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NEW DEVELOPMENTS IN THE 1-aza-dieLS-ALDER REACTION – VERSATILE ROUTES TO PYRIDINES

Timothy E. Hurst

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

August 2008

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.
Abstract

In Chapter one a review of the 1-aza-Diels-Alder reaction is presented. The hetero-Diels-Alder reaction of 1-aza-1,3-butadienes with both alkene and alkyne dienophiles has been shown to be an efficient and versatile method for the preparation of a large range of nitrogen-containing six-membered heterocycles. The use of electron-rich 1-azadienes in the normal electron-demand Diels-Alder reaction is primarily examined, followed by a brief look at the synthetic applications of the inverse electron-demand process.

In Chapter two the intermolecular hetero-Diels-Alder cycloadditions of 3-siloxy-1-aza-1,3-butadienes with electron-deficient dienophiles is presented as an efficient route to tri- and tetra-substituted pyridine core of the thiopeptide antibiotic nosiheptide. A series of α,β-unsaturated oximes and hydrazones were prepared and subsequently shown to participate readily in the hetero-Diels-Alder reaction with dimethyl acetylenedicarboxylate.

In Chapter three, the intramolecular Diels-Alder reaction is presented as a versatile method for the preparation of chromeno[c]pyridines. First a series of model systems was prepared and shown to undergo thermally induced intramolecular cycloaddition. This methodology was then utilised in the rapid preparation of the penta-substituted pyridine core of the antitumour antibiotic streptonigrin.

Chapter four contains experimental procedures for all of the work detailed above.
Acknowledgments

First and foremost I would like to thank my supervisor, Professor Chris Moody for giving me the opportunity to work on such a challenging and interesting project, as well as for his constant support and patience over the past few years. I would also like to thank GlaxoSmithKline for providing funding and in particular to my industrial supervisor Dr. Tim Miles for his help and suggestions.

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Finally I would like to thank my parents, without whom I would not have had the opportunity to study for my PhD in the first place. Also, I would especially like to thank my girlfriend Liz for her constant love, support and understanding over the past several years.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-DCB</td>
<td>ortho-Dichlorobenzene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAD</td>
<td>Dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>HFIP</td>
<td>Hexafluoroisopropanol</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>IMDA</td>
<td>Intramolecular Diels-Alder</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>PFP</td>
<td>Pentafluorophenyl</td>
</tr>
<tr>
<td>PMB</td>
<td><em>para</em>-Methoxybenzyl</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SOD</td>
<td>Superoxide Dismutase</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td><em>tert</em>-Butyldimethylsilyl</td>
</tr>
</tbody>
</table>
THF  Tetrahydrofuran
THP  Tetrahydropyryl
TMS  Trimethylsilyl
Chapter 1

Introduction

The 1-Aza-Diels-Alder Reaction
1.1 Introduction to the 1-Aza-Diels-Alder Reaction

Since the pioneering work by Diels and Alder in 1928, the Diels-Alder cycloaddition has become one of the most widely used and flexible methods for the synthesis of six-membered rings; reasons for this include the high degree of chemo-, regio- and diastereoselectivity observed with this reaction.

The Diels-Alder reaction itself may be classified into 3 different types based on the lowest energy gap between the frontier molecular orbitals involved in the transformation (Figure 1). The first type is the 'normal' electron-demand reaction which is controlled by the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The second type is the 'neutral' electron-demand reaction, where the HOMO_{diene}-LUMO_{dienophile} and HOMO_{dienophile}-LUMO_{diene} energy gaps are equivalent. The third type is the 'inverse' electron-demand Diels-Alder, and occurs where the lowest energy separation is between the LUMO of the diene and the HOMO of the dienophile.

![Figure 1.](image-url)
The rate of cycloaddition may be increased by improving the interaction between the relevant molecular orbitals by reducing the energy gap between them. This may be achieved through the introduction of appropriate substituents onto the diene or dienophile, or by the use of appropriate catalysts. Thus, for a ‘normal’ demand Diels-Alder reaction addition of electron-donating substituents into the diene and electron-withdrawing groups into the dienophile serves to increase the reaction rate. Conversely, electron-withdrawing groups on the diene and electron-donating groups on the dienophile increase the rate in the ‘inverse’ demand reaction.

Diels-Alder methodology has been extended to the synthesis of heterocyclic compounds through substitution of one or more of the carbon atoms in either the diene or the dienophile with a combination of C, N, O or S atoms. In the synthesis of nitrogen-containing six-membered heterocycles, three complementary strategies have been developed, namely the 1-aza, 2-aza and imino-Diels-Alder reactions (Figure 2). In this discussion, the focus will be on the 1-aza-Diels-Alder reaction.

![Figure 2.](image)
Introduction of the electron-withdrawing nitrogen atom at the 1-position of the diene lowers its reactivity in the 'normal' demand Diels-Alder reaction with electron-deficient dienophiles, which has limited the synthetic potential of unactivated 1-azadienes. Exceptions to this include the use of o-quinone methide imines as dienes and certain intramolecular reactions. The use of N-alkyl-1-azadienes has been extended only in recent years through the introduction of appropriately activating substituents into the C-2, C-3 and C-4 positions of the diene. However, they shall not be considered further in this discussion.²

Incorporation of an electron-releasing substituent in the form of an alkoxy, siloxy or dialkylamino group at the N-terminus of the 1-azadiene furnishes a comparatively electron-rich system that is more reactive towards electron-poor dienophiles (Figure 3). For this reason, these systems, in particular the α,β-unsaturated N,N-dialkylhydrazones 3, have received much attention in the literature for the synthesis of six-membered nitrogen heterocycles.²⁻⁸

\[
\begin{align*}
&\text{OR} & \text{OSiR}_3 & \text{NR}_2 \\
&1 & 2 & 3
\end{align*}
\]

Figure 3. Examples of electron-rich 1-aza-1,3-butadienes
More recently, elegant work by Boger\textsuperscript{9-15} and Fowler\textsuperscript{16-21} has demonstrated the synthetic potential of the ‘inverse’ demand 1-aza-Diels-Alder reactions of various \(N\)-sulfonyl-1-aza-1,3-butadienes \(4\) and 2-cyano-1-azadienes \(5\) (Figure 4).

![Figure 4.](image)

A representative evaluation of the inter- and intramolecular hetero-Diels-Alder reactions of electron-rich 1-aza-1,3-butadienes with alkene and alkyne dienophiles will be presented, followed by those of electron-deficient 1-aza-1,3-butadienes.

1.2 Hetero-Diels-Alder Reactions of Electron-Rich 1-Azadienes with Alkene Dienophiles

The hetero-Diels-Alder reaction of \(\alpha,\beta\)-unsaturated \(N,N\)-dimethylhydrazones has been extensively employed in the synthesis of six-membered nitrogen-containing heterocycles.\textsuperscript{2,8} Pioneering work in this area was carried out by Léon Ghosez and coworkers, who first rationalised that the strongly electron-releasing nature of the dimethylamino substituent would enhance 1-azadiene reactivity towards electron-deficient dienophiles.\textsuperscript{22}

The first 1-azadiene \(7\) used by Ghosez bears a simple methyl substituent at C-3, and may be readily prepared by condensation of methacrolein with \(N,N\)-
dimethylhydrazine. Introduction of this additional electron-releasing substituent into the C-3 position was found to be beneficial in the [4+2]-cycloaddition of 1-azabutadienes with electron-deficient dienophiles (Scheme 1). For example, treatment of methacrolein N,N-dimethylhydrazone 7 with acrylonitrile 8 or methyl acrylate 9 gave superior yields (Table 1, entries 3-4) compared to the acrolein derivative 6 (Table 1, entries 1-2).

\[
\text{Scheme 1. Reagents and conditions: a. benzene, 120 °C, sealed tube, 6-8 h.}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R</th>
<th>Dienophile</th>
<th>X</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>H</td>
<td>8</td>
<td>CN</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>H</td>
<td>9</td>
<td>CO_2Me</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>Me</td>
<td>8</td>
<td>CN</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Me</td>
<td>9</td>
<td>CO_2Me</td>
<td>13</td>
<td>70</td>
</tr>
</tbody>
</table>

Treatment of 1-azadiene 7 with dimethyl fumarate 14 (R^1 = CO_2Me, R^2 = H) or dimethyl maleate 15 (R^1 = H, R^2 = CO_2Me) afforded exclusively the trans-cycloadduct 16 (Scheme 2). The authors attributed this result to the isomerisation of dimethyl maleate 15 to the more stable trans-isomer prior to cycloaddition. Higher yields and lower reaction times have been obtained by carrying out the reaction under ultrasonic irradiation (50 °C, 49 h, 95-99%), although the trans-cycloadduct 16 was still the only observed product.
New Developments in the 1-Aza-Diels-Alder Reaction

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Scheme 2. Reagents and conditions: a. MeCN, reflux, 133-136 h.

In order to obtain the cis-cycloadduct 19, maleic anhydride 17 was used as the dienophile under very mild conditions, followed by ring-opening and esterification with diazomethane (Scheme 3).4,22

Scheme 3. Reagents and conditions: a. CH2Cl2, rt, 20 min; b. MeOH; c. CH3N2.

Treatment of the n-propyl analogue 20 with N-phenylmaleimide 21 generated the expected tetrahydropyridine 22, which was then be converted to the dihydropyridine derivative 23 upon heating with silica gel in toluene. Oxidation to the pyridine 24 was achieved using MnO2 in acetic acid (Scheme 4).25
New Developments in the 1-Aza-Diels-Alder Reaction

Scheme 4. Reagents and conditions: a. MeCN, 55 °C; b. SiO₂, toluene, reflux; c. MnO₂, AcOH, 60 °C.

An asymmetric variant of the hetero-Diels-Alder reaction was reported by Ghosez and coworkers. High degrees of diastereoselectivity were obtained for the cycloaddition between 1-azadiene 25, derived from Enders’ hydrazine, and various dienophiles including N-phenylmaleimide 21 (Scheme 5).²⁶

Waldner has shown that introduction of a halogen atom into the dieneophile allows direct formation of the dihydropyridine cycloadduct 28 via base induced elimination of hydrogen chloride. Aromatisation was then carried out with hydrochloric acid in dioxane (Scheme 6). 2-Chloroacrylonitrile was also successfully used as the dienophile.\textsuperscript{27}

![Scheme 6](image)

\textbf{Scheme 6.} \textit{Reagents and conditions:} a. MeCN, Et\textsubscript{3}N, 70 °C; b. HCl, dioxane, rt.

