the synthesis of thioacetals 397 involved oxidation of commercially available 2-nitro-phenethyl alcohol 400 to yield aldehyde 401, which could then be converted into the corresponding thioacetal 401 (Scheme 162). Work in this area was carried out by an undergraduate project student, who found that this strategy although successful, gave poor results on reaction scale-up. Both the Parikh-Doering modified Swern\(^{237}\) (activation by pyridine-sulfur trioxide complex) and pyridinium chlorochromate\(^{238}\) (PCC) oxidations, were attempted. Improved results were obtained when the aldehyde was converted into the thioacetal without isolation (Scheme 162). Presumably, the ortho-nitro moiety causes problems with the standard oxidation methods, and 14\% was the best yield obtained for the two step process. Employing PCC oxidation, I encountered similar problems, with by-products being formed during oxidation even when carefully monitoring the reaction progress by TLC.

Scheme 162
The use of the commercially available Dess-Martin periodinane allowed the oxidation of 2-nitro-phenethyl alcohol to aldehyde 401 with >90% conversion determined from the $^1$H NMR spectrum of the crude mixture (Scheme 163). Although the exact mechanism of the reaction is unknown it is believed to proceed via an intermediate such as 403 which, could collapse to yield the aldehyde 401 with elimination of acetic acid. Aldehyde 401 was not isolated as we abandoned this route because no other 2-nitro-phenethyl alcohols are commercially available, and as a result a more general synthesis of thioacetal substrates was developed.

![Scheme 163](image)

We envisaged an improved strategy would involve Wittig alkenation of 2-nitrobenzaldehydes 334 (a range of which are available) to form the corresponding enol ethers 404 which could then be converted into thioacetals 405 (Scheme 164).

![Scheme 164](image)

The phosphonium salt 406 of methoxymethyl chloride (MOMCl) was prepared by a literature procedure, heating a slight excess of MOMCl with triphenylphosphine under reflux in DCM (Scheme 165). This was then converted into phosphonium ylid 407 employing tert-butyllithium in THF. The Wittig reaction then proceeded upon addition of the 2-nitrobenzaldehydes 334a-c to the phosphonium ylid 407 in THF at low temperature, followed by warming to room temperature to yield enol ethers 408a-c. Thus, 2-nitrobenzaldehyde 334a was converted into enol ethers 408a, isolated as a mixture of geometrical isomers (predominantly the $E$ isomer). Enol ethers 408a were not purified but were converted into thioacetal 409a directly, following work-up of the Wittig reaction. During thioacetal formation, a white precipitate formed, which was filtered off once TLC confirmed complete consumption of starting material. $^1$H NMR spectroscopy confirmed that this solid consisted of triphenylphosphine containing products. Presumably the boron
trifluoride complexes of triphenyl phosphine and triphenyl phosphine oxide are insoluble in toluene. Thus, after work-up thioacetal 409a was isolated in good purity. In a similar fashion, 2-nitrobenzaldehydes (R = -3-OMe 334b, R = -4,5-OCH₂O 334c) yielded the respective enol ethers 408b and 408c, as mixtures of isomers. These were then directly converted into thioacetals 409b and 409c, respectively, with removal of most of the triphenyl phosphine and triphenyl phosphine oxide impurities, as above. Only small portions of thioacetals 409a-c were purified by recrystallisation for characterisation. The bulk of the nitro compounds 409a-c were reduced to give anilines 410a-c (Scheme 165). Anilines 410a and 410b were not isolated, but were converted into carbamates 411a and 411b, respectively, by heating with di-tert-butyldicarbonate. Aniline 410c was converted into the corresponding imide 412 before mono-deprotecting using TFA in DCM to yield carbamate 411c. Purification by recrystallisation gave pure carbamates 411a-c in good yields over 4-5 steps. N-Silylation as before, then gave pure N-silyl carbamates 413a-c in good yields, which were again of low stability making full characterisation difficult.

Scheme 165
12.3 Synthesis of Quinolines

N-Silyl carbamate 413a was subjected to our standard solid phase reaction sequence, using resin-bound ester 309a' and we obtained ketone 414, presumably via resin-bound enol ether 415 (Scheme 166). A range of Boc deprotection/cyclisation strategies were tested, including treating the ketone with stronger TFA under an oxygen atmosphere and use of acidic oxidant nitric acid. Both gave dissapointing results, yielding complex mixtures of compounds by \(^1\)H NMR spectroscopy, which did contain quinoline 416aa', but some uncyclised compounds were also present.

\[
\begin{align*}
413a & \xrightarrow{\text{i}} \text{Cp}_2\text{Ti}[\text{P(OEt)}_3]_2 \quad 74 \\ & \xrightarrow{\text{ii}} \text{NHBOC} \\ & \xrightarrow{\text{iii}} \text{wash resin}
\end{align*}
\]

Scheme 166

Employing 10\% TFA in DCM and leaving for 1 h, gave cleavage from the resin and concommitant Boc deprotection to yield the aniline trifluoroacetate salt 417aa' (Scheme 167). Simply heating salt 417aa' in DCM gave the desired quinoline 416aa' in good purity (see appendix 1 for \(^1\)H NMR spectra of trifluoroacetate salt 417aa' and quinoline 416aa'). However, this was not completely reproducible, and we found that adding 5 eq. of manganese dioxide and heating under reflux, in DCM for 1-2 h lead to excellent conversion to quinoline 416aa' in high purity (Scheme 167).
Using the standard Takeda conditions, the new procedure for cleavage from the resin, and the oxidative cyclisation strategy, a range of quinolines were synthesised in moderate to good yields and high purity. The intermediate TFA salts 417 were not always pure, and in some cases significant amounts of quinoline products along with other intermediate compounds were present, after the cleavage from the resin. Therefore salts 417a-c were not isolated but simply converted into quinolines 416a-c (Scheme 168). The impurities in the trifluoroacetate salts 417 must be converted into the quinoline products, as these are isolated in high purity.

\[
\begin{align*}
\text{i. } & \text{Cp}_2\text{Ti}[\text{P(}\text{OEt})_3]_2 & \rightarrow & \text{R}_1\text{NBOc} & \text{thiophene} \\
\text{ii. } & 0.33 \text{ eq. } & \text{0} & \text{309a', d', e', and f'} & \text{reduction} \\
\text{iii. } & 10\% \text{ TFA/DCM, 1h} & \rightarrow & \text{416a-c} & 42-67\% \\
\end{align*}
\]

Scheme 168

A couple of more interesting esters were employed, including the successful use of fluorine and a heterocycle in the resin-bound ester (Figure 34). Only one example failed to yield the quinoline in good purity; namely quinoline 416cd' which failed to cyclise cleanly. The other examples were formed in excellent purity, although it was difficult to obtain $^1$H NMR spectra without the presence of water, and these quinolines are thought to be hygroscopic.

\[
\begin{align*}
\text{416aa'} & 67\% \\
\text{416ba'} & 46\% \\
\text{416ca'} & 52\% \\
\text{416bd'} & 59\% \\
\text{416cd'} & \text{impure} \\
\text{416be'} & 51\% \\
\text{416ce'} & 41\% \\
\text{416cf'} & 54\% \\
\end{align*}
\]

Figure 34
12.4 Future Work

The extension of this methodology to synthesise 2,4-disubstituted quinolines 399, employing titanium alkylidenes derived from thioacetals 397 (which could be prepared as above from readily available 2-nitrophenones 418), is ongoing within our group (Scheme 169).

It may also be possible to extend our methodology to the synthesis of N-, 2-, 4-trisubstituted tetrahydroquinolines 419 (Scheme 170), employing a reductive cyclisation of ketones 420 (utilising titanium alkylidenes derived from N-alkyl-N-Boc thioacetals 421).
Chapter 13 - Unsuccessful Resin-bound Esters

It is important to discuss the functional group tolerance within the Merrifield resin-bound esters (Section 3.2). The esters used in the attempted synthesis of 2,3-fused indoles, bis-indoles, and iso-serotonin derivatives are discussed elsewhere (Chapter 11). Also, all successful esters have already been discussed earlier.

Esters 303g', 303h' and 303i' were however, unsuccessful when treated with the titanium alkylidene derived from thioacetal 342a under our standard conditions (Scheme 421).

Heteroaromatic substituents are tolerated as with the successful use of furanyl ester 303f'. However, the 2'-thiophenyl substituent in ester 303g' does not give clean products and the $^1$H NMR spectra contained large CpTiLn singlets, presumably due to the thienyl moiety acting as a ligand towards titanium. Although the 2'-position of the heteroatom could account for extra co-ordination to titanium intermediates, previous work within the group showed that the 3'-thiophenyl substituent gave a similar result in the benzofuran series. Ester 303h' resulted in poor mass recovery and CpTiLn contaminated mixtures of products. This failure could be due to a variety of reasons including the low reactivity of the sterically hindered ester carbonyl, competing alkylidenation with the Boc carbonyl, and co-ordination of titanium intermediates between the ester and Boc carboxyls. The failure of ester 303i' is not surprising as we have already shown that acidic protons tend to quench the titanium carbenes (see section 8.4).
General Experimental details

All reactions were carried out under an inert atmosphere unless otherwise stated, using oven-dried or flame-dried glassware. Solutions were added via syringe unless otherwise stated. THF, was freshly distilled from sodium-benzophenone; dichloromethane, toluene, triethylphosphite and pyridine were distilled from CaH₂ prior to use. Petroleum ether refers to the fraction boiling at 40-60 °C. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Purification by column chromatography was carried out using Fisher Matrex TM silica gel (mesh size 35-70 μm) or neutral alumina (mesh size 35-70 μm) as the stationary phase. Melting points are uncorrected. IR spectra were recorded using a Nicolet Impact 410 FTIR or JASCO FT/IR 410 spectrometer. NMR spectra were recorded using a Bruker DPX-400, DPX-360 or DPX-250 spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane using residual CHCl₃ as an internal standard (7.26 ppm). Chemical shifts in ¹³C NMR spectra are given in ppm relative to CDCl₃ as internal standard (77.00 ppm). All NMR J Values are given in Hz. Mass spectra were recorded on a JEOL JMS700 spectrometer. Combustion analysis was carried out using a Carlo-Erba 1106 or Exeter Analytical inc. CE 440 elemental analyser. For X-ray crystallography, single crystals of suitable size were attached to a glass fibre using acrylic resin, and mounted on a goniometer head in a general position. Data were collected on an Enraf-Nonius KappaCCD diffractometer, running under Nonius Collect software, and using graphite monochromated X-radiation (λ=0.71073 Å). Precise unit cell dimensions were determined by post-refinement of a significant percentage of the data sets. The frame images were integrated using Denzo(SMN) and the resultant raw intensity files processed using a locally modified version of DENZOX. Data were then sorted and merged using SORTVX and an empirical absorption correction applied at this stage. All non-H atoms were allowed anisotropic thermal motion. Aliphatic and aromatic C-H hydrogen atoms were included at calculated positions, with C-H = 0.96 Å, and were refined with a riding model. Refinement with SHELXL97-2 used full-matrix least-squares on F² and all the unique data were included in the refinements. The absolute configuration of compound 346c was confirmed by the refinement of the Flack absolute structure parameter, which refined to zero within error. Calculations using PLATON indicated that there were no voids in the lattices capable of containing any further solvent molecules. Thermal ellipsoid plots were obtained using the program ORTEP-3 for Windows. All calculations were carried out using the WinGX package of crystallographic programs.
General Experimental Procedures

Merrifield resin-bound esters 303 - Method A

\[ \text{O} - \text{R} \]

Six Kans with chloromethyl polystyrene resin (each containing 150 mg of resin, 0.28 mmol/kan, 1.68 mmol) in DMF (150 cm\(^3\)) were stirred with the corresponding caesium carboxylate [prepared by adding CsOH (50% H\(_2\)O) drop-wise to an ethanol solution of the carboxylic acid (1.50 mmol) until pH 7 was achieved] at 50-60 °C for 15 h. The Kans were then washed with DMF (x 2), water (x 2) and then alternately with MeOH and DCM (x 5), before finally washing with MeOH and diethyl ether and dried under vacuum.

Merrifield resin-bound esters 303a'-c', g' and h' - Method B

\[ \text{O} - \text{R} \]

Chloromethyl polystyrene resin (3.00 g, 6.00 mmol) and the caesium carboxylate [prepared as for method A, (30 mmol)] in DMF (25 cm\(^3\)), were agitated on a Quest Controller apparatus, at 50 °C for 20 h. The resin was then washed with DMF (x 5), alternately with MeOH/DCM (x 5), before finally washing with MeOH and EtOAc to give the desired resin bound esters 303a-c which were dried under vacuum. Magic angle spinning (MAS) proton NMR confirmed greater than 90% loading was achieved for esters 303a'-c', g' and h'.

Solid-phase Takeda reaction – general method A

Titanocene dichloride (1.51 g, 6.00 mmol, 20.0 eq.), magnesium turnings (0.20 g, 8.23 mmol) and 4Å molecular sieves (0.60 g) were heated briefly under vacuum. After allowing to cool, the reaction flask was purged with argon, and THF (6.0 cm\(^3\)) and triethylphosphite (2.1 cm\(^3\), 12.2 mmol) were added and the reaction mixture was stirred, cooling using an ice bath for 30 mins. After stirring for a further 2-2.5 h, a THF (6.0 cm\(^3\)) solution of the thioacetal (1.50 mmol, 5.0 eq.) was added, and the solution stirred for 15 mins. The reaction mixture was added via syringe into a flask containing 1 Kan of resin bound ester (0.28-0.31 mmol, 1 eq.), pre-swollen in THF (3 cm\(^3\)). The mixture was stirred under argon for 15-18 h. After this time, the Kan was removed and then washed with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and finally with diethyl ether. The resin was then dried under vacuum.
Solid-phase Takeda reaction – general method B
Titanocene dichloride (0.90 g, 3.60 mmol, 12.0 eq.), magnesium turnings (0.10 g, 3.96 mmol) and 4Å molecular sieves (0.20 g) were heated briefly under vacuum. After allowing to cool, the reaction flask was purged with argon, and THF (5.0 cm³) and triethylphosphite (1.2 cm³, 7.2 mmol) were added and the reaction mixture was stirred, cooling using an ice bath for 30 mins. After stirring for a further 2-2.5 h, a THF (4.0 cm³) solution of the thioacetal (0.90 mmol, 3.0 eq.) was added, and the solution stirred for 15 mins. The reaction mixture was added via syringe into a flask containing 1 Kan of resin bound ester (0.28-0.31 mmol, 1 eq.), pre-swollen in THF (3 cm³). The mixture was stirred under argon for 15-18 h. The kan was then washed and dried as for solid-phase Takeda reaction Method A.

Solid-phase Takeda reaction – general method C
Titanocene dichloride (0.45 g, 1.80 mmol, 6.0 eq.), magnesium turnings (0.05 g, 2.00 mmol) and 4Å molecular sieves (0.10 g) were heated briefly under vacuum. After allowing to cool, the reaction flask was purged with argon, and THF (4.0 cm³) and triethylphosphite (0.6 cm³, 2.0 mmol) were added and the reaction mixture was stirred for 30 mins. After stirring for a further 2-2.5 h, a THF (4.0 cm³) solution of the thioacetal (0.60 mmol, 2.0 eq.) was added, and the solution stirred for 20-30 mins. The reaction mixture was added via syringe into a flask containing 1 Kan of resin bound ester (0.28-0.31 mmol, 1 eq.), pre-swollen in THF (3 cm³). The mixture was stirred under argon for 15-18 h. The kan was then washed and dried as for solid-phase Takeda reaction Method A.

Solid-phase Takeda reaction – general method D
Titanocene dichloride (3.60 g, 14.4 mmol, 12.0 eq.), magnesium (0.38 g, 15.8 mmol) and 4Å molecular sieves (1.20 g) were heated briefly in vacuo and then allowed to cool. The reaction flask was purged with argon before adding THF (24 cm³) and triethylphosphite (4.80 cm³, 28.8 mmol). The reaction mixture was cooled using an ice bath and stirred for 30 mins. After stirring for a further 2.5 h at rt, a THF (16 cm³) solution of the thioacetal (3.60 mmol, 3.0 eq.) was added, and the mixture was stirred for 15 mins. After this time the reaction mixture was added in four equal portions via syringe, into four flasks each containing 1 Kan of resin-bound ester (0.30 mmol, 1.0 eq.), each pre-swollen in THF (6 cm³). The kan was then washed and dried as for solid-phase Takeda reaction Method A.
General solution-Phase Takeda reaction
Titanocene dichloride (2.04 g, 8.18 mmol), magnesium turnings (0.23 g, 9.82 mmol) and 4Å molecular sieves (0.81 g) were heated briefly under vacuum, allowed to cool, and the reaction flask was purged with argon. THF (20 cm³) and triethylphosphite (2.8 cm³, 16.6 mmol) were then added, and the reaction mixture was allowed to stir for 3 h under argon. After this time, a THF (3.0 cm³) solution of the thioacetal (3.00 mmol) was added, and the reaction mixture was stirred for 2 h at rt. The reaction was quenched by adding aqueous HCl (20 cm³, 2 mol dm⁻³) and the residue was then filtered through wet celite washing with DCM (2 x 40 cm³). The combined organic phases were then washed with water (2 x 40 cm³), dried over sodium sulfate, and concentrated in vacuo.

Cleavage from Merrifield resin - general procedure A
Following the Takeda reaction, the resin bound product (1 Kan) was treated with 1% TFA in DCM (5 cm³, 0.65 mmol) and placed on a shaker for 30 min. The Kan was washed with DCM (3 x 5 cm³) and the organic washings were combined and then concentrated.

Cleavage from Merrifield resin - general procedure B
Following the Takeda reaction, the resin bound product (1 Kan) was treated with 10% TFA in DCM (5 cm³, 6.50 mmol) and placed on a shaker for 1 h. The Kan was washed with DCM (3 x 5 cm³) and the organic washings were combined and then concentrated.

General Indole-Boc deprotection method
Following a literature procedure, trifluoroacetic acid (0.5 cm³, 6.50 mmol) was added to a solution of the Boc-protected indole in DCM (2.0 cm³), at 0 °C under argon, and the reaction mixture was allowed to warm to rt and stirred for 1 h. After this time, the reaction mixture was concentrated in vacuo to yield the desired indole.

General procedure for carbamate alkylation
Sodium hydride [60% in mineral oil, (0.66 g, 16.5 mmol)], was added portion-wise to a solution of carbamate 335a (4.04 g, 13.0 mmol) and alkyl halide (16.5 mmol), in DMF at 0 °C under argon. The reaction mixture was then allowed to warm to rt and stirred for 2-3 h. After this time the reaction mixture was carefully poured into iced water and extracted into ethyl acetate (2 x 50 cm³). The combined organic phases were then washed with water (3 x 150 cm³), dried with magnesium sulphate, and concentrated to yield the desired amine.
General procedure for ketone cyclisation
TFA (0.5 cm³, 6.50 mmol) was added dropwise to a solution of the crude ketone in DCM (5 cm³), at 0 °C under argon, allowed to warm to rt and was then stirred for 1-3 h. After this time, the reaction mixture was poured into saturated sodium bicarbonate and extracted into DCM (2 x 10 cm³). The combined organic phases were then washed with saturated sodium bicarbonate (20 cm³), water (20 cm³), dried over sodium sulphate, and concentrated to yield the resulting N-alkyl indole.

Cyclisation/Oxidation - general method for forming quinolines
Manganese dioxide (0.09 g, 1.00 mmol) was added to a solution of the crude amine salt in DCM (10 cm³) and the reaction mixture was heated under reflux for 1-2 h. After this time, the reaction mixture was filtered through a celite plug, washing with DCM (10 cm³). The combined organic phases were washed with saturated sodium bicarbonate (20 cm³), dried over sodium sulfate, and concentrated to yield the desired quinoline.

[Manganese dioxide was synthesised by adding potassium permanganate (10 g, 63.3 mmol) in water (500 cm³) to manganese sulfate tetrahydrate (16.9 g, 75.8 mmol) in water (500 cm³) at 0 °C. The reaction mixture was stirred for 5 mins and then filtered. The resulting black solid was then washed with water (500 cm³) and dried in an oven at 120 °C.]

Bis(phenylthio)phenylmethane 241 285

Thiophenol (7.70 cm³, 75.1 mmol) was added to a solution of benzaldehyde (3.19 g, 30.1 mmol), acetic acid (20 cm³) and boron trifluoride diethyletherate (3.2 cm³, 27.0 mmol) in toluene (30 cm³), under nitrogen, and stirred for 68 h at rt. After this time, the reaction mixture was quenched by adding water (40 cm³) and extracted with diethyl ether (3 x 40 cm³). The combined organic phases were washed with saturated sodium bicarbonate solution until the acid was neutralised, dried over magnesium sulfate, and concentrated to yield a yellow oil. Crystallisation from Pet. ether gave bis(phenylthio)phenylmethane 240 285 as needles (7.87 g, 25.6 mmol, 85%); Mpt: 47-49 °C (Lit. 241 Mpt: 52-53 °C); δH (400 MHz, CDCl3): 5.42 [1H, s, CH(SPh)2], 7.20 (15H, m, Ar-H); δC (100 MHz, CDCl3): 60.4 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.8 (CH), 132.5 (CH), 134.5 (C) 139.5(C); m/z, EI+ (%): 308 (M++ , 2), 199 (M++ -C₆H₅S, 100).
Finely powdered molecular sieves 4Å (0.30 g), magnesium turnings (0.66 g, 2.70 mmol), and titanocene dichloride (0.56 g, 2.25 mmol), were heated briefly under vacuum and then allowed to cool to rt. The flask was then purged with argon, before adding THF (4 cm³) and triethylphosphite (0.77 cm³, 4.50 mmol). The reaction mixture was then allowed to stir at rt, for 3 h under argon. Thioacetal 285 (0.17 g, 0.55 mmol) in THF (1 cm³) was added to the reaction mixture, and was then further stirred for 10 mins, before cyclohexanone (0.05 g, 0.50 mmol) in THF (1.5 cm³), was added drop-wise over 15 mins and then allowed to stir at rt for 15 h. The reaction mixture was quenched by the addition of hexane (15 cm³), the resulting insoluble materials were removed by filtration through celite, and the solution was then concentrated to yield a red oil. Kugelrohr distillation of the residue (80-90 °C / 1mm Hg) removed some triethylphosphate and triethylphosphite to leave the crude desired product, which was purified by flash column chromatography (SiO₂, Pet. ether: ethyl acetate 19: 1) to yield phenylmethylidenecyclohexane 286 (0.05 g, 0.29 mmol, 57%) as a yellow oil; R₆ (Pet. ether: ethyl acetate 19: 1): 0.45; δ₁H (400 MHz, CDCl₃): 0.85-0.90 (2H, m, CH₂), 1.52-1.67 (4H, m, CH₂), 2.26 (2H, t, J 5.5, CH₂), 2.36 (2H, t, J 5.5, CH₂), 6.22 (1H, s, CH=C), 7.15-7.35 (5H, m, Ar-H).

2-[Bis(phenylthio)methyl]–4,4,5,5-tetramethyl-1,3,2-dioxaborolane 287

Following the procedure of Mendoza and Matteson, n-butyllithium (17.1 cm³, 42.6 mmol, 2.5 mol dm⁻³ in hexane) was added to a solution of bis(phenylthio)methane (10.00 g, 42.6 mmol) in THF (50 cm³), at 0 °C under nitrogen, and stirred for 30 mins. After this time, the reaction mixture was cooled to -78 °C and trimethylborate (4.9 cm³, 42.6 mmol) was added. The reaction mixture was then warmed to rt and stirred for 2 h, before cooling to -60 °C and quenching with aqueous HCl (90 cm³, 2 mol dm⁻³). The resulting mixture was diluted with water (100 cm³) and extracted with diethyl ether (2 x 50 cm³). Precipitation of the ether soluble material was achieved by adding hexane (100 cm³) to give a 7: 4 ratio of 2-[bis(phenylthio)methyl]boronic acid 203 A: bis(phenylthio)methane B as a white solid (10.35 g, 88%); δ₁H (400 MHz, CDCl₃): 4.16 (1H, s, CHB), 4.35 (2H, s, CH₂), 5.10 (2H, s, OH), 7.25-7.51 (10H, m, Ar-H). Pinacol (5.28 g, 44.8 mmol) was
added to a solution of the crude 2-[bis(phenylthio)methyl]boronic acid (10.00 g, 42.6 mmol) in THF (50 cm³), under nitrogen at rt, and stirred for 18 h. After this time, the reaction mixture was concentrated to leave a colourless oil. Purification by Kugelrohr distillation (70-80 °C, 1 mm Hg), removed pinacol and bis(phenylthio)methane. Further Kugelrohr distillation (200-220 °C, 1 mm Hg), gave the impure product as an oil (8.33 g) which upon low temperature crystallisation (freezer) from Pet. ether, yielded 2-[bis(phenylthio)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane\(^{203}\) \(287\) as plates (5.37 g, 15 mmol, 2 steps 33%); Mpt: 34-37 °C, (Lit.\(^{203}\) : oil); \(\nu_{\text{max}}^\text{KBr}/\text{cm}^{-1}\) 3059 (CH), 2680 (CH), 1583 (C=C), 1391 (B-O), 847 (B-C), 747 (CH), 689 (CH); \(\delta_H\) (400 MHz, CDCl\(_3\)): 1.13 (12H, s, CH\(_3\)), 4.20 (1H, s, CHB), 7.17-7.30 (6H, m, Ar-H), 7.48-7.50 (4H, m, Ar-H); \(\delta_C\) (100 MHz, CDCl\(_3\)): 24.9 (CH\(_3\)), 85.1 (C), 127.6 (CH), 129.1 (CH), 131.8 (CH), 135.7 (C), 138.5 (C); m/z, EI\(^+\) (%): 358 (M\(^+\), 100), 249 (M\(^+\)SC\(_6\)H\(_5\), 100), 149 (95); Accurate mass: C\(_{19}\)H\(_{23}\)BO\(_2\)S\(_2\): requires 357.1269, found 357.1264, C\(_{19}\)H\(_{23}\)BO\(_2\)S\(_2\): requires 358.1233, found 358.1230; Microanalysis Found: C 63.64%, H 6.41%; Theoretical: C 63.72%, H 6.47%.

1,3-Dithian-2-yl-1,3,2-dioxaborolane \(288\)

\(n\)-Butyllithium (7.5 cm\(^3\), 18.8 mmol, 2.5 mol dm\(^{-3}\) in hexane) was added to a solution of 1,3-dithiane (2.25 g, 18.8 mmol) in THF (20 cm\(^3\)), under nitrogen at 0 °C, and stirred for 30 mins. After this time, the reaction mixture was cooled to -78 °C, and trimethylborate (2.2 cm\(^3\), 18.8 mmol) was added. The reaction mixture was then warmed to 25 °C and stirred for 2 h, before cooling to -60 °C and quenched with aqueous HCl (2 mol dm\(^{-3}\), 40 cm\(^3\)). The resulting mixture was then diluted with water (50 cm\(^3\)) and extracted with diethyl ether (2 x 50 cm\(^3\)). Precipitation of the ether-soluble material by adding hexane (100 cm\(^3\)) proved unsuccessful and so the solution was concentrated under vacuum to leave a yellow oil, which solidified on standing to yield a yellow solid (2.99 g). Pinacol (4.43 g, 18.8 mmol) was added to a solution of this crude material (2.99 g, 18.4 mmol, 97%, assuming pure boronic acid) in THF (10 cm\(^3\)), under nitrogen at rt and stirred for 16 h. After this time, the reaction mixture was concentrated to leave a colourless oil. Purification by Kugelrohr distillation (80-100 °C, 1.1 mm Hg), removed pinacol and 1,3-dithiane. Further Kugelrohr distillation (100-160 °C, 1.1 mm Hg), yielded 1,3-dithian-2-yl-1,3,2-dioxaborolane \(288\) (A) as a colourless oil [70% pure, contaminated with pinacol and an unknown impurity (B)] that crystallised on standing in the freezer (3.05 g, 12.4 mmol, 2.
steps 66%); bp 100-160 °C (1.1 mm Hg); ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 2980 (CH), 2926 (CH<sub>2</sub>), 2845 (CH<sub>2</sub>), 1458 (B-O), 847 (B-C); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 1.24 (12H<sup>B</sup>, s) 1.27 (12H<sup>A</sup>, s, CCH<sub>3</sub>), 2.02-2.04 (2H<sup>A</sup> + 2H<sup>B</sup>, m, CH<sub>2</sub>), 2.77-2.93 (4H<sup>A</sup> + 4H<sup>B</sup>, m, SCH<sub>2</sub>), 3.72 (1H<sup>B</sup>, bs, CH/B), 3.78 (1H<sup>B</sup>, m); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 24.6 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 24.9 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 84.6 (C) 138.1 (C); m/z, El+ (%): 246 (M<sup>+</sup>, 8), 120 (M<sup>+</sup>-C<sub>6</sub>H<sub>12</sub>O<sub>2</sub>, 53), 59 (100); Accurate mass: C<sub>10</sub>H<sub>19</sub>O<sub>2</sub>B<sub>2</sub> requires 245.0956, found 245.0955, C<sub>10</sub>H<sub>19</sub>1<sub>B</sub>O<sub>2</sub>S<sub>2</sub> requires 246.0920, found 246.0922.