In 1991 Gilchrist and coworkers undertook a study designed to investigate the effect of different hydrazone substituents in hetero-Diels-Alder reactions (Scheme 7). Treatment of the N-benzoylhydrazone 29 with N-phenylmaleimide 21 afforded the desired pyridine 32 in good yield after elimination and formal oxidation (Table 2, entry 1). The N-tosyl and dinitrophenyl derivatives 30-31 performed less well (Table 2, entries 2-3), presumably because the stronger electron-withdrawing groups deactivate the diene too greatly for efficient cycloaddition to take place.\textsuperscript{28,29}

![Scheme 7](image)

\textbf{Scheme 7.} \textit{Reagents and conditions:} a. xylene or mesitylene, reflux, 24-45 h.
Table 2. Effect of varying hydrazone substituents on 1-azadiene reactivity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>X</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>NHCOPh</td>
<td>32</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>NHTs</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>NHC₆H₃(NO₂)₂</td>
<td>32</td>
<td>42</td>
</tr>
</tbody>
</table>

Oxazoles and isoxazoles may also participate as dienophiles in hetero-Diels-Alder cycloadditions when substituted with a suitable electron-withdrawing group, which also serves to control the regiochemistry (Scheme 8). Spontaneous loss of nitrous acid and dimethylamine afforded the pyridine derivatives 33 and 34, without isolation of the primary cycloadducts.³⁰,³¹

![Scheme 8](image)

Scheme 8. Reagents and conditions: a. 4-nitro-2-phenyloxazole, CHCl₃, 55 °C, 48 h; b. 4-nitro-3-phenylisoxazole, CHCl₃, 55 °C, 48 h.

The 1-azadiene 35, bearing a trimethylsiloxy group at C-3 was readily prepared from the mono(dimethyl)hydrazone of methylglyoxal on treatment with a slight excess of trimethylbromosilane. Addition of this electron-releasing group further increases the reactivity of the 1-aza-1,3-butadiene towards electron-deficient dienophiles, although the cycloadduct formed was relatively unstable and needed to be isolated under an inert atmosphere (Scheme 9).²³
Scheme 9. Reagents and conditions: a. benzene, 110 °C, sealed tube, 2.5 h.

Ghosez and coworkers have also shown the benefit of introducing a siloxy group at the C-3 position of 1-azadienes. In this case the bulkier TBDMS group in 1-azadiene 37 (prepared in two steps from pyruvic aldehyde dimethylacetal by condensation with N,N-dimethylhydrazine followed by treatment with TBDMS triflate) proved more hydrolytically stable, allowing the tetrahydropyridine cycloadduct 38 to be isolated in excellent yield (Scheme 10). Dimethyl fumarate 14 and dimethyl maleate 15 were also shown to be efficient partners in [4+2]-cycloadditions with 37.4

Scheme 10. Reagents and conditions: a. benzene, 100 °C.

The presence of a dimethylamino group enhances the reactivity of 1-azadiene 39 to the extent that cycloaddition was almost instantaneous at room temperature, with concomitant loss of dimethylamine and oxidation to the substituted pyridine 40 (Scheme 11). A slower reaction and lower yield was observed with methyl acrylate 9.23
New Developments in the 1-Aza-Diels-Alder Reaction

[Chemical structure images]


In 1997, Cuerva and coworkers reported the hetero-Diels-Alder reaction of tributylstannane 41 with N-methylmaleimide 42 in quantitative yield (Scheme 12). Quinonic dienophiles were also investigated.³²

Scheme 12. Reagents and conditions: a. toluene, 70 °C, 48 h.

High reactivity in the 1-aza-Diels-Alder reaction may also be achieved by constraining the 1-azadiene into the favoured s-cis geometry. For example α-methylene cyclohexanone dimethylhydrazone 44 reacts in high yield with a range of dienophiles (Scheme 13, Table 3). Cyclic dienophiles including N-phenylmaleimide 21 and benzoquinone were also investigated.³³

Scheme 13. Reagents and conditions: a. benzene, 110 °C, 2 h.
Table 3. Diels-Alder reaction of hydrazone 44 with electron-poor dienophiles 8-9 and 45.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>X</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>CN</td>
<td>46</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>CO₂Me</td>
<td>47</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>COMe</td>
<td>48</td>
<td>69</td>
</tr>
</tbody>
</table>

The introduction of a methyl group at the C-2 position of the 1-azadiene, however, lowers its reactivity in the hetero-Diels-Alder reaction (Scheme 14). For example, treatment of the unsubstituted diene 6 with naphthoquinone 50 afforded the cycloadduct 51 in good yield as assessed by ¹H nuclear magnetic resonance (NMR) analysis of the crude reaction mixture (Table 4, entry 1). The C-2 methylated analogue 49 on the other hand, failed to react under the same conditions (Table 4, entry 2).


Table 4. Hetero-Diels-Alder reaction of hydrazones 6 and 49 with naphthoquinone 50.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>H</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>Me</td>
<td>52</td>
<td>0</td>
</tr>
</tbody>
</table>
The authors attributed this effect to the increased steric hindrance between the methyl group at C-2 and the $N,N$-dimethylamino substituent (Figure 5). This pushes the nitrogen lone pair out of conjugation with the $\pi$-system, causing loss of activation of the diene, and hence lower reactivity.\(^4\),\(^22\)

![Figure 5. Deactivation of 1-aza-1,3-butadienes by C-2 substitution.](image)

Strongly electron-releasing substituents such as a tert-butyldimethylsilyloxy group at C-3 compensate for this by increasing the electron density of the 1-azadiene, allowing cycloaddition to take place, albeit in modest yield (Scheme 15, Table 5).\(^4\)

![Scheme 15. Reagents and conditions: a. benzene, 100 °C, sealed tube.](image)

Table 5. Hetero-Diels-Alder reaction of hydrazones 50 and 54 with dimethyl fumarate 14.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>H</td>
<td>Me</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>OTBDMS</td>
<td>Me</td>
<td>55</td>
<td>36</td>
</tr>
</tbody>
</table>
Incorporation of an electron-withdrawing substituent into the C-2 position of the diene also lowers its reactivity, presumably through both steric and electronic interactions, as can be seen from the increased reaction times for 1-aza-dienes 56-57 with N-phenylmaleimide 21 versus diene 7 (Scheme 16, Table 6).33


Table 6. Hetero-Diels-Alder reaction of hydrazones 7 and 56-57 with N-phenylmaleimide 21.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R</th>
<th>Time/d</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>H</td>
<td>1</td>
<td>58</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>CN</td>
<td>14</td>
<td>59</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>CO₂Me</td>
<td>3</td>
<td>60</td>
<td>76</td>
</tr>
</tbody>
</table>

Stereospecific cycloaddition of 1-aza-dienes 7 and 56 with dimethyl fumarate 14 and dimethyl maleate 15 has also been achieved in the presence of lithium trifluoromethanesulfonimide as a Lewis acid catalyst, although reaction times are still relatively long (Scheme 17, Table 7).33

Scheme 17. Reagents and conditions: a. LiNTf₂, Et₂O, rt, 19 h; b. LiNTf₂, MeCN, 50 °C, 72 h.
Table 7. Hetero-Diels-Alder reaction of hydrazones 7 and 56 under Lewis acid catalysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R</th>
<th>Method</th>
<th>Dienophile</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>H</td>
<td>a</td>
<td>14</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>CN</td>
<td>b</td>
<td>14</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>CN</td>
<td>b</td>
<td>15</td>
<td>62</td>
<td>68</td>
</tr>
</tbody>
</table>

Benzoquinone 63 and naphthoquinone 50 are both very reactive dienophiles, and form cycloadducts with a range of 1-azadienes.

Treatment of Ghosez’s diene 7 with benzoquinone 63 afforded the cycloadduct 64, which arises from nucleophilic attack of the liberated dimethylamine at C-6 of the quinone (Scheme 18). Similar results were obtained under ultrasonic irradiation.24


3-Methylquinoline-5,8-dione 65 may however be obtained in good yield by addition of a chloroformyl-polystyrene scavenger resin, which completely removes dimethylamine from the reaction mixture (Scheme 19).35
Scheme 19. Reagents and conditions: a. benzene, scavenger resin, rt

Cycloaddition of 3-siloxy-1-azadiene 37 with benzoquinone 63 afforded the dimethylamino-substituted product 66, which also forms from displacement of the tert-butyldimethylsilyloxy group by the dimethylamine which is liberated in the aromatisation step (Scheme 20).4


Ghosez and coworkers have also reported the use of naphthoquinone 50 as a dienophile. Cycloaddition under mild conditions afforded the tetrahydro-cycloadduct 67 in 80% yield by NMR analysis. The fully aromatised product 68 may be obtained in one pot by carrying out the reaction at higher temperature in the presence of palladium on charcoal (Scheme 21).4, 22 Once again, ultrasonic irradiation has been employed in the formation of 67, followed by air oxidation to 68 in 81% yield over 2 steps.24
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Scheme 21. Reagents and conditions: a. naphthoquinone 50, MeCN, -20 °C to rt; b. naphthoquinone 50, 10% Pd/C, MeCN, 75 °C.

Potts et al. have shown that juglone 69 and its derivatives are also efficient dienophiles in the 1-aza-Diels-Alder reaction (Scheme 22). Thus, treatment of 1-azadiene 7 with juglone 69 afforded the 8-hydroxylated cycloadduct 71 with complete regiocontrol (Table 8, entry 1). This reactivity may be explained by the strong electron-withdrawing nature of the hydroxyl group on the adjacent carbonyl via hydrogen bonding, making C-2 electron-deficient. The opposite regiochemistry was obtained with methyljuglone 70 due to the electron-donating nature of the methoxy group (Table 8, entry 2).

Table 8. Hetero-Diels-Alder reactions of hydrazone 7 with juglones 69-70.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>R¹</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>OH</td>
<td>71</td>
<td>H</td>
<td>OH</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>OMe</td>
<td>72</td>
<td>OMe</td>
<td>H</td>
<td>62</td>
</tr>
</tbody>
</table>
The reaction of oxygenated 1-azadiene 73 with juglone 69 and its derivatives has been investigated under two sets of conditions (Scheme 23).\textsuperscript{38, 39} Firstly, treatment of 73 with 69 in the presence of acetic anhydride proceeded with complete regioselectivity to give the dihydro-cycloadduct 74 in excellent yield. The role of acetic anhydride was to scavenge the dimethylamine liberated on cycloaddition, preventing it from adding to the starting quinone. In contrast, reaction of methyl juglone 70 with 73 in the presence of MnO\textsubscript{2} gave the N-dimethylamino dihydro-cycloadduct 75. As expected, the methoxy group in methyl juglone 70 directs the cycloaddition with complete regioselectivity for the opposite isomer. In both cases, aromatisation to the pyridines was achieved on treatment with an appropriate oxidant.

Scheme 23. Reagents and conditions: a. juglone 69, Ac\textsubscript{2}O; b. methyljuglone 70, MnO\textsubscript{2}.

Unsymmetrical disubstituted naphthoquinones have also been used as dienophiles (Scheme 24).\textsuperscript{40} With 76 as the dienophile, the reinforcing directing effects of the hydroxyl and methoxy groups gave the desired product as a single regioisomer 79 (Table 9, entry 1). A single regioisomer is also obtained with 77 (Table 9, entry 2).\textsuperscript{41} The authors attributed this to the stronger hydrogen bonding between the hydroxyl group and its adjacent carbonyl compared to that between the amine group and its adjacent carbonyl. Competing activation of the C-1 and C-4 carbonyl groups in dienophile 78 leads to the formation of a mixture of cyclisation products 81 and 84, although the hydroxyl group still dominates the regioselectivity (Table 9, entry 3).
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Scheme 24. Reagents and conditions: a. CH₂Cl₂, 8 h-20 d.

Table 9. Diels-Alder reaction of hydrazone 7 with disubstituted naphthoquinones 76-78.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>R¹</th>
<th>R²</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>OMe</td>
<td>OH</td>
<td>98 (79)</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>NH₂</td>
<td>OH</td>
<td>93 (80)</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>NHAc</td>
<td>OH</td>
<td>70 (81)</td>
</tr>
</tbody>
</table>

Treatment of 1-azadiene 7 with quinoline-5,8-dione 85 afforded predominantly the 1,8-diazaanthraquinone 86 after cycloaddition and oxidation (Scheme 25).³⁴ ³⁶ The expected regioselectivity was obtained by virtue of the electron-Withdrawing effect of the ring nitrogen atom on the C-8 carbonyl, directing attack of the C-4 end of the diene to C-6 of the dienophile. Application of ultrasonic conditions to the formation of 86 led to a decrease in reaction time, but with a loss of regioselectivity.²⁴

Scheme 25. Reagents and conditions: a. benzene, rt, 12 h; b. EtOH, reflux, 2 h.
Opposite regioselectivity may be obtained by choosing a dienophile system that overrides the effect of the ring nitrogen atom and makes the C-5 carbonyl more electron-deficient. Thus, the ethoxycarbonyl group in tetrahydroquinoline-5,8-dione 88 promotes the exclusive formation of the 1,5-isomer 90 after cycloaddition, deprotection and oxidation (Scheme 26).\(^{42}\)

\[
\begin{array}{c}
\text{NMe}_2 \quad 6 \\
\text{NMe}_2 \quad 88
\end{array}
\xrightarrow{a} \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array} \xrightarrow{b,c} \begin{array}{c}
\text{NMe}_2 \\
\text{NMe}_2
\end{array}
\]

Scheme 26. Reagents and conditions: a. CH\(_2\)Cl\(_2\), rt, 16 h; b. deprotection; c. DDQ

The 1-aza-Diels-Alder reaction between diene 73 and quinoline-5,8-dione 85 has also been studied in detail. Interestingly, traces of acid and oxygen accelerated a competing stepwise process, affording the furoquinoline 91 as the major product, with only small amounts (8%) of the desired [4+2]-cycloadduct (Scheme 27). The desired [4+2]-dihydro-cycloadduct 92 was obtained in 63 % yield (3:2 mixture of regioisomers) by carrying out the reaction in degassed toluene under nitrogen.\(^{39, 43, 44}\)

\[
\begin{array}{c}
\text{Me} \quad \text{EtO} \\
\text{EtO} \quad \text{Me}
\end{array}
\xrightarrow{a} \begin{array}{c}
\text{NMe}_2 \\
\text{NMe}_2
\end{array} \xrightarrow{b} \begin{array}{c}
\text{EtO} \\
\text{Me}
\end{array}
\]

Scheme 27. Reagents and conditions: a. quinoline-5,8-dione 85, CHCl\(_3\), rt, 1 h; b. quinoline-5,8-dione 85, toluene (degassed), rt 15 min.
Hetero-Diels-Alder reaction between 1-azadiene 7 and quinoline-2,5,8-triones 93-97 substituted with a variety of groups at C-3 proceeded with complete regioselectivity to give the aromatic cycloadducts 98-102 (Scheme 28, Table 10). As expected, the regiochemistry is controlled by the presence of the amide nitrogen and the C-2 carbonyl.

Scheme 28. Reagents and conditions: a. CHCl₃ or THF, rt, 5-45 min.

Table 10. Hetero-Diels-Alder reaction between hydrazone 7 and quinoline-2,5,8-triones 93-97.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>R</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>Me</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>Ph</td>
<td>99</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
<td>CHO</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>COMe</td>
<td>101</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>CO₂H</td>
<td>102</td>
<td>66</td>
</tr>
</tbody>
</table>

In contrast, Diels-Alder cycloaddition of 1-azadiene 103, substituted with a methyl group at C-4, afforded the dihydro-cycloadducts 107-109 as the major products (Scheme 29, Table 11). This may be attributed to the increased steric interaction of the C-5 substituent with the adjacent carbonyl in the planar aromatic product. In many cases, addition of dimethylamine (liberated during the reaction) to the starting quinone was observed, giving rise to the moderate yields. Addition of a chloroformyl-
polystyrene resin or silica gel has been used to suppress by-product formation, leading to increased yields (80-90%).

![Scheme 29](image.png)

**Scheme 29. Reagents and conditions:** a. CHCl₃, rt.

**Table 11.** Hetero-Diels-Alder reaction of hydrazone 103 with quinoline-2,5,8-triones 104-106.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>107</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>108</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>106</td>
<td>CH₂OAc</td>
<td>H</td>
<td>Me</td>
<td>109</td>
<td>76</td>
</tr>
</tbody>
</table>

Treatment of substituted chromanquinone 110 with 1-azadiene 7 gave the aromatic product 111 after cycloaddition and in situ oxidation (Scheme 30). The observed regiochemistry is controlled by electron donation from the ring oxygen atom. Hydrogen bonding between the hydroxyl group and the C-5 carbonyl is unfavourable as they are not coplanar, hence cannot influence the regiochemical outcome.

![Scheme 30](image.png)

**Scheme 30. Reagents and conditions:** a. CH₂Cl₂, rt, 3 h; b. Ag₂O, SiO₂ or DDQ.
Läckner has shown that the regioselectivity in the hetero-Diels-Alder of isochromanquinone 112 may be controlled by the substitution pattern of the diene. Thus, 1-azadienes lacking a substituent at C-4 gave the 2,5-cycloadduct 113 after cycloaddition and subsequent oxidation with MnO₂, whilst diene 103 afforded the 2,8-isomer 114 (Scheme 31).²⁵

\begin{align*}
\text{Me} &\quad \text{O}^2 \\
\text{113} &\quad \text{a,b} \quad 53\% \\
\text{112} &\quad \text{c,d} \quad 47\% \\
\text{Me} &\quad \text{O}^2 \\
\text{114} &
\end{align*}

Scheme 31. Reagents and conditions: a. 7, benzene, rt, 18 h; b. MnO₂, CHCl₃; c. 103, benzene, rt, 18 h; d. MnO₂, CHCl₃.

Hetero-Diels-Alder reactions involving unsymmetrical dienophiles often lead to mixtures of regioisomeric products. One of the most successful ways to combat this problem is the incorporation of a halogen atom into the dienophile. Frequently this allows selective formation of both regioisomers, without the need for complicated separations.

For example, treatment of 1-azadiene 7 with chloroquinones 115-118 gave the aromatic products 119-122 in moderate to good yield as single regioisomers (Scheme 32, Table 12). In each case, the C-4 end of the diene is directed to the less hindered end of the dienophile.²⁵
Scheme 32. Reagents and conditions: a. CH$_2$Cl$_2$, rt.

Table 12. Hetero-Diels-Alder reaction of hydrazone 7 with chloroquinones 115-118.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115</td>
<td>H</td>
<td>Cl</td>
<td>119</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>Cl</td>
<td>H</td>
<td>120</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>H</td>
<td>OMe</td>
<td>121</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>OMe</td>
<td>H</td>
<td>122</td>
<td>73</td>
</tr>
</tbody>
</table>

Chlorinated analogues of juglone and methyl juglone allow formation of both the 5- and 8-substituted cycloadducts with 1-azadiene 7. As was shown in Scheme 22, the hydroxyl group in juglone 69 and the methoxy group in methyljuglone 70 control the regiochemistry under normal conditions, leading to selective formation of the 8- and 5-substituted products respectively. However, introduction of a halogen at C-2 or C-3 of the dienophile exerts stronger regiochemical control than that of the C-5 substituent (Scheme 33). Thus, C-2 halogenated dienophiles 123 and 125 allow selective formation of the 8-substituted products (Table 13, entries 1 and 3). The opposite regioisomers 127 and 72 were obtained from the C-3 halogenated dienophiles 124 and 126 (Table 13, entries 2 and 4). As with the chlorobenzoquinone dienophiles, the C-4 (electron-rich) end of the diene attacks the unsubstituted end of the dienophile.\textsuperscript{51}
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Scheme 33. Reagents and conditions: a. CH₂Cl₂ or MeCN, rt, 48-120 h.

Table 13. Hetero-Diels-Alder reaction of hydrazone 7 with chlorinated juglones 123-126.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123 H Cl H OH</td>
<td>71 H OH</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>124 Cl H H OH</td>
<td>127 OH H</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>125 H Cl H OMe</td>
<td>128 H OMe</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>126 Cl H H OMe</td>
<td>72 OMe H</td>
<td>66</td>
</tr>
</tbody>
</table>

Diazaanthraquinones may also be formed selectively via a halogenated dienophile approach. For example, 1,8-diazaanthraquinone 130 was synthesised from 7-bromo-4-methoxy-2-phenylquinoline-5,8-dione 129 (Scheme 34). The opposite regioisomer was obtained in 50% yield from 6-bromo-4-methoxy-2-phenylquinoline-5,8-dione.⁵²

Scheme 34. Reagents and conditions: a. benzene, rt, 15 min.