**Attempted formation of Alkenyl boronate 289 - using thioacetals 287 or 288**

Cp<sub>2</sub> Ti[P(OEt) <sub>3</sub>]<sub>2</sub> 74 was prepared on the same scale and by the same method as in the procedure for alkene 286. After allowing the low-valent titanium 74 mixture to stir for 3 h, thioacetal 287 (195 mg, 0.55 mmol) or thioacetal 288 (135 mg, 0.55 mmol) in THF (1 cm<sup>3</sup>) was added, and the reaction mixture was then allowed to stir for 10 mins. Cyclohexanone (0.05 g, 0.50 mmol) in THF (2 cm<sup>3</sup>), was then added drop-wise over 10 mins, the reaction mixture was stirred for 18 h, and then quenched by the addition of hexane (20 cm<sup>3</sup>). The resulting insoluble materials were removed by filtering through celite and the solution was then concentrated to yield a red oil. Distillation of the residue (100 °C / 1mm Hg) removed triethylphosphite and the <sup>1</sup>H NMR spectrum of the resulting residue confirmed there was no sign of the desired product 289, in both cases.

**Wang resin-bound ester 290**

Six Kans of Wang resin (each containing 168 mg resin, 0.29 mmol/kan, 1.74 mmol) were stirred in THF (100 cm<sup>3</sup>) at rt with hydrocinnamic acid (1.28 g, 8.53 mmol, 4.9 eq.) and DMAP (0.20 g, 1.64 mmol, 0.94 eq.). 1,3-Diisopropylcarbodiimide DIC (1.3 cm<sup>3</sup>, 8.5 mmol) was added drop-wise and the reaction mixture was stirred for a further 24 h. The THF solution was removed and the Kans were then washed with THF, MeOH/DCM alternate (x 4), MeOH and finally with diethyl ether. The resin was then dried under vacuum overnight and re-treated as above. Washing and drying of the resin as before yielded the desired resin-bound ester 290: δ<sub>C</sub> (90 MHz, Gel-Phase, CDCl<sub>3</sub>): 30.8 (CH<sub>2</sub>),
35.8 (CH$_2$), 40.2 (Wang CH$_2$), 66.0 (Wang CH$_2$), 126.2 (Wang C), 127.9 (Wang CH), 128.2 (CH), 128.4 (CH), 128.7 (Wang CH), 129.1 (C), 130.0 (C), 132.1 (Wang C), 128.2 (CH), 128.4 (CH), 128.7 (Wang CH), 129.1 (C), 130.0 (C), 132.1 (Wang C), 172.5 (C).

**Attempted formation of boronate 291**

![Diagram](image_url)

Following the general solid-phase Takeda reaction (method A), employing thioacetal 287 (0.52 g, 1.45 mmol) and Wang resin-bound ester 290 (0.29 mmol), and then subjecting the resin to the standard Merrifield resin cleavage conditions - A, a brown solid was obtained (0.016 g). $^1$H NMR spectroscopy confirmed that this was mostly dihydrocinamic acid and triethylphosphite with some other unknown impurities.

**General procedure for lithiation of bis(phenylthio)phenylmethane 285 and quenching with trimethylborate**

$n$-Butyllithium (2.6 cm$^3$, 6.50 mmol, 2.5 mol dm$^{-3}$ in hexane) was added to a solution of bis(phenylthio)phenylmethane 285 (2.00 g, 6.50 mmol) in THF (10 cm$^3$), under nitrogen at 0 °C and stirred for 30 min. After this time, the dark orange mixture was cooled to -78 °C, and trimethylborate (0.8 cm$^3$, 6.50 mmol) was added. The reaction mixture was then warmed to 25 °C and stirred for 2 h, before cooling to -60 °C and then quenched with aqueous HCl (2 mol dm$^{-3}$, 10 cm$^3$). The resulting mixture was then diluted with water (20 cm$^3$) and extracted with diethyl ether (2 x 25 cm$^3$). The combined organic phases were then dried over sodium sulphate, and concentrated under vacuum to leave a yellow oil. $^1$H NMR spectroscopy confirmed that a 8: 5: 5 mixture of bis(phenylthio)phenylmethane 285 (A): 1-(phenylthio)butane$^{205}$ (B): (phenylthio)phenylmethane$^{204}$ 294 (C) remained; $\delta$$_{H}$ (400 MHz, CDCl$_3$): 0.87 (3H, t, J 7.6, CH$_3$-CH$_2$), 1.40-1.54 (2H, m, CH$_2$), 1.60-1.67 (2H, m, CH$_2$), 2.90 (2H, t, J 7.4, CH$_2$-S), 4.11 (2H, s, CH$_2$), 5.42 (1H, s, CH), 7.15-7.37 (15H, m, Ar-H).
As above, 1,3-propanedithiol (6.0 cm$^3$, 60.0 mmol), benzaldehyde (3.10 cm$^3$, 30.0 mmol), acetic acid (20 cm$^3$) and boron trifluoride diethyletherate (3.2 cm$^3$, 27.0 mmol) in toluene (30 cm$^3$), followed by the same work-up as for thioacetal 285, yielded the desired thioacetal 297 as a white solid. Recrystallisation from Pet. ether gave 2-phenyl-1,3-dithiane 297 as needles (4.92 g, 25.0 mmol, 84%); Mpt: 67-69 °C, (Lit.$^{243}$ Mpt: 69-70 °C); $\delta_H$ (400 MHz, CDCl$_3$): 1.89-1.97 (1H, m, CH$_{ax}$), 2.14-2.21 (1H, m, CH$_{eq}$), 2.89-2.94 (2H, m, CH$_2$-S), 3.03-3.11 (2H, m, CH$_2$-S), 5.30 (1H, s, PhCH), 7.26-7.48 (5H, m, Ar-H); $\delta_C$ (100 MHz, CDCl$_3$): 25.1 (CH$_2$), 32.1 (CH$_2$), 51.5 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 139.1 (C); m/z, EI+ (%): 196 (M$^+$, 100), 122 (M$^+$-C$_3$H$_6$S, 60), 121 (M$^+$-C$_3$H$_7$S, 61).

General procedure for lithiation of 2-phenyl-1,3-dithiane 297 and formation of benzoin propylenethioacetal$^{244}$ 298

$n$-Butyllithium (0.6 cm$^3$, 1.30 mmol, 2.5 mol dm$^{-3}$ in hexane) was added to a solution of 2-phenyl-1,3-dithiane 297 (0.25 g, 1.27 mmol) in THF (5 cm$^3$), under nitrogen at -30 °C, and stirred for 1 h. After this time, the dark green reaction mixture was cooled to -78 °C, and benzaldehyde (0.15 cm$^3$, 1.50 mmol) was added. The resulting yellow solution was then warmed to 25 °C and stirred for 18 h. After this time, the reaction mixture was poured into saturated ammonium chloride solution (10 cm$^3$) and extracted with chloroform (2 x 10 cm$^3$). The combined organic phases were then washed with water (20 cm$^3$) and brine (20 cm$^3$), dried over sodium sulphate and concentrated in vacuo to leave a yellow oil. $^1$H NMR spectroscopy confirmed that this was a mixture of the desired product 298 (A)$^{244}$: thioacetal 297 starting material (B): benzaldehyde (C), 5: 1: 1; $\delta_H$ (400 MHz, CDCl$_3$): 1.75-1.95 (2H$^A$, m, CH$_2$), 1.89-1.97 (1H$^B$, m, CH$_{ax}$), 2.14-2.21 (1H$^B$, m, CH$_{eq}$), 2.55-2.70 (4H$^A$, m, CH$_2$-S), 2.89-3.11 (1H$^A$ + 4H$^B$, m, CH$_A$OH + CH$_B$-S), 4.98 (1H$^A$, s, OH), 5.30 (1H$^B$, S, PhCH), 6.84-6.86 (2H$^A$, m, Ar-H), 7.08-7.12 (2H$^A$, m, Ar-H), 7.16-7.20(1H$^A$, m, Ar-H), 7.24-7.48 (4H$^A$ + 5H$^B$, m, Ar-H), 7.50-7.52 (1H$^A$, m, Ar-H), 7.66-7.69 (3H$^C$, m, Ar-H), 7.85-7.87 (2H$^C$, m, Ar-H), 9.95 (1H$^C$, s, CHO).
Boron trifluoride diethyletherate (1.0 cm³, 8.00 mmol) was added drop-wise to a solution of cinnamaldehyde (2.64 g, 20.0 mmol) and propane-1,3-dithiol (2.2 cm³, 20.0 mmol) in dry diethyl ether (40 cm³) at 0 °C under nitrogen. The ice bath was then removed and the reaction mixture was stirred for 3 h at rt, and then quenched by pouring into aqueous sodium hydroxide (10%, 50 cm³). The resulting mixture was then extracted with chloroform (3 x 40 cm³) and the combined chloroform extracts were then washed with water (50 cm³) and brine (50 cm³), dried over sodium sulfate, and concentrated under vacuum to yield a yellow oil which crystallised on standing (4.40 g). Recrystallisation from hexane, gave 2-(1-styryl)-1,3-dithiane 299, as a yellow solid (3.51 g, 15.8 mmol, 79%); Mpt: 57-59 °C, (Lit. 212 Mpt: 57-58 °C); δ_H (400 MHz, CDCl3): 1.85-1.95 (1H, m, CH₉), 2.10-2.17 (1H, m, CH₂), 2.86-3.10 (4H, m, CH₂-S), 4.80 (1H, d, J 7.7, S₂CH), 6.23 (1H, dd, J 7.7 and 16.0, CH=CHPh), 6.74 (1H, d, J 16.0, CH=CHPh), 7.23-7.39 (5H, m, Ar-H); δ_C (100 MHz, CDCl3): 25.2 (CH₂), 30.2 (CH₂), 47.7 (CH), 126.0 (CH), 126.7 (CH), 128.1 (CH), 128.6 (CH), 133.4 (CH), 136.1(C).

General procedure for lithiation of 2-(1-styryl)-1,3-dithiane 299 in the formation of thioacetal 300

n-Butyllithium (0.40 cm³, 1.00 mmol, 2.5 mol dm⁻³ in hexane) was added to a solution of 2-(1-styryl)-1,3-dithiane 299 (0.20 g, 0.90 mmol) in THF (5 cm³), under nitrogen at -40 °C, warmed to -20 °C and stirred for 1 h. After this time, the dark orange reaction mixture was cooled to -40 °C, and D₂O (0.20 cm³, 10.0 mmol) was added. The yellow solution was then warmed to 25 °C and stirred for 45 mins. The reaction mixture was poured into saturated brine (10 cm³) and extracted with chloroform (2 x 10 cm³). The combined organic phases were then washed with water (30 cm³) and brine (30 cm³), dried over sodium sulphate and concentrated under vacuum to leave a yellow oil. ¹H NMR spectroscopy confirmed this contained a mixture of 2-deuterio-2-(1-styryl)-1,3-dithiane 300 A: 2-(1-styryl)-1,3-dithiane 299 B (4: 1); δ_H (400 MHz, CDCl₃): 1.85-1.95 (1H₂⁺⁺, m, CH₉), 2.10-2.17 (1H₂⁺⁺, m, CH₂), 2.86-3.10 (4H₂⁺⁺, m, CH₂-S), 4.80 [1H⁺, d, J 7.7, S₂CH], 6.23 (1H⁺, d, J 16.0, CH=CHPh), 6.24 (1H⁺, dd, J 7.7 and 16.0, CH=CHPh), 6.74 (1H⁺⁺, d, J 16.0, CH=CHPh), 7.19-7.39 (5H⁺⁺, m, Ar-H).
Boron trifluoride diethyletherate (2.0 cm$^3$, 16.0 mmol) was added dropwise to a solution of 2-aminooacetophenone (1.35 g, 10 mmol) and propanedithiol (2.2 cm$^3$, 20.0 mmol) in diethyl ether (10 cm$^3$), and the reaction mixture was heated under reflux for 60 h. After this time the reaction mixture was washed with sodium hydroxide (1 mol dm$^{-3}$, 3 x 10 cm$^3$) and water (30 cm$^3$), dried over sodium sulfate, and concentrated to leave a yellow oil. The crude $^1$H NMR spectrum confirmed 87% conversion to the desired product. Purification by column chromatography (SiO$_2$, DCM), resulted in elimination of the thioacetal moiety explaining the poor yield obtained as the majority of the product was contaminated with 2-aminoacetophenone. Some of the desired product 310 was obtained in moderate purity as a yellow oil (0.72 g, 3.20 mmol, 32%, 95% pure); $R_f$ (SiO$_2$, DCM): 0.15, $\delta_H$ (400 MHz, CDCl$_3$): 1.97-1.99 (5H, m, CH$_2$ and CH$_3$), 2.83-2.86 (4H, m, CH$_2$-S), 4.88 (2H, s, NH$_2$), 6.65 (1H, dd, $J$ 1.2 and 7.9, H-3'), 6.77 (1H, dt, $J$ 1.3 and 8.2, H-5'), 7.10 (1H, dt, $J$ 1.5 and 7.9, H-4'), 7.78 (1H, dd, $J$ 1.4 and 8.0, H-6'); $\delta_C$ (100 MHz, CDCl$_3$): 24.6 (CH$_2$), 27.5 (CH$_3$), 28.2 (CH$_2$), 53.0 (C), 118.1 (CH), 118.6 (CH), 124.6 (C), 128.9 (CH), 130.5 (CH), 145.9 (C).

2-(2'-Aminophenyl)-2-methyl-1,3-dithiane 310

\[
\begin{align*}
\text{S} & \text{S} \\
\text{NH}_2 & \\
\end{align*}
\]

Boron trifluoride diethyletherate (7.8 cm$^3$, 60.8 mmol) was added drop-wise to a solution of 2-aminobenzophenone (6.0 g, 30.4 mmol) in 1,3-propanedithiol (6.6 cm$^3$, 60.8 mmol), and the reaction mixture was stirred for 20 h at rt. After this time DCM (30 cm$^3$) was added and the residue was washed with sodium hydroxide (1 mol dm$^{-3}$, 3 x 30 cm$^3$) and water (30 cm$^3$), dried over sodium sulfate, and concentrated to leave a yellow solid (8.44 g, 29.4 mmol, 97%). Recrystallisation from ethyl acetate gave 2-(2'-aminophenyl)-2-phenyl-1,3-dithiane 311 as needles (7.19 g, 24.9 mmol, 82%); $R_f$ (SiO$_2$, DCM): 0.30; Mpt: 113-116 °C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 3433 (NH$_2$), 3330 (NH$_2$), 1443 (CH), 1484 (CH); $\delta_H$ (400 MHz, CDCl$_3$): 1.95-2.03 (2H, m, CH$_2$), 2.71-2.96 (4H, m, CH$_2$-S), 4.50 (2H, s, NH$_2$), 6.64 (1H, dd, $J$ 1.1 and 7.9, H-3') 6.71 (1H, m, H-5'), 7.11 (1H, m, H-4'), 6.97 (1H, d, $J$ 8.0, H-6'),
7.28-7.36 (2H, m, Ar-H), 7.50 (1H, d, J 7.8, Ar-H), 7.65 (2H, d, J 7.7, Ar-H); δC (100 MHz, CDCl3): 24.4 (CH2), 29.5 (CH2), 61.4 (C), 117.5 (CH), 118.4 (CH), 124.1 (C), 127.9 (CH), 128.6 (CH) 128.8 (CH), 129.1 (CH), 132.2 (CH), 141.2 (C), 145.7 (C); m/z, EI+ (%): 287 (M++, 25), 213 (M++-C3H6S, 30), 212 (M++-C3H7S', 32), 180 (100); Accurate mass: C16H16NS2: requires 287.4497, found 287.4477; Microanalysis Found: C 66.79%, H 5.82%, N 4.73%; Theoretical C16H16OS2: C 66.89%, H 5.92%, N 4.88%.

2-(2'-Hydroxyphenyl)-1,3-dithiane

Following a known procedure for thioacetallisation,220 tellerium tetrachloride (0.27 g, 1.00 mmol) was added to a solution of salicaldehyde (2.44 g, 20.0 mmol) and 1,3-propanedithiol (2.0 cm³, 20.0 mmol) in dichloroethane (30 cm³), and was stirred at rt for 3 h. After this time 0.60 g of sodium bicarbonate was added and the residue were filtered off. The organic phases were then dried over sodium sulfate and concentrated to leave a pale yellow solid (4.23 g, 19.9 mmol, 99.5%). Washing the resultant solid with cold Pet. ether and drying under vacuum gave 2-(2'-hydroxyphenyl)-1,3-dithiane 314 as a white solid (4.03 g, 19.0 mmol, 95%): Mpt: 125-127 °C (Lit.245 Mpt: not quoted); νmax (KBr)/cm⁻¹ 3319 (OH), 2980 (CH), 1591 (CH), 1498 (CH2), 1498 (CH2), 1248 (OH), 758 (CH); δH (400 MHz, CDCl3): 1.89-2.00 (1H, m, CHax), 2.16-2.22 (1H, m, CHeq), 2.91-2.95 (2H, m, CH2), 3.04-3.11 (2H, m, CH2), 5.41 (1H, s, CH), 6.33 (1H, s, OH), 6.86-6.90 (2H, m, H-3' and H-6'), 7.19 (1H, dt, J 1.6 and 7.7, H-5'), 7.82 (1H, dt, J 1.7 and 8.0, H-4'); δC (100 MHz, CDCl3): 24.9 (CH2), 31.6 (CH2), 47.5 (CH), 117.4 (CH), 120.8 (CH), 123.5 (C), 129.1 (CH), 130.1 (CH), 154.5 (C); m/z, EI+ (%): 212 (M+++, 100), 138 (96), 137 (80); Accurate mass: C10H12OS2: requires 212.0330, found 212.0328; Microanalysis Found: C 56.64%, H 5.34%; Theoretical C10H12OS2: C 56.87%, H 5.21%.
Triethylamine (2.3 cm³, 16.5 mmol), was added to a solution of 2-(2’-hydroxyphenyl)-1,3-dithiane 314 (3.18 g, 15.0 mmol), tert-butylidimethylchlorosilane (2.49 g, 16.5 mmol), imidazole (1.12 g, 16.5 mmol), in DMF (15 cm³) and was allowed to stir for 16 h. The reaction mixture was poured into sat. sodium bicarbonate solution (30 cm³) and extracted into diethyl ether (3 x 30 cm³). The combined organic phases were washed with water (5 x 100 cm³), dried over sodium sulfate and concentrated to yield a pale yellow solid (4.88 g, 16.5 mmol, 100%). Recrystallisation from Pet. ether gave 2-(2’-tert-butyldimethylsilyloxyphenyl)-1,3-dithiane 316 as needles (3.66 g, 11.2 mmol, 75%); Mpt: 77-80 °C; v max (KBr)/cm⁻¹ 2952 (CH), 2856 (CH), 1286 (SiMe₂), 1089 (O-Si), 909 (O-Si), 831 (SiMe₂); δ H (400 MHz, CDCl₃): 0.26 (6H, s, SiMe₂), 1.06 (9H, s, CMe₃), 1.91-1.98 (1H, m, CH₉), 2.13-2.19 (1H, m, CH₉), 2.87-2.93 (2H, m, CH₂-S), 3.00-3.07 (2H, m, CH₂-S), 5.60 (1H, s, CH), 6.78 (1H, dd, J 1.1 and 8.1, H-3’), 6.93 (1H, dt, J 1.1 and 7.5, H-5’), 7.12 (1H, dt, J 1.8 and 7.5, H-4’), 7.52 (1H, dd, J 1.7 and 7.7, H-6’); δ c (100 MHz, CDCl₃): -4.4 (CH₃), 18.3 (C), 25.3 (CH₃), 25.8 (CH₃), 32.5 (CH₂), 44.8 (CH), 118.8 (CH), 121.7 (CH), 129.0 (CH), 129.2 (CH), 129.8 (C), 138.1 (C); m/z, El+ (%): 326 (M⁺, 20), 269 (100), 223 (16), 195 (87), 161 (34), 135 (20), 82.9 (16), 73 (86); Accurate mass: C₁₆H₁₆O₅S₂Si: requires 326.5973 found 326.5976; Microanalysis Found: C 58.83%, H 7.80%; Theoretical C₁₆H₁₆O₅S₂Si: C 58.89%, H 7.97%.

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing thioacetal 316 (0.48 g, 1.45 mmol) and Wang resin-bound ester 290 (0.29 mmol), yielded 1-(2’-tert-butyldimethylsilyloxyphenyl)-4-phenylbutan-2-one 318 as an oil (0.070 g, 0.210 mmol, 71%): δ H (400 MHz, CDCl₃): 0.20 (6H, s, Me₂Si), 0.97 (9H, s, t-BuSi), 2.69 (2H, t, J 8.0, CH₂), 2.83 (2H, t, J 7.9, CH₂), 3.64 (2H, s, CH₂), 6.81 (1H, d, J 8.1, H-3’), 6.87 (1H, dt, J 7.4 and 1.0, H-5’), 7.06-7.12 (5H, m, Ar-H), 7.22-7.25 (2H, m, Ar-H).
1,3-Propanedithiol (13.4 cm³, 124 mmol) was added to a solution of 2-hydroxyacetophenone (10.0 g, 73.5 mmol), and boron trifluoride diethyletherate (15 cm³, 118 mmol) in THF (40 cm³), under nitrogen, and stirred for 15 h at rt. After this time, the reaction mixture was quenched by adding water (80 cm³) and extracted with diethyl ether (3 x 60 cm³). The combined organic phases were then washed with saturated sodium bicarbonate solution until the acid was neutralised, dried over sodium sulfate, and concentrated in vacuo to yield a colourless oil [(16.81 g, 74.3 mmol, 101%), [due to poor separation between Rf of product and starting material in all solvents tried, the crude product (approx 86% conversion) was protected without purification]. Triethylamine (14 cm³, 100 mmol) was added to a crude mixture of thioacetal 315 [(assume 73.5 mmol), 86:14 mole ratio thioacetal 315: 2-hydroxyacetophenone by ¹H NMR with some 1,3-propanedithiol], imidazole (6.81 g, 100 mmol), and tert-butyldimethylchlorosilane (15.07 g, 100 mmol) in DMF (50 cm³) under nitrogen, and stirred for 16 h. The reaction mixture was quenched into sodium bicarbonate solution (30 cm³) and extracted into diethyl ether (2 x 40 cm³). The combined organic phases were then washed with water (3 x 100 cm³), dried over sodium sulphate and concentrated to leave a yellow oil (27.1 g). Column chromatography of a 3.00 g portion [SiO₂, DCM: Pet. ether 1: 1], gave the desired product 319 (2.14 g, 6.28 mmol). Recrystallisation of the white solid from Pet. ether gave the desired product as plates (1.73 g, 5.08 mmol). The remainder was then purified by crystallisation from Pet. ether, induced by seeding, to yield 2-(2'-tert-butylidimethylsilyloxyphenyl)-2-methyl-1,3-dithiane 319 as plates (12.24 g, 35.9 mmol, 44% for 2 steps); Rf (DCM: Pet ether 1: 1): 0.40; Mpt: 56-59 °C; νmax (KBr)/cm⁻¹ 2960 (CH), 2856 (CH), 1251 (SiMe₂), 1058 (O-Si), 911 (O-Si), 825 (SiMe₂); δH (400 MHz, CDCl₃): 0.32 (6H, s, SiMe₂), 1.04 (9H, s, CMe₃), 1.89-1.97 (2H, m, CH₂), 2.00 (3H, s, CH₃), 2.75-2.82 (4H, m, CH₂-S), 6.85 (1H, dd, J 1.0 and 8.0, H-3'), 6.90 (1H, dt, J 1.1 and 7.8, H-5'), 7.13 (1H, dt, J 1.7 and 7.8, H-4'), 7.92 (1H, dd, J 1.7 and 7.9, H-6'); δC (100 MHz, CDCl₃): -3.3 (CH₃), 19.1 (C), 24.8 (CH₂), 26.5 (CH₃), 28.4 (CH₂), 28.7 (CH₃), 118.4 (CH), 119.7 (CH), 128.4 (CH), 131.1 (CH), 132.3 (C), 134.1 (C); m/z, EI+ (%): 340 (M⁺, 16), 283 (16), 209 (100); Accurate mass: C₁₇H₂₈O₅Si₂: requires 340.6262, found 340.6245; Microanalysis Found: C 59.60%, H 8.21%; Theoretical C₁₆H₁₆O₅Si₂: C 60.00%, H 8.23%.
**N,N-Dibenzyl-2-bromoaniline 321**

![Chemical Structure](image)

Benzyl bromide (11.6 cm$^3$, 93.0 mmol), was added to a solution of 2-bromoaniline (4.0 g, 23.3 mmol) and potassium carbonate (12.9 g, 93.0 mmol) in NMP (25 cm$^3$) under nitrogen, and the reaction mixture was heated at 60-70 °C for 16 h. After allowing to cool, water (50 cm$^3$) was added and stirred for 10 min. The mixture was extracted with diethyl ether (3 x 30 cm$^3$), and the combined organic phases were washed with water (10 x 80 cm$^3$) and dried over sodium sulfate, before concentrating *in vacuo* to yield a yellow oil. Column chromatography (SiO$_2$, eluting with Pet. ether and then DCM) yielded *N,N*-dibenzyl-2-bromoaniline 321 as a colourless oil (6.44 g, 18.3 mmol, 79%): $R_f$ (SiO$_2$, Pet. ether): 0.10; $\nu_{\text{max}}$ (Thin Film)/cm$^{-1}$ 3061 (CH), 3026 (CH), 783 (CH), 753 (CH); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 4.17 (4H, s, NCH$_2$), 6.83 (1H, dt, $J$ 1.6 and 7.5, H-4), 6.89 (1H, dd, $J$ 1.5 and 8.0, H-6), 7.07 (1H, dt, $J$ 1.5 and 8.1, H-5) 7.17-7.35 (1OH, m, Ar-H), 7.56 (1H, dd, $J$ 1.5 and 7.9, H-3); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 56.4 (CH$_2$), 121.4 (C), 124.5 (CH), 124.7 (CH), 127.0 (CH), 127.6 (CH), 128.2 (CH), 128.6 (CH), 133.8 (CH), 138.0 (C), 148.8 (C); m/z, EI+ (%): 351 (M$^{+}$, 22), 260 (M$^{+}$-CH$_2$Ph, 19), 180 (20), 91 (100); Accurate mass: C$_{20}$H$_{18}$N$_7$Br: requires 351.0623, found 351.0625, C$_{20}$H$_{18}$N$_8$1Br: requires 353.0604, found 353.0601; Microanalysis: Found C 68.13%, H 5.10%, N 3.98%, Br 22.80%; Theoretical C$_{20}$H$_{18}$NBr: C 68.18%, H 5.11%, N 3.98%, Br 22.73%.

**N-Benzyl-N-phenyl-N-(1'-phenylpent-1'-yl) 324**

$n$-Butyllithium (1.80 cm$^3$, 4.40 mmol, 2.5 mol dm$^{-3}$ in hexane) was added to a solution of *N,N*-dibenzyl-2-bromoaniline 321 (1.30g, 3.69 mmol) in THF (12 cm$^3$), under nitrogen at -78 °C, and slowly allowed to warm to -40 °C over 30 mins. After this time, DMF (0.80 cm$^3$, 10.4 mmol) was added and the reaction mixture was then slowly warmed to 25 °C and stirred for 1 h. The reaction mixture was then poured into water (30 cm$^3$) and extracted with diethyl ether (2 x 30 cm$^3$). The combined organic phases were then washed with water (2 x 30 cm$^3$) and brine (30 cm$^3$), dried over sodium sulfate and concentrated to give a yellow solid (1.20 g). Recrystallisation from propan-2-ol gave *N*-benzyl-*N*-phenyl-*N*-(1'-phenylpent-1'-yl) 324 as golden yellow needles (0.90 g, 2.90 mmol, 78%); Mpt: 98-101 °C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 2945 (CH), 2926 (NCH$_2$), 2840 (NCH$_2$), 753 (CH), 726 (CH), 700 (CH);
N,N-Dibenzyl-4-methylaniline

Benzyl bromide (14.0 cm³, 112 mmol) was added to a solution of p-toluidine (3.00 g, 28.0 mmol) and potassium carbonate (15.5 g, 112 mmol) in NMP (30 cm³) under nitrogen, and the reaction mixture was heated at 60-70 °C for 60 h. After cooling, water (100 cm³) was added and stirred for 10 mins before extracting with diethylether (3 x 30 cm³). The combined organic phases were washed with water (4 x 60 cm³), dried over sodium sulfate and concentrated in vacuo, to give an orange oil (8.91 g). Column chromatography of a 1.00 g portion (SiO₂, DCM), gave the desired amine 325 as a white solid (0.37 g). Recrystallisation from DCM/ propan-2-ol gave the desired product 325, as needles (0.27 g). The remainder of the reaction mixture was purified by crystallisation, induced by seeding, to give N,N-dibenzyl-4-methylaniline 325 as needles (5.94 g, 20.7 mmol, 74%); Mpt: 53-56 °C (Lit. 246, Oil); δH (400 MHz, CDCl₃): 2.22 (3H, s, CH₃), 4.62 (4H, s, NCH₂), 6.64 (2H, d, J 8.4, H-2 and H-6), 6.97 (2H, d, J 8.3, H-3 and H-5), 7.22-7.33 (10H, m, Ar-H); δC (100 MHz, CDCl₃): 20.2 (CH₃), 54.4 (CH₂), 112.6 (CH), 126.7 (CH), 126.8 (CH), 128.6 (CH), 129.7 (CH), 138.1 (C), 138.8 (C), 196.1 (C); m/z, EI+ (%): 287 (M⁺, 100), 210 (M⁺-C₆H₅, 27), 180 (M⁺-C₇H₇, 27), 91 (100); Microanalysis: Found C 87.85%, H 7.45%, N 4.85%; Theoretical C2₁H₂₁N: C 87.81%, H 7.32%, N 4.88%. 