Finally, a double hetero-Diels-Alder reaction may be carried out with the appropriately substituted dienophile such as 2,6-dibromobenzoquinone 131 to give 3,6-dimethyl-1,8-diazaanthraquinone 132 (Scheme 35).⁵³
Many examples of 1-aza-Diels-Alder reactions are known where the dihydro- or tetrahydropyridine cycloadduct is isolated directly from the cycloaddition. Formation of the aromatic product is usually achieved in a separate step through treatment with a suitable oxidising agent, typically activated MnO₂ or palladium on charcoal. One method for the formation of the aromatic products in one pot is to use an acetylenic dienophile instead of an alkene.

Furukawa et al. first reported the reaction of a range of 3-siloxy-1-aza-1,3-butadienes 133-135 (readily prepared from the α-ketoximes on treatment with trimethylchlorosilane, sodium iodide and base) with dimethyl acetylenedicarboxylate (DMAD) 136 (Scheme 36). A poor yield was obtained with the C-2 unsubstituted diene 133 (Table 14, entry 1), which may be due to the instability of either the starting material or product under the reaction conditions. Introduction of a methyl or methoxycarbonyl substituent raised the yield considerably (Table 14, entries 2-3), in contrast to the trend observed with the equivalent N,N-dimethylhydrazones. Hetero-Diels-Alder reaction of a 1-azadiene substituted with a methyl group at C-3 was also investigated, although no product was observed after 48 hours under reflux in toluene.
Scheme 36. Reagents and conditions: a. benzene, reflux, 8 h.

Table 14. Hetero-Diels-Alder reaction of oximes 133-135 with DMAD 136.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133</td>
<td>H</td>
<td>137</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>134</td>
<td>Me</td>
<td>138</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>135</td>
<td>CO₂Me</td>
<td>139</td>
<td>62</td>
</tr>
</tbody>
</table>

A further example is the [4+2]-cycloaddition of 1-azadiene 7 with DMAD 136. Although no reaction occurred under standard thermal heating, both ultrasonic and microwave irradiation have been successfully employed to afford the desired pyridine dicarboxylate 140 in 60% and 50% yield respectively (Scheme 37).

Scheme 37. Reagents and conditions: a. ultrasound, 50 °C, 50 h; b. MW, Et₂O, 10 min.

Unlike 7, the fluorinated 1-azadiene 141 reacted with DMAD 136 under normal thermal conditions. However, the initial product isolated was the stable dihydro-cycloadduct 142, which had to be aromatised to the pyridine 143 by elimination of dimethylamine on treatment with acid (Scheme 38).
1.4 Intramolecular Hetero-Diels-Alder Reactions of Electron-Rich 1-Azadienes

The first example of an intramolecular hetero-Diels-Alder (IMDA) reaction of α,β-unsaturated hydrazones was reported by Dolle and coworkers in 1988. Although [4+2]-cyclisation failed to take place with an unsubstituted allyl ether due to a competing [3,3]-Claisen rearrangement, incorporation of halogens into the dienophile portion allowed smooth reaction to take place (Scheme 39).57

The same authors reported two examples of IMDA reactions involving acetylenic dienophiles. Thus, cyclisation was induced on heating in xylene to give the expected pyridines 148-149 after 18 hours (Scheme 40, Table 15).57
Scheme 40. Reagents and conditions: a. xylene, reflux, 18 h.

Table 15. IMDA cycloadditions of hydrazones 146-147.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>146</td>
<td>H</td>
<td>148</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>147</td>
<td>Ph</td>
<td>149</td>
<td>74</td>
</tr>
</tbody>
</table>

Moody and coworkers have exploited a double hetero-Diels-Alder reaction of aromatic ethers and amides as a novel route to 2,2'-bipyridines (Scheme 41, Table 16). Once again, a lower yield was observed where the 1-azadiene was substituted at the C-2 position (Table 16, entry 2).58, 59

Scheme 41. Reagents and conditions: a. xylene or mesitylene, reflux. Alkynes drawn non-linear for clarity.
Table 16. IMDA cycloadditions of hydrazones 150-152.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>H</td>
<td>O</td>
<td>153</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>151</td>
<td>Me</td>
<td>O</td>
<td>154</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>152</td>
<td>H</td>
<td>NBz</td>
<td>155</td>
<td>68</td>
</tr>
</tbody>
</table>

The double IMDA reaction of unsaturated $N,N$-dimethylhydrazones linked through an aliphatic chain was also shown to proceed in good yield (Scheme 42).\textsuperscript{58,59}

\[ \text{Scheme 42. Reagents and conditions: a. xylene, reflux.} \]

Boger and coworkers have utilised an intramolecular hetero-Diels-Alder reaction of $O$-alkyl $\alpha,\beta$-unsaturated oximes 158-159 as the key step in their synthesis of the tropoloalkaloid rubrolone 160. Although no reaction was observed at temperatures below 140 °C, cyclisation was subsequently found to occur between 175-185 °C using triisopropylbenzene as the solvent (Scheme 43).\textsuperscript{60}

\[ \text{Scheme 43. 158: R=Me, 159: R=Bn; Reagents and conditions: a. triisopropylbenzene, 175-185 °C, 36 h.} \]
Quinonic dienophiles have also been investigated in the intramolecular 1-aza-Diels-Alder reaction, through activation of the secondary nitrogen as the trifluoroacetamide, followed by cycloaddition and elimination (Scheme 44, Table 17).\textsuperscript{61}

\begin{align*}
\text{Scheme 44. Reagents and conditions: a. NaH, TFAA, THF, rt; b. TFA, CH}_2\text{Cl}_2, \text{rt, 1 h.}
\end{align*}

Table 17. IMDA cycloadditions of hydrazones 161-162.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161</td>
<td>CH</td>
<td>163</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>162</td>
<td>N</td>
<td>164</td>
<td>47</td>
</tr>
</tbody>
</table>

Gilchrist \textit{et al.} have reported acyl hydrazones as efficient systems in intramolecular Diels-Alder reactions. For instance, unsaturated hydrazone 165 undergoes cycloaddition under reflux in \textit{o}-dichlorobenzene in good yield (Scheme 45). The presence of an alkyl substituent at C-3 in the diene fragment was found to be crucial, as the corresponding compound with a proton at this position failed to cyclise at temperatures up to 180 °C, and decomposed above this.\textsuperscript{28, 29} This observation is in accordance with the results reported by Ghosez and others.
Once again, introduction of an acetylenic dienophile afforded the 2,5-disubstituted pyridine after heating in o-dichlorobenzene for 2 days (Scheme 46). Analogous unsaturated oximes were found to be unreactive compared to the acylhydrazones, which was attributed to superior electron donation of the acylamino substituent into the diene.  

The IMDA reaction of α,β-unsaturated oximes 169 to give the corresponding nitrones 170-171 has been explored. Thus, intramolecular cycloaddition of (E)-169 gave nitrone 170 as a single isomer in 30% yield. Subsequent treatment with DMAD 136 led to formation of the tricyclic product 172 as the only isolable product (Scheme 47). The observed stereoselectivity is dictated by the proximal ester group, which directs the approach of the dipolarophile to the less hindered lower (re) face. The opposite nitrone diastereomer 171 was obtained by heating (Z)-169 in glacial acetic acid.

Subsequent 1,3-dipolar cycloaddition gave a 1:0.28 mixture of the two possible
stereoisomers 173, which was attributed to partial blocking of the upper (si) face by the remote isopropyl group.\(^{62}\)

Scheme 47. Reagents and conditions: a. (E)-169, CH\(_2\)Cl\(_2\), rt, 4 d; b. DMAD 136, toluene, rt, 30 min; c. (Z)-169, AcOH, 100 °C, 4 h; d. DMAD 136, toluene, 65 °C, 2 h (major isomer shown).

Saito and coworkers have recently reported the Rh(I)-catalysed IMDA reaction of various ω-alkynyl-vinyl oximes in the formation of bicyclic pyridines. An optimised catalyst system of 5 mol% [RhCl(cod)]\(_2\) and 13 mol% AgSbF\(_6\) in hexafluoroisopropanol (HFIP) was found to promote facile cycloaddition of ω-alkynyl-vinyl oximes 174-176 to the desired annulated pyridines 177-179 in 58-79% yield (Scheme 48, Table 18). Terminal acetylenes however failed to cyclise under the same conditions.\(^{63}\)
Scheme 48. Reagents and conditions: a. 5 mol% [RhCl(cod)]₂, 13 mol% AgSbF₆, HFIP, rt-80 °C, 3-23 h.

Table 18. Rh(I)-catalysed IMDA reactions of 𝝀-alkynyl-vinyl oximes 174-176.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>174</td>
<td>Me</td>
<td>O</td>
<td>177</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>175</td>
<td>Me</td>
<td>NTs</td>
<td>178</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>176</td>
<td>Ph</td>
<td>NTs</td>
<td>179</td>
<td>61</td>
</tr>
</tbody>
</table>

1.5 Inverse Electron-Demand 1-Aza-Diels-Alder Reactions

The synthetic application of inverse electron-demand 1-aza-Diels-Alder reactions has been pioneered primarily by Boger and coworkers have shown that various N-benzenesulfonylimines act as efficient 1-azadienes with a range of electron-rich dienophiles. Such is the effect of the N-benzenesulfonyl group on the activation of the 1-azadiene that reactions are routinely performed at room temperature or below.

The required hetero-Diels-Alder substrates 183-185 were prepared either from the 𝝀,𝝌-unsaturated ketones 180 by direct condensation with an arylsulfonylamide (method a), or from the free oximes 181 by homolytic rearrangement of their O-sulfinyl derivatives 182 formed in situ using either an arylsulfonyl chloride (method b) or
sulfonyl cyanide (method c) and triethylamine as reagents (Scheme 49). Some examples of 1-azadienes prepared in this way are shown in Table 19.

Scheme 49. Reagents and conditions: a. $R^3\text{SO}_2\text{NH}_2$, MgSO₄, toluene or TiCl₄, CH₂Cl₂; b. R³SOCl, Et₃N, CCl₄, 0 °C to rt, 12 h; c. R³SO₂CN, Et₃N, CCl₄, 0 °C to rt, 10 h.

Table 19. Preparation of N-sulfonyl-1-aza-1,3-butadienes 183-185.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>183</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>CO₂Et</td>
<td>Ph</td>
<td>Ph</td>
<td>184</td>
<td>69%</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>Me</td>
<td>Ph</td>
<td>p-Tol</td>
<td>185</td>
<td>63%</td>
</tr>
</tbody>
</table>

Treatment of N-sulfonyl-1-azadiene 186, prepared using the above methodology, with ethyl vinyl ether 187 in dichloromethane gave the tetrahydro-cycloadduct 188 in excellent yield (Scheme 50). The corresponding free oxime and O-methyl oxime failed to react under the same conditions.⁹
Incorporation of a noncomplementary electron-withdrawing group into the 1-azadiene further accelerates their reaction with electron-rich dienophiles, such as the hetero-Diels-Alder reaction of ethoxycarbonyl-substituted dienes 184 and 189-190 with ethyl vinyl ether 187 (Scheme 51, Table 20).11, 12

This rate enhancement was further demonstrated by competition experiments between 4-ethoxycarbonyl-N-sulfonyl-1-azadiene 190 and 4-phenyl-N-sulfonyl-1-azadiene 183 for the same dienophile (Scheme 52). The product distribution was shown to be >20:1 in favour of the ethoxycarbonyl-substituted product 193. Similar results were obtained
for competition experiments involving 2-ethoxycarbonyl-\(N\)-sulfonyl-1-aza-1,3-butadiene.\(^{11}\)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{Ph} \\
\text{N} & \quad \text{SO}_2\text{Ph} \\
190 & \\
\text{N} & \quad \text{SO}_2\text{Ph} \\
183 & \\
\text{LEt} & \\
187 & \\
\text{a} \rightarrow & \\
\text{CO}_2\text{Me} & \quad \text{Ph} \\
\text{N} & \quad \text{SO}_2\text{Ph} \\
193 & \\
\text{N} & \quad \text{SO}_2\text{Ph} \\
194 & \\
\text{20:1} & \quad \text{193:194}
\end{align*}
\]

**Scheme 52.** Reagents and conditions: a. \(\text{CH}_2\text{Cl}_2\), rt.

Boger and coworkers have applied this methodology towards the total synthesis of a number of complex natural products, including (+)-camptothecin 199. The key inverse electron-demand Diels-Alder reaction was carried out between \(N\)-sulfonyl-1-azadiene 195 and 1,1,3,3-tetraethoxypropene 196, followed by aromatisation to give the trisubstituted pyridine 198 in 60-70% yield, which was further converted to the natural product (Scheme 53).\(^{64}\)
Fowler and coworkers have successfully demonstrated that incorporation of a 2-cyano group renders the 1-azadiene (prepared by addition of trimethyl cyanide into the imine) sufficiently reactive to undergo hetero-Diels-Alder cycloaddition with a range of dienophiles, including electron-rich and electron-poor alkenes (Scheme 54, Table 21). The reaction proceeds with high levels of endo selectivity to give the cis-substituted products 204-213.\(^\text{18, 19}\)

Scheme 54. Reagents and conditions: a. benzene, rt to reflux, 24-48 h; b. neat, rt to reflux, 24-48 h; c. neat, 110 °C, 8 d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R¹</th>
<th>Dienophile</th>
<th>R²</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>OAc</td>
<td>203</td>
<td>Ph</td>
<td>79(204)</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>OAc</td>
<td>187</td>
<td>OEt</td>
<td>0 (205)</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>OAc</td>
<td>9</td>
<td>CO₂Me</td>
<td>0 (206)</td>
</tr>
<tr>
<td>4</td>
<td>201</td>
<td>CO₂Me</td>
<td>187</td>
<td>OEt</td>
<td>0 (207)</td>
</tr>
<tr>
<td>5</td>
<td>202</td>
<td>Ph</td>
<td>203</td>
<td>Ph</td>
<td>0 (208)</td>
</tr>
</tbody>
</table>

Frontier orbital calculations have confirmed that cycloadditions between 1-azadienes 200-202 and electron-rich dienophiles do indeed proceed via an inverse electron-demand process. Further evidence for this is the complete endo- and regioselectivity observed in these reactions. In contrast, cycloadditions between 1-azadienes 200-202 and electron-deficient dienophiles are most likely normal electron-demand reactions, often leading to a mixture of regioisomers.¹⁶

1.6 Conclusions

The 1-aza-Diels-Alder reaction has been shown to be an efficient and versatile method for the preparation of a large variety of nitrogen-containing six-membered heterocycles. The cycloaddition of electron-rich 1-aza-1,3-butadienes with alkene dienophiles has been extensively examined to give the dihydro- or tetrahydropyridine cycloadducts. Oxidation to the corresponding pyridines was frequently achieved using oxidants such as manganese dioxide or palladium on charcoal. Alkyne dienophiles have also been employed in the hetero-Diels-Alder reaction, allowing formation of the aromatic products directly from the reaction mixture.
The use of benzoquinone dienophiles has often been hampered by addition of nucleophilic amines (liberated on aromatisation during the reaction) into both the starting material and product. This problem has been solved by the addition of an appropriate amine scavenger into the reaction medium. The observed regiochemistry is often controlled by the electronic properties of the quinonic dienophile. Incorporation of a halogen atom into the quinone double bond has proved a valuable strategy to achieve complete regiocontrol. Several examples of intramolecular hetero-Diels-Alder reactions involving both alkene and alkyne dienophiles have also been reported.

The inverse electron-demand hetero-Diels-Alder reaction of N-sulfonyl- and 2-cyano-1-azadienes with electron-rich dienophiles has been explored by Boger and Fowler respectively. Excellent yields and high degrees of endo selectivity were observed in a range of cases. This methodology has subsequently been employed in the synthesis of several complex natural products.
Chapter 2

Results and Discussion

- Intermolecular 1-Aza-Diels-Alder Reactions
2.1 Introduction

The pyridine ring appears in a range of bioactive compounds, both naturally occurring and synthetic, often in highly substituted form; examples of particular interest to our research group include the thiopeptide antibiotic nosiheptide 214 and the antitumour antibiotic streptonigrin 215 (Figure 6). Although focus will remain on synthetic efforts towards streptonigrin 215, a brief study on model systems related to the tetra-substituted pyridine core of nosiheptide 214 will also be presented.

Figure 6.

Nosiheptide 214 is a member of the thiopeptide antibiotics, a class of sulfur containing highly modified cyclic peptides characterised by the presence of a heterocyclic centrepiece consisting of a tri- or tetra-substituted pyridine embedded in a macrocyclic array.65
The natural product was first isolated from *Streptomyces actuous* 40037 in 1961, and was characterised through degradation and X-ray crystallographic studies. Nosiheptide 214 is currently used commercially as a feed additive to promote weight gain in poultry and pigs.

Although nosiheptide 214 has yet to succumb to total synthesis, several approaches to various fragments, including the pyridine core, have been reported. Shin and coworkers first completed the tetra-substituted pyridine unit 220 of nosiheptide 214 in stepwise fashion starting from 5-bromo-3-hydroxypyridine 216 (Scheme 55). Key steps in this synthesis included the conversion of a C-5 cyano group into the thioamide and subsequent Hantzsch reaction to form the 5-thiazoyl pyridine 217. A Reissert reaction was used to install a second cyano group at C-2, followed by conversion into 2-thiazoyl pyridine 218 as before. A further Reissert reaction was employed to form the pyridone, which was converted into the third thiazoyl unit via triflation, Stille cross-coupling, bromination and a final Hantzsch reaction to give protected pyridine 220.
Moody and coworkers have recently reported a different approach based on the ozonolysis of quinoline 223, readily prepared from acetanilide 221 using a double Vilsmeier reaction followed by Baeyer-Villiger oxidation. Ozonolysis of the benzene ring revealed the orthogonally protected pyridine 224 suitable for further elaboration (Scheme 56).
Previous work in this laboratory focused on the reaction of bis-trimethylsilyl protected dienes such as 225 with a range of dienophiles.\textsuperscript{83} Thus, cycloaddition of 1-aza-1,3-butadiene 225 with DMAD 136 was carried out under reflux in toluene to afford the corresponding 3-hydroxypyridine 226 in moderate yield (Scheme 57) after 14 days.\textsuperscript{54} The poor yields may be explained by hydrolysis of the labile silyl enol ether moiety in the diene under the reaction conditions prior to cycloaddition.

Scheme 57. Reagents and conditions: a. toluene, reflux, 14 d.
The reactivity of these 1-azadienes with unsymmetrical dienophiles was also assessed, including methyl propiolate 228 \((R^2 = \text{CO}_2\text{Me})\) and 3-butyn-2-one 229 \((R^2 = \text{COMe})\), both of which react with complete regioselectivity to afford the 2,3,6-trisubstituted pyridines 230-231 in poor to moderate yield (Scheme 58, Table 22).\(^{83}\)

![Scheme 58. Reagents and conditions: a. toluene, 120 °C, sealed tube, 20 h-4 d.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R(^1)</th>
<th>Dienophile</th>
<th>R(^2)</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>135</td>
<td>Me</td>
<td>228</td>
<td>\text{CO}_2\text{Me}</td>
<td>230</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>227</td>
<td>Bn</td>
<td>229</td>
<td>\text{COMe}</td>
<td>231</td>
<td>39</td>
</tr>
</tbody>
</table>

The application of microwave irradiation has been shown to accelerate the rate of many organic reactions.\(^ {84,85}\) Indeed, several examples of hetero-Diels-Alder reactions have been reported under microwave conditions, including both 1- and 2-azadienes.\(^ {21,86-88}\) Therefore at the start of this project it was envisaged that the long reaction times previously observed might be reduced by performing the reaction under these conditions. In order to address the issue of the poor yields observed, the use of a more hydrolytically stable silicon-based protecting group was also investigated.
2.3 Synthesis and Cycloadditions of $\alpha,\beta$-Unsaturated Oximes

A range of 3-tert-butyldimethylsiloxy-$\alpha,\beta$-unsaturated oximes was prepared, and their reactivity in the intermolecular hetero-Diels-Alder reaction investigated. Thus, $O$-methyl oximes 236-237 were prepared from the free oximes 232-233 in two steps via $O$-alkylation and formation of the tert-butyldimethylsilyl enol ether on treatment with TBDMS triflate and DIPEA (Scheme 59, Table 23).50