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2-N,N-Dimethylamino-5-methyl benzaldehyde 326

Phosphorous oxychloride (5.70 cm³, 60.0 mmol) was added to DMF (14 cm³) at 0 °C, and was allowed to stir for 15 min. After this time N,N-dimethyl-p-toluidine (2.20 cm³, 20 mmol) was added and the reaction was allowed to warm to 60 °C stirred for 16 h. After this time the reaction was then poured into sodium hydroxide (2 mol dm⁻³, 40 cm³) and extracted into diethyl ether (3 x 30 cm³). The combined organic phases were then washed with water (6 x 100 cm³), dried over sodium sulfate and concentrated to yield a yellow oil (2.76 g, 16.9 mmol). Column chromatography (SiO₂, hexane: diethyl ether 9: 1) gave the desired product 2-N,N-dimethylamino-5-methyl benzaldehyde 326 as a yellow oil (1.99 g, 12.2 mmol, 61%): Rf (SiO₂, hexane: diethyl ether 9: 1): 0.10; νmax (KBr)/cm⁻¹ 2945 (NMe₂), 2837 (NMe₂), 2792 (NMe₂), 1686 (C=C); δH (400 MHz, CDCl₃): 2.31 (3H, s, Ar-CH₃), 2.87 (6H, s, NMe₂), 6.97 (1H, d, J 8.3, H-3), 7.27 (1H, dd, J 2.2 and 8.3, H-4), 6.97 (1H, d, J 1.8, H-6); δC (100 MHz, CDCl₃): 20.3 (CH₃), 45.8 (CH₃), 118.0 (CH), 127.3 (C), 130.4 (CH), 130.6 (C), 135.4 (CH), 154.1 (C), 191.6 (CH); m/z, El⁺ (%): 163 (M⁺, 100), 134 (M⁺-CHO, 45), 120 (M⁺-C₂H₃O, 64); Accurate mass: C₁₀H₁₃NO: requires 163.2193, found 163.2201; Microanalysis Found: C 73.42%, H 7.97%, N 8.57%; Theoretical: C₁₀H₁₃NO: C 73.61%, H 7.98%, N 8.59%.

2-[2'-(N,N-Dimethylamino)-5-methylphenyl]-1,3-dithiane 327

Boron trifluoride diethyletherate (2.6 cm³, 20.0 mmol) was added to a mixture of 2-(N,N-dimethylamino)-5-methylbenzaldehyde 326 (1.60 g, 9.80 mmol) and 1,3-propanedithiol (2.0 cm³, 20.0 mmol), was heated at 70 °C for 15 h. The reaction mixture was worked up as for thioacetal 319 to yield a yellow oil (2.09 g, 84%). Column chromatography (SiO₂, DCM) gave the desired product as a colourless oil (1.36 g, 5.68 mmol, 58%). Recrystallisation from DCM/ Pet. ether gave 2-[2'-(N,N-dimethylamino)-5-methylphenyl]-1,3-dithiane 327 as needles (0.99 g, 3.92 mmol, 40%): Rf (SiO₂, DCM): 0.45; Mpt: 54-57 °C; δH (400 MHz, CDCl₃): 1.90-2.00 (1H, m, CH₃ax), 2.15-2.20 (1H, m, CH₃eq), 2.29 (3H, s, CH₃), 2.72 (6H, s, NMe₂), 2.86-2.91 (2H, m, CH₂-S), 3.07-3.15 (2H, m, CH₂-S), 5.75 (1H, s, S₂CH), 6.99-7.05 (2H, m, H-3' and H-6'), 7.41 (1H, s, H-4'); δC (100 MHz, CDCl₃): 20.7
(CH₃), 25.4 (CH₂), 32.6 (CH₂), 45.7 (CH), 45.8 (CH₃), 119.5 (CH), 129.7 (CH), 130.0 (CH), 130.1 (C), 133.5 (C); m/z, EI⁺ (%): 253 (M⁺⁺, 77), 238 (M⁺⁺-CH₃, 16), 220 (17), 146 (100); Accurate mass: C₁₃H₁₉NS₂: requires 253.4326, found 253.4305; Microanalysis Found: C 61.27%, H 7.60%, N 5.24%; Theoretical C₁₆H₁₆O₂: C 61.66%, H 7.51%, N 5.53.

1-(2'-N,N-Dimethylamino-5'-methylphenyl)-4-phenylbutan-2-one 328

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing 2-(2'-N,N-dimethylamino-5'-methylphenyl)-1,3-dithiane 327 (0.37 g, 1.45 mmol), and resin-bound ester 309a (0.30 mmol, Method A), yielded 1-(2'-N,N-Dimethylamino-5'-methylphenyl)-4-phenylbutan-2-one 328 as a yellow oil (0.044 g, 0.16 mmol, 53%); v max (Soln, CDCl₃)/cm⁻¹: 2940 (CH), 2900 (CH), 2825 (NMe₂); δH (400 MHz, CDCl₃): 2.34 (3H, s, CR 3 ), 2.91-2.98 (4H, m, CH₂CH₂Ph), 3.21 (6H, s, NMe₂), 4.15 (2H, s, CH₂CO), 6.85 (1H, s, H-6'), 7.19-7.31 (7H, m, Ar-H); δC (100 MHz, CDCl₃): 20.8 (CH₃), 29.7 (CH₂), 43.9 (CH₂), 46.1 (CH₂), 47.6 (CH₃), 119.7 (CH), 126.0 (CH), 127.5 (C), 128.4 (CH), 128.5 (CH), 130.0 (CH), 133.7 (CH), 140.1 (C), 140.7 (C), 140.9 (C), 206.4 (C); m/z, EI⁺ (%): 281.1 (M⁺⁺, 54), 162.1 (25), 148.1 (100); Accurate mass: C₁₉H₂₁NO: requires 281.3997, found 281.3992.

2'-Nitro-(bisthiophenyl)benzaldehyde thioacetal²⁴⁷ 330

Thiophenol (7.70 cm³, 75.0 mmol) was added to a solution of 2-nitrobenzaldehyde (4.53 g, 30.0 mmol), acetic acid (20 cm³) and boron trifluoride diethyletherate (3.9 cm³, 30.0 mmol) in toluene (25 cm³), under nitrogen, and stirred for 30 h at rt. Work up as for thioacetal 315 gave 2'-nitro-(bisthiophenyl)benzaldehyde thioacetal 330 as a yellow solid, which was analytically pure (8.82 g, 21.0 mmol, 70%). Recrystallisation of a 0.50 g portion from diethyl ether gave the desired 2'-nitro-(bisthiophenyl)benzaldehyde thioacetal 330 as yellow needles (0.35 g, 1.00 mmol, 58%); Mpt: 98-101 °C, (Lit.²⁴⁷ Mpt: 101 °C); v max (KBr)/cm⁻¹ 1526 (NO₂), 1361 (NO₂); δH (400 MHz, CDCl₃): 6.43 (1H, s, CH-S₂), 7.22-7.26 (6H, m, SPh), 7.34-7.36 (5H, m, SPh + H-5'), 7.52 (1H, dt, J 1.2 and 7.7, H-4'), 138
2-(2'-Nitrophenyl)-1,3-dithiane 329a

1,3-Propanedithiol (12.0 cm³, 120 mmol) was added to a solution of 2-nitrobenzaldehyde (15.0 g, 99.0 mmol) and boron trifluoride diethyletherate (13.5 cm³, 120 mmol) in toluene (50 cm³), under nitrogen and stirred for 16 h at rt. After this time, the reaction was quenched by adding water (50 cm³) and then extracted into DCM (2 x 50 cm³). The combined organic phases were washed with sodium hydroxide (1 mol dm⁻³, 2 x 50 cm³), water (2 x 100 cm³), dried over sodium sulfate and concentrated under vacuum to give a yellow solid. Recrystallisation from propan-2-ol gave 2-(2'-nitrophenyl)-1,3-dithiane 329a as yellow needles (20.72 g, 86.0 mmol, 87%): Rᵣ(SiO₂, DCM): 0.48; Mpt: 114-116 °C; ν_max (KBr)/cm⁻¹: 2954 (CH), 2832 (CH), 1524 (NO₂), 1351 (NO₂); δ₁H (400 MHz, CDCl₃): 1.89-2.01 (1H, m, CH₆), 2.17-2.24 (1H, m, CH₆a), 2.90-2.96 (2H, m, CH₂-S), 3.09-3.16 (2H, m, CH₄S), 5.89 (lH, s, CH-S₂), 7.42 (1H, dt, J 1.3 and 8.2, H-4'), 7.60 (1H, dt, J 1.2 and 7.6, H-5'); δ₁C (100 MHz, CDCl₃): 25.4 (CH₂), 32.7 (CH₂), 46.4 (CH), 125.1 (CH), 126.2 (C), 129.5 (CH), 131.1 (CH), 133.9 (CH), 138.5 (C); m/z, EI+ (%): 241 (M⁺-OH, 17), 224 (M⁺-O₂H, 6), 166 (49), 147 (24), 135 (32), 106 (100); Accurate mass: C₁₀H₁₁N₀₂S₂: requires 241.0231, found 241.0233; Microanalysis Found: C 49.80%, H 4.49% N 5.81%; Theoretical C₁₀H₁₁N₀₂S₂: C 49.79%, H 4.56% N 5.81%

2-(3'-Methoxy-2'-nitrophenyl)-1,3-dithiane 329b

As above, using 1,3-propanedithiol (3.30 cm³, 33.0 mmol), 3-methoxy-2-nitrobenzaldehyde (5.00 g, 27.6 mmol) and boron trifluoride diethyletherate (3.70 cm³, 33.0 mmol) in toluene (40 cm³), gave pure desired product (6.64 g, 23.5 mmol, 85%).
Recrystallisation of a 1.00 g portion from propan-2-ol, gave 2-(3'-methoxy-2'-nitrophenyl)-1,3-dithiane 329b as yellow needles (0.90 g, 3.30 mmol, 77%): Rf (DCM, SiO2): 0.60; Mpt: 188-191 °C; v_max (KBr)/cm⁻¹ 2843 (COMe), 1607 (C=C), 1534 (NO₂), 1369 (NO₂), 1283 (OMe); δ_H (400 MHz, CDCl₃): 1.86-1.97 (1H, m, CHax), 2.13-2.20 (1H, m, CHeq), 2.86-2.92 (2H, m, CH₂-S), 3.01 (2H, td, J 14.7 and 2.3, CH₂-S), 3.88 (1H, s, OCH₃), 5.14 (1H, s, CH-S₂), 6.98 (1H, dd, J 0.9 and 8.3, H-4'), 7.34 (1H, dd, J 1.1 and 7.9, H-6'), 7.41 (1H, t, J 8.1 H-5'); δ_C (100 MHz, CDCl₃): 24.8 (CH₂), 32.1 (CH₂), 45.5 (CH), 56.5 (CH₃), 112.6 (CH), 120.9 (CH), 131.5 (CH), 132.0 (C), 150.5 (C); m/z, EI+ (%): 271 (M⁺, 7), 254 (M⁺-OH, 10), 119 (44), 106 (100); Accurate mass: C₁₁H₁₃N₀₃S₂: requires 271.0337, found 271.0339; Microanalysis Found: C 48.76%, H 4.87% N 5.14%; Theoretical C₁₁H₁₃N₀₃S₂: C 48.69%, H 4.83%, N 5.13%.

2-(4',5'-Methylenedioxy-2'-nitrophenyl)-1,3-dithiane 329c

As above, using 1,3-propanedithiol (3.10 cm³, 30.1 mmol), 2-nitropiperonal (4.90 g, 25.1 mmol) and boron trifluoride diethyletherate (3.40 cm³, 30.1 mmol) in toluene (70 cm³), gave thioacetal 329c (6.99 g, 24.5 mmol, 98%). Recrystallisation of a 0.40 g portion from propan-2-ol, yielded 2-(4',5'-methylenedioxy-2'-nitrophenyl)-1,3-dithiane 329c as yellow needles (0.35 g, 1.23 mmol, 86%): Rf (SiO₂, DCM): 0.60; Mpt: 156-158 °C; v_max (KBr)/cm⁻¹ 2913 (OCH₂O), 1521 (NO₂), 1377 (NO₂); δ_H (250 MHz, CDCl₃): 1.84-2.00 (1H, m, CHax), 2.14-2.17 (1H, m, CHeq), 2.87-2.96 (2H, m, CH₂-S), 3.06-3.18 (2H, m, CH₂-S), 5.99 (1H, s, CH-S₂), 6.12 (2H, s, OCH₂O), 7.32 (1H, s, H-6'), 7.41 (1H, s, H-3'); δ_C (63 MHz, CDCl₃): 25.0 (CH₂), 32.3 (CH₂), 46.4 (CH), 103.2 (CH₂), 105.6 (CH), 109.6 (CH), 130.2 (C), 141.8 (C), 147.7 (C), 152.0 (C); m/z, EI+ (%): 285 (M⁺, 10), 268 [(M⁺-OH, 24)], 179 (42), 106 (80), 83 (100); Accurate mass: C₁₁H₁₁NO₄S₂: requires 285.0130, found 285.0133; Microanalysis Found: C 46.46%, H 3.97%, N 4.81%; Theoretical C₁₁H₁₁NO₄S₂: C 46.31%, H 3.86%, N 4.91%.
2-(5'-Hydroxy-2'-nitrophenyl)-1,3-dithiane 329d

The reaction was carried out as above, employing 1,3-propanedithiol (4.20 cm³, 40.7 mmol), 5-hydroxy-2-nitrobenzaldehyde (5.67 g, 33.9 mmol) and boron trifluoride diethyletherate (4.60 cm³, 40.7 mmol) in DCM (80 cm³). The reaction mixture was quenched into saturated sodium bicarbonate (80 cm³). The organic phases were separated and then washed with water (2 x 100 cm³), dried over sodium sulfate, and concentrated under vacuum to yield a yellow solid (8.88 g, 102%). Recrystallisation from toluene, gave 2-(5'-hydroxy-2'-nitrophenyl)-1,3-dithiane 329d as yellow needles (6.70 g, 26.1 mmol, 77%): Rf (SiO₂, DCM): 0.46; Mpt: 156-159 °C; νmax (KBr)/cm⁻¹: 3441 (NH₂), 1583 (C=C), 1520 (NO₂), 1333 (NO₂), 1304 (OH); δH (400 MHz, CDCl₃): 1.88-2.00 (1H, m, CHax), 2.17-2.24 (1H, m, CHeq), 2.91-2.95 (2H, m, CH₂-S), 3.10-3.18 (2H, m, CH₂-S), 5.82 (1H, bs, OH), 6.07 (1H, s, CH-S₂), 6.83 (1H, dd, J 9.0 and 2.3, H-4'), 7.30 (1H, d, J 2.8, H-6'), 7.95 (1H, d, J 9.0 H-3'); δC (100 MHz, CDCl₃): 25.1 (CH₂), 32.3 (CH₂), 46.2 (CH), 115.7 (CH), 117.2 (CH), 128.1 (CH), 136.8 (C), 160.1 (C); m/z, EI⁺ (%): 257 (M⁺, 7), 240 (M⁺-OH, 27), 160.0 (100); Accurate mass C₁₀H₁₁NO₃S₂: requires 257.0180, found 257.0178; Microanalysis Found: C 46.76%, H 4.33%, N 5.54%; Theoretical C₁₀H₁₁NO₃S₂: C 46.67%, H 4.31%, N 5.44%.

2-(5'-Chloro-2'-nitrophenyl)-1,3-dithiane 234 329f

As above, using 1,3-propanedithiol (8.20 cm³, 81.7 mmol), 5-chloro-2-nitrobenzaldehyde [15% 4-chloro-2-nitrobenzaldehyde (12.63 g, 68.1 mmol)] and boron trifluoride diethyletherate (9.20 cm³, 81.7 mmol) in toluene (100 cm³), gave a yellow solid (19.86 g). Two recrystallisations from propan-2-ol yielded a 12: 1 mixture of thioacetal 329f 234 (A): 2-(4'-chloro-2'-nitrophenyl)-1,3-dithiane (B), as yellow needles (14.50 g, 52.6 mmol, 77%): Rf (DCM, SiO₂): 0.67; δH (400 MHz, CDCl₃): 1.94-1.98 (1H⁺B, m, CHax), 2.17-2.22 (1H⁺B, m, CHeq), 2.91-2.97 (2H⁺B, m, CH₂-S), 3.08-3.15 (2H⁺B, m, CH₂-S), 5.11
2-(2'-Aminophenyl)-1,3-dithiane\textsuperscript{234} \textsuperscript{331a}

\begin{center}
\includegraphics[width=0.2\textwidth]{2-(2'-Aminophenyl)-1,3-dithiane.png}
\end{center}

THF (150 cm\textsuperscript{3}) was added to a 3-necked flask charged with argon, containing 2-(2'-nitrophenyl)-1,3-dithiane \textsuperscript{329a} (20.7 g, 86.0 mmol) and the reaction mixture was cooled using an ice bath. Palladium on charcoal (5% loading/50% water, 13.8 g) was added, followed by sodium borohydride (11.13 g, 294 mmol) in three equal portions over 10 min, and the reaction mixture was allowed to stir at rt for 18 h. After this time, the mixture was acidified to pH 6 with hydrochloric acid (2 mol dm\textsuperscript{-3}). Chloroform (150 cm\textsuperscript{3}) was added and the mixture stirred for 10 mins. The solution was then filtered and the organic layer was washed with water (2 x 200 cm\textsuperscript{3}), dried over sodium sulfate and concentrated to leave a yellow solid. Recrystallisation from propan-2-ol gave 2-(2'-aminophenyl)-1,3-dithiane\textsuperscript{234} \textsuperscript{331a} as needles (15.42 g, 73.0 mmol, 85%), R\textsubscript{f} (SiO\textsubscript{2}, DCM): 0.14; Mpt: 112-115 °C (Lit.\textsuperscript{234} 114-115 °C); \textit{v} max (KBr)/cm\textsuperscript{-1}: 3434 (NH\textsubscript{2}), 3340 (NH\textsubscript{2}), 1623 (NH\textsubscript{2}); \textit{\delta} (400 MHz, CDCl\textsubscript{3}): 1.88-1.99 (1H, m, CH\textsubscript{ax}), 2.15-2.22 (1H, m, CH\textsubscript{eq}), 2.90-2.95 (2H, m, CH\textsubscript{2}-S), 3.06-3.13 (2H, m, CH\textsubscript{2}-S), 4.15 (2H, bs, NH\textsubscript{2}), 5.30 (1H, s, S\textsubscript{2}CH), 6.68 (1H, dd, J 1.0 and 7.9, H-3'), 6.75 (1H, dt, J 1.1 and 7.5, H-5'), 7.09 (1H, dt, J 1.5 and 7.5, H-4'), 7.30 (1H, dd, J 1.4 and 7.7, H-6'); \textit{\delta} (100 MHz, CDCl\textsubscript{3}): 25.3 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 48.7 (CH), 117.0 (CH), 119.1 (CH), 123.1 (C), 128.5 (CH), 129.3 (CH), 144.4 (C); m/z, EI+ (%): 211 (M\textsuperscript{+}, 70), 178 (M\textsuperscript{+}-SH, 17), 136 (100); Accurate mass: C\textsubscript{10}H\textsubscript{13}NS\textsubscript{2}: requires 211.0489, found 211.0490; Microanalysis Found: C 66.79%, H 5.82%, N 4.73%; Theoretical C\textsubscript{10}H\textsubscript{13}NS\textsubscript{2}: C 66.89%, H 5.92%, N 4.88%.

Diazine-\textit{n}-oxide \textsuperscript{333}

\begin{center}
\includegraphics[width=0.2\textwidth]{Diazine-\textit{n}-oxide.png}
\end{center}

THF (150 cm\textsuperscript{3}) was added to a 3-necked flask, charged with argon, containing 2-(2'-nitrophenyl)-1,3-dithiane \textsuperscript{329a} (14.15 g, 58.6 mmol) and the reaction was cooled using an ice bath. Palladium on charcoal (5% loading/50% water, 4.38 g) followed by sodium borohydride (5.54 g, 147 mmol) in three equal portions over 15 mins were added, and the
reaction was stirred at rt for 18 h. After this time the reaction was worked up exactly as for 2-(2'-aminophenyl)-1,3-dithiane 331a above to leave an orange oil (13.52 g). ¹H NMR spectroscopy confirmed that an 18: 8: 2 mixture of aniline 331a: dimer 333: starting material 329a was obtained. Column chromatography (SiO₂, CHCl₃) gave pure starting material 329a (0.50 g, 2.07 mmol), aniline 331a (5.21 g, 24.7 mmol) and dimer 333 (1.93 g, 4.43 mmol) which was recrystallised from ethyl acetate to give the pure diazine-N-oxide 333 as orange/yellow needles (1.59 g, 3.65 mmol); Rf (SiO₂, CHCl₃): 0.25; Mpt: 202-204 °C; vₘₐₓ (KBr)/cm⁻¹: 1630 (CH), 1460 (N=NO), 1390 (N=NO), 765 (CH), 575 (1H, s, S₂CH), 6.00 (1H, s, S₂CH), 7.41-7.47 (3H, m, Ar-H), 7.53-7.54 (1H, m, Ar-H), 7.71 (1H, dd, J 1.2 and 7.9, Ar-H), 7.81-7.83 (1H, m, Ar-H), 7.89 (1H, dd, J 1.3 and 7.8, Ar-H), 8.55-8.57 (1H, m, Ar-H); δC (100 MHz, CDCl₃): 25.0 (CH₂), 25.1 (CH₂), 32.0 (CH₂), 32.1 (CH₂), 45.6 (CH), 122.0 (CH), 124.1 (CH), 128.4 (CH), 129.0 (CH), 129.1 (CH), 130.0 (CH), 130.1 (CH), 130.7 (CH), 132.1 (C), 136.5 (C), 140.2 (C), 147.8 (C); m/z, EI⁺ (%): 435 [(M+H)⁺, 15], 417 [(M+H)⁺-H₂O, 23], 311 (45), 237 (42), 221 (100); Accurate mass: C₂₀H₂₂N₂O₆ requires 435.0693, found 435.0693; Microanalysis: Found C 55.21%, H 5.05%, N 6.43%; Theoretical C₂₀H₂₂N₂O₆: C 55.14%, H 5.09%, N 6.43%.

2-(2'-Amino-3'-methoxyphenyl)-1,3-dithiane 331b

Following the above procedure, 2-(3'-methoxy-2'-nitrophenyl)-1,3-dithiane 329b (6.24 g, 23.0 mmol), palladium on charcoal (5% loading/ 50% water, 3.69 g) and sodium borohydride (2.61 g, 69.0 mmol) in THF (50 cm³), gave the pure desired aniline 331b as a white crystalline solid (4.64 g, 19.2 mmol, 83%). Recrystallisation of a 0.50 g portion from propan-2-ol, gave 2-(2'-amino-3'-methoxyphenyl)-1,3-dithiane 331b as tiny needles (0.43 g, 1.87 mmol, 71%): Rf (SiO₂, DCM): 0.17; Mpt: 121-124 °C; vₘₐₓ (KBr)/cm⁻¹: 3421 (NH₂), 3333 (NH₂), 1617 (NH₂), 1480 (OCH₃); δH (400 MHz, CDCl₃): 1.88-2.00 (1H, m, CH₃), 2.15-2.19 (1H, m, CH₃), 2.89 (2H, dt, J 3.3 and 14.3, CH₂-S), 3.06-3.13 (2H, m, CH₂-S), 3.83 (3H, s, OCH₃), 4.16 (2H, bs, NH₂), 5.33 (1H, s, S₂CH), 6.71-6.76 (2H, m, H-4' and H-5'), 6.96 (1H, dd, J 2.2 and 6.8, H-6'), δC (100 MHz, CDCl₃): 25.3 (CH₂), 31.8 (CH₂), 48.4 (CH), 55.7 (CH₃), 110.0 (CH), 118.2 (CH), 120.3 (CH), 123.2 (C), 134.2 (C), 147.7 (C); m/z, EI⁺ (%): 241 (M⁺⁺, 100), 224 (5), 208 [(M⁺⁺-CH₃O), 17], 116 (C₁₀H₁₄S, 75), 152 (27); Accurate mass: C₁₁H₁₅NOS₂ requires 241.0595, found 241.0597;
Microanalysis Found: C 54.72%, H 6.15%, N 5.78%; Theoretical C_{11}H_{13}NOS_2: C 54.74%, H 6.26%, N 5.80%.

2-(2'-Amino-4',5'-methylenedioxyphenyl)-1,3-dithiane 331c

![Chemical structure of 331c](image)

Following a literature procedure, a mixture of iron powder (4.70 g, 28.0 mmol), 2-(4',5'-methylenedioxy-2'-nitrophenyl)-1,3-dithiane 329c (8.00 g, 50.0 mmol) and ammonium chloride (7.49 g, 140 mmol), in ethanol (125 cm^3) and water (75 cm^3), was heated under reflux for 1 h. After allowing to cool, the reaction mixture was filtered through celite, washing with ethanol. The dark green solution was then concentrated in vacuo. The resulting slurry was partitioned between ethyl acetate (150 cm^3) and brine (200 cm^3). The organic phases were then separated and washed with water (2 x 100 cm^3), dried over magnesium sulfate, and concentrated in vacuo to yield 2-(2'-amino-4',5'-methylenedioxyphenyl)-1,3-dithiane 331c which was one product by both ^1H NMR spectroscopy and TLC analysis and was not further purified due to it's instability in previous purification attempts), as a yellow solid (7.69 g, 108%): R_f (SiO_2, DCM): 0.42; $\delta_H$ (400 MHz, CDCl_3): 1.85-1.97 (1H, m, CH_αx), 2.13-2.20 (1H, m, CH_eq), 2.88 (2H, dt, J 3.2 and 14.5, CH_2-S), 3.05 (2H, td, J 14.5 and 2.5, CH_2-S), 5.25 (1H, s, CH-S_2), 5.86 (2H, s, OCH_2O), 6.31 (1H, s, H-3'), 6.87 (1H, s, H-6'); m/z, EI+ (%): 255 (M^{+}, 78), 180 (100); Accurate mass: C_{11}H_{13}NOS_2: requires 255.0388, found 255.0385.

2-(2'-Amino-5'-hydroxyphenyl)-1,3-dithiane 331d

![Chemical structure of 331d](image)

Following the above procedure, iron powder (7.54 g, 135 mmol) was added to a solution of 2-(5'-hydroxy-2'-nitrophenyl)-1,3-dithiane 329d (12.87 g, 50.0 mmol) and ammonium chloride (12.04 g, 225 mmol), in ethanol (200 cm^3) and water (200 cm^3) and heated under reflux for 2 h. Work up as above yielded pure aniline 331d as a yellow solid (9.87 g, 43.4 mmol, 87%). Recrystallisation of a 0.30 g portion from propan-2-ol, gave 2-(2'-amino-5'-hydroxyphenyl)-1,3-dithiane 331d as needles (0.24 g, 70%); $R_f$ (SiO_2, EtOAc): 0.46; Mpt: 156-159 °C; $\nu_{max}$ (KBr)/cm^{-1} 3441 (NH_2), 1583 (C=C), 1520 (NO_2), 1333 (NO_2), 1304 (OH); $\delta_H$ (250 MHz, C_2D_6SO): 1.61-1.77 (1H, m, CH_αx), 2.08-2.15 (1H, m, CH_eq), 2.80-
2.88 (2H, m, CH₂-S), 3.04-3.16 (2H, m, CH₂-S), 4.57 (2H, bs, NH₂), 5.39 (1H, s, CH-S₂), 6.43-6.49 (2H, m, H-4' and H-6'), 6.69 (1H, d, J 2.5, H-3'), 8.51 (1H, s, OH); oe (63 MHz, C₂D₆SO): 25.5 (CH₂), 31.6 (CH₂), 46.0 (CH), 114.8 (CH), 116.3 (CH), 117.3 (CH), 123.6 (C), 137.5 (C), 148.9 (C); m/z, EI+ (%): 257 (M⁺, 7), 240 [(M⁺-OH), 27], 160 (100); Accurate mass: C₁₀H₁₃NOS₂: requires 257.0180, found 257.0178; Microanalysis Found: C 52.86%, H 5.76%, N 6.13%; Theoretical C₁₀H₁₃NOS₂: C 52.86%, H 5.73%, N 6.17%.

2-(2'-Amino-5'-chlorophenyl)-1,3-dithiane

Following the above procedure, iron powder (8.81 g, 158 mmol) was added to a solution of a 12: 1 mixture of 2-(5'-chloro-2'-nitrophenyl)-1,3-dithiane 329f and 2-(4'-chloro-2'-nitrophenyl)-1,3-dithiane (14.50 g, 52.6 mmol), ammonium chloride (14.07 g, 263 mmol), in ethanol (200 cm³) and water (100 cm³), and heated under reflux for 2 h. Following work up as above, yielded aniline 331f as a yellow solid (9.64 g, 39.2 mmol). Two recrystallisations from propan-2-ol, gave 2-(2'-amino-5'-chlorophenyl)-1,3-dithiane 331f as yellow needles (6.55 g, 51%); Rf (SiO₂, DCM): 0.45; Mpt: 99-101 °C (Lit. oil); δ₂ (250 MHz, CDCl₃): 1.84-2.00 (1H, m, CH ax), 2.14-2.18 (1H, m, CH eq), 2.88-2.97 (2H, m, CH₂-S), 3.02-3.14 (2H, m, CH₂-S), 4.15 (2H, bs, NH₂), 5.22 (1H, s, CH-S₂), 6.60 (1H, d, J 8.5, H-3'), 7.04 (1H, dd, J 8.5 and 2.4, H-4'), 7.29 (1H, d, J 2.4, H-6').

2-[2'-(N,N-Di-tert-butyloxycarboxyamino)phenyl]-1,3-dithiane 334

Sodium hexamethyldisilazane (22.0 cm³, 22.0 mmol, 1 mol dm⁻³ in THF) was added to a solution of 2-(2'-aminophenyl)-1,3-dithiane 331a (2.11 g, 10.0 mmol) and di-tert-butyl-dicarbonate (5.46 g, 25.0 mmol) in THF (50 cm³) at 0 °C under nitrogen. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was then quenched by pouring into water (50 cm³), extracted into DCM (2 x 30 cm³). The combined organic phases were then washed with water (2 x 50 cm³), dried over sodium sulfate and concentrated to yield a yellow solid (3.53 g). Recrystallisation from Pet. ether gave 2-[2'- (N,N-di-tert-butyloxycarboxyamino)phenyl]-1,3-dithiane 334 as needles (3.21 g, 7.80 mmol, 78%); Rf (SiO₂, Hexane: DCM 1: 9): 0.10; Mpt: 106-109 °C; v max (KBr)/cm⁻¹: 2983
Following a known procedure, a solution of 2-(2’-aminophenyl)-1,3-dithiane 331a (3.18 g, 15.0 mmol) and di-tert-butyl-dicarbonate (3.60 g, 16.5 mmol) in THF (25 cm³) was heated under reflux, under nitrogen for 5 h. After this time the reaction mixture was poured into water (50 cm³) and extracted into DCM (2 x 30 cm³). The combined organic phases were washed with water (2 x 50 cm³), dried over sodium sulfate and concentrated to yield a yellow solid (4.34 g). Recrystallisation from propan-2-ol gave 2-[2’-(N-tert-butyloxycarboxyamino)phenyl]-1,3-dithiane 335a as golden plates (4.00 g, 12.8 mmol, 86%), Rf (SiO₂, DCM): 0.32; Mpt: 142-144 °C; v_max (KBr)/cm⁻¹: 3400 (NH), 2980 (CH), 2965 (CH), 1737 s (CO); δ_H (400 MHz, CDCl₃): 1.54 [9H, s, (CH₃)₃], 1.88-1.99 (1H, m, CH₉), 2.17-2.23 (1H, m, CH₉), 2.91-2.95 (2H, m, CH₂-S), 3.07-3.14 (2H, m, CH₂-S), 4.75 (1H, s, NH), 5.30 (1H, s, S₂CH), 7.05 (1H, dt, J 1.0 and 7.6, H-5’), 7.27 (1H, dt, J 1.5 and 8.6, H-4’), 7.40 (1H, dd, J 1.2 and 7.7, H-6’), 7.30 (1H, bd, J 7.1, H-3’); δ_C (100 MHz, CDCl₃): 25.1 (CH₂), 28.4 (CH₃), 31.9 (CH₂), 48.3 (CH), 80.5 (C), 122.9 (CH), 124.1 (CH), 128.3 (CH), 129.1 (CH), 136.1 (C), 138.1 (C), 153.2 (C); m/z, EI+ (%): 311 (M⁺⁺, 10), 255 (M⁺⁺-C₄H₁₀, 100), 254 (70); Accurate mass: C₁₅H₂₁NO₂S₂: requires 311.1014, found 311.1014; Microanalysis Found: C 57.95%, H 6.80%, N 4.40%; Theoretical C₁₅H₂₁NO₂S₂: C 57.84%, H 6.80%, N 4.50%.
Use of 2-[2'-(N,N-Di-tert-butylcarboxyamino)phenyl]-1,3-dithiane 334 under solution-phase Takeda conditions

Employing thioacetal 334 (1.23 g, 3.00 mmol), under the conditions described above, yielded an orange oil (0.95 g). $^1$H NMR analysis confirmed that a mixture of products (337: 338: 339/ 1: 1: 9) was obtained with considerable amounts of triethylphosphite and other impurities present. Column chromatography (SiO$_2$, EtOAc: Pet. ether 1:1) of a 0.50 g portion gave N,N-di-tert-butyloxycarboxyamino-2-toluidine 337 as a white solid (0.26 g): $R_f$ (SiO$_2$, EtOAc: Pet. ether 1:1): 0.11; $\delta_H$ (400 MHz, CDCl$_3$): 1.66 [18H, s, C(CH$_3$)$_3$], 3.65 (3H, s, CH$_3$), 7.11 (1H, t, J 7.6, H-4'), 7.23 (1H, d, J 7.3, H-6'), 7.28 (1H, t, J 7.8, H-5'), 7.77 (1H, d, J 8.3, H-3'); N-tert-butyloxycarboxyamino-2-toluidine 338 as a white solid (0.24 g): $R_f$ (SiO$_2$, EtOAc: Pet. ether 1:1): 0.40; Mpt: 79-81 °C (Lit. Mpt: 82-83 °C); $\delta_H$ (400 MHz, CDCl$_3$): 1.52 [9H, s, C(CH$_3$)$_3$], 2.25 (3H, s, CH$_3$), 6.25 (IH, s, NH), 6.97 (1H, dt, J 0.9 and 7.5, H-4'), 7.13 (1H, d, J 7.4, H-6'), 7.17 (1H, t, J 7.4, H-5'), 7.78 (1H, d, J 8.3, H-3'); and the corresponding thiol 339 (most of this compound appeared to be converted to the corresponding disulfide on silica) was obtained as a colourless oil (0.07 g): $R_f$ (SiO$_2$, EtOAc: Pet. ether 1:1): 0.35, $v_{max}$ (Thin film)/cm$^{-1}$: 3443 (NH), 3158 (NH), 3054 (SH), 2973 (OH), 2936 (OH), 2895 (OH), 1787 (CO), 1719 (CO), 1447 (NH), 1380 (OH), 1167 (COC); $\delta_H$ (400 MHz, CDCl$_3$): 1.33 (1H, t, J 8.1, SH), 1.64 [9H, s, C(CH$_3$)$_3$], 1.87-1.93 (2H, m, CH$_2$CH$_2$CH$_2$), 2.60 (2H, q, J 7.3, CH$_2$-SH), 2.71 (1H, td, J 7.4 and 12.8, CH$^A$CH$^B$CH$_2$SH), 2.92 (1H, td, J 6.8 and 12.8, CH$^A$CH$^B$CH$_2$SH), 3.72 (1H, t, J 7.6, H-5'), 7.32 (1H, t, J 7.8, H-4'), 7.38 (1H, d, J 7.4, H-6), 7.80 (1H, d, J 8.4, H-6); $\delta_C$ (100 MHz, CDCl$_3$): 23.7 (CH$_3$), 28.5 (CH$_3$), 29.0 (CH$_2$), 33.3 (CH$_2$), 45.4 (CH), 85.0 (C), 115.5 (CH), 124.8 (C), 125.1 (CH), 125.4 (CH), 129.8 (CH), 140.4 (C), 149.5 (C), 173.8 (C).
Use of 2-[2'-[N-tert-Butyloxycarboxyamino]phenyl]-1,3-dithiane 335a under solution-phase Takeda conditions

![Diagram of chemical reaction]

Employing thioacetal 335a (1.23 g, 3.00 mmol) under the conditions described above, yielded a red oil (1.93 g). $^1$H NMR analysis confirmed that a mixture of products (338: 341 2: 9) was obtained with considerable amounts of triethylphosphite and impurities with signals corresponding to cyclopentadienylligands. Column chromatography (Al$_2$O$_3$, Et$_2$O: Pet. ether 1: 1) of a 0.50 g portion of the crude material gave N-tert-butyloxycarboxyamino-2-toluidine 338 as a white solid (0.09 g): $R_f$ (Al$_2$O$_3$, Et$_2$O: Pet. ether 1: 1): 0.30, $^1$H NMR as before; and ring opened thiol 341 (most of this compound appeared to be converted to the corresponding disulfide on Al$_2$O$_3$ gel) was obtained as a colourless oil (0.20 g): $R_f$ (Al$_2$O$_3$, Et$_2$O: Pet. ether 1: 1): 0.20; $\nu_{\text{max}}$ (Thin film)/cm$^{-1}$: 3675 (NH), 3036 (NH), 3054 (SH), 1702 (CO), 1553 (C=C), 1472 (NH), 1169 (COC); $\delta$H (400 MHz, CDCl$_3$): 1.28 (1H, t, $J$ 8.1, SH), 1.53 [9H, s, C(CH$_3$)$_3$], 1.80 (2H, qu, $J$ 7.0 CH$_2$CH$_2$CH$_2$), 2.49 (2H, t, $J$ 7.1, CH$_2$-S-CH$_2$), 2.55 (2H, td, 7.0 and 7.9, CH$_2$SH), 3.72 (2H, s, ArCH$_2$S-), 6.98 (1H, dt, $J$ 1.2 and 7.5, H-5), 7.11 (1H, dd, $J$ 1.5 and 7.6, H-3), 7.26 (1H, dt, $J$ 1.6 and 7.6, H-4), 7.82 (1H, d, $J$ 8.0, H-6); $\delta$C (100 MHz, CDCl$_3$): 23.3 (CH$_3$), 28.4 (CH$_3$), 29.7 (CH$_2$), 32.9 (CH$_2$), 33.5 (CH$_2$), 80.5 (C), 122.6 (CH), 123.4 (CH), 126.5 (C), 128.5 (CH), 130.4 (CH), 137.0 (C), 153.2 (C); m/z, EI+ (%): 313 (M$^{+*}$, 4), 257 (7), 151 (41), 106 (50), 57 (100); Accurate mass: C$_{15}$H$_{23}$NO$_2$S$_2$: requires 313.1168, found 313.1170.

2-[2'-{(N-tert-Butyloxycarboxyamino)-3'-methoxyphenyl}-1,3-dithiane 335b

Following the procedure for carbamate 335a, a solution of 2-(2'-amino-3'-methoxyphenyl)-1,3-dithiane 331b (4.10 g, 17.0 mmol) and di-tert-butyl-dicarbonate (4.08 g, 18.7 mmol) in THF (30 cm$^3$), was heated under reflux for 40 h. After this time the reaction mixture was poured into water (50 cm$^3$) and extracted into diethylether (2 x 60 cm$^3$). The combined organic phases were washed with water (2 x 100 cm$^3$), dried over sodium sulfate and
concentrated to yield a white solid (4.76 g). Recrystallisation, from propan-2-ol, yielded 2-[2-\((N\text{-tert-butyl}o\text{xycarboxyamino})\)-3'-methoxyphenyl]-1,3-dithiane 335b as needles (4.34 g, 12.7 mmol, 75%), Mpt: 174-177 °C; \(\nu_{\text{max}} \text{(KBr)/cm}^{-1} \): 3317 (NH), 2359 (NCO), 1714 (CO), 1496 (C=C), 1473 (COMe); \(\delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.49 [9H, s, (CH\(_3\)_3)], 1.87-1.98 (1H, m, CH\(_{ax}\)), 2.13-2.20 (1H, m, CH\(_{eq}\)), 2.87 (2H, dt, J 14.4 and 4.0, CH\(_2\)-S), 3.03 (2H, td, J 2.4 and 14.6, CH\(_2\)-S), 3.83 (3H, s, OMe), 5.40 (1H, s, CH), 6.03 (1H, bs, NH), 6.83-6.87 (1H, m, H-5'), 7.20-7.24 (2H, m, H-4' and H-6'); \(\delta_{\text{C}} \) (100 MHz, CDCl\(_3\)): 25.3 (CH\(_2\)), 28.2 (CH\(_3\)), 32.3 (CH\(_2\)), 47.3 (CH\(_3\)), 55.8 (CH), 80.2 (C), 111.1 (CH), 120.3 (CH), 123.6 (C), 127.8 (CH), 136.9 (C), 154.7 (C); m/z, EI+ (%): 341 (M\(^{++}\), 12), 285 (M\(^{+}\)-C\(_4\)H\(_8\), 63), 284 (40), 240 (M\(^{+}\)-C\(_3\)H\(_9\)O, 63), 178 (100); Accurate mass: C\(_{16}\)H\(_{23}\)N\(_2\)O\(_3\)S\(_2\): requires 341.1119, found 341.1112; Microanalysis Found: C 56.40%, H 6.83%, N 4.17%; Theoretical C\(_{16}\)H\(_{23}\)N\(_2\)O\(_3\)S\(_2\): C 56.27%, H 6.79%, N 4.10%.

2-[2'-(N-tert-Butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane 335c

Following the procedure for carbamate 335a, a solution of 2-(2'-amino-4',5'-methylenedioxyphenyl)-1,3-dithiane 331c (5.61 g, 22.0 mmol) and di-tert-butyl-dicarbonate (11.52 g, 52.8 mmol) in THF (75 cm\(^3\)), was heated under reflux for 15 h. After this time the reaction mixture was poured into water (100 cm\(^3\)) and extracted into ethyl acetate (2 \(\times\) 60 cm\(^3\)). The combined organic phases were washed with brine (100 cm\(^3\)) and water (100 cm\(^3\)), dried over sodium sulfate, and concentrated to yield 2-[2'-(N-Di-tert-butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane with was contaminated with some di-tert-butyl-dicarbonate as a brown/green solid (15.04 g, 120%); \(R_f \) (SiO\(_2\), DCM): 0.52, \(\delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.55 [18H, s, (CH\(_3\)_3)], 1.87-1.98 (1H, m, CH\(_{ax}\)), 2.13-2.22 (1H, m, CH\(_{eq}\)), 2.91-2.95 (2H, m, CH\(_2\)-S), 3.07-3.14 (2H, m, CH\(_2\)-S), 5.24 (1H, s, CH-S\(_2\)), 5.96 (2H, s, OCH\(_2\)O), 6.96 (1H, s, H-3'), 6.28 (1H, s, H-6'). Trifluoroacetic acid (2.6 cm\(^3\), 33.0 mmol) was added drop-wise to the crude 2-[2'-(N-di-tert-butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane (15.04 g, assumed 22.0 mmol) in DCM (250 cm\(^3\)) and the reaction mixture was stirred for 15 h. After this time the reaction mixture was washed with sodium bicarbonate (2 \(\times\) 100 cm\(^3\)) and water (100 cm\(^3\)), dried over sodium sulfate and concentrated to yield a yellow solid (6.89 g). Recrystallisation from propan-2-ol gave 2-[2'-(N-tert-Butyloxycarboxyamino)-4',5'-methylenedioxyphenyl]-1,3-dithiane 335c as needles (4.34 g, 12.7 mmol, 75%).
methylene dioxyphenyl]-1,3-dithiane 335c as yellow needles (6.53 g, 18.4 mmol, 83% from 329c), Rf (SiO2, DCM): 0.15; Mpt: 156-158 °C; v_max (KBr/cm⁻¹): 3404 (NH), 2975 (OCH₂O), 1727 (CO), 1508 C=C), 1154 (COC); δ_H (400 MHz, CDCl₃): 1.53 [9H, s, (CH₃)₃], 1.85-1.95 (1H, m, CH₉ax), 2.15-2.21 (1H, m, CHeq), 2.88 (2H, dt, J 14.4 and 3.3, CH₂-S), 3.05-3.12 (2H, m, CH₂-S), 5.22 (1H, s, CH-S₂), 5.93 (2H, s, OCH₂O), 6.94 (1H, s, H-3'), 6.24 (1H, s, H-6'); δ_C (90 MHz, CDCl₃): 25.1 (CH₂), 28.4 (CH₃), 32.0 (CH₂), 47.7 (CH), 80.5 (C), 101.5 (CH₂), 105.6 (C), 107.7 (CH), 130.1 (C), 144.6 (C), 147.9 (C), 153.5 (C); m/z, EI⁺ (%): 355 (~O, 50), 298 (~O-C₄H₉, 55), 282 (M⁺-C₆H₆O, 29), 225 (M⁺-C₆H₁₀O₅, 58), 192 (M⁺-C₆H₁₂NO₄, 100); Accurate mass: C₁₆H₂₁NO₃S₂: requires 355.0912, found 355.0914; Microanalysis Found: C 54.23%, H 6.05%, N 3.86%; Theoretical C₁₆H₂₁NO₃S₂: C 54.08%, H 5.91%, N 3.94%.

2-[2'-(N-tert-Butyloxycarboxyamino)-5'-hydroxyphenyl]-1,3-dithiane 335d

Following the procedure for carbamate 335a, a solution 2-(2'-amino-5'-hydroxyphenyl)-1,3-dithiane 331d (9.09 g, 40.0 mmol) and di-tert-butyl-dicarbonate (10.48 g, 48.0 mmol) in THF (100 cm³), was heated under reflux for 64 h. After this time the reaction mixture was poured into water (50 cm³), extracted into ethyl acetate (2 x 60 cm³). The combined organic phases were washed with brine (100 cm³) and water (100 cm³), dried over sodium sulfate and concentrated to yield a yellow solid (15.8 g, 114%). Recrystallisation, from ethanol/ water and subsequent drying in a vacuum oven yielded 2-[2'-(N-tert-butyloxycarboxyamino)-5'-hydroxyphenyl]-1,3-dithiane 335d as needles (10.0 g, 30.6 mmol, 76%); Mpt: 155-157 °C; v_max (KBr/cm⁻¹): 3426 (OH), 3310 (NH), 1685 (CO), 1584 (C=C), 1504 (OH), 1157 (COC); δ_H (250 MHz, CDCl₃): 1.53 [9H, s, (CH₃)₃], 1.88-1.94 (1H, m, CH₉ax), 2.15-2.21 (1H, m, CHeq), 2.87 (2H, dt, J 14.3 and 4.0, CH₂-S), 3.03 (2H, td, J 2.5 and 14.6, CH₂-S), 5.23 (1H, s, S₂CH), 5.57 (1H, s, OH), 6.03 (1H, bs, NH), 6.65 (1H, dd, J 8.7 and 2.9, H-4'), 6.92 (1H, d, J 2.9, H-6'), 7.37 (1H, bd, J 8.4, H-3'); δ_C (63 MHz, CDCl₃): 25.2 (CH₂), 28.4 (CH₃), 31.9 (CH₂), 47.6 (CH), 80.6 (C), 115.1 (CH), 116.1 (CH), 128.0 (C), 153.3 (C), 154.3 (C); m/z, EI⁺ (%): 327 (M⁺⁺, 28), 271 (M⁺⁺-C₆H₆, 100), 270 (50), 253 (M⁺⁺-C₆H₉O, 29), 152 (98); Accurate mass: C₁₆H₂₁NO₃S₂: requires 327.0963, found 327.0959; Microanalysis Found: C 55.01%, H 6.65%, N 4.09%; Theoretical C₁₆H₂₁NO₃S₂: C 55.09%, H 6.47%, N 4.28%.
Trimethylsilyl chloride (3.1 cm³, 24.0 mmol) was added dropwise to a solution of 2-[2'-(N-tert-butyloxycarboxyamino)-5'-hydroxyphenyl]-1,3-dithiane 335d (6.54 g, 20.0 mmol) in dry pyridine (40 cm³) and the reaction mixture was stirred under argon for 15 h. After this time the solvent was removed in vacuo and diethyl ether (50 cm³) was added. The resulting precipitate was filtered off and the ethereal solution was concentrated to leave a white solid. Recrystallisation, from propan-2-ol, gave 2-[2'-(N-tert-butyloxycarboxyamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane 335e as a white powder (6.63 g, 16.6 mmol, 83%); Mpt: 116-119 °C; ν<sub>max</sub> (KBr)/cm<sup>-1</sup>: 3433 (NH), 1716 (CO), 1509 (C=C), 1253 (SiMe₃), 1158 (COC); δ<sub>H</sub> (400 MHz, CDCl₃): 0.25 [9H, s, Si(CH₃)₃], 1.53 [9H, s, (CH₃)₃], 1.91-1.98 (1H, m, CH<sub>ax</sub>), 2.16-2.22 (1H, m, CH<sub:eq</sub>), 2.89 (2H, dt, J = 14.4 and 3.9, CH<sub>1-S</sub>), 3.06-3.13 (2H, m, CH<sub>2-S</sub>), 5.22 (1H, s, SlCH), 6.75 (1H, dd, J = 8.8 and 2.8, H-4'), 6.96 (1H, d, J = 2.7, H-6'), 7.52 (1H, bs, H-3'); δ<sub>C</sub> (90 MHz, CDCl₃): 0.2 (CH₃), 25.2 (CH<sub>2</sub>), 28.4 (CH₃), 32.0 (CH₂), 47.6 (CH), 80.4 (C), 114.8 (C), 115.9 (C), 119.6 (CH), 120.4 (CH), 125.4 (C), 129.2 (C), 153 8 (C); m/z, EI+ (%): 399 (M<sup>+</sup>, 31), 343 (M<sup>+</sup>-C₂H₅, 65), 236 (100); Accurate mass: C<sub>18</sub>H<sub>29</sub>N₃O₃S₂Si: requires 399.1358, found 399.1358.

2-[2'-(N-tert-butyloxycarboxyamino)-5'-chlorophenyl]-1,3-dithiane 335f

A solution of 2-(2'-amino-5'-chlorophenyl)-1,3-dithiane 331f (6.14 g, 25.0 mmol) and di-tert-butyl-dicarbonate (6.55 g, 30.0 mmol) in THF (75 cm³) was heated under reflux for 64 h. After this time the reaction mixture was poured into water (100 cm³), extracted into diethylether (2 x 75 cm³). The combined organic phases were washed with water (2 x 150 cm³), dried over sodium sulfate and concentrated to yield a yellow solid (9.40 g). Recrystallisation, from propan-2-ol gave 2-[2'-(N-tert-butyloxycarboxyamino)-5'-chlorophenyl]-1,3-dithiane 335f as yellow needles (7.65 g, 22.1 mmol, 89%); Mpt: 125-127 °C; ν<sub>max</sub> (KBr)/cm<sup>-1</sup>: 3398 (NH), 1734 (CO), 1496 (C=C), 1150 (COC); δ<sub>H</sub> (250 MHz, CDCl₃): 1.54 [9H, s, (CH₃)₃], 1.90-1.96 (1H, m, CH<sub>ax</sub>), 2.18-2.19 (1H, m, CH<sub>eq</sub>), 2.89 (2H,
A solution of lithium di-isopropylamine (7.2 cm$^3$, 14.4 mmol, 2.0 mol dm$^{-3}$ in THF, ethyl benzene and heptanes) in THF (22.8 cm$^3$) was added dropwise to a solution of carbamate 335a (3.74 g, 12.0 mmol) and chlorotrimethylsilane (2.0 cm$^3$, 14.4 mmol) in THF (70 cm$^3$), at -78 °C under argon. The reaction mixture was allowed to warm to rt over 45 mins and was allowed to stir for a further 1 h at this temperature. After this time, the solvent was removed in vacuo and ether (100 cm$^3$) was added. The resulting precipitate was filtered off and the ethereal solution was concentrated to yield 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)phenyl]-1,3-dithiane 342a (1H and 13C NMR were carried out at 52 °C to allow rapid rotation around the C2'-N1 bond on the NMR timescale) as a white solid (3.95 g, 10.3 mmol, 86%); Mpt: 100-103 °C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 1680 (CO), 1250 (SiMe$_3$), 1162 (Si-N), 850 (SiMe$_3$); $\delta_{\text{H}}$ (400 MHz, 52 °C, CDCl$_3$): 0.23 [9H, s, Si(CH$_3$)$_3$], 1.43 [9H, s, C(CH$_3$)$_3$], 1.90-1.99 (1H, m, CH$_{ax}$), 2.11-2.16 (1H, m, CH$_{eq}$), 2.85-3.02 (4H, m, CH$_S$), 5.22 (1H, s, S$_2$CH), 6.93 (1H, dd, J 1.1 and 7.0, H-6'), 7.18-7.25 (2H, m, H-4' and 5'), 7.62 (1H, dd, J 1.9 and 7.4, H-3'); $\delta_{\text{C}}$ (100 MHz, 52 °C, CDCl$_3$): 0.0 (CH$_3$), 25.3 (CH$_2$), 28.1 (CH$_3$), 32.7 (CH$_2$), 32.8 (CH$_2$), 46.9 (CH), 80.4 (C), 127.4 (CH), 128.5 (CH), 129.0 (CH), 129.3 (CH), 137.2 (C), 138.7 (C), 156.7 (C); m/z, El+ (%): 383 (M$^{+}$, 7), 327 (M$^{+}$-C$_4$H$_9$, 73), 282 (M$^{+}$-C$_7$H$_{18}$, 100); Accurate mass: C$_{18}$H$_{29}$NO$_2$S$_2$Si: requires 383.1409, found 383.1413; Microanalysis Found: C 56.26%, H 7.66%, N 3.44%; Theoretical C$_{18}$H$_{29}$NO$_2$S$_2$Si: C 56.35%, H 7.62%, N 3.65%.
2-[2'-{(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-3'-methoxyphenyl}-1,3-dithiane 342b

Exactly as for thioacetal 342a, employing carbamate 335b (4.10 g, 12.0 mmol) gave 2-[2'-{(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-3'-methoxyphenyl}-1,3-dithiane 342b (a 50:50 mixture of the two geometrical isomers a:b) as a yellow solid (4.52 g, 10.9 mmol, 91%); υ<sub>max</sub> (G Gate)/cm<sup>-1</sup>: 2837 (OCH<sub>3</sub>), 1684 (CO), 1253 (SiMe<sub>3</sub>), 1157 (Si-N), 840 (SiMe<sub>3</sub>); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 0.23 [9H, s, Si(CH<sub>3</sub>)<sub>3</sub>], 1.35 [9H<sup>a</sup>, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.58 [9H<sup>b</sup>, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.94-2.02 (1H<sup>ab</sup>, m, CH<sub>ax</sub>), 2.16-2.20 (1H<sup>ab</sup>, m, CH<sub>eq</sub>), 2.89-3.02 (4H<sup>ab</sup>, m, CH<sub>2</sub>-S), 5.26 (1H<sup>ab</sup>, s, S<sub>2</sub>CH), 6.82 (1H<sup>ab</sup>, bd, J 7.4, H-6'), 7.19-7.34 (2H<sup>ab</sup>, m, H-4' and H-5'); m/z, EI+ (%): 413 (M<sup>+</sup>, 20), 356 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>, 70), 312 (M<sup>+</sup>-C<sub>5</sub>H<sub>9</sub>O<sub>2</sub>, 77), 250 (79), 73 (100); Accurate mass: C<sub>19</sub>H<sub>31</sub>N<sub>0</sub>3S<sub>2</sub>Si: requires 413.1515, found 413.1513.

2-[2'-{(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-4',5'-methyleneedioxy}-1,3-dithiane 342c

Exactly as for thioacetal 342a, employing carbamate 335c (3.55 g, 10.0 mmol), yielded 2-[2'-(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-4',5'-methyleneedioxy]-1,3-dithiane 342c as yellow needles; (4.01 g, 9.39 mmol, 94%); υ<sub>max</sub> (G Gate)/cm<sup>-1</sup>: 2765 (OCH<sub>2</sub>O), 1677 (CO), 1246 (SiMe<sub>3</sub>), 1157 (Si-N), 845 (SiMe<sub>3</sub>); δ<sub>H</sub> (250 MHz, CDCl<sub>3</sub>): 0.10 [9H, s, Si(CH<sub>3</sub>)<sub>3</sub>], 1.30 [9H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.69-1.79 (1H, m, CH<sub>ax</sub>), 1.94-1.99 (1H, m, CH<sub>eq</sub>), 2.71-2.86 (4H, m, CH<sub>2</sub>-S), 5.02 (1H, s, S<sub>2</sub>CH), 5.77-5.79 (2H, s, OCH<sub>2</sub>O), 6.28 (1H, s, H-3'), 6.97 (1H, s, H-6'); m/z, EI+ (%): 427 (M<sup>+</sup>, 23), 371 (M<sup>+</sup>-C<sub>4</sub>H<sub>8</sub>, 70), 326 (M<sup>+</sup>-C<sub>5</sub>H<sub>9</sub>O<sub>2</sub>, 48), 265 (61), 73 (100); Accurate mass: C<sub>19</sub>H<sub>29</sub>N<sub>0</sub>4S<sub>2</sub>Si: requires 427.1307, found 427.1308.
2-[2'-((N-tert-Butyloxycarboxy-N-trimethylsilylamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane 342e

Exactly as for thioacetal 342a, employing carbamate 335e (4.80 g, 12.0 mmol) gave 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)-5'-trimethylsilyloxyphenyl]-1,3-dithiane 342e as a yellow oil; (3.57 g, 7.56 mmol, 63%); \( \nu_{\text{max}} \) (Thin Film)/cm\(^{-1}\): 1683 (CO), 1292 (SiMe\(_3\)), 1248 (SiMe\(_3\)), 1159 (Si-O), 842 (SiMe\(_3\)); \( \delta_{\text{H}} \) (250 MHz, CDCl\(_3\)): 0.07 [9H, s, Si(CH\(_3\))\(_3\)], 0.11 [9H, s, Si(CH\(_3\))\(_3\)], 1.28 [9H, s, C(CH\(_3\))\(_3\)], 1.82-1.90 (1H, m, CH\(_{ax}\)), 2.10-2.16 (1H, m, CH\(_{eq}\)), 2.89-3.00 (4H, m, CH\(_2\)-S), 4.98 (1H, d, J 8.5 and 2.8, H-4'); 6.61 (1H, d, J 8.5, H-3'); 6.97 (1H, d, J 2.7, H-6'); m/z, EI+ (%): 471 (M\(^{+}\), 10), 415 (M\(^{+}\)-C\(_6\)H\(_5\), 48), 370 (M\(^{+}\)-C\(_6\)H\(_5\)O\(_2\)), 30, 309 (70), 73 (100); Accurate mass: C\(_{21}\)H\(_{37}\)N\(_2\)O\(_3\)S\(_2\)Si: requires 471.1753, found 471.1755.