![Scheme 59](image)

Scheme 59. Reagents and conditions: a. 10% NaOH (aq.), Me$_2$S0$_4$, rt 30 min then reflux 5 min; b. K$_2$CO$_3$, Me$_2$S0$_4$, acetone, 4 °C, 24 h; c. TBDMSOTf, DIPEA, CH$_2$Cl$_2$, 0 °C, 3 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\alpha$-ketoxime</th>
<th>R</th>
<th>$O$-Methyl Oxime</th>
<th>Yield/%</th>
<th>1-Azadiene</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>232</td>
<td>Me</td>
<td>234</td>
<td>78</td>
<td>236</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>233</td>
<td>CO$_2$Me</td>
<td>235</td>
<td>89</td>
<td>237</td>
<td>54</td>
</tr>
</tbody>
</table>

The analogous TBDMS oxime derivatives 238-239 were also prepared in high yield from the free oximes 232-233 in a single step on treatment with TBDMS triflate and DIPEA (Scheme 60).50
The intermolecular hetero-Diels-Alder reactions of 3-siloxy-1-aza-1,3-butadienes 236-237 and 238-239 were next investigated. Unfortunately, only traces of the expected pyridines was observed on heating O-methyl oxime ethers 236-237 with DMAD 136 at 150 °C under microwave heating, as well as significant decomposition of the starting materials (Table 25, entries 1-2). This result mirrors those of Gilchrist29 and Boger,9 who have also found O-alkyl oxime ethers to be unreactive in certain hetero-Diels-Alder reactions. One possible reason for this is that the O-methyl oximes 236-237 are not sufficiently electron-rich to interact with electron-deficient dienophiles due to an unfavourable HOMO_diene-LUMO_dienophile energy separation.

However, treatment of the more electron-rich 238 and 239 with either 1 or 2 equivalents of DMAD 136 in a sealed tube at 150 °C under microwave irradiation proceeded smoothly to afford the protected pyridines 240-241 in moderate yields after cycloaddition and concomitant loss of tert-butyl dimethylsilanol in only a few hours (Table 25, entries 4, 6, 8). The primary dihydro-pyridine cycloadducts were not observed under the reaction conditions. As may be expected, introduction of the
electron-withdrawing ester moiety at C-2 of the diene lowered its reactivity towards the electron-deficient dienophile, leading to slightly longer reaction time and lower yield (Table 25, entry 8). Increasing the temperature to 180 °C shortened the reaction time even further (Table 25, entries 5, 7, 9, 10). A control reaction performed in a sealed tube at 150 °C gave the expected pyridine 240 in 57% yield after 6 hours (Table 25, entry 3). However, the use of microwave irradiation remains a safe, clean, and efficient means of performing high temperature reactions and was used in the following studies on hydrazone derived 1-azadienes.

![Scheme 61](image-url)

Scheme 61. Reagents and conditions: a. toluene or toluene/THF, Δ, MW.
Table 25. Cycloaddition of $\alpha,\beta$-unsaturated oximes 238-239 with DMAD 136 under microwave heating.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>R</th>
<th>X</th>
<th>DMAD (equiv.)</th>
<th>Temp. /°C</th>
<th>Time /h</th>
<th>Product</th>
<th>Yield /%$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>236</td>
<td>Me</td>
<td>OMe</td>
<td>2.0</td>
<td>150</td>
<td>2</td>
<td>240</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>237</td>
<td>CO$_2$Me</td>
<td>OMe</td>
<td>2.0</td>
<td>150</td>
<td>0.5</td>
<td>241</td>
<td>-</td>
</tr>
<tr>
<td>3$^c$</td>
<td>238</td>
<td>Me</td>
<td>OTBDMS</td>
<td>2.0</td>
<td>150</td>
<td>6</td>
<td>240</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>238</td>
<td>Me</td>
<td>OTBDMS</td>
<td>2.0</td>
<td>150</td>
<td>6</td>
<td>240</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>238</td>
<td>Me</td>
<td>OTBDMS</td>
<td>2.0</td>
<td>180</td>
<td>2</td>
<td>240</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>238</td>
<td>Me</td>
<td>OTBDMS</td>
<td>1.0</td>
<td>150</td>
<td>8</td>
<td>240</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>238</td>
<td>Me</td>
<td>OTBDMS</td>
<td>1.0</td>
<td>180</td>
<td>3</td>
<td>240</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>239</td>
<td>CO$_2$Me</td>
<td>OTBDMS</td>
<td>2.0</td>
<td>150</td>
<td>10</td>
<td>241</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>239</td>
<td>CO$_2$Me</td>
<td>OTBDMS</td>
<td>2.0</td>
<td>180</td>
<td>6</td>
<td>241</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>239</td>
<td>CO$_2$Me</td>
<td>OTBDMS</td>
<td>1.0</td>
<td>180</td>
<td>8</td>
<td>241</td>
<td>45</td>
</tr>
</tbody>
</table>

$^a$ reactions were carried out in a CEM Discover™ microwave reactor.

$^b$ isolated yield after chromatography on silica gel.

$^c$ reaction carried out in a sealed tube under standard thermal heating.

2.4 Synthesis and Cycloadditions of $\alpha,\beta$-Unsaturated Hydrazones

As discussed above, the most commonly used 1-azadienes in hetero-Diels-Alder reactions are the $N,N$-dimethylhydrazones,$^{2-8}$ as they are generally considered to be more electron-rich than their equivalent oximes due to the increased electron donation of the dimethylamino group compared to the alkoxy or siloxy group. Thus, $\alpha,\beta$-unsaturated hydrazones exhibit greater reactivity towards highly electron-deficient dienophiles such as DMAD 136 based on the likely frontier orbital interactions (HOMO$_\text{diene}$/LUMO$_\text{dienophile}$), assuming that a normal electron-demand cycloaddition is in operation. A number of reactions of $\alpha,\beta$-unsaturated hydrazones with electron-
deficient alkenes and benzoquinones as dienophiles have therefore been reported.\textsuperscript{2, 4, 8} Reactions with alkynes however are less common. The C-3 oxygenated hydrazones are also known, although no Diels-Alder reactions of these dienes with alkynes have been reported.

A series of 3-siloxy-\(\alpha,\beta\)-unsaturated hydrazones was therefore prepared in order to probe the reactivity of these 1-azadienes towards electron-deficient acetylenes (Scheme 62). The required \(\alpha\)-ketohydrazones 248-252 were prepared by condensation of 2,3-butanedione 242 with the appropriate hydrazines 243-247. Although 243-244 and 247 are commercially available, 1-\textit{tert}-butoxycarbonyl- and 1-benzyloxycarbonyl-1-methyl-hydrazines 245 and 246 had to be synthesised by protection of methylhydrazine with di-\textit{tert}-butyl dicarbonate\textsuperscript{91} and benzyl chloroformate\textsuperscript{92} in 92% and 58% yield respectively. Silyl enol ether formation was achieved under standard conditions in excellent yield (Table 26, entries 1-2, 4-5), except for \textit{N}-\textit{tert}-butoxycarbonylhydrazone 250, which suffered loss of the protecting group under the reaction conditions (Table 26, entry 4).\textsuperscript{50}

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {\textbf{Scheme 62. Reagents and conditions:} a. EtOH, 0 °C, 16 h; b. TBDMSOTf, DIPEA, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 5-18 h.};
\end{tikzpicture}
\end{center}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazine</th>
<th>X</th>
<th>α-keto-hydrazone</th>
<th>Yield/%</th>
<th>1-Azadiene</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMe₂</td>
<td>243</td>
<td>248</td>
<td>72</td>
<td>53</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>piperidinyl</td>
<td>244</td>
<td>249</td>
<td>62</td>
<td>253</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>NMeBoc</td>
<td>245</td>
<td>250</td>
<td>96</td>
<td>254</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>NMeCbz</td>
<td>246</td>
<td>251</td>
<td>78</td>
<td>255</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>phthalimido</td>
<td>247</td>
<td>252</td>
<td>87</td>
<td>256</td>
<td>79</td>
</tr>
</tbody>
</table>

Initial work on the hydrazone series focused on the cycloaddition of known 3-tert-butylidimethylsiloxy-2-methyl-1-aza-1,3-butadiene 53 with DMAD 136 (Scheme 63). In a control experiment, treatment of 53 with 136 gave the desired cycloadduct 240 in 53% yield after 20 hours under reflux in toluene (Table 27, entry 1). Again, no evidence of the primary cycloadduct was detected. Once again the use of microwave irradiation was investigated in an attempt to decrease the reaction time and improve the yield.

Irradiation of equimolar amounts of 1-azadiene 53 and DMAD 136 at 150 °C in toluene in a sealed tube for 2 hours afforded the desired pyridine 240, still protected as the TBDMS ether and in poor yield, due to the competing formation of the conjugate addition product dimethyl 2-(dimethylamino)fumarate 257, caused by reaction between the dienophile and dimethylamine liberated upon aromatisation of the initial Diels-Alder adduct (Table 27, entry 2). Thus, 2 equivalents of the dienophile were necessary to achieve complete consumption of the 1-azadiene, allowing the product to be isolated in comparable yield to the thermal reaction in only 2 hours (Table 27, entry 3). Once again, increasing the temperature to 180 °C shortened the reaction time even further (Table 27, entry 4). A control reaction performed in a sealed tube at 150
°C under thermal conditions gave the anticipated pyridine 240 in 46% yield after 2 hours.

Scheme 63. Reagents and conditions: a. toluene or toluene/THF, Δ, MW.

Table 27. Cycloaddition of α,β-unsaturated hydrazones 53 and 253-256 with DMAD 136 under microwave heating.^

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-Azadiene</th>
<th>X</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>NMe₂</td>
<td>110</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>NMe₂</td>
<td>150</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>NMe₂</td>
<td>150</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>NMe₂</td>
<td>180</td>
<td>0.75</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>253</td>
<td>piperidiny</td>
<td>150</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>255</td>
<td>NMeCbz</td>
<td>150</td>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>256</td>
<td>phthalimido</td>
<td>180</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>256</td>
<td>phthalimido</td>
<td>180</td>
<td>4</td>
<td>54</td>
</tr>
</tbody>
</table>

^

reactions were carried out in a CEM Discover™ microwave reactor using 2 equivalents of DMAD 136.

isolated yield after chromatography on silica gel.

reaction carried out under reflux in toluene.