2-[2'-((N-tert-Butyloxycarboxy-N-trimethylsilylamino)-5'-chlorophenyl]-1,3-dithiane 342f

Exactly as for thioacetal 342a, employing carbamate 335f (4.15 g, 12.0 mmol) gave 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)-5'-chlorophenyl]-1,3-dithiane 342f as yellow needles (4.43 g, 10.6 mmol, 88%); \( \nu_{\text{max}} \) (G Gate)/cm\(^{-1}\): 1677 (CO), 1246 (SiMe\(_3\)), 1155 (Si-N), 843 (SiMe\(_3\)); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 0.23 [9H, s, Si(CH\(_3\))\(_3\)], 1.44 [9H, s, C(CH\(_3\))\(_3\)], 1.92-1.95 (1H, m, CH\(_{ax}\)), 2.14-2.18 (1H, m, CH\(_{eq}\)), 2.87-3.01 (4H, m, CH\(_2\)-S), 5.13 (1H, d, J 8.3, H-6'), 7.18 (1H, d, J 8.3 and 2.5, H-4'); 7.63 (1H, d, J 2.5, H-3'); m/z, EI+ (%): 417 (M\(^{+}\), 3), 361 (M\(^{+}\)-C\(_6\)H\(_5\)), 70, 316 (M\(^{+}\)-C\(_6\)H\(_5\)O\(_2\)), 49, 73 (91), 57 (100); Accurate mass: C\(_{18}\)H\(_{28}\)Cl\(_{3}\)NO\(_2\)S\(_2\)Si: requires 417.1019, found 417.1016; C\(_{18}\)H\(_{28}\)Cl\(_{3}\)NO\(_2\)S\(_2\)Si: requires 419.0994, found 419.0992.
Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342a (0.58 g, 1.50 mmol) and resin-bound ester 309a' (Method B, 0.28 mmol), yielded \textit{N-tert-butyloxycarboxy-2-phenethyl indole} 336aa' in excellent purity as a grey oil (0.062 g, 0.195 mmol, 69%); \(\nu_{\text{max}}\) (Solvent, CDCl\(_3\))/cm\(^{-1}\): 3065 (C=C), 1749 (CO), 1454 (CH); \(\delta\) (400 MHz, CDCl\(_3\)): 1.68 [9H, s, (CH\(_3\))\(_3\)], 3.00 (2H, t, \(J=8.4\), CH\(_2\)), 3.32 (2H, t, \(J=8.4\), CH\(_2\)), 6.34 (1H, d, \(J=0.6\), H-3), 7.16-7.30 (7H, m, Ar-H), 7.42 (1H, dd, \(J=1.0\) and 7.7, H-4), 8.07 (1H, d, \(J=8.3\), H-7); \(\delta\) (100 MHz, CDCl\(_3\)): 28.3 (CH\(_3\)), 31.8 (CH\(_2\)), 35.2 (CH\(_2\)), 83.8 (C), 107.4 (CH), 115.6 (CH), 119.8 (CH), 122.6 (CH), 123.3 (CH), 126.0 (CH), 128.4 (CH), 129.3 (C), 136.5 (C), 141.5 (C), 141.6 (C), 150.6 (C); m/z, EI\(^+\) (%): 321 (M\(^{++}\), 21), 265 (M\(^{++}\)-C\(_4\)H\(_8\), 58), 220 (M\(^{++}\)-C\(_3\)H\(_9\)O\(_2\), 10), 174 (80), 130 (100); Accurate mass: C\(_{21}\)H\(_{23}\)N\(_2\)O\(_2\): requires 321.1729, found 321.1726.

**\textit{N-tert-Butyloxycarboxy-2-phenethyl indole} 336aa'**

Following the solid-phase Takeda Method B and resin-cleavage procedure \(A\), employing silylated carbamate 342a (0.35 g, 0.90 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded \textit{N-tert-butyloxycarboxy-2-phenethyl indole} 336aa' in excellent purity as a grey oil (0.059 g, 0.180 mmol, 61%); \(\delta\) (400 MHz, CDCl\(_3\)): as above.

**\textit{N-tert-Butyloxycarboxy-2-phenyl indole} \(249\) 336ab'**

Following the solid-phase Takeda Method A and resin-cleavage procedure \(A\), employing silylated carbamate 342a (0.58 g, 1.50 mmol) and resin-bound ester 309b' (Method B, 0.28 mmol), yielded \textit{N-tert-butyloxycarboxy-2-phenyl indole} \(249\) 336ab' in excellent purity as a white solid (0.048 g, 0.165 mmol, 59%); Mpt: 75-78 °C; \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\): 2980 (C=C), 1728 (CO), 1454 (CH); \(\delta\) (400 MHz, CDCl\(_3\)): 1.30 [9H, s, (CH\(_3\))\(_3\)], 6.55 (1H, s, H-3), 7.23-7.43 (7H, m, Ar-H), 7.54 (1H, d, \(J=7.6\), H-4), 8.07 (1H, d, \(J=8.3\), H-7); \(\delta\) (100 MHz, CDCl\(_3\)): 27.5 (CH\(_3\)), 83.3 (C), 109.9 (CH), 115.2 (CH), 120.4 (CH), 122.9 (CH), 124.3
(CH), 127.5 (CH), 127.8 (CH), 128.7 (CH), 129.2 (C), 135.0 (C), 137.3 (C), 140.5 (C), 150.2 (C); m/z, El+ (%): 293 (M++, 8), 237 (M++-C4H8, 23), 193 (M++-C3H6O2, 50), 85 (63), 83 (100); Accurate mass: C19H19N02: requires 293.1416, found 293.1418.

**N-tert-Butyloxyacarboxy-2-methyl indole**

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342a (0.58 g, 1.50 mmol) and resin-bound ester 309c' (Method B, 0.28 mmol), yielded N-tert-butyloxyacarboxy-2-methyl indole in excellent purity as a white solid (0.038 g, 0.165 mmol, 59%); Mpt: 49-52 °C; νmax (KBr)/cm⁻¹: 2950 (C=C), 1724 (CO), 1338 (CH); δH (400 MHz, CDCl3): 1.68 [9H, s, (CH3)3], 2.59 (3H, s, CH3), 6.31 (1H, s, H-3), 7.15-7.25 (2H, m, H-5 and H-6), 7.41-7.43 (1H, m, H-4), 8.09 (1H, d, J 8.2, H-7); δC (100 MHz, CDCl3): 17.1 (CH3), 28.3 (CH3), 83.6 (C), 107.9 (CH), 115.4 (CH), 119.4 (CH), 122.5 (CH), 123.0 (CH), 129.3 (C), 136.5 (C), 137.8 (C), 150.7 (C); m/z, El+ (%): 231 (M++, 4), 175 (M++-C4H8, 10), 131 (M++-C3H6O2, 12), 83 (100); Accurate mass: C14H17N02: requires 231.1256, found 231.1259.

**N-tert-Butyloxyacarboxy-2-(2'-methyl-propenyl) indole**

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342a (0.58 g, 1.50 mmol) and resin-bound ester 309d' (Method B, 0.311 mmol), yielded N-tert-butyloxyacarboxy-2-(2'-methyl-propenyl) indole in excellent purity as a yellow oil (0.064 g, 0.236 mmol, 76%); νmax (Thin film)/cm⁻¹: 3052 (NH), 2977 (CH), 1731 (CO), 1454 (CH), 802 (CH=CMes2); δH (400 MHz, CDCl3): 1.68 [9H, s, (CH3)3], 1.94 (3H, s, CH3=C), 1.97 (3H, s, CH3=C), 6.42 (1H, s, C=CH), 6.51 (1H, s, H-3), 7.21 (1H, dt, J 1.2 and 7.3, H-6), 7.26 (1H, dt, J 1.4 and 7.5, H-5), 7.50 (1H, d, J 7.3, H-4) 8.13 (1H, d, J 8.2, H-7); δC (100 MHz, CDCl3): 19.9 (CH3), 26.5 (CH3), 28.2 (CH3), 83.5 (C), 109.3 (CH), 115.5 (CH), 118.0 (CH), 122.6 (CH), 123.6 (CH), 129.5 (C), 135.9 (C), 136.3 (C), 137.7 (C), 150.6 (C); m/z, El+ (%): 271 (M++, 17), 215 (M++-C4H8, 100), 171 (M++-C6H12O2, 42), 130 (M++-C7H15O2, 39); Accurate mass: C17H21NO2: requires 271.1572, found 271.1570.
Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342b (0.62 g, 1.50 mmol) and resin-bound ester 309a' (Method B, 0.28 mmol), yielded \textit{N}-\textit{tert}-butyloxycarboxy-7-methoxy-2-phenethyl indole 336ba' in excellent purity as a grey oil (0.058 g, 0.162 mmol, 59%); \( \nu_{\text{max}} \) (Solt\({ }^a\), CDCl\(_3\))/cm\(^{-1}\): 2957 (C=C), 2832 (COCH\(_3\)), 1445 (CH); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.53 [9H, s, (CH\(_3\))\(_3\)], 2.91 (2H, t, \( J \) 8.6, CH\(_2\)), 3.05-3.09 (2H, m, CH\(_2\)), 3.83 (3H, s OCH\(_3\)), 6.17 (1H, s, H-3), 6.61 (1H, dd, \( J \) 7.8 and 1.8, H-6), 6.98-7.04 (2H, m, H-4 and H-5), 7.09-7.23 (5H, m, Ar-H); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)): 27.7 (CH\(_3\)), 30.1 (CH\(_2\)), 35.4 (CH\(_2\)), 55.1 (CH\(_3\)), 83.4 (C), 104.6 (CH), 112.7 (CH), 122.7 (CH), 125.5 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 131.2 (C), 141.1 (C), 141.4 (C), 147.4 (C), 151.0 (C); m/z, EI\(^+\) (%): 351 (M\(^{++}\), 15), 251 (M\(^{++}\)-C\(_3\)H\(_8\)O\(_2\), 25), 160 (M\(^{++}\)-C\(_2\)H\(_3\)O\(_2\)H, 100); Accurate mass: C\(_{22}\)H\(_{23}\)N\(_2\)O\(_2\): requires 351.1834, found 351.1837.

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342c (0.64 g, 1.50 mmol) and resin-bound ester 309a' (Method B, 0.28 mmol), yielded \textit{N}-\textit{tert}-butyloxycarboxy-5,6-methylenedioxy-2-phenethyl indole 336ca' in excellent purity as a white/brown solid (0.071 g, 0.195 mmol, 69%); Mpt: 102-105 °C; \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 2974 (C=C), 2930 (OCH\(_2\)O), 1465 (CH); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.66 [9H, s, (CH\(_3\))\(_3\)], 2.98 (2H, t, \( J \) 8.4, CH\(_2\)), 3.25-3.29 (2H, m, CH\(_2\)), 5.93 (1H, s, OCH\(_2\)O), 6.21 (1H, s, H-3), 6.82 (1H, s, H-4), 7.17-7.30 (5H, m, Ar-H), 7.65 (1H, s H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)): 28.2 (CH\(_3\)), 31.8 (CH\(_2\)), 35.3 (CH\(_2\)), 83.8 (C), 97.6 (CH), 98.8 (CH), 100.8 (CH\(_2\)), 107.4 (CH), 123.2 (C), 125.9 (CH), 128.3 (CH), 128.4 (CH), 131.1 (C), 140.2 (C), 141.5 (C), 144.0 (C), 145.2 (C), 150.4 (C); m/z, EI\(^+\) (%): 365 (M\(^{++}\), 10), 309 (M\(^{++}\)-C\(_4\)H\(_8\), 17), 218 (M\(^{++}\)-C\(_1\)H\(_1\)O\(_2\), 59), 174 (M\(^{++}\)-C\(_2\)H\(_3\)O\(_2\)H, 48), 83 (100); Accurate mass: C\(_{22}\)H\(_{23}\)N\(_2\)O\(_4\): requires 365.1627, found 365.1629.
N-tert-Butyloxycarboxy-5,6-methylenedioxy-2-phenyl indole 336cb'

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342c (0.64 g, 1.50 mmol) and resin-bound ester 309b' (Method B, 0.28 mmol), yielded N-tert-butyloxycarboxy-5,6-methylenedioxy-2-phenyl indole 336cb' in excellent purity as a brown oil (0.066 g, 0.20 mmol, 70%); ν max (Soln, CDCl3)/cm⁻¹: 3149 (C=C), 2980 (OCH2O), 1730 (CO), 1464 (CH); δ H (400 MHz, CDCl3): 1.28 [9H, s, (CH3)3], 5.97 (1H, s, OCH2O), 6.41 (1H, s, H-3), 6.92 (1H, s, H-4), 7.31-7.38 (5H, m, Ar-H), 7.76 (1H, s, H-7); δ C (100 MHz, CDCl3): 27.5 (CH3), 83.4 (C), 97.0 (CH), 99.0 (CH), 101.0 (CH2), 109.9 (CH), 123.1 (C), 127.3 (CH), 127.7 (CH), 128.6 (CH), 132.4 (C), 135.1 (C), 139.2 (C), 144.4 (C), 146.0 (C), 150.2 (C); m/z, EI+ (%): 337 (M⁺, 18), 281 (M⁺-C4H8, 58), 237 (M⁺-C5H9O2, 100); Accurate mass: C20H19N04: requires 337.1682, found 337.1678.

N-tert-Butyloxycarboxy-2-methyl-5,6-methylenedioxy indole 336cc'

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342c (0.64 g, 1.50 mmol) and resin-bound ester 309c' (Method B, 0.28 mmol), yielded N-tert-butyloxycarboxy-2-methyl-5,6-methylenedioxy indole 336cc' in excellent purity as a white/brown solid (0.044 g, 0.160 mmol, 58%); Mpt: 95-98 °C; ν max (KBr)/cm⁻¹: 2982 (C=C), 2927 (OCH2O), 1726 (CO); δ H (400 MHz, CDCl3): 1.66 [9H, s, (CH3)3], 2.52 (3H, s, CH3), 5.93 (1H, s, OCH2O), 6.17 (1H, s, H-3), 6.81 (1H, s, H-4), 7.66 (1H, s, H-7); δ C (100 MHz, CDCl3): 17.2 (CH3), 28.2 (CH3), 83.7 (C), 96.7 (CH), 98.5 (CH), 100.8 (CH2), 108.0 (CH), 123.3 (C), 131.0 (C), 136.3 (C), 144.0 (C), 145.0 (C), 150.6 (C); m/z, EI+ (%): 275 (M⁺, 14), 219 [(M⁺-C4H8), 44], 175 [(M⁺-C5H9O2), 45], 83 (100); Accurate mass: C15H17N04: requires 275.1161, found 275.1158.
Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342e (0.71 g, 1.50 mmol) and resin-bound ester 309a' (Method B, 0.28 mmol), yielded \( \text{N-tert-butyloxycarboxy-5-hydroxy-2-phenethyl indole 336da'} \) in excellent purity as a yellow oil (0.064 g, 0.190 mmol, 68%); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 3432 (OH), 2925 (C=C), 1731 (CO), 1382 (OH); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.66 [9H, s, (CH\(_3\))\(_3\)], 2.98 (2H, t, \( J = 8.4 \), CH\(_2\)), 3.29 (2H, t, \( J = 7.4 \), CH\(_2\)), 4.97 (1H, s, OH), 6.24 (1H, s, H-3), 6.74 (1H, dd, \( J = 8.9 \) and 2.5, H-6), 6.86 (1H, d, \( J = 2.4 \), H-4), 7.17-7.30 (5H, m, Ar-H), 7.92 (1H, d, \( J = 8.9 \), H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)): 28.2 (CH\(_3\)), 32.7 (CH\(_2\)), 35.1 (CH\(_2\)), 83.7 (C), 105.1 (CH), 107.1 (CH), 111.9 (CH), 116.4 (CH), 126.0 (CH), 128.4 (CH), 130.3 (C), 131.4 (C), 141.4 (C), 142.7 (C), 150.5 (C); m/z, EI\(^+\) (%): 337 (M\(^+\), 12), 281 (M\(^+\)-C\(_4\)H\(_5\), 26), 237 (M\(^+\)-C\(_3\)H\(_6\)O\(_2\), 20), 190 (51), 146 (100); Accurate mass: C\(_{21}\)H\(_{23}\)N\(_2\)O\(_3\): requires 337.1682, found 337.1678.

\( \text{N-tert-Butoxycarboxy-5-hydroxy-2-phenyl indole 336db'} \)

Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342e (0.71 g, 1.50 mmol) and resin-bound ester 309b' (Method B, 0.28 mmol), yielded \( \text{N-tert-butoxycarboxy-5-hydroxy-2-phenyl indole 336db'} \) in excellent purity as a yellow oil (0.062 g, 0.201 mmol, 72%); \( \nu_{\text{max}} \) (Solt\(^6\), CDCl\(_3\))/cm\(^{-1}\): 3696 (OH), 3600 (OH), 3152 (HC=C), 1476 (CH), 1384 (OH); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.29 [9H, s, (CH\(_3\))\(_3\)], 6.34 (1H, s, OH), 6.44 (1H, s, H-3), 6.84 (1H, dd, \( J = 8.9 \) and 2.6, H-6), 6.97 (1H, d, \( J = 2.4 \), H-4), 7.33-7.41 (5H, m, Ar-H), 8.05 (1H, d, \( J = 8.9 \), H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)): 27.5 (CH\(_3\)), 83.5 (C), 105.7 (CH), 109.7 (CH), 113.1 (CH), 116.0 (CH), 127.6 (CH), 127.8 (CH), 128.7 (CH), 130.2 (C), 132.3 (C), 134.8 (C), 138.1 (C), 141.4 (C), 150.3 (C); m/z, EI\(^+\) (%): 309 (M\(^+\), 15), 253 (M\(^+\)-C\(_4\)H\(_5\), 32), 209 (M\(^+\)-C\(_3\)H\(_6\)O\(_2\), 100); Accurate mass: C\(_{19}\)H\(_{19}\)N\(_2\)O\(_3\): requires 309.1364, found 309.1364.
Following the solid-phase Takeda Method A and resin-cleavage procedure A, employing silylated carbamate 342e (0.71 g, 1.50 mmol) and resin-bound ester 309c' (Method B, 0.28 mmol), yielded N-tert-butyloxycarboxy-5-hydroxy-2-methyl indole 336dc' in excellent purity as a pink oil (0.048 g, 0.196 mmol, 70%); \(\nu_{\max} (\text{Soln, CDCl}_3)/\text{cm}^{-1}: 3691 (\text{OH}), 3601 (\text{OH}), 3154 (\text{C=C}), 1474 (\text{CH}), 1379 (\text{OH}); \delta_H (400 \text{ MHz, CDCl}_3): 1.67 [9H, s, (CH)_3], 2.56 (3H, s, CH_3), 5.94 (1H, s, OH), 6.73 (1H, s, H-3), 6.73 (1H, dd, \(J=8.9\) and 2.5, H-4), 6.86 (1H, d, \(J=2.5\), H-4), 7.93 (1H, d, \(J=8.9\), H-3); \delta_C (100 \text{ MHz, CDCl}_3): 17.0 (CH_3), 28.3 (CH_3), 83.7 (C), 105.0 (CH), 107.7 (CH), 111.7 (CH), 116.2 (CH), 120.4 (C), 130.4 (C), 131.4 (C), 138.9 (C), 150.7 (C); m/z, El+ (%): 247 (M`, 12), 191 (M`-C_4H_8, 28), 147 (M`-C_2H_6O_2, 40), 83 (100); Accurate mass: C_{14}H_{17}NO_3: requires 247.1208, found 247.1212.

Titanocene dichloride (2.26 g, 9.00 mmol), magnesium turnings (0.30 g, 12.6 mmol) and 4Å molecular sieves (0.90 g) were heated briefly in vacuo, allowed to cool and then the reaction flask was purged with argon. THF (9.0 cm³) and triethylphosphite (3.2 cm³, 18.6 mmol) were then added and the reaction mixture stirred, cooling using an ice bath for 30 mins. After stirring for a further 2 h at rt, a THF (18.0 cm³) solution of the thioacetal 342f (1.56 g, 4.50 mmol) was added, and the solution stirred for 15 mins. The reaction mixture was then added via syringe, in three equal portions, into three separate flasks each containing 1 Kan of resin bound ester 309a' (Method B, 3 x 0.28 mmol), pre-swollen in THF (3 x 3 cm³). The mixture was stirred under argon for 15h. The Kans were then washed as in the standard Takeda procedures, and one Kan when treated under the standard resin-cleavage conditions A, yielded N-tert-butyloxycarboxy-5-chloro-2-phenethyl indole 336fa' as a yellow oil (0.015 g, 0.04 mmol, 14%); \(\delta_H (400 \text{ MHz, CDCl}_3): 1.68 [9H, s, (CH)_3], 3.01 (2H, t, J=8.3, CH_2), 3.33 (2H, t, J=8.3, CH_2), 6.28 (1H, s, H-3), 7.16-7.21 (6H, m, Ar-H), 7.39 (1H, d, J=2.0, H-4), 7.99 (1H, d, J=8.8, H-7).
2-Phenyl-1H-indole<sup>250</sup> 332ab'

Following the general Boc deprotection procedure, using N-Boc indole 336ab' (0.048 g, 0.164 mmol), yielded 2-phenyl-1H-indole<sup>249</sup> 332ab' as a grey solid (0.031 g, 0.16 mmol, 97%); Mpt: 178-181 °C (Lit. 249 Mpt: 189-200 °C); $\nu_{\text{max}}$ (Solt<sup>3</sup>, CDCl<sub>3</sub>/cm<sup>-1</sup>): 3441 (NH), 2925 (CH), 1635 (HC=C); $\delta_H$ (400 MHz, CDCl<sub>3</sub>): 6.82 (1H, s, H-3), 7.12 (1H, t, $J$ 7.8, H-6), 7.19 (1H, td, $J$ 7.6 and 1.0, H-5), 7.32 (1H, t, $J$ 7.4, Ar-H), 7.35-7.45 (3H, m, Ar-H), 7.64-7.66 (3H, m, Ar-H), 8.31 (1H, bs, NH); $\delta_C$ (100 MHz, CDCl<sub>3</sub>): 99.8 (CH), 110.7 (CH), 120.1 (CH), 120.5 (CH), 122.2 (CH), 125.0 (CH), 127.5 (CH), 128.8 (C), 132.2 (C), 136.4 (C), 137.5 (C); m/z, EI+ (%): 193 (M<sup>+</sup>, 100), 165 (15), 84 (28); Accurate mass: C<sub>14</sub>H<sub>11</sub>N: requires 193.0891, found 193.0894.

7-Methoxy-2-phenethyl-1H-indole 332ba'

Following the general Boc deprotection procedure, using N-Boc indole 336ba' (0.033 g, 0.09 mmol), yielded 7-methoxy-2-phenethyl-1H-indole 332ba' as a purple solid (0.024 g, 0.09 mmol, 100%); Mpt: 85-88 °C; $\nu_{\text{max}}$ (Solt<sup>3</sup>, CDCl<sub>3</sub>/cm<sup>-1</sup>): 3151 (NH), 3095 (HC=C), 2932 (COCH<sub>3</sub>), 1791 (HC=C); $\delta_H$ (400 MHz, CDCl<sub>3</sub>): 2.96-3.09 (4H, m, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.93 (3H, s OCH<sub>3</sub>), 6.24 (1H, d, $J$ 2.2, H-3), 6.56 (1H, dd, $J$ 2.3 and 7.6, H-6), 6.96 (1H, dt, $J$ 7.8 and 3.1, H-4), 7.13 (1H, d, $J$ 7.9, H-5), 7.13-7.25 (3H, m, Ar-H), 7.28-7.31 (2H, m, Ar-H), 8.04 (1H, bs, NH); $\delta_C$ (100 MHz, CDCl<sub>3</sub>): 30.2 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>), 100.1 (CH), 101.3 (CH), 112.8 (CH), 119.9 (CH), 126.1 (CH), 128.4 (CH), 128.5 (CH), 129.0 (C), 130.0 (C), 138.5 (C), 141.2 (C), 145.6 (C); m/z, EI+ (%): 251 (M<sup>+</sup>, 42), 160 (M<sup>+</sup>-C<sub>7</sub>H<sub>8</sub>, 100), Accurate mass: C<sub>17</sub>H<sub>17</sub>NO: requires 251.1310, found 251.1308.
7-Methoxy-2-phenyl-1H-indole 332bb'

Following the solid-phase Takeda Method A, resin-cleavage procedure A and general Boc deprotection procedure, employing silylated carbamate 342b (0.62 g, 1.50 mmol) and resin-bound ester 309b' (Method B, 0.28 mmol), yielded 7-methoxy-2-phenyl-1H indole 332bb' as a pale green solid (0.043 g, 0.19 mmol, 69% from 309b'); Mpt: 82-85 °C; \( \nu_{\max} \) (KBr)/cm\(^{-1}\): 3440 (NH), 2925 (COCH\(_3\)), 1681 (HC=C); \( \delta_H \) (400 MHz, CDCl\(_3\)): 3.97 (3H, s OCH\(_3\)), 6.63 (1H, d, \( J = 7.7, \) H-6), 6.79 (1H, d, \( J = 1.9, \) H-3), 7.01-7.05 (1H, m, Ar-H), 7.22-7.33 (2H, m, Ar-H), 7.39-7.44 (2H, m, Ar-H), 7.64-7.56 (2H, m, Ar-H), 8.57 (1H, bs, NH); \( \delta_C \) (100 MHz, CDCl\(_3\)): 55.3 (CHl), 100.2 (CH), 102.2 (CH), 113.3 (CH), 120.5 (CH), 125.1 (CH), 127.2 (C), 127.5 (CH), 128.9 (CH), 130.4 (C), 132.3 (C), 137.5 (C), 145.9 (C); m/z, EI+ (%): 223 (M\(^{+}\), 77), 180 (42), 83 (100); Accurate mass: C\(_{15}\)H\(_{13}\)NO: requires 223.0997, found 223.0998.

5,6-Methylenedioxy-2-phenyl-1H-indole 332cb'

Tetrabutylammonium fluoride [(TBAF), 1 mol dm\(^{-3}\) in THF, 0.7 cm\(^3\), 70 mmol] was added drop-wise, to a solution of N-Boc indole 336cb' (0.033 g, 0.10 mmol), in THF (2 cm\(^3\)) under argon in THF. The reaction mixture was then heated under reflux for 30 h. After this time the reaction mixture was poured into water (10 cm\(^3\)) and extracted into ethyl acetate (2 x 5 cm\(^3\)). The combined organic phases were then washed with water (2 x 10 cm\(^3\)) dried over sodium sulphate, and concentrated to yield a 10:1 mixture of indole 332cb': indole 336cb' (starting material) and some tetrabutylammonium salts (0.020 g). Tritteration of the mixture from chloroform, yielded 5,6-methylenedioxy-2-phenyl-1H-indole 332cb' as a white solid (0.011 g, 0.050 mmol, 50%); \( \delta_H \) (400 MHz, CDCl\(_3\)): 5.95 (2H, s, OCH\(_2\)O), 6.70 (1H, s, H-3), 6.87 (1H, s, H-4), 7.00 (1H, s, H-7), 7.29 (1H, d, \( J = 7.4, \) H-4'), 7.42 (2H, t, \( J = 7.5, \) H-3' and H-5'), 7.59 (2H, d, \( J = 7.3, \) H-2' and H-6'), 8.21 (1H, s, NH); m/z, EI+ (%): 237 (M\(^{+}\), 100). However in an attempt to obtain a \( ^{13}\)C NMR spectrum, substantial decomposition occurred, and so no further characterisation of indole 332cb' was possible.
5-Hydroxy-2-phenethyl-1H-indole\textsuperscript{251} 332da'

Following the general Boc deprotection procedure, using N-Boc indole \textsuperscript{336}da' (0.048 g, 0.142 mmol), followed by column chromatography (SiO\textsubscript{2}, DCM: MeOH, 19: 1), yielded the desired 5-hydroxy-2-phenethyl-1H-indole\textsuperscript{251} 332da' as a grey solid (0.021 g, 0.09 mmol, 62%); \(R_f\) (SiO\textsubscript{2}, DCM: MeOH, 19: 1): 0.31; \(\delta:H\) (400 MHz, CDCl\textsubscript{3}): 3.00-3.08 (4H, \textit{m}, \(\text{CH}_2\text{CH}_2\text{Ph}\)), 4.42 (1H, s, OH), 6.16 (1H, d, \(J 1.4\), H-3), 6.67 (1H, dd, \(J 2.4\) and 8.6, H-6), 6.94 (1H, d, \(J 2.4\), H-4), 7.10 (1H, d, \(J 8.6\), H-7), 7.20-7.32 (5H, m, Ar-H), 7.64 (1H, s, NH); \(m/z\), EI+ (%): 237 (M\textsuperscript{+}, 38), 146 (M\textsuperscript{+}-C\textsubscript{7}H\textsubscript{7}, 100); Accurate mass: C\textsubscript{16}H\textsubscript{15}NO: requires 237.1154, found 237.1157.