1 equiv. of DMAD 136 used.
It was envisaged that by altering the nature of the leaving group in the aromatisation step it would be possible to limit the formation of the competing Michael adducts, and so improve the yield of the desired product.

As may be expected, the piperidinyl derivative 253 displayed similar reactivity to 53 (Table 27, entry 5), including the formation of unwanted conjugate addition product 257. Introduction of a single electron-withdrawing substituent onto the leaving group in 1-azadiene 255 also failed to prevent by-product formation (Table 27, entry 6). However, the introduction of a second electron-withdrawing group onto hydrazone 256, derived from N-aminophthalimide,93 completely suppressed Michael addition of the nitrogen leaving group into the dienophile, leading to an increased yield, although higher temperature was necessary to effect the cyclisation (Table 27, entry 7). Only a single equivalent of DMAD 136 was therefore required with this diene (Table 27, entry 8).

The reactivity of unsymmetrical dienophiles, in particular methyl propiolate 228 and 3-butyn-2-one 229, was also investigated. The most reactive 1-azadiene 53 was chosen for this study as longer reaction times were expected as less electron-deficient (and hence less reactive) dienophiles were being employed (Scheme 64). Indeed, increasing the reaction temperature to 180 °C for 6 hours was necessary to achieve complete consumption of the 1-azadiene (Table 28, entries 1-2). Poor yields of a single regioisomer were obtained in each case, as assigned by 1H NMR spectroscopy based on the coupling constants (8.3 Hz) between the two ortho aromatic protons. Other unsymmetrical dienophiles such as 4-phenyl-3-butyn-2-one, 4-trimethylsilanyloxybut-2-ynoic acid ethyl ester and methyl trimethylsilylpropiolate were examined and
found to be unreactive under the reaction conditions, presumably due to steric as well as electronic considerations.

\[
\text{TBDMSO} \quad + \quad \begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{NMe}_2
\end{array}
\end{array} \quad \xrightarrow{\text{a}} \quad \begin{array}{c}
\begin{array}{c}
\text{TBDMSO} \\
\text{Me} \\
\text{N} \\
\text{R}
\end{array}
\end{array}
\]

Scheme 64. Reagents and conditions: a. toluene/THF, Δ, MW.

Table 28. Cycloaddition of 53 with unsymmetrical acetylenes 228-229 under microwave heating.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>R</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Product</th>
<th>Yield/%(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>228</td>
<td>CO(_2)Me</td>
<td>180</td>
<td>6</td>
<td>258</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>229</td>
<td>COMe</td>
<td>180</td>
<td>6</td>
<td>259</td>
<td>28</td>
</tr>
</tbody>
</table>

\(^a\) reactions were carried out in a CEM Discover™ microwave reactor (300 W) with simultaneous cooling using 2 equivalents of dienophile.

\(^b\) isolated yield after chromatography on silica gel.

This methodology has very recently been extended by Arndt and coworkers, who utilised a hetero-Diels-Alder reaction as the key step in their synthesis of the pyridine core of nosiheptide 214 (Scheme 65).\(^{94}\)
Synthesis of 1-azadienes bearing a triflate group at the C-3 position would allow direct formation of highly-substituted pyridines bearing a leaving group suitable for further elaboration by transition-metal catalysed cross-coupling reactions. Two hydrazones were chosen for this study, namely N-methyl-N-Cbz protected hydrazone 255 and phthalimido derivative 256, as they both bear electron-withdrawing substituents on the hydrazone which should prevent substitution of the triflate group by the amine liberated in the aromatisation step through a competing SNAr process.

Attempted formation of the vinyl triflates from hydrazones 255 and 256 was carried out under a range of conditions (Scheme 66). Initially, trifluoromethanesulfonic anhydride was used as the electrophile, but N-phenylbis(trifluoromethane)sulfonimide was chosen for the bulk of the study due to ease of handling of the reagent. A range of bases and solvents were also screened, as well as the addition of DMPU as a co-solvent. However all reactions failed to give any of the desired product, and this work was therefore abandoned.
Scheme 66. Reagents and conditions: a. see table.

Table 29. Attempted synthesis of vinyl triflates and nonaflates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazone</th>
<th>X</th>
<th>Conditions</th>
<th>Product</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>255</td>
<td>NMeCbz</td>
<td>Tf₂O, DIPEA, CH₂Cl₂</td>
<td>263</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>255</td>
<td>NMeCbz</td>
<td>Tf₂O, Et₃N, CH₂Cl₂</td>
<td>263</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>255</td>
<td>NMeCbz</td>
<td>PhNTf₂, DIPEA, CH₂Cl₂</td>
<td>263</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>255</td>
<td>NMeCbz</td>
<td>PhNTf₂, KHMDS, THF</td>
<td>263</td>
<td>decomp.</td>
</tr>
<tr>
<td>5</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, DIPEA, CH₂Cl₂</td>
<td>264</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, Et₃N, CH₂Cl₂</td>
<td>264</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, NaH, THF</td>
<td>264</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, Cs₂CO₃, THF</td>
<td>264</td>
<td>SM</td>
</tr>
<tr>
<td>9</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, KHMDS, THF</td>
<td>264</td>
<td>SM</td>
</tr>
<tr>
<td>10</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, n-BuLi, THF</td>
<td>264</td>
<td>decomp.</td>
</tr>
<tr>
<td>11</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, LiHMDS, DMPU, THF</td>
<td>264</td>
<td>decomp.</td>
</tr>
<tr>
<td>12</td>
<td>256</td>
<td>phthalimido</td>
<td>PhNTf₂, NaH, DMPU, THF</td>
<td>264</td>
<td>trace</td>
</tr>
</tbody>
</table>

2.6 Attempted Synthesis of Intramolecular Substrates

A brief study on the synthesis of intramolecular hetero-Diels-Alder substrates was also undertaken. First, alkylation of 2,3-butanedione monoxime 232 was attempted using a variety of bases with either tosylate⁹⁵ 265 or iodide⁹⁶ 266 as the electrophile (Scheme 67, Table 30). Unfortunately, recovery of the starting materials or decomposition was observed in all cases.
New Developments in the 1-Aza-Diels-Alder Reaction

Scheme 67. Reagents and conditions: a. see table.

Table 30.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>X</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>265</td>
<td>OTs</td>
<td>10% NaOH (aq.)</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>265</td>
<td>OTs</td>
<td>NaH, THF</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>266</td>
<td>I</td>
<td>10% NaOH (aq.)</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>266</td>
<td>I</td>
<td>n-BuLi, THF</td>
<td>decomp.</td>
</tr>
</tbody>
</table>

Next, hydrazones 268 and 269 were prepared from 2,3-butanedione 232 via condensation with the appropriate hydrazine. Alkylation of the hydrazone nitrogen was then examined under a range of conditions (Scheme 68, Table 31), though once again none of the desired product was obtained.

Scheme 68. Reagents and conditions: a. see table.
Table 31. Attempted alkylation of hydrazones 268-269.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazone</th>
<th>R</th>
<th>Electrophile</th>
<th>X</th>
<th>Conditions</th>
<th>Product</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>268</td>
<td>Me</td>
<td>265</td>
<td>OTs</td>
<td>Cs$_2$CO$_3$, acetone</td>
<td>270</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>268</td>
<td>Me</td>
<td>266</td>
<td>I</td>
<td>Cs$_2$CO$_3$, acetone</td>
<td>270</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>268</td>
<td>Me</td>
<td>266</td>
<td>I</td>
<td>$n$-BuLi, THF</td>
<td>270</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>269</td>
<td>Cbz</td>
<td>266</td>
<td>I</td>
<td>K$_2$CO$_3$, EtOAc</td>
<td>271</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>269</td>
<td>Cbz</td>
<td>266</td>
<td>I</td>
<td>NaH, DMF</td>
<td>271</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>269</td>
<td>Cbz</td>
<td>266</td>
<td>I</td>
<td>$n$-BuLi, THF</td>
<td>271</td>
<td>SM</td>
</tr>
</tbody>
</table>

Finally, incorporation of the side-chain onto the nitrogen atom prior to formation of the hydrazone was attempted. Thus, following procedures reported by Gilchrist and coworkers, pent-4-ynoic acid 272 was converted to hydrazide 273 via the acid chloride and treatment with methyl hydrazine (Scheme 69). Reaction of 2,3-butanedione 242 with hydrazide 273 and subsequent formation of the silyl enol ether delivered the IMDA substrate 275. Intramolecular cycloaddition was attempted under microwave heating, but after 10 hours at 180 °C only decomposition of the starting material was observed. This work was therefore abandoned.
Series of α,β-unsaturated oximes and hydrazones have been prepared, and their reactivity in the hetero-Diels-Alder cycloaddition with electron-deficient acetylenes evaluated. In general, the bis-silylated oximes proved to be less reactive than the corresponding hydrazones, requiring much longer reaction times to obtain complete consumption of the starting materials. This is due to the superior electron donation of the dimethylamino substituent into the diene, thereby further raising the energy of the HOMO of the diene. However, as described in the next chapter, in the intramolecular mode, oxime containing dienes do participate in hetero-Diels-Alder reactions with appropriate dienophiles.
Changing the electronic properties of the N-1 substituent has a strong effect on the reactivity of the $\alpha,\beta$-unsaturated hydrazones. The stronger the electron-donating group, the more reactive the 1-azadiene, and the shorter the reaction time observed for Diels-Alder cycloaddition. However, side-products were observed due to addition of the nucleophilic amine liberated after aromatisation into the starting materials. Introducing electron-withdrawing groups onto the hydrazone nitrogen lowered the reactivity of the 1-azadiene, leading to longer reaction times for cycloaddition, though suppression of the unwanted side-reactions was obtained.