2-Methyl-5-hydroxy-1H-indole 332dc'

Following the general Boc deprotection procedure, but leaving for 64 h, using N-Boc indole \textsuperscript{336}dc' (0.036 g, 0.145 mmol), followed by column chromatography (SiO\textsubscript{2}, DCM), yielded 2-methyl-5-hydroxy-1H-indole 332dc' as a grey solid (0.017 g, 0.12 mmol, 81%); \(R_f\) (SiO\textsubscript{2}, DCM): 0.10; \(\delta:H\) (400 MHz, CDCl\textsubscript{3}): 2.41 (3H, s, CH\textsubscript{3}), 4.44 (1H, s, OH), 6.10 (1H, s, H-3), 6.67 (1H, dd, \(J 2.4\) and 8.6, H-6), 6.92 (1H, d, \(J 2.4\), H-4), 7.12 (1H, d, \(J 8.6\), H-7), 7.72 (1H, s, NH); \(m/z\), EI+ (%): 147 (M\textsuperscript{+}, 88), 146 (M\textsuperscript{+}-H, 92), 84 (100); Accurate mass: C\textsubscript{9}H\textsubscript{9}NO: requires 147.0684, found 147.0682.

\textit{N}-Deutero-3-deutero-5-deuteroxy-2-methyl indole 345dc'

Dissolving indole 332dc' in d-4 MeOH in an NMR tube, gave \textit{N}-deutero-3-deutero-5-deuteroxy-2-methyl indole 345dc'; Mpt: 120-123 °C; \(\delta:H\) (400 MHz, d-4 MeOH): 2.25 (3H, s, CH\textsubscript{3}), 6.45 (1H, dd, \(J 2.4\) and 8.6, H-6), 6.69 (1H, d, \(J 2.2\), H-4), 6.95 (1H, d, \(J 8.6\), H-7); \(\delta:C\) (100 MHz, d-4 MeOH): 13.9 (CH\textsubscript{3}), 105.0 (CH), 111.1 (CH), 111.9 (CH), 131.6 (C), 133.3 (C), 137.7 (C), 151.5 (C).
Lithium di-isopropylamine [generated by adding n-butyl lithium (2.70 cm³, 6.60 mmol, 2.5 mol dm⁻³ in hexanes), to a solution of di-isopropylamine (1.20 cm³, 7.20 mmol) in THF (8.0 cm³) at -78 °C and stirring at this temperature for 1 h], was added drop-wise to a solution of carbamate 335a (1.86 g, 6.00 mmol) and the reaction was allowed to warm to rt over 1 h. After this time, a white precipitate resulted from which the solvent was removed in vacuo, and DCM (30 cm³) was added. The reaction mixture was allowed to stir for a further 1 h before methyl iodide (1.80 cm³, 30.0 mmol) was added and stirred for 22 h at rt. The reaction mixture was worked up by pouring into water and extracting with DCM (20 cm³). The DCM extracts were then dried over sodium sulfate and concentrated to yield a yellow oil (1.26 g, 65%). "H NMR analysis confirmed that a 12: 5 mixture of starting material 335a: product 346a remained. Column chromatography (SiO₂, DCM) gave pure starting material 335a (0.58 g, 1.87 mmol, 31%) and 2-[2'-((N-tert-butyloxycarboxy-N-methylamino)phenyl)-1,3-dithiane 346a (0.54 g, 1.66 mmol, 28%); Rf (SiO₂, DCM): 0.13; Mpt: 103-105 °C; νmax (KBr)/cm⁻¹: 2822 (NMe), 1688 (CO), 1363 (NCO); δH (400 MHz, CDCl₃): 1.35 [9H, s, (CH₃)₃], 1.88-1.99 (1H, m, CHax), 2.13-2.20 (1H, m, CHEq), 2.85-3.11 (4H, m, CH₂-S), 3.22 (3H, s, NCH₃), 5.24 (1H, d, J 6.4, H-3'), 7.10 (1H, d, J 6.4, H-3'), 7.26-7.32 (2H, m, H-4' and H-6') 7.67 (1H, dt, J 6.6 and 1.9, H-5'); δC (100 MHz, CDCl₃): 25.1 (CH₂), 28.0 (CH₃), 32.1 (CH₂), 32.5 (CH₂), 37.5 (CH₃), 45.9 (CH), 80.2 (C), 127.7 (CH), 128.0 (CH), 129.0 (CH), 129.2 (CH), 136.6 (C), 140.8 (C), 155.1 (C); m/z, EI+ (%): 325 (M²⁺, 9), 269 (M²⁺-C₄H₈, 64), 224 (M²⁺-C₈H₁₁O₂, 62), 162 (100); Accurate mass: C₁₆H₂₃N₀₂S₂: requires 325.1170, found 325.1172; Microanalysis Found: C 59.05%, H 7.12%, N 4.35%; Theoretical C₁₆H₂₃N₀₂S₂: C 59.04%, H 7.12%, N 4.30%.

Following the general procedure for carbamate alkylation, using methyl iodide (1.10 cm³, 16.5 mmol) in DMF (60 cm³), and allowing to stir for 2 h, gave pure amine 346a as a pale yellow solid (3.85 g, 11.8 mmol, 91%); δH (400 MHz, CDCl₃): as above.
Following the general procedure for carbamate alkylation, using benzyl bromide (2.50 cm$^3$, 16.5 mmol) in DMF (60 cm$^3$), and allowing to stir for 2 h, gave a yellow solid (6.09 g). Recrystallisation, from propan-2-ol, yielded 2-[2'-(N-benyl-N-tert-butyloxycarboxyamino)phenyl]-1,3-dithiane 346b as white needles (3.82 g, 9.51 mmol, 76%); R$_f$ (SiO$_2$, DCM): 0.35; Mpt: 128-130 °C; $\nu_{max}$ (KBr)/cm$^{-1}$: 2931 (NCH$_2$), 1691 (CO), 1388 (NCO); $\delta_H$ (400 MHz, CDCl$_3$): 1.37 [9H, s, (CH$_3$)$_3$], 1.86-1.98 (1H, m, CH$_ax$), 2.12-2.18 (1H, m, CH$_eq$), 2.82-3.03 (4H, m, CH$_2$-S), 4.33 (1H, d, J 18.5, NCH$_AH_B$), 5.20-5.24 (2H, m, NCH$_AH_B$ and S$_2$CH), 6.68 (1H, s, H-3'), 7.09 (1H, t J 7.4, Ar-H), 7.22-7.28 (6H, m, Ar-H), 7.64 (1H, dd, J 7.8 and 1.2, H-6'); $\delta_C$ (100 MHz, CDCl$_3$): 25.2 (CH$_2$), 28.1 (CH$_3$), 32.2 (CH$_2$), 32.5 (CH$_2$), 46.3 (CH), 53.5 (CH$_2$), 80.5 (C), 127.3 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.9 (CH), 129.3 (CH), 129.4 (CH), 136.7 (C), 138.2 (C), 139.2 (C), 155.3 (C); m/z, EI+ (%): 401 (M$^+$, 4), 345 (M$^{+*}$-C$_4$H$_8$, 37), 300 (M$^{+*}$-C$_5$H$_9$O$_2$, 58), 254 (100); Accurate mass: C$_{22}$H$_{27}$N$_2$O$_2$S$_2$: requires 401.1483, found 401.1486; Microanalysis: Found: C 65.51%, H 6.84%, N 3.54%; Theoretical C$_{22}$H$_{27}$N$_2$O$_2$S$_2$: C 65.87%, H 6.78%, N 3.49%.

Following the general procedure for carbamate alkylation, using prenyl bromide (1.90 cm$^3$, 16.5 mmol) in DMF (60 cm$^3$), and allowing to stir for 2.5 h, the pure desired product 346c was obtained as a yellow solid (5.23 g). Recrystallisation from hexane, yielded 2-[2'-(N-tert-butyloxycarboxy-N-prenylamino)phenyl]-1,3-dithiane 346c as plates (3.03 g, 8.00 mmol, 61%); Mpt: 96.5-98.5 °C; $\nu_{max}$ (KBr)/cm$^{-1}$: 2929 (NCH$_2$), 1687 (CO), 1391 (NCO), 870 (CH); $\delta_H$ (400 MHz, CDCl$_3$): 1.35 [9H, s, (CH$_3$)$_3$], 1.42 (3H, s, CCH$_3$), 1.67 (3H, s, CCH$_3$), 1.88-1.99 (1H, m, CH$_ax$), 2.14-2.18 (1H, m, CH$_eq$), 2.85-2.91 (2H, m, CH$_2$-S), 2.95-3.08 (2H, m, CH$_2$-S), 4.03 (1H, dd, J 14.8 and 7.8, NCH$_AH_B$), 4.46 (1H, dd, J 14.5 and 5.9, NCH$_AH_B$), 5.25 (1H, s, S$_2$CH), 5.34 (1H, t J 7.5, NCH$_2$CH$_2$), 7.03 (1H, d J 6.9, H-3'), 7.21-7.30 (1H, m, Ar-H), 7.65 (1H, dd, J 7.6 and 1.2, H-6'); $\delta_C$ (100 MHz, CDCl$_3$):
Following the general procedure for carbamate alkylation, using allyl bromide (1.40 cm³, 16.5 mmol) in DMF (60 cm³), and allowing to stir for 2.5 h, gave the pure desired amine 346d was obtained as a yellow solid (4.50 g, 12.8 mmol, 98%). Recrystallisation of a 0.50 g portion, from propan-2-ol, gave 2-[2'-(N-allyl-N-tert-butyloxy-carboxyamino)phenyl]-1,3-dithiane 346d as white prisms (0.32 g, 0.91 mmol, 63%); R_f (SiO₂, DCM): 0.35; M.pt: 87-90 °C; ν_max (KBr)/cm⁻¹: 2929 (NCH₂), 1697 (CO), 1385 (NCO); δ_H (400 MHz, CDCl₃): 1.36 [9H, s, (CH₃)₃], 1.88-1.99 (1H, m, CH₃), 2.13-2.20 (1H, m, CH₂), 2.85-2.93 (2H, m, CH₂-S), 2.97-3.08 (2H, m, CH₂-S), 3.91 (1H, dd, J 15.0 and 7.2, NCH₂), 4.46 (1H, d, J 11.0, NCH₂), 5.10-5.15 (2H, m, CH-CH₂), 5.22 (1H, s, S₂), 5.92-6.02 (1H, m, CH=CH₂), 7.06 (1H, d J 6.8, H-3'), 7.25 (1H, dt, J 1.5 and 7.4, Ar-H), 7.30 (1H, dt, J 1.3 and 7.4, Ar-H), 7.68 (1H, dd, J 7.6 and 1.6, H-6'); δ_C (100 MHz, CDCl₃): 25.2 (CH₂), 28.1 (CH₃), 32.2 (CH₂), 32.4 (CH₂), 46.2 (CH), 52.8 (CH₂), 80.4 (C), 117.9 (CH₂), 128.1 (CH), 128.6 (CH), 129.0 (CH), 129.3 (CH), 133.7 (CH), 136.8 (C), 139.4 (C), 154.8 (C); m/z, EI+ (%): 351 (M⁺, 10), 295 (M⁺-C₄H₈, 64), 250 (M⁺-C₇H₉O₂, 50), 188 (100); Accurate mass: C₁₈H₂₅NO₂S₂: requires 351.1327, found 351.1328; Microanalysis: Found: C 61.40%, H 7.12%, N 3.95%; Theoretical C₁₈H₂₅NO₂S₂: C 61.50%, H 7.17%, N 3.98%. -- 166
The general solid-phase Takeda Method A using amine 346a (0.47 g, 1.45 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), followed by the general resin-cleavage procedure A, yielded 1-(2'-N-tert-butyloxycarboxy-N-methylamino-5-phenyl)-4-phenylbutan-2-one 347 as a black oil [a mixture of diasteriomers of geometrical isomers, see chapter 9.3, (0.055 g, 0.16 mmol, 54%); \( \nu_{\text{max}} \) (Solt\( a \), CDCl\( 3 \))/cm\(^{-1} \): 2980 (NMe), 1792 (CO), 1690 (NCO\( 2 \)); \( \delta_{h} \) (360 MHz, 253 K, CDCl\( 3 \)): 1.29 and 1.50 [9H, s, 2 x C(CH\( 3 \)\( 3 \)], 2.79 (2H, t, J 7.1, CH\( 2 \)), 2.87-2.92 (2H, m, CH\( 2 \)), 3.04 and 3.06 (3H, 2 x s, NCH\( 3 \)), 3.54-3.78 (2H, complex AB system, \( \text{CH}^A\text{H}^B\text{CO} \), 7.11-7.33 (9H, m, Ar-H); \( \delta_{h} \) (360 MHz, 273 K, CDCl\( 3 \)): 1.30 and 1.50 [9H, s, 2 x C(CH\( 3 \)\( 3 \)], 3.06 (3H, s, NCH\( 3 \)), 3.57-3.72 (2H, AB system, \( \text{CH}^A\text{H}^B\text{CO} \), 7.12-7.28 (9H, m, Ar-H); \( \delta_{h} \) (360 MHz, 333 K, CDCl\( 3 \)): 1.37 [9H, s, C(CH\( 3 \)\( 3 \)], 2.73-2.77 (2H, m, CH\( 2 \)), 2.89 (2H, t, J 7.2, CH\( 2 \)), 3.09 (3H, s, NCH\( 3 \)), 3.61 (1H, s, \( \text{CH}^A\text{H}^B\)), 3.60 (1H, s, \( \text{CH}^A\text{H}^B\text{CO} \), 7.10-7.27 (9H, m, Ar-H); m/z, EI+ (%): 353 (M\(^+ \), 3), 297 (M\(^+\)·C\(_4\)H\(_8\), 18), 253 (M\(^+\)·C\(_5\)H\(_8\)NO\(_2\), 50), 120.1 (100); Accurate mass: \( \text{C}_{22}\text{H}_{27}\text{N}_{03}\): requires 353.1991, found 353.1987.

**N-Methyl-2-phenethyl indole 348aa**

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346a (0.42 g, 1.50 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded \( N \)-methyl-2-phenethyl indole 348aa' in excellent purity as a yellow oil (0.028 g, 0.126 mmol, 44% from ester 309a'); \( R_t \) (SiO\(_2\), DCM): 0.64; \( \nu_{\text{max}} \) (Solt\( a \), CDCl\( 3 \))/cm\(^{-1} \): 3055 (HC=C), 3025 (CH), 2925 (NCH\( 3 \)), 1468 (CH), 1454 (CH); \( \delta_{h} \) (400 MHz, CDCl\( 3 \)): 3.05 (4H, s, CH\(_2\) CH\(_2\)Ph), 3.61 (3H, s, NCH\( 3 \)), 6.31 (1H, s, H-3), 7.05-7.09 (1H, m, Ar-H), 7.16 (1H, dt, J 1.1 and 7.1, Ar-H), 7.21-7.32 (6H, m, Ar-H), 7.53 (1H, d, J 7.8, H-7); \( \delta_{c} \) (100 MHz, CDCl\( 3 \)): 28.9 (CH\(_2\)), 29.3 (CH\(_3\)), 35.1 (CH\(_2\)), 98.8 (CH), 108.7 (CH), 119.3 (CH), 119.7 (CH), 120.7 (CH), 126.2 (CH), 128.4 (CH), 128.5 (CH), 137.4 (C), 138.1 (C), 140.5 (C), 141.3 (C); m/z, EI+ (%):
Accurate mass: C\textsubscript{17}H\textsubscript{17}N: requires 235.1361, found 235.1359.

**N-Methyl-2-phenethyl indole 348aa'**

![N-Methyl-2-phenethyl indole 348aa']

Following the general solid-phase Takeda Method B, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346a (0.29 g, 0.90 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded N-methyl-2-phenethyl indole 348aa' (0.314 g, 0.133 mmol, 45% from ester 309a'); \(\delta_H\) (400 MHz, CDCl\textsubscript{3}): as above.

**N-Methyl-2-phenyl indole\textsuperscript{252} 348aa'**

![N-Methyl-2-phenyl indole 348aa']

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346a (0.42 g, 1.50 mmol) and resin-bound ester 309b' (Method A, 0.30 mmol), yielded N-methyl-2-phenyl indole\textsuperscript{252} 348aa' as a white solid (0.012 g, 0.057 mmol, 32% from ester 309b'); Mpt: 98-101 °C; (Lit.\textsuperscript{252} Mpt 99-101 °C); \(\delta_H\) (400 MHz, CDCl\textsubscript{3}): 3.75 (3H, s, NCH\textsubscript{3}), 6.56 (1H, s, H-3), 7.14-7.16 (1H, m, Ar-H), 7.24-7.27 (1H, m, Ar-H), 7.35-7.53 (6H, m, Ar-H), 7.63 (1H, dd, \(J\) 7.8 and 0.8, H-7).

**N-Benzyl-2-phenethyl indole 348ba'**

![N-Benzyl-2-phenethyl indole 348ba']

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346b (0.60 g, 1.50 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded N-benzyl-2-phenethyl indole 348ba' in excellent purity as a grey solid (0.051 g, 0.165 mmol, 55% from ester 309a'); \(R_f\) (SiO\textsubscript{2}, DCM): 0.58; Mpt: 66-69 °C; \(\nu\textsubscript{max}\) (KBr)/cm\textsuperscript{-1}: 3027 (HC=C), 2925 (NCH\textsubscript{2}), 1463 (CH), 1452 (CH); \(\delta_H\) (400 MHz, CDCl\textsubscript{3}): 2.93-3.02 (4H, m, CH\textsubscript{2}CH\textsubscript{2}Ph), 5.25 (2H, s, NCH\textsubscript{2}Ph), 6.40 (1H, s, H-3), 6.88-6.93 (2H, m, Ar-H), 6.98-7.38 (11H, m, Ar-H), 7.56-7.60 (1H, m, Ar-H); \(\delta_C\) (100 MHz, CDCl\textsubscript{3}): 28.6 (CH\textsubscript{2}), 35.1 (CH\textsubscript{2}), 46.3 (CH\textsubscript{2}), 99.7...
N-Benzyl-2-(2-methyl-propenyl) indole 348bd'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346b (0.60 g, 1.50 mmol) and resin-bound ester 309d' (Method A, 0.30 mmol), yielded N-benzyl-2-(2-methyl-propenyl) indole 348bd' in excellent purity as a light brown solid (0.038 g, 0.147 mmol, 49% from ester 309d'); Mpt: 80-83 °C; \( \nu_{\text{max}} \) (KBr)/cm\(^{-1} \): 3043 (HC=C), 2966 (NCH\(_2\)), 2929 (CH\(_2\)), 1450 (CH\(_3\)), 842 (CH), 792 (CH); \( \delta \)\(_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.89 (3H, s, CH\(_3\)), 1.99 (3H, s, CH\(_3\)), 5.28 (2H, s, NCH\(_2\)Ph), 6.04 [1H, s, CHC(CH\(_3\))\(_2\)], 6.40 (1H, s, H-3), 6.92 (2H, d, J 7.1, Ar-H), 6.98-7.20 (6H, m, Ar-H), 7.52-7.54 (1H, m, H-7); \( \delta \)\(_{\text{C}} \) (100 MHz, CDCl\(_3\)): 17.3 (CH\(_3\)), 23.9 (CH\(_3\)), 43.6 (CH\(_2\)), 98.8 (CH), 106.8 (CH), 111.3 (CH), 116.6 (CH), 117.1 (CH), 118.3 (CH), 123.0 (CH), 124.1 (CH), 125.2 (C), 125.6 (CH), 133.5 (C), 134.5 (C), 135.1 (C), 137.2 (C); m/z, EI\(^+\) (%): 261 (M\(^+\), 100), 246 (M\(^+\)-CH\(_3\), 66), 170 (37); Accurate mass: C\(_{19}\)H\(_{19}\)N: requires 261.1517, found 261.1517.

2-Phenethyl-N-prenyl indole 348ca'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346c (0.57 g, 1.50 mmol) and resin-bound 309a' (Method A, 0.30 mmol), yielded 2-phenethyl-N-prenyl indole 348ca' in excellent purity as a yellow/brown oil (0.060 g, 0.210 mmol, 70% from ester 309a'); Mpt: 64-67 °C; \( \nu_{\text{max}} \) (KBr)/cm\(^{-1} \): 3054 (HC=C), 3023 (HC=C), 2927 (NCH\(_2\)), 1461 (CH\(_3\)), 781 (C=CH), 744 (C=CH); \( \delta \)\(_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.68 (3H, d, J 1.0, CH\(_3\)), 1.80 (3H, s, CH\(_3\)), 2.99-3.08 (4H, m, CH\(_2\)CH\(_2\)Ph), 4.63-4.69 (2H, m, CH\(_2\)CH), 5.11-5.15 (1H, m, NCH\(_2\)CH\(_2\)), 6.31 (1H, s, H-3), 7.06 (1H, dt, J 1.0 and 7.3, H-5), 7.13 (1H, dt, J 1.1 and 7.0, H-6), 7.17-7.32 (6H, m, Ar-H), 7.49 (1H, d, J 7.6, H-7); \( \delta \)\(_{\text{C}} \) (100 MHz, CDCl\(_3\)): 18.1 (CH\(_3\)), 25.5
(CH₃), 28.8 (CH₂), 35.1 (CH₂), 41.3 (CH₂), 99.0 (CH), 119.2 (CH), 119.9 (CH), 120.6 (CH), 120.9 (CH), 126.1 (CH), 128.0 (C), 128.3 (CH), 128.5 (CH), 134.1 (C), 136.5 (C), 140.1 (C), 141.4 (C); m/z, EI+ (%): 289 (M⁺, 56), 198 (M⁺-C₇H₇, 100); Accurate mass: C₂₁H₂₃N: requires 289.1830, found 289.1831.

2-(2-Methyl-propenyl)-N-prenyl-indole 348cd'

Following the general solid-phase Takeda Method A, resin-cleavage procedure A, and general ketone cyclisation procedure, employing amine 346c (0.57 g, 1.50 mmol) and resin-bound ester 309d' (Method A, 0.30 mmol), yielded 2-(2-methyl-propenyl)-N-prenyl-indole 348cd' in excellent purity as a yellow/brown oil (0.036 g, 0.150 mmol, 50% from ester 309d'); v_max (KBr)/cm⁻¹: 3053 (He=e), 3029 (He=e), 2925 (NeH₂), 1460 (eH₃), 777 (eH=C), 792 (CH=C); δ_H (400 MHz, CDCl₃): 1.69 (3H, d, J 0.8, CH₃), 1.81 (3H, s, CH₃), 1.95 (3H, d, J 0.5, CH₃), 1.97 (3H, s, CH₃), 4.67 (2H, d, J 6.4, NCH₂CH), 5.16-5.20 (1H, m, NeH₂), 6.18 (1H, d, J 0.7, CH=CMe₂), 6.38 (1H, s, H-3), 7.06 (1H, dt, J 0.9 and 7.8, H-5), 7.14 (1H, dt, J 1.0 and 7.1, H-6), 7.27 (1H, m, H-4), 7.56 (1H, d, J 7.7, H-7); δ_C (100 MHz, CDCl₃): 18.0 (CH₃), 20.2 (CH₃), 25.5 (CH₃), 26.9 (CH₃), 41.5 (CH₂), 101.3 (CH), 109.2 (CH), 114.7 (CH), 119.3 (CH), 120.9 (CH), 128.2 (C), 134.0 (C), 136.0 (C), 137.1 (C), 139.5 (C); m/z, EI+ (%): 239 (M⁺, 100), 171 (M⁺-C₅H₃, 80); Accurate mass: C₁₇H₂₁N: requires 239.1674, found 239.1676.

2-[2'-(N-Methyloxycarboxyamino)phenyl]-1,3-dithiane 350

Methylchloroformate (0.80 cm³, 12.0 mmol) was added dropwise to a solution of amine 331 (2.11 g, 10.0 mmol), saturated sodium bicarbonate (0.80 cm³), in dioxane (60 cm³) and the reaction mixture was allowed to stir for 16 h. After this time, the reaction mixture was poured into water (60 cm³) and extracted into diethyl ether (2 x 60 cm³). The combined organic phases were then washed with water (2 x 60 cm³), brine (60 cm³), dried over magnesium sulphate, and concentrated to yield a white solid (2.41 g, 90%, 8.96 mmol). Recrystallisation of a 0.50 g portion, from propan-2-ol, yielded 2-[2'-(N-
methylloxycarboxyamino)phenyl]-1,3-dithiane 350 as white needles (0.36 g, 72%); Rf (SiO2, DCM): 0.30; Mpt: 95-97 °C; νmax (KBr/cm\(^{-1}\)): 3295 (NH), 2851 (OCH3), 1731 (CO); δH (400 MHz, CDCl3): 1.89-1.99 (1H, CHax), 2.17-2.22 (1H, CHeq), 2.91-2.94 (2H, CH2-S), 3.05-3.12 (2H, CH2-S), 3.81 (3H, OCH3), 5.31 (1H, CH3), 7.06 (1H, t, J 7.4, H-5'), 7.30 (1H, t, J 7.6, H-4'), 7.39 (1H, d, J 7.6, H-6'), 7.62 (1H, s, H-3'), 7.89 (1H, s, NH); δC (100 MHz, CDCl3): 25.0 (CH2), 31.9 (CH2), 48.8 (CH), 52.5 (CH3), 122.6 (C), 124.6 (CH), 128.6 (CH), 129.3 (CH), 136.0 (C), 154.3 (C); m/z, EI+ (%): 269 (M+, 80), 163 (C10H11S, 30), 136 (100); Accurate mass: C12H15NO2S2: requires 269.0544, found 269.0544; Microanalysis Found: C 53.43%, H 5.60%, N 5.28%; Theoretical C12H15NO2S2: C 53.57%, H 5.62%, N 5.21%.

2-[2'-(N-Methyl-N-methyloxycarboxyamino)phenyl]-1,3-dithiane 349

![Image](349)

Lithium di-isopropylamine (3.75 cm\(^3\), 7.50 mmol, 2.0 mol dm\(^{-3}\) in THF, ethyl benzene and heptanes), in THF (4.0 cm\(^3\)) was added drop-wise to a solution of carbamate 350 (1.88 g, 7.00 mmol) in THF (20 cm\(^3\)), under argon at -78 °C, and the reaction mixture was allowed to warm to rt and then stirred for 1 h. The reaction mixture was then cooled to -40 °C before methyl iodide (1.80 cm\(^3\), 30.0 mmol) was added and the reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was then poured into water and extracted with ethyl acetate (2 x 30 cm\(^3\)). The combined organic phases were then washed with water (3 x 100 cm\(^3\)), dried over sodium sulfate and concentrated to yield a yellow solid (1.79 g) containing mostly the desired product 349 and a small amount of starting material 350. Recrystallisation from propan-2-ol, yielded 2-[2'-(N-methyl-N-methyloxycarboxyamino)phenyl]-1,3-dithiane 349 as a white solid (1.15 g, 4.06 mmol, 58%); Mpt: 105-107 °C; νmax (KBr/cm\(^{-1}\)): 2925 (NCH3), 1700 (CO); δH (400 MHz, CDCl3): 1.87-1.98 (1H, CHax), 2.14-2.21 (1H, CHeq), 2.85-2.92 (2H, CH2-S), 3.02-3.10 (2H, CH2-S), 3.28 (3H, s, NCH3), 3.64 (3H, OCH3), 5.24 (1H, CH3), 7.14 (1H, d, J 7.1, H-3'), 7.29-7.36 (2H, CH-4' and H-5'), 7.71 (1H, dd, J 7.2 and 1.8, H-6'); δC (100 MHz, CDCl3): 25.2 (CH2), 32.1 (CH2), 32.4 (CH2), 38.4 (CH3), 45.7 (CH), 53.1 (CH3), 127.9 (CH), 128.5 (CH), 129.3 (CH), 129.7 (CH), 136.6 (C), 140.1 (C), 156.6 (C); m/z, EI+ (%): 283 (M+, 37), 208 (20), 177 (100); Accurate mass: C13H17N02S2: requires 283.0701, found 283.0703; Microanalysis Found: C 55.13%, H 5.98%, N 4.83, S 22.72%; Theoretical C13H17N02S2: C 55.09%, H 6.05%, N 4.94, S 22.63%.
Following a known procedure, benzylchloroformate (2.20 cm³, 15.0 mmol) was added dropwise to a solution of amine 331 (3.17 g, 15.0 mmol) and sodium bicarbonate (2.52 g, 30.0 mmol), in acetone: water (4: 1, 125 cm³) at 0 °C. The reaction mixture was allowed to warm to rt and then further stirred for 2 h. After this time the reaction mixture was concentrated in vacuo, water (100 cm³) was added, and the mixture was extracted with ethyl acetate (2 x 50 cm³). The combined organic phases were then washed with water (2 x 100 cm³), dried over magnesium sulphate, and concentrated to yield crude carbamate 351 as a yellow oil (5.28 g). DMF (90 cm³) and methyl iodide (1.90 cm³, 30 mmol) were added and the mixture was cooled to 0 °C, under argon. Sodium hydride [60% in mineral oil, (0.75 g, 18.8 mmol)], was then added portion-wise over 10 mins and the reaction mixture was allowed to warm to rt and stirred for 3 h. After this time the reaction mixture was carefully poured into iced water and extracted into ethyl acetate (2 x 80 cm³). The combined organic phases were then washed with water (2 x 200 cm³), dried over sodium sulphate, and concentrated to yield a yellow/orange oil (1.15 g, 4.06 mmol, 58%). Column chromatography (SiO₂, DCM) yielded 2-[2'-(N-benzyloxycarboxy-N-methylamino)phenyl]-1,3-dithiane 351 as a yellow oil (0.98 g, 2.73 mmol, 18%); Rf (SiO₂, DCM): 0.25; νmax (KBr)/cm⁻¹: 2908 (NMe), 1699 (CO), 781 (CH); δH (400 MHz, CDCl₃): 1.82-1.94 (1H, m, CH₃), 2.05-2.13 (1H, m, CH₂), 2.79-3.02 (4H, m, CH₂-S), 3.28 (3H, s, NCH₃), 5.05 (1H, d, J 12.7, NCH₂CH₃), 5.10 (1H, d, J 12.6, NCH₂CH₃), 5.23 (1H, s, S₂CH), 7.11 (1H, d, J 7.2, H-3'), 7.23-7.34 (7H, m, Ar-H), 7.71 (1H, dd, J 7.6 and 1.7, H-6'); δC (100 MHz, CDCl₃): 24.9 (CH₂), 31.9 (CH₂), 32.2 (CH₂), 38.3 (CH₃), 45.7 (CH), 67.0 (CH₂), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 129.2 (CH), 129.4 (CH), 136.5 (C), 136.6 (C), 139.9 (C), 155.7 (C); m/z, EI+ (%): 359 (M⁺, 18), 268 [(M⁺-C₃H₇), 64], 91 (100); Accurate mass: C₁₉H₂₁NO₂S₂: requires 359.1014, found 359.1012; Microanalysis Found: C 63.46%, H 5.83%, N 4.02%, S 18.05%; Theoretical C₁₉H₂₁NO₂S₂: C 63.48%, H 5.84%, N 3.90%, S 17.84%.
Attempted solid-phase Diels-Alder reaction

Following the general Takeda procedure B, using N-silyl carbamate 342a (0.58 g, 1.50 mmol) and resin-bound ester 309d' (0.311 mmol), the corresponding enol ether 360 was obtained as a bright red coloured resin. Following a literature procedure,124 N-methylmaleimide (0.33 g, 3.00 mmol) was added to a flask containing enol ether 360 (1 Kan, 0.311 mmol) and toluene (40 cm³), and the reaction mixture was allowed to stir at 70 °C for 40 h. After this time, the Kan was washed with toluene (x 5), alternatively with MeOH/ DCM, MeOH and finally with diethyl ether to leave an orange coloured resin. Subsequent subjection to the above standard resin cleavage conditions A, yielded N-Boc indole 336ad' (1H NMR as before) in very high purity and good yield (60%), with no sign of any other compound present the 1H NMR spectrum.

Attempted formation of Ketone 363

Following the general Takeda procedure B using thioacetal 285 (0.46 g, 1.50 mmol) and REM resin (0.300 mmol, 1.43 mmol g⁻¹), followed by the standard resin-cleavage procedure method A generated an orange solid (0.016 g). 1H NMR spectroscopy confirmed a mixture of products was obtained, including what may have been the desired ketone 363. Large singlets (corresponding to cyclopentadienyl ligands) were also observed, suggesting that titanium residues remained also.
Resin-bound ester 368

Methyl oxalyl chloride (0.6 cm$^3$, 6.00 mmol) was added drop-wise to a reaction flask, containing 3 Kans of hydroxymethyl polystyrene (each containing 230 mg resin, 0.87 mmol g$^{-1}$, 0.20 mmol/kan, 0.6 mmol), triethylamine (0.85 cm$^3$, 6.00 mmol) and dimethylamino pyridine (0.07 g, 0.60 mmol) in DCM (50 cm$^3$), at -10 °C under argon, and allowed to stir at this temperature for 30 mins. The reaction mixture was then allowed to warm to rt and stirred for 15 h. The Kans were washed with DCM (x 2), and then alternately with MeOH and DCM (x 4), before finally washing with MeOH and dried under vacuum to yield resin-bound ester 368; $\nu_{\text{max}}$ (G Gate)/cm$^{-1}$: 1766 (CO), 1741 (CO).

Resin-bound ester 369

Oxalyl chloride (0.6 cm$^3$, 6.00 mmol) was added drop-wise to a reaction flask, containing 3 Kans of hydroxymethyl polystyrene (each containing 230 mg resin, 0.87 mmol g$^{-1}$, 0.20 mmol/kan, 0.6 mmol), triethylamine (0.85 cm$^3$, 6.00 mmol) and dimethylamino pyridine (0.07 g, 0.60 mmol) in DCM (50 cm$^3$), at 0 °C under argon, and allowed to warm to rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, dry ethanol was added drop-wise, and the reaction mixture was allowed to warm to rt and stirred for 15 h. The Kans were then washed with DCM (x 2), and then alternately with MeOH and DCM (x 5), before finally washing with MeOH and dried under vacuum to yield resin-bound ester 369; $\nu_{\text{max}}$ (G Gate)/cm$^{-1}$: 1758 (CO), 1743 (CO).
Attempted formation of bis-indole 370

Titanocene dichloride (1.20 g, 4.80 mmol, 24.0 eq.), magnesium turnings (0.13 g, 5.30 mmol) and 4Å molecular sieves (0.30 g) were heated briefly in vacuo and then allowed to cool. The reaction flask was purged with argon before adding THF (10 cm³) and triethylphosphite (1.60 cm³, 9.60 mmol). The reaction mixture was cooled using an ice bath and stirred for 30 mins. After stirring for a further 3 h at rt, a THF (8 cm³) solution of thioacetal 342a (0.46 g, 1.20 mmol, 6.0 eq.) was added, and the mixture was stirred for 15 mins. After this time the reaction mixture was added via syringe, into a flask containing 1 Kan of resin-bound ester 368 or 369 (0.20 mmol, 1.0 eq.), pre-swollen in THF (8 cm³). The mixture was stirred under argon for 15-18 h, before washing the Kan with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and dried under vacuum. The Kan was then treated with 5% TFA in DCM (5 cm³, 3.25 mmol) and placed on a shaker for 30 mins. The Kan was washed with DCM (3 x 5 cm³) and the organic washings were combined and then concentrated to yield a red oil (<10 mg). ¹H NMR spectroscopy confirmed that only titanium residues (large singlets corresponding to cyclopentadienyl ligands were observed), triethylphosphite and THF remained.

General method for the synthesis of resin-bound β- amino esters

The dialkyl amine (18 mmol, 10 eq), was added to a flask containing six Kans of REM resin (each containing approximately, 0.30 mmol/kan, 1.80 mmol) in DMF (100 cm³) at rt and stirred for 15 h. The Kans were then washed with DMF (x 2), and then alternately with MeOH and DCM (x 4), before finally washing with MeOH and diethyl ether to give the desired resin-bound β- amino esters.
Resin-bound β–amino ester 378

Following the general method for β-amino ester synthesis, employing six Kans with GSK in-house REM resin 377 (each containing 176 mg resin, 1.64 mmol g⁻¹, 0.29 mmol/kan, 1.74 mmol) and morpholine (1.60 cm³, 18 mmol, 10 eq) yielded β-amino ester 378; ν_max (G Gate)/cm⁻¹: 1735 s (CO).

4-Morpholin-4-yl-1-phenyl-butan-2-one²⁵³ 379

The general solid-phase Takeda procedure C and general resin-cleavage conditions-A, employing thioacetal 285 (0.19 g, 0.60 mmol) and resin-bound ester 378 (0.30 mmol), yielded 4-morpholin-4-yl-1-phenyl-butan-2-one²⁵³ 379 as a yellow oil (0.070 g, 0.30 mmol, 104%); ν_max (Thin film)/cm⁻¹: 1720 (CO); δ_H (400 MHz: CDCl₃): 2.83 (2H, t, J 9.7, NCH₂CH₂), 3.05 (2H, t, J 6.3, COCH₂CH₃), 3.28 (2H, t, J 6.3, COCH₂CH₃), 3.39 (2H, d, J 11.7, NCH₂CH₃), 3.74 (2H, s, PhCH₂CO), 3.80-3.94 (4H, m, NCH₂CH₂O), 7.17 (2H, d, J 6.7, H-1' and H-6'), 7.26-7.38 (3H, m, Ar-H); δ_C (100 MHz: CDCl₃): 35.5 (CH₂), 49.7 (CH₂), 51.8 (CH₂), 52.4 (CH₂), 63.7 (CH₃), 127.5 (CH), 128.9 (CH), 129.4 (CH), 132.9 (C), 204.3 (C); m/z, EI⁺ mode (%): 233 (M⁺, 40), 114 (C₆H₁₂NO, 16), 100 (C₅H₁₀NO, 100); Accurate mass: C₁₄H₁₉N₃O₂: requires 233.1416, found 233.1415.

1,4-Diphenyl-butan-2-one²⁵⁴ 381

The general solid-phase Takeda method C and general resin-cleavage procedure A employing thioacetal 285 (0.19 g, 0.60 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded 1,4-diphenyl-butan-2-one²⁵⁴ 381 (0.041 g, 0.184 mmol, 61%); δ_H (400 MHz, CDCl₃): 2.68-2.81 (4H, m, CH₂CH₂Ph), 3.59 (2H, s, COCH₂Ph), 7.21-7.32 (10H, m, Ar-H).
Merrifield resin-bound β-amino ester 383

Following the general method for β-amino ester synthesis, employing six Kans of Polymerlabs REM resin 382 (each containing 188 mg resin, 1.60 mmol g⁻¹, 0.30 mmol/kan, 1.80 mmol) and morpholine (1.60 cm³, 18.0 mmol, 10 eq) yielded β-amino ester 383; νmax (G Gate)/cm⁻¹: 1732 (CO).

Wang resin-bound β-amino ester 385

Six Kans of Wang resin (each containing 176 mg resin, 1.70 mmol g⁻¹, 0.30 mmol/kan, 1.80 mmol) were stirred in THF (100 cm³) at rt with acrylic acid (0.60 cm³, 9.00 mmol) and DMAP (0.22 g, 1.80 mmol). 1,3-Diisopropylcarbodiimide DIC (1.4 cm³, 9.00 mmol) was added drop-wise and the reaction mixture was stirred for 24 h at rt. The THF solution was removed and the Kans were then washed with THF, MeOH/DCM alternate (x 4), MeOH and finally with diethyl ether. The resin was then dried under vacuum overnight and re-treated as above to yield Wang REM resin 384. Following the general method for β-amino ester synthesis, employing six Kans of Wang REM resin 384 (1.80 mmol) and morpholine (1.60 cm³, 18.0 mmol, 10 eq) yielded β-amino ester 385.

Wang resin-bound β-amino ester 387

Wang REM resin 384 was synthesised as for ester 385. Following the general method for β-amino ester synthesis, employing two Kans of Wang REM resin 384 (0.60 mmol) and piperidine (0.30 cm³, 3.00 mmol, 5 eq) yielded β-amino ester 387.
Formation of crude indole 389

Following the general solid-phase Takeda method B and general resin-cleavage procedures but using 10% TFA in DCM, employing thioacetal 342a (0.35 g, 0.90 mmol) and resin-bound ester 387 (0.30 mmol), yielded crude indole 396 as an impure mixture (0.032 g, 30%). The crude $^1$H spectrum contained signals corresponding to the indole 396 [δH (400 MHz, CDCl3): 1.41-1.46 (6H, m, NCH2CH2), 1.70 [9H, s, C(CH3)3], 2.45-2.76 (4H, m, NCH2CH2), 2.93-3.00 (2H, m, ArCH2CH2N), 3.33-3.36 (2H, m, ArCH2CH2N), 6.44 (1H, s, H-3), 7.14-7.19 (2H, m, Ar-H), 7.20-7.30 (4H, m, Ar-H), 7.45 (1H, d, J 7.3, Ar-H), 7.45 (1H, d, J 8.0, Ar-H)] with some other signals which could not be interpreted.

Resin-bound β-amino ester 394

Following a literature procedure,122 4 Kans containing Merrifield resin (each containing 164 mg resin, 1.83 mmol g$^{-1}$, 0.30 mmol/kan, 1.20 mmol) were stirred with acrylic acid (0.40 cm$^3$, 6 mmol, 5 eq), cesium carbonate (1.96 g, 6.00 mmol, 5 eq) and potassium iodide (0.12 g, 6.00 mmol, 5 eq) in DMF (60 cm$^3$), at 70 °C for 18 h. The Kans were then washed with DMF (x 2), water (x 2), and then alternately with MeOH and DCM (x 5), before finally washing with MeOH and diethyl ether, and drying under vacuum to leave REM resin 393. Following the general method for β-amino ester synthesis, employing two Kans of REM resin 393 (0.60 mmol) and morpholine (0.60 cm$^3$, 6.00 mmol, 10 eq), yielded β-amino ester 394.

2-Ethylmorpholin-4-yl-N-benzyl-indole 396

The general solid-phase Takeda method A, general resin-cleavage procedure A, and ketone cyclisation conditions employing thioacetal 346b (0.60 g, 1.50 mmol) and resin-bound ester 394 (0.30 mmol), yielded crude indole 396 as an impure mixture (0.017 g, 0.08 mmol, 28%). Purification by column chromatography (SiO2, ethyl acetate), yielded 2-
ethylmorpholin-4-yl-N-benzyl-indole 396 as a yellow solid (0.04 g, 0.02 mmol, 6%); \( R_f \) (SiO\(_2\), ethyl acetate) 0.13; \( \delta_H \) (400 MHz, CDCl\(_3\)): 2.45-3.50 (4H, m, NCH\(_2\)CH\(_2\)O), 2.67 (2H, t, \( J \) 7.2, CH\(_2\)CH\(_2\)N), 2.88 (2H, t, \( J \) 7.4, CH\(_2\)CH\(_2\)N), 3.68-3.71 (4H, m, NCH\(_2\)CH\(_2\)O), 5.35 (2H, s, NCH\(_2\)Ph), 6.37 (1H, s, H-3), 6.95 (2H, dd, \( J \) 8.2 and 1.6, Ar-H), 7.06-7.13 (2H, m, Ar-H), 7.20-7.30 (4H, m, Ar-H), 7.57 (1H, dd, \( J \) 6.6 and 1.8, Ar-H).

2-(2'-Nitrophenyl)acetaldehyde 401

2'-Nitrophenethyl alcohol (0.15 cm\(^3\), 1.00 mmol) in DCM (2 cm\(^3\)), was added dropwise to a solution of the Dees-Martin periodinane reagent (0.51 g, 1.20 mmol) in DCM (3 cm\(^3\)), at rt under argon, for 30 mins. After this time, the reaction mixture was quenched by pouring into sodium hydroxide (1.0 mol dm\(^{-3}\), 40 cm\(^3\)) and diethyl ether (30 cm\(^3\)) was added. The resulting white precipitate was filtered. The organic layer was separated, washed with water (2 x 50 cm\(^3\)), dried over magnesium sulfate and concentrated to yield a yellow oil (0.11 g, 67%). The crude \(^1\)H spectrum confirmed that greater than 95% conversion to aldehyde 401 was achieved [\( \delta_H \) (400 MHz, CDCl\(_3\)): 4.03 (2H, s, CH\(_2\)CHO), 7.24 (1H, dd, \( J \) 7.6 and 0.8, H-6'), 7.42 (1H, t, \( J \) 7.6, H-5'), 7.42 (1H, t, \( J \) 7.6, H-4'), 7.80 (1H, dd, \( J \) 7.6 and 1.1, H-3'), 9.24 (1H, s, CHO)] along with some other signals which could not be interpreted.

Methoxymethyl triphenylphosphonium chloride\(^{239} \) 406

Methoxymethyl chloride (10.0 cm\(^3\), 110 mmol) was added slowly to a solution of triphenylphosphine (26.2 g, 100 mmol) in DCM (150 cm\(^3\)) and the reaction mixture was heated under reflux for 15 h. Toluene (150 cm\(^3\)) was added and the solution was evaporated to dryness and then repeated to yield methoxymethyl triphenylphosphonium chloride 406 as a white crystalline solid (34.0 g, 99.0 mmol, 99%); \( \delta_H \) (400 MHz, CDCl\(_3\)): 3.74 (1H, s, OCH\(_3\)), 6.00 (2H, d, \( J \) 3.9, CH\(_2\)PPh\(_3\)), 7.67-7.71 (6H, m, Ar-H), 7.79-7.86 (9H, m, Ar-H).
tert-Butyllithium (1.50 mol dm$^{-3}$ in hexane, 53.3 cm$^3$, 80 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride 406 (15.0 g, 99.0 mmol) in THF (180 cm$^3$), at -78 °C under argon. The reaction mixture was stirred at -78 °C for 15 mins, and then warmed to -40 °C over 15 mins, and stirred at this temperature for 30 mins. The reaction mixture was then cooled to -78 °C and a solution of 2-nitrobenzaldehyde 334a (9.06 g, 60.0 mmol) in THF (120 cm$^3$) was added via canula, stirred at this temperature for 15 mins before allowing to warm to rt and allowed to stir for 18h. After this time, the reaction mixture was quenched by pouring into water (200 cm$^3$) and extracted into DCM (2 x 100 cm$^3$). The combined organic phases were then washed with water (2 x 150 cm$^3$), brine (200 cm$^3$), dried over sodium sulfate, and concentrated to yield a brown solid (29.83 g). Signals in the $^1$H NMR (400 MHz, CDCl$_3$) spectrum confirmed that this was the desired enol ether 408a as a 5:1 mixture of trans A: cis B isomers [$\delta$ 3.75 (3H A, s, OCH$_3$), 3.80 (3H B, s, OCH$_3$), 5.70 (1H B, d, $J$ 7.2, CH=CHOCH$_3$), 6.31 (1H B, d, $J$ 7.2, CH=CHOCH$_3$), 6.39 (1H A, d, $J$ 12.8, CH=CHOCH$_3$), 7.05 (1H A, d, $J$ 12.8, CH=CHOCH$_3$)] with significant amounts of triphenylphosphine-containing side-products remaining but no evidence of any aldehyde starting material. 1,3-Propanedithiol (6.6 cm$^3$, 66 mmol) was added to a solution of crude enol ether 408a (assume 60.0 mmol), acetic acid (60 cm$^3$) and boron trifluoride diethyletherate (23.0 cm$^3$, 180 mmol) in toluene (100 cm$^3$), under nitrogen, and stirred for 20 h at rt. After this time, the resulting white solid was filtered off and the filtrate was poured into water (200 cm$^3$) and extracted into ethyl acetate (2 x 50 cm$^3$). The combined organic phases were washed with water (100 cm$^3$), sodium hydroxide (2 mol dm$^{-3}$, 2 x 100 cm$^3$), water (200 cm$^3$), brine (200 cm$^3$), dried over sodium sulfate, and concentrated to yield a brown solid (16.99 g). $^1$H NMR analysis confirmed that this was the desired thioacetal 409a with significant amounts of triphenylphosphine-containing impurities remaining. Recrystallisation of a 0.50 g portion from propan-2-ol, yielded 2-(2’-nitrobenzyl)-1,3-dithiane 409a as orange/yellow needles (0.32 g, 1.25 mmol): R$_f$ (SiO$_2$, DCM): 0.48; $\nu_{\text{max}}$ (GGate)/cm$^{-1}$: 2925 (CH$_2$), 2896 (CH), 1512 (NO$_2$), 1495 (NO$_2$); $\delta_H$ (400 MHz, CDCl$_3$): 1.83-1.93 (1H, m, CH$_{ax}$), 2.08-2.17 (1H, m, CH$_{eq}$), 2.79-2.91 (4H, m, CH$_2$-S), 3.39 (2H, d, $J$ 7.4, CH$_2$CHS), 4.36 (1H, t, $J$ 7.5, CH$_2$CHS), 7.42-7.45 (2H, m, H-4' and H-6'), 7.56 (1H, dt, $J$ 1.2 and 7.0, H-5'), 8.01 (1H, dd, $J$ 1.2 and 7.1, H-3'); $\delta_C$ (100 MHz, CDCl$_3$): 25.6 (CH$_2$), 30.1 (CH$_2$), 38.9 (CH$_2$), 46.6 (CH), 125.1 (CH), 149.5 (NO$_2$), 1512 (NO$_2$), 2925 (CH$_2$), 2896 (CH), 1512 (NO$_2$), 1495 (NO$_2$).
128.3 (CH), 132.4 (C), 132.8 (CH), 133.5 (CH), 149.1 (C); m/z, EI+ (%): 255 (M⁺, 8), 119 (100); Accurate mass: C₁₁H₁₃NO₂S₂: requires 255.0387, found 255.0388.

2-(3'-Methoxy-2'-nitrobenzyl)-1,3-dithiane 409b

As for thioacetal 409a, tert-Butyllithium (1.50 mol dm⁻³ in hexane, 37.0 cm³, 55 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride 406 (20.6 g, 60.0 mmol) in THF (120 cm³), at -78 °C under argon. The reaction mixture was stirred at -78 °C for 15 mins, and then warmed to -40 °C over 30 mins and stirred at this temperature for 30 mins. The reaction mixture was then cooled to -78 °C and a solution of 3-methoxy-2-nitrobenzaldehyde 334b (7.25 g, 40.0 mmol) in THF (40 cm³) at rt was added via syringe, stirred at -78 °C for 15 mins before allowing to warm to rt over 1 h and allowing to further stir for 18 h. After this time, the reaction was quenched by pouring into water (400 cm³) and extracted into DCM (2 x 200 cm³). The combined organic phases were then washed with water (3 x 300 cm³), brine (300 cm³), dried over sodium sulfate, and concentrated to yield a brown solid (20.14 g). Signals in the ¹H NMR spectrum (400 MHz, CDCl₃), confirmed that this was the desired enol ether 408b as a 2: 1 mixture of trans A: cis B isomers [8 5.03 (1H₈, d, J 7.2, CHCHOCH₃), 5.62 (1H₈, d, J 12.8, CHCHOCH₃), 6.26 (1H₈, d, J 7.1, CHCHOCH₃), 7.07 (1H₈, d, J 12.8, CHCHOCH₃)] with significant amounts of triphenylphosphine-containing by-products remaining, but no evidence of any aldehyde starting material. Following the procedure for the formation of thioacetal 409a, employing crude enol ether 409b (20.14 g, assumed 40.0 mmol), 1,3-propanedithiol (4.40 cm³, 44.0 mmol), acetic acid (40 cm³), and boron trifluoride diethyletherate (19.0 cm³, 150 mmol) in toluene (100 cm³), and following the same work-up procedure, yielded a brown solid (12.03 g). ¹H NMR analysis confirmed that this was the desired thioacetal 409b; δH (400 MHz, CDCl₃): 1.81-1.92 (1H, m, CH₃), 2.04-2.13 (1H, m, CH₃), 2.80-2.87 (4H, m, CH₂-S), 3.03 (2H, d, J 7.7, CH₂CH₃), 3.88 (3H, s, OCH₃), 4.23 (1H, t, J 7.7, CH₂CH₃), 6.95 (1H, d, J 7.8, H-4'), 7.16-7.18 (1H, d, m, H-6'), 7.36 (1H, t, J 8.1, H-5'); Rₜ (SiO₂, DCM): 0.42; with no sign of the enol ether remaining although significant amounts of triphenylphosphine-containing impurities did remain and attempts to recrystallise a 0.40 g portion of this mixture were unsuccessful. This crude mixture was simply used to form the aniline and then Boc protected.
As for thioacetal 409a, using tert-Butyllithium (1.50 mol dm\(^{-3}\) in hexane, 37 cm\(^3\), 55.0 mmol) was added drop-wise to a solution of methoxymethyltriphenylphosphonium chloride 406 (20.6 g, 60.0 mmol) in THF (120 cm\(^3\)), at -78 °C under argon. The reaction mixture was stirred at -78 °C for 15 mins, and then warmed to -40 °C over 30 mins and stirred at this temperature for 30 mins. The reaction mixture was then cooled to -78 °C and a solution of 2-nitropiperanal 334c [(7.80 g, 40.0 mmol) in THF (60 cm\(^3\)) at rt] was added via syringe, stirred at -78 °C for 15 mins before allowing to warm to rt over 1 h and then allowed to stir for 18 h. After this time, the reaction mixture was quenched by pouring into water (400 cm\(^3\)) and extracted with DCM (2 x 200 cm\(^3\)). The combined organic phases were then washed with water (3 x 300 cm\(^3\)), brine (300 cm\(^3\)), dried over sodium sulfate, and concentrated to yield a brown solid (20.96 g). Signals in the \(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum confirmed that this was the desired enol ether 408c as a 4: 3 mixture of trans A cis B isomers [\(\delta\) 5.52 (1H\(^A\), d, J 12.8, CHCHOCH\(_3\)), 5.83 (1H\(^B\), d, J 7.3, CHCHOCH\(_3\)), 6.24 (1H\(^B\), d, J 7.3, CHCHOCH\(_3\)), 6.95 (1H\(^A\), d, J 12.8, CHCHOCH\(_3\))] with significant amounts of triphenylphosphine-containing side-products remaining. Following the procedure for the formation of thioacetal 409a, employing crude enol ether 408c (20.96 g, assume 40.0 mmol), yielded a brown solid (12.85 g). \(^1\)H NMR analysis confirmed that this was thioacetal 409c with significant amounts of triphenylphosphine-containing impurities but no evidence of any aldehyde starting material remained. Recrystallisation of a 0.40 g portion from propan-2-ol, gave 2-(4',5'-methylenedioxy-2'-nitrobenzyl)-1,3-dithiane 409c as yellow needles (0.28 g, 0.94 mmol): \(R_f\) (SiO\(_2\), DCM): 0.42; Mpt: 136-138 °C; \(\nu_{\text{max}}\) (GGate)/cm\(^{-1}\): 2962 (CH\(_2\)), 2900 (CH), 1496 (NO\(_2\)), 1477 (NO\(_2\)) ; \(\delta_H\) (400 MHz, CDCl\(_3\)): 1.83-1.94 (1H, m, CH\(_{ax}\)), 2.08-2.15 (1H, m, CH\(_{eq}\)), 2.81-2.89 (4H, m, CH\(_2\)-S), 3.33 (2H, d, J 7.4, CH\(_2\)CHS), 4.37 (1H, t, J 7.5, CH\(_2\)CHS), 6.11 (2H, s, OCH\(_2\)O), 6.80 (1H, s, H-6'), 7.56 (1H, s, H-3'); \(\delta_C\) (100 MHz, CDCl\(_3\)): 25.7 (CH\(_2\)), 30.2 (CH\(_2\)), 39.6 (CH\(_2\)), 46.8 (CH), 103.0 (CH\(_2\)), 106.0 (CH), 112.0 (CH), 129.6 (C), 129.7 (C), 147.3 (C), 151.4 (C); m/z, EI\(^+\) (%): 299 (M\(^+\), 5), 282 (M\(^+\)-OH, 8), 193 (18), 119.0 (100); Accurate mass: C\(_{12}\)H\(_{13}\)N\(_2\)O\(_4\)S\(_2\): requires 299.0286, found 299.0286; Microanalysis Found: C 48.15%, H 4.27%, N 4.53%, S 21.38%; Theoretical C\(_{12}\)H\(_{13}\)N\(_2\)O\(_4\)S\(_2\): C 48.14%, H 4.38%, N 4.68%, S 21.42%.
Iron powder (10.05 g, 180 mmol) was added to the crude thioacetal 409a (assuming 60 mmol) and ammonium chloride (16.05 g, 300 mmol), in an ethanol (200 cm$^3$) and water (100 cm$^3$) solution, and the reaction mixture was heated under reflux for 4 h. After cooling, the reaction mixture was filtered through celite, washing with ethyl acetate (100 cm$^3$) and then concentrated in vacuo. The resulting slurry was partitioned between ethyl acetate (100 cm$^3$) and water (150 cm$^3$) and the organic phases were then washed with water (2 x 150 cm$^3$), brine (150 cm$^3$), dried over magnesium sulfate, and concentrated under vacuum to give a brown oil; (14.16 g). $^1$H NMR analysis confirmed that this was the desired amine 410a [R$_f$ (SiO$_2$, DCM): 0.12] with significant amounts of triphenylphosphine-containing by-products remaining. Di-tert-butyl-dicarbonate (13.10 g, 60.0 mmol), was added to a solution of the crude amine 410a in THF (120 cm$^3$) and was heated under reflux, under nitrogen, for 20 h. After this time, the reaction mixture was poured into water (200 cm$^3$) and extracted into diethyl ether (2 x 100 cm$^3$). The combined organic phases were washed with water (2 x 200 cm$^3$), brine (2 x 200 cm$^3$), dried over sodium sulfate and concentrated to yield a white/brown solid (18.16g). Recrystallisation from cyclohexane: propan-2-ol (4:1) yielded 2-[2'-(N-tert-butyloxycarboxyamino)benzyl]-1,3-dithiane 411a as a pale yellow solid (8.61 g, 26.5 mmol, 44% from 334a), R$_f$ (SiO$_2$, DCM): 0.17; Mpt: 130-133 °C; $\nu_{max}$ (GGate)/cm$^{-1}$: 3300 (NH), 2976 (CH$_2$), 2927 (CH), 2898 (CH), 1685 (CO); $\delta_{H}$ (400 MHz, CDCl$_3$): 1.52 [9H, s, (CH$_3$)$_3$], 1.85-1.92 (1H, m, CH$_ax$), 2.09-2.14 (1H, m, CH$_eq$), 2.84-2.86 (4H, m, CH$_2$-S), 3.03 (2H, d, J 7.1, CH$_2$CHS), 4.21 (1H, t, J 7.5, CH$_2$CHS), 6.51 (1H, s, NH), 7.10 (1H, dt, J 1.1 and 8.0, H-5'), 7.22-7.28 (2H, m, H-4' and H-6'), 7.65 (1H, bd, J 7.8, H-3'); $\delta_{C}$ (100 MHz, CDCl$_3$): 25.2 (CH$_2$), 28.3 (CH$_3$), 30.4 (CH$_2$), 37.4 (CH$_2$), 47.8 (CH), 80.5 (C), 124.0 (CH), 124.6 (CH), 127.9 (CH), 129.3 (C), 130.6 (CH), 136.1 (C), 153.5 (C); m/z, EI+ (%): 325 (M$^+$, 42), 268 (M$^+$-C$_6$H$_9$, 64), 119 (100); Accurate mass: C$_{16}$H$_{23}$NO$_2$S$_2$: requires 325.1170, found 325.1173; Microanalysis Found: C 59.16%, H 7.12%, N 4.30%, S 19.70%; Theoretical C$_{16}$H$_{23}$NO$_2$S$_2$: C 59.04%, H 7.16%, N 4.33%, S 19.71%. 