The synthesis of 1-azadienes bearing a triflate group at the 3-position was attempted. A variety of reaction conditions were screened, but this work was unsuccessful. An intramolecular hetero-Diels-Alder substrate was also constructed, although cycloaddition could not be achieved under microwave heating.
Chapter 3

Results and Discussion

- Towards the Formal Synthesis of Streptonigrin
3.1 Introduction

Streptonigrin\textsuperscript{99} \textbf{215} was first isolated by Rao and Cullen\textsuperscript{100} in 1959 from \textit{Streptomyces flocculus} and was shown to exhibit activity against several animal tumours.\textsuperscript{101-105} Streptonigrin \textbf{215} has also been isolated from other \textit{Streptomyces} strains, namely \textit{S. rufochromogenes} and \textit{S. echinatus},\textsuperscript{106} as well as from \textit{Actinomyces albus var. bruneomycini} (Figure 7).\textsuperscript{107, 108} Two further closely related antibiotics \textit{streptonigrone}\textsuperscript{109} \textbf{277} and \textit{lavendamycin} \textbf{278} have since been isolated.\textsuperscript{110, 111} Lavendamycin \textbf{278} has also been postulated as a possible biosynthetic precursor to \textit{streptonigrin} \textbf{215} and related analogues.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Figure 7.}
\end{figure}
The structure of streptonigrin 215 was first reported by Woodward and coworkers in 1963 on the basis of spectroscopic and degradative studies. Further evidence for this structure was reported in 1975 by Chiu and Lipscomb through X-ray diffraction analysis. More recent NMR studies by Lown and Begleiter, and Harding and coworkers have confirmed the structure as 215.

The AB- and C-rings of 215 are held coplanar due to an internal hydrogen bond between the pyridine amino group and the quinoline nitrogen (Figure 8). Streptonigrin 215 is also optically active due to hindered rotation about the CD-biaryl bond. Although initially assigned as the $P$-isomer by Dholakia and Gillard, subsequent work by Tennent and Rickards suggested that streptonigrin 215 adopts the $M$-configuration. More recent work by Bringmann and coworkers has confirmed that the $M$-isomer is indeed the correct structure.

![Figure 8.](image-url)
3.2 Biological Activity of Streptonigrin

Streptonigrin 215 has been shown to exhibit potent antiviral activity against both Gram-positive and Gram-negative bacteria, as well as strong antitumour activity towards a range of both animal and human cancer cell lines. However, clinical use has been precluded due to severe side effects including prolonged bone marrow depression.

The mechanism of action for the anticancer activity of streptonigrin 215 has been the source of much interest. It has been shown to inhibit DNA and RNA synthesis and cause DNA strand breaks in vitro and in vivo, as well as promote mammalian topoisomerase II-induced cell death. Streptonigrin 215 binds irreversibly to DNA in the presence of certain metal ions, in particular zinc and copper, followed by reduction of the quinone moiety by either a one- or two-electron process to the hydroquinone or semiquinone radical. Hydrogen peroxide (formed from the superoxide radical via a superoxide dismutase (SOD) catalysed process) then induces oxidation back to the quinone and formation of hydroxyl radicals, leading to its DNA damaging effects.

Due to its unique structural properties and potent biological activity, it is unsurprising that streptonigrin 215 has provided much inspiration to the synthetic chemist. Indeed, considerable effort has been made to prepare analogues of streptonigrin that maintain the high degrees of biological activity displayed by the natural product yet lack the toxic side effects.
3.3 Previous Syntheses of Streptonigrin

Three previous total syntheses of streptonigrin \(215\) have been reported. The first was presented by Weinreb and coworkers\(^{120-122}\) in 1980, followed closely by Kende\(^{123-125}\) in 1981 and Boger in 1985.\(^{126-128}\)

Weinreb’s approach was centred on two key reactions; an imino-Diels-Alder reaction for the formation of the CD-ring fragment, followed by a modified Friedländer reaction to install the quinoline ring. Weinreb’s synthesis started with readily available aldehyde \(279\), which was converted into the homoallylic alcohol \(280\) in three steps (Scheme 70). Oxidation to the aldehyde and Wittig reaction gave the desired diene fragment \(281\). A Diels-Alder reaction with a dienophile formed \textit{in situ} from hydantoin \(282\) proceeded smoothly to afford a 3:1 mixture of regioisomeric products \(283\) and \(284\) in favour of the desired isomer. The mixture was not separated at this stage but converted into the key pyridine intermediate \(285\) in a further three steps.
Installation of the remaining amino substituent into the C-5 position of the pyridine was accomplished in a further ten steps (Scheme 71). Key transformations included the Polonovski-type N-oxide rearrangement (285 to 286), a further [2,3]-sigmatropic shift to functionalise C-5 (287 to 288) and the Yamada modification of the Curtius rearrangement to give the desired aminopyridine (288 to 289).
New Developments in the 1-Aza-Diels-Alder Reaction

Scheme 71. Reagents and conditions: a. m-CPBA, CH₂Cl₂; b. Ac₂O, 120 °C; c. K₂CO₃, MeOH; d. SOCl₂, benzene; e. N-(cyanomethyl)pyrrolidine, DMSO; f. KO'Bu, THF, DMSO; g. (CO₂H)₂, THF, H₂O; h. TFPAA, Na₂HPO₄, CH₂Cl₂; i. KMnO₄, acetone, H₂O; j. (PhO)₂PON₃, benzene, H₂O.

A second Polonovski-type rearrangement was then carried out, followed by oxidation, formation of the β-ketophosphonate 290 and Wadsworth-Emmons reaction with known aldehyde 291 to afford the nitrochalcone (Scheme 72). Reduction and cyclisation proceeded smoothly, followed by deprotection and oxidation to the quinone 292, which was converted into streptonigrin 215 following standard procedures. In total, the natural product was prepared in over 30 steps in 0.034% overall yield from readily available starting materials.
Kende’s approach to streptonigrin 215 also featured a Friedländer condensation to assemble the quinoline fragment. The synthesis started from the known ketoenamine 293, which was condensed with methyl acetoacetate to afford the pyridone. Reduction of the C-3 acetyl group to the secondary alcohol proceeded smoothly on treatment with sodium borohydride. Chlorination and dehydration to the vinyl group was achieved using phenylphosphoryl dichloride, followed by heating for 3 hours. Treatment with copper cyanide and addition of methylmagnesium bromide gave the key vinylpyridine 294 (Scheme 73).
A Friedländer condensation was then carried out between 294 and iminoaniline 295 using potassium tert-butoxide in tert-butanol to give the tetracyclic compound 296. Deprotection, nitration and methylation of the phenol gave 297. The vinyl unit was then cleaved under oxidative conditions to install the carboxylic acid, and oxidation of the methyl group adjacent to the pyridine nitrogen was achieved with selenium dioxide, followed by sodium chlorite. Selective esterification of the less hindered acid and a modified Curtius rearrangement afforded intermediate 298. Reduction of the nitro group and oxidation to the quinone gave advanced intermediate 292, which had previously been prepared by Weinreb. Synthesis of this compound therefore constituted a formal total synthesis of streptonigrin 215. The clever use of the vinyl unit as a masking group for the amino group shortened the synthesis considerably when compared to Weinreb’s, allowing the natural product to be obtained in 22 steps and in 0.069% overall yield.
Scheme 73. Reagents and conditions: a. methyl acetoacetate, xylene, reflux; b. NaBH₄, THF, IPA; c. PhPOCl₂; d. CuCN, DMF, reflux; e. MeMgBr, benzene; f. KO'Bu, toluene, 'BuOH; g. TFA; h. HNO₃, MeNO₂; i. Me₂SO₄, K₂CO₃, acetone, reflux; j. OsO₄, NMO, acetone, 'BuOH, H₂O; k. NaIO₄, 1,4-dioxane, H₂O, 80 °C; l. SeO₂, AcOH, reflux; m. NaClO₂, H₂NSO₂H, NaOAc, dioxane, H₂O; n. MeOH, AcCl; o. (PhO)₂PON₃, Et₂N, benzene, H₂O; p. Na₂S₂O₄, THF, MeOH, H₂O, reflux; q. Fremy's salt, Na₂HPO₄, acetone, H₂O.
Boger and coworkers have also reported a formal synthesis of streptonigrin 215. The key steps involved two sequential inverse electron-demand hetero-Diels-Alder reactions, with concomitant loss of nitrogen in each case. The starting material for this synthesis was 6-methoxyquinoline 299, which was first converted into 2-cyano-6-methoxyquinoline, followed by nitration and formation of the thioamide using hydrogen sulfide in diethylamine (Scheme 74). Treatment of the thioamide with iodomethane gave the desired S-methylthioimidate, which underwent hetero-Diels-Alder reaction with 1,2,4,5-tetrazine-3,6-dicarboxylate, followed by extrusion of nitrogen, to deliver the desired triazine 300.

A further hetero-Diels-Alder reaction with enamine 301 gave a 2.8:1 mixture of the regioisomers 302 and 303. The desired isomer 302 was hydrolysed to the diacid with the sodium salt of phenylselenol, which unfortunately also effected O-demethylation of the aromatic ether. Selective esterification, modified Curtius rearrangement and remethylation of the phenolic hydroxyl group afforded the advanced intermediate 298 which could be converted into streptonigrin 215 using the methodology previously described by Weinreb and Kende. This synthesis has proved to be the most efficient, comprising a total of 13 steps from readily available starting materials and in 1.8% overall yield.
Scheme 74. Reagents and conditions: a. TsCl, KCN, CH₂Cl₂, H₂O; b. HNO₃, H₂SO₄; c. H₂S, Et₂NH, 1,4-dioxane; d. Mel, MeCN; e. dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, 1,4-dioxane, 80 °C; f. CH₂Cl₂, 6.2 kbar; g. NaSePh, THF-HMPA, 70 °C; h. HCl, MeOH, H₂O; i. (PhO)₃PON₃, benzene, H₂O; j. Mel, K₂CO₃, THF.
Three syntheses of the CD-rings of streptonigrin 215 have also been reported. The first was reported by Cheng and coworkers in 1976 in stepwise fashion starting from pyrogallol.\textsuperscript{129} Cheng later reported a more convergent synthesis based on an unsymmetrical Ullmann reaction.\textsuperscript{130} Thus, known 2,3-dimethyl-4-nitropyridine 304 was first converted into 4-chloro-2,3-dimethyl-5-nitropyridine 305 in 4 steps (Scheme 75). The second partner 306 for biaryl cross-coupling was prepared from 2,3-dimethoxyphenol by protection of the free hydroxyl group and iodination. The key unsymmetrical Ullmann coupling was carried out in 33% yield using copper dust in DMF at 140 °C to deliver 307. Oxidation of the pyridine methyl group to the carboxylic acid was carried out in 2 steps on treatment with selenium dioxide under reflux in dioxane followed by silver oxide in basic aqueous ethanol. Hydrolysis of the acetate protecting group was also effected under the reaction conditions. Final reduction of the nitro group was carried out under catalytic hydrogenolysis to afford the streptonigrin CD-rings 308.
Scheme 75. Reagents and conditions