![Image of molecular structure](image-url)
Iron powder (6.70 g, 120 mmol), was added to a solution of crude thioacetal 409b (12.03 g, assumed 40.0 mmol) and ammonium chloride (10.70 g, 200 mmol), in ethanol (120 cm³) and water (40 cm³) and heated under reflux for 2 h. After allowing to cool, the reaction mixture was filtered through celite, washing with ethyl acetate (200 cm³). The dark green solution was then concentrated in vacuo. The resulting brown solid was partitioned between ethyl acetate (250 cm³) and water (400 cm³). The organic phases were separated and washed with water (400 cm³), brine (200 cm³), dry over magnesium sulfate and concentrated under vacuum to yield a brown oil (9.73 g). ¹H NMR confirmed that this was mostly the desired aniline 410b [Rf (SiO₂, DCM): 0.48] in good purity although contaminated with small amounts of starting material and triphenylphosphine-containing by-products. Di-tert-butyl-dicarbonate (8.73 g, 40.0 mmol) was added to this crude material in THF (150 cm³), and the mixture was heated under reflux for 42 h. After this time, the reaction mixture was poured into water (150 cm³) and extracted into diethyl ether (2 x 80 cm³). The combined organic phases were then washed with water (2 x 150 cm³), brine (150 cm³), dry over sodium sulfate and concentrated to yield a brown oil (8.13 g). Crystallisation, from propan-2-ol/cyclohexane, yielded 2-[2’-(N-tert-butyloxycarboxyamino)-3’-methoxybenzyl]-1,3-dithiane 411b as needles (3.82 g, 10.7 mmol, 27% from 334b): Rf (SiO₂, DCM): 0.17; Mpt: 125-126 °C; v max (GGate)/cm⁻¹: 3300 (NH), 2978 (C H₂), 2908 (CH), 1685 (CO); δ_H (400 MHz, CDCl₃): 1.50 [9H, s, (CH₃)₃], 1.81-1.92 (1H, m, CH₆₆(ax)), 2.05-2.13 (1H, m, CH₆₆(eq)), 2.78-2.87 (4H, m, CH₂-S), 3.13 (2H, d, J 7.4, CH₂CHS₂), 3.82 (3H, s, OCH₃), 4.21 (1H, t, J 7.5, CH₂CHS₂), 5.99 (1H, s, NH), 6.81 (1H, d, J 8.2, H-4’), 6.90 (1H, d, J 7.5, H-6’), 7.17 (1H, t, J 8.0, H-5’); δ_C (100 MHz, CDCl₃): 25.8 (CH₂), 28.3 (CH₃), 30.3 (CH₂), 37.8 (CH₂), 47.6 (CH), 55.7 (CH₃), 80.1 (C), 109.8 (CH), 122.5 (CH), 124.9 (C), 127.1 (CH), 136.4 (C), 154.8 (C), 154.8 (C); m/z, EI+ (%): 355 (M⁺, 10), 299 (M⁺-C₄H₈, 12) 148 (30), 199 (100); Accurate mass: C₁₇H₂₅NO₃S₂: requires 355.1276, found 355.1278; Microanalysis Found: C 57.29%, H 7.12%, N 3.86%; Theoretical C₁₇H₂₅NO₃S₂: C 57.43%, H 7.09%, N 3.94%.

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Using both exactly the same reagent quantities and procedure as for the reduction of thioacetal 409b, employing crude thioacetal 409c (12.03 g, assumed 40.0 mmol), yielded amine 410c as a brown oil (9.89 g). $^1$H NMR confirmed that this was mostly the desired aniline 410c [R$_f$ (SiO$_2$, DCM): 0.41] although contaminated with significant amounts of triphenylphosphine-containing by-products. Di-tert-butyl-dicarbonate (17.5 g, 80.0 mmol) was added to this crude material in THF (150 cm$^3$), and the mixture was heated under reflux for 42 h. After this time the reaction mixture was poured into water (200 cm$^3$) and extracted into ethyl acetate (2 x 100 cm$^3$). The combined organic phases were washed with water (3 x 100 cm$^3$), brine (200 cm$^3$), dried over sodium sulfate, and concentrated to yield the corresponding imide 412 [R$_f$ (SiO$_2$, DCM): 0.54] which was contaminated with some di-tert-butyl-dicarbonate and triphenylphosphine-containing by-products, as a brown solid (13.35 g). Trifluoroacetic acid (3.1 cm$^3$, 40.0 mmol) was added drop-wise to the crude imide (13.35 g, assumed 44.0 mmol) in DCM (400 cm$^3$) and the mixture was stirred for 18 h. After this time the reaction mixture was washed with sodium bicarbonate (2 x 100 cm$^3$) and then water (3 x 100 cm$^3$), dried over sodium sulfate, and concentrated to yield carbamate 411c as a brown solid (11.82 g). Recrystallisation from propan-2-ol, yielded 2-[2'-(N-tert-butyloxycarboxyamino)-4',5'-methyleneoxybenzyl]-1,3-dithiane 411c as tiny needles (5.50 g, 14.9 mmol, 37% from 334c), R$_f$ (SiO$_2$, DCM): 0.19; Mpt: 163-165 °C; $\nu_{max}$ (KBr)/cm$^{-1}$: 3246 (NH), 2900 (CH$_2$), 1672 (CO), 1157 (COC); $\delta_H$ (400 MHz, CDCl$_3$): 1.50 [9H, s, (CH$_3$)$_3$], 1.84-1.93 (1H, m, CH$_{ax}$), 2.09-2.14 (1H, m, CH$_{eq}$), 2.81-2.86 (4H, m, CH$_2$-S), 2.94 (2H, d, J 7.1, CH$_2$CHS$_2$), 4.16 (1H, t, J 7.1, CH$_2$CHS$_2$), 5.93 (2H, s, OCH$_2$O), 6.32 (1H, s, NH), 6.70 (1H, s, H-6'), 7.04 (1H, s, H-3'); $\delta_C$ (100 MHz, CDCl$_3$): 25.6 (CH$_2$), 28.5 (CH$_3$), 30.4 (CH$_2$), 37.3 (CH$_2$), 48.3 (CH), 80.4 (C), 101.4 (CH$_2$), 106.7 (CH), 109.5 (CH), 124.4 (C), 145.2 (C), 146.9 (C), 154.0 (C); m/z, El$^+$ (%): 369 (M$^{+}$, 22), 313 (M$^{+}$-C$_4$H$_8$, 8), 150 (27), 119 (100); Accurate mass: C$_{17}$H$_{23}$NO$_4$S$_2$: requires 369.1069, found 369.1069; Microanalysis Found: C 55.36%, H 6.17%, N 3.65%, S 17.29%; Theoretical C$_{17}$H$_{23}$NO$_4$S$_2$: C 55.26%, H 6.27%, N 3.79%, S 17.36%.
Lithium di-isopropylamine (1.2 cm³, 2.40 mmol, 2.0 mol dm⁻³ in THF, ethyl benzene and heptanes) was added drop-wise to a solution of carbamate 411a (0.65 g, 2.00 mmol) and chlorotrimethylsilane (0.45 cm³, 3.50 mmol) in THF (15 cm³), at -78 °C under argon. The reaction mixture was allowed to warm to rt over 30 mins and was then allowed to stir for a further 30 mins at this temperature. After this time the solvent was removed in vacuo and diethyl ether (15 cm³) was added. The resulting precipitate was filtered off and the ethereal solution was concentrated to yield 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)benzyl]-1,3-dithiane 413a as a pale yellow solid (0.69 g, 1.72 mmol, 86%); δ_H (400 MHz, CDCl₃): 0.21 [9H, s, Si(CH₃)₃], 1.51 [9H, s, C(CH₃)₃], 1.80-1.91 (1H, m, CH₆), 2.06-2.11 (1H, m, CH₆), 2.78-2.88 (5H, m, CH₂-S and CH₆H₆CHS₂), 3.02 (1H, dd, J 14.3 and 5.6, CH₆H₆CHS₂), 4.29 (1H, dd, J 8.8 and 5.6, CH₆H₆CHS₂), 6.96 (1H, d, J 7.1, H-3'), 7.16-7.52 (3H, m, H-4', H-5' and H-6'); m/z, EI⁺ (%): 397 (M⁺, 18), 341 (M⁺-C₄H₆, 33), 119 (100); Accurate mass: C₁₉H₃₁N₁O₂S₂Si: requires 397.1566, found 397.1564.

Exactly as for carbamate 413a, employing lithium di-isopropylamine (2.75 cm³, 5.50 mmol, 2.0 mol dm⁻³ in THF, ethyl benzene and heptanes), carbamate 411b (1.78 g, 5.00 mmol) and chlorotrimethylsilane (1.00 cm³, 8.25 mmol) in THF (40 cm³), gave 2-[2'-((N-tert-butyloxycarboxy-N-trimethylsilylamino)-3'-methoxybenzyl]-1,3-dithiane 413b as a yellow oil (1.80 g, 4.20 mmol, 84%); δ_H (400 MHz, CDCl₃): 0.19 [9H, s, Si(CH₃)₃], 1.59 [9H, s, C(CH₃)₃], 1.81-1.90 (1H, m, CH₆), 2.07-2.11 (1H, m, CH₂O), 2.77-2.90 (5H, m, CH₂CH₂CH₂-S and CH₆H₆CHS₂), 2.98 (1H, dd, J 14.1 and 5.8, CH₆H₆CHS₂), 3.77 (3H, s, OCH₃), 4.29 (1H, dd, J 8.6 and 5.8, CH₆H₆CHS₂), 6.79 (1H, dd, J 8.2, Ar-H), 6.90 (1H, bd, J 7.6, Ar-H), 7.13 (1H, t, J 7.9, H-5').
2-[2'-{(N-tert-Butyloxycarboxy-N-trimethylsilylamino)-4',5'-methylenedioxy]-1,3-dithiane 413c

Exactly as for carbamate 413a, employing lithium di-isopropylamine (3.00 cm³, 6.00 mmol, 2.0 mol dm⁻³ in THF, ethyl benzene and heptanes), carbamate 411c (2.00 g, 5.40 mmol) and chlorotrimethylsilane (1.00 cm³, 8.25 mmol) in THF (40 cm³), yielded 2-[2'-(N-tert-butyloxycarboxy-N-trimethylsilylamino)-4',5'-methylenedioxy]-1,3-dithiane 413c as a yellow oil which solidified on standing (2.18 g, 4.90 mmol, 91%); δH (400 MHz, CDCl₃): 0.22 [9H, s, Si(CH₃)₃], 1.50 [9H, s, C(CH₃)₃], 1.79-1.90 (1H, m, CH₆), 2.05-2.12 (1H, m, CH₇), 2.63-2.85 (5H, m, CH₂CH₂CH₂-S and CH₃H₉CHS₂), 2.93 (1H, dd, J 14.2 and 5.6, CH₃H₉CHS₂), 4.21 (1H, dd, J 9.1 and 5.3, CH₃H₉CHS₂), 5.91-5.96 (2H, m, OCH₂O), 6.47 (1H, s, H-3'), 6.97 (1H, s, H-6').

1-(2'-{N-tert-Butyloxycarboxyamino-5'-phenyl}-4-phenylpentan-2-one 414

Following the general solid-phase Takeda Method D and resin-cleavage procedure A, employing silylated carbamate 413a (1.43 g, 3.60 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded 1-(2'-{N-tert-butyloxycarboxyamino-5'-phenyl}-4-phenylpentan-2-one 414 in good purity as a yellow oil (0.063 g, 0.178 mmol, 59%); δH (400 MHz, CDCl₃): 1.47 [9H, s, C(CH₃)₃], 2.61 (2H, t, J 7.8, CH₂CH₂), 2.68-2.76 (4H, m, CH₂CH₂), 2.79 (2H, t, J 7.8, CH₂CH₂), 6.92-7.19 (8H, m, Ar-H), 7.34 (1H, s, NH), 7.62 (1H, d, J 7.9, H-6').
1-(2'-Amoniumtrifluoroacetate-5'-phenyl)-4-phenylpentan-2-one 417aa'

Following the general solid-phase Takeda method D and resin-cleavage procedure B, employing silylated carbamate 413a (1.43 g, 3.60 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded 1-(2'-amoniumtrifluoroacetate-5'-phenyl)-4-phenylpentan-2-one 417aa' in good purity as a yellow oil (0.086 g, 0.234 mmol, 78%); δ_H (400 MHz, CDCl₃): 2.79 (4H, s, CH₂CH₂), 3.04 (2H, t, J 7.3, CH₂CH₂), 3.07 (2H, t, J 7.3, CH₂CH₂), 6.04-7.36 (9H, m, Ar-H), 11.13 (3H, s, NH₃); δ_C (100 MHz, CDCl₃): 20.9 (CH₂), 29.0 (CH₂), 32.9 (CH₂), 39.7 (CH₂), 121.7 (CH), 126.4 (C), 127.9 (CH), 128.5 (C), 129.1 (CH), 129.3 (CH), 129.6 (CH), 131.9 (CH), 132.4 (C), 137.7 (C), 187.9 (C).

All the quinolines below were synthesised following the general solid-phase Takeda method D and resin-cleavage procedure B, and then subjecting the crude material to the cyclisation/oxidation conditions (see general procedures).

2-Phenethyl-quinoline²⁵⁵ 416aa'

Following the above procedures, employing silylated carbamate 413a (1.43 g, 3.60 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded 2-phenethyl-quinoline²⁵⁵ 416aa' as a yellow oil (0.049 g, 0.202 mmol, 67%); ν_max (Thin Film)/cm⁻¹: 3032 (CH), 2952 (CH), 2912 (CH), 1618 (C=C), 1589 (C=C), 1512 (C=C), 1495 (C=C), 729 (CH), 696 (CH); δ_H (400 MHz, CDCl₃): 3.15-3.19 (2H, m, CH₂), 3.29-3.33 (2H, m, CH₂), 7.19-7.31 (6H, m, Ar-H), 7.50 (1H, dt, J 1.0 and 7.5, H-6), 7.68-7.73 (1H, m, H-7), 7.79 (1H, d, J 8.1, H-5), 8.06 (1H, d, J 8.6, H-4), 8.08 (1H, d, J 8.8, H-8); δ_C (100 MHz, CDCl₃): 35.9 (CH₂), 40.8 (CH₂), 121.5 (CH), 125.9 (CH), 126.8 (C), 127.5 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.5 (CH), 136.4 (CH), 141.5 (C), 161.8 (C); m/z, EI+ (%): 234 (M⁺, 20), 233 (M⁺-H, 100), 233 (M⁺-H₂, 92); Accurate mass: C₁₇H₁₆N: requires 234.1283, found 234.1280.
8-Methoxy-2-phenethyl-quinoline 416ba' 

Following the above procedures, employing silylated carbamate 413b (1.54 g, 3.60 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded 8-methoxy-2-phenethyl-quinoline 416ba' as a yellow oil (0.037 g, 0.139 mmol, 46%); \( \lambda_{max} \) (Thin Film)/cm\(^{-1}\): 3060 (CH\(_2\)), 3026 (CH\(_2\)), 2954 (CH), 2930 (CH), 2852 (OCH\(_3\)), 1602 (C=C), 1564 (C=C), 1503 (C=C), 751 (CH), 700 (CH); \( \delta_H \) (400 MHz, CDCl\(_3\)): 3.14-3.18 (2H, m, CH\(_2\)), 3.35-3.39 (2H, m, CH\(_2\)), 4.10 (3H, s, OCH\(_3\)), 7.05 (1H, d, \( J = 7.5 \)), 7.09-7.31 (6H, m, Ar-H + H-5), 7.35-7.44 (2H, m, H-6 and H-7), 8.02 (1H, d, \( J = 8.4 \)), \( \delta_C \) (100 MHz, CDCl\(_3\)): 36.1 (CH\(_2\)), 50.0 (CH\(_2\)), 56.2 (CH\(_3\)), 107.8 (CH), 119.5 (CH), 122.0 (CH), 125.9 (CH), 126.0 (CH), 128.0 (C), 128.4 (CH), 128.5 (CH), 136.2 (CH), 139.8 (C), 141.6 (C), 155.0 (C), 161.0 (C); m/z, EI\(^+\) (%): 263 (M\(^+\), 100), 262 (M\(^+\)-H, 54); Accurate mass: C\(_{18}\)H\(_{17}\)NO: requires 263.1310, found 263.1308.

8-Methoxy-2-(2'-methyl-propenyl)-quinoline 416bd' 

Following the above procedures, employing silylated carbamate 413b (1.54 g, 3.60 mmol) and resin-bound ester 309d' (Method A, 0.30 mmol), yielded 8-methoxy-2-(2'-methyl-propenyl)-quinoline 416bd' as a yellow oil (0.038 g, 0.176 mmol, 59%); \( \lambda_{max} \) (Thin Film)/cm\(^{-1}\): 3047 (CH\(_2\)), 2966 (CH), 2929 (CH), 2835 (OCH\(_3\)), 1649 (C=C), 1600 (C=C), 1556 (C=C), 1498 (C=C); \( \delta_H \) (400 MHz, CDCl\(_3\)): 2.00 (3H, d, \( J = 1.2 \)), 2.14 (3H, d, \( J = 1.2 \)), 4.07 (3H, s, OCH\(_3\)), 6.62 [1H, t, \( J = 1.2 \), CHC(CH\(_3\))\(_2\)], 7.02 (1H, dd, \( J = 7.5 \) and 1.2, H-3), 7.33-7.44 (3H, m, H-5, H-6 and H-7), 8.05 (1H, d, \( J = 8.5 \)), \( \delta_C \) (100 MHz, CDCl\(_3\)): 19.9 (CH\(_3\)), 27.3 (CH\(_3\)), 55.9 (CH\(_3\)), 107.6 (CH), 119.2 (CH), 122.7 (CH), 125.8 (CH), 126.2 (CH), 127.3 (C), 135.5 (CH), 139.8 (C), 141.4 (C), 155.2 (C), 156.6 (C); m/z, EI\(^+\) (%): 213 (M\(^+\), 7), 212 (M\(^+\)-H, 10), 82 (100); Accurate mass: C\(_{14}\)H\(_{15}\)NO: requires 213.1154, found 213.1153.
2-(4'-Fluoro-phenyl)-8-methoxy-quinoline 416be' Following the above procedures, employing silylated carbamate 413b (1.54 g, 3.60 mmol) and resin-bound ester 309e' (Method A, 0.30 mmol), yielded 2-(4'-fluoro-phenyl)-8-methoxy-quinoline 416be' as a yellow oil (0.039 g, 0.154 mmol, 51%); $\nu_{\text{max}}$ (Thin Film)/cm$^{-1}$: 3002 (CH), 2960 (CH), 2937 (CH), 2836 (OCH$_3$), 1615 (C=C), 1601 (C=C), 1559 (C=C), 1497 (C=C), 1330 (CF), 753 (CF); $\delta_H$ (400 MHz, CDCl$_3$): 4.10 (3H, s, OCH$_3$), 7.07 (1H, d, $J_{7.4}$, H-5), 7.15-7.21 (2H, m, H-3' and H-5'), 7.39-7.47 (2H, m, H-6 and H-7), 8.02 (1H, d, $J_{8.6}$, H-3), 8.08-8.13 (3H, m, H-4, H-2' and H-6'); $\delta_C$ (100 MHz, CDCl$_3$): 56.1 (CH$_3$), 107.2 (CH), 115.7 (d, $J_{21.4}$, CH), 119.1 (CH), 119.3 (CH), 126.6 (CH), 128.2 (C), 129.5 (d, $J_{8.2}$, CH), 135.9 (C), 136.9 (CH), 140.1 (C), 155.2 (C), 155.5 (C), 163.3 (d, $J_{249}$, CF); m/z, EI+ (%): 253 (M$^+$, 95), 252 (M$^+\cdot$H, 100), 224 (M$^+\cdot$CHO, 57), 223 (M$^+\cdot$CH$_2$O, 51); Accurate mass: C$_{16}$H$_{12}$FNO: requires 253.0903, found 253.0904.

6,7-Methylenedioxy-2-phenethyl-quinoline 416ca' Following the above procedures, employing silylated carbamate 413c (1.59 g, 3.60 mmol) and resin-bound ester 309a' (Method A, 0.30 mmol), yielded 6,7-methylenedioxy-2-phenethyl-quinoline 416ca' as a yellow oil (0.046 g, 0.202 mmol, 52%); $\nu_{\text{max}}$ (Thin Film)/cm$^{-1}$: 3032 (CH$_2$), 2952 (CH$_2$), 2912 (CH), 2856 (CH), 1618 (C=C), 1589 (C=C), 1512 (C=C), 1495 (C=C), 729 (CH), 696 (CH); $\delta_H$ (400 MHz, CDCl$_3$): 3.10-3.15 (2H, m, CH$_2$), 3.19-3.24 (2H, m, CH$_2$), 6.09 (2H, s, OCH$_2$O), 7.02 (1H, s, H-5), 7.03 (1H, d, $J_{8.3}$, H-3), 7.17-7.30 (5H, m, Ar-H), 7.38 (1H, s, H-8), 7.85 (1H, d, $J_{8.3}$, H-4); $\delta_C$ (100 MHz, CDCl$_3$): 36.1 (CH$_2$), 40.6 (CH$_2$), 101.6 (CH$_2$), 102.6 (CH), 105.5 (CH), 119.7 (CH), 123.5 (C), 125.9 (CH), 128.3 (CH), 128.5 (CH), 135.1 (CH), 141.6 (C), 146.1 (C), 147.2 (C), 155.6 (C), 159.5 (C); m/z, EI+ (%): 277 (M$^+$, 100), 200 (M$^+\cdot$C$_6$H$_5$, 50); Accurate mass: C$_{18}$H$_{15}$NO$_2$: requires 277.1103, found 277.1102.
2-(4'-Fluorophenyl)-6,7-methylenedioxy-quinoline 416ce'

Following the above procedures, employing silylated carbamate 413c (1.59 g, 3.60 mmol) and resin-bound ester 309e' (Method A, 0.30 mmol), yielded 2-(4'-fluorophenyl)-6,7-methylenedioxy-quinoline 416ce' as a yellow solid (0.033 g, 0.124 mmol, 41%); Mpt: 139-142 °C; \( \nu_{\text{max}} \) (GGate)/cm\(^{-1} \): 2962 (CH), 2915 (CH), 2848 (CH), 2784 (CH\(_2\)), 1617 (C=C), 1600 (C=C), 1498 (C=C), 1330 (CF), 757 (CF); \( \delta_H \) (400 MHz, CDCl\(_3\)): 6.11 (2H, s, OCH\(_2\)O), 6.77 (1H, s, H-5), 7.17-7.20 (2H, m, H-3' and H-5'), 7.43 (1H, s, H-8), 7.66 (1H, d, J 8.5, H-3), 8.01 (1H, d, J 8.5, H-4), 8.09-8.11 (2H, m, H-2' and H-6'); \( \delta_C \) (100 MHz, CDCl\(_3\)): 101.7 (CH\(_2\)), 102.5 (CH), 106.0 (CH), 115.7 (d, J 21.4, CH), 116.9 (CH), 124.0 (C), 126.6 (CH), 128.4 (C), 129.0 (d, J 8.6, CH), 135.6 (CH), 146.4 (C), 147.8 (C), 151.0 (C), 154.2 (C), 163.7 (d, J 249, CF); m/z, El+ (%): 267 (M\(^+\), 100), 208 (43); Accurate mass: C\(_{16}\)H\(_9\)FN\(_3\)O\(_2\): requires 267.0696, found 267.0695.

2-(3'-Furyl)-6,7-methylenedioxy-quinoline 416cf'

Following the above procedures, employing silylated carbamate 413c (1.59 g, 3.60 mmol) and resin-bound ester 309f' (Method A, 0.30 mmol), yielded 2-(3'-furyl)-6,7-methylenedioxy-quinoline 416cf' as a yellow solid (0.039 g, 0.162 mmol, 54%); Mpt: 124-127 °C; \( \nu_{\text{max}} \) (GGate)/cm\(^{-1} \): 2914 (CH), 2848 (CH), 1618 (C=C), 1577 (C=C), 1513 (C=C), 1494 (C=C); \( \delta_H \) (400 MHz, CDCl\(_3\)): 6.09 (2H, s, OCH\(_2\)O), 7.02 (1H, s, H-5), 7.04 (1H, d, J 1.6, H-5'), 7.37 (1H, s, H-8), 7.44 (1H, d, J 8.4, H-3), 7.52 (1H, d, J 1.6, H-4'), 7.93 (1H, d, J 8.4, H-4), 8.08 (1H, s, H-2'); \( \delta_C \) (100 MHz, CDCl\(_3\)): 101.8 (CH\(_2\)), 102.7 (CH), 105.8 (CH), 109.0 (CH), 117.1 (CH), 123.9 (C), 127.5 (C), 135.3 (CH), 141.4 (CH), 143.8 (CH), 146.5 (C), 147.5 (C), 149.6 (C), 150.8 (C); m/z, El+ (%): 239 (M\(^+\), 100), 211 (M\(^+\)-CHO, 18), 153 (12); Accurate mass: C\(_{14}\)H\(_9\)NO\(_3\): requires 239.0582, found 239.0581.
REFERENCES


Brase, S., Chimica Oggi-Chemistry Today, 2000, 18, 14.


APPENDIX - 1

Representative NMR spectra of selected products
Current Data Parameters
NAME: D-83 Free Indole
EXPNO: 10
PRNO: 1

F2 - Acquisition Parameters
Data: 20010618
Time: 13:31
INSTRUM: G24400
PULPROG: 5 mm Quad1-13
PULPROG: f30
DG: 30208
SOLVENT: CDCl3
MT: 10
DS: 0
SM: 6023.056 MHz
TMES: 0.250967 MHz
KG: 5.932344 sec
RG: 180
DM: 50.660 usec
DE: 6.000 usec
TE: 298.0 K
DS: 0.00000000 sec

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PI: 9.260 usec
PL: -5.20 dB
SFS: 400.13244 MHz

F2 - Processing parameters
SI: 32768
SF: 400.13244 MHz
KOFF: 9.91
COB: 180
LB: 0.30 Hz
GB: 0
PC: 4.00

D warn alert parameters
CA: 39.51 cm
C2P: 0.250 ppm
C1: 3701.20 Hz
C2P: -0.500 ppm
C2: -300.00 ppm
Pinch: 0.24992 ppm/cm
KSW: 0.000099 Hz/cm
User - Calum Macleod

G-58.6 Cleavage to salt

Current Data Parameters
NAME: 020513-CH2-50
PROD: 20
PRDENG: 1

F2 - Acquisition Parameters
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Time: 13:24
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PULPROG: p30
TD: 37500
SOLVENT: CDCl3
NS: 15
DS: 8202 666 Hz
NCHRES: 0 255087 Hz
AD: 1988 344 sec
BG: 90.5
DW: 0.800000 sec
OE: 6.60 usec
TE: 298.0
TO: 0.000000 sec

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NUC1 1M
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FL1: 3.00 mHz
SF01: 400.1324893 kHz

F2 - Processing parameters
SS: 30760
SF: 400.1324893 kHz
CW: 6 kHz
DR: 0
LB: 0
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PC: 6 dB

SD scale plot parameters
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FXP: 9.250 ppm
FXT: 3710.20 Hz
FP: -3500 ppm
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PHCNW: 0.249800 ppm/cm
HNC: 99.99999 Hz/cm
Current Data Parameters

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Instrument: DD-400
Mode: 5 mm Dual 13
Pulprog: 6130
TD: 3360
Solvent: CCI3
MX: 15
D1: 32768
805
PULPROG: 30 Hz
TO: 2921.800 sec
FIDRES: 0 25006 Hz
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DM: 60.000 usec
DE: 0 00 usec
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---------- CHANNEL 1 ----------

NUT: 920 usec
PLL: -0.00 Hz
SFD1: 402.182085 Hz

USER - Calum Macleod
H-65.7 Crude Quinoline
APPENDIX -2
Selective Crystallographic Information

Crystal Structure of Diazine-N-oxide 333
Selected Molecular Geometrical Measurements of N(Boc)$_2$ Imide

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<td>C1&quot;-O2 - 1.3288(14)</td>
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Selected Molecular Geometrical Measurements of NHBoc Carbamate

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**Selected Molecular Geometrical Measurements of N(Me)Boc Carbamate**

346a

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**Selected Molecular Geometrical Measurements of N(Prenyl)Boc Carbamate**

346c

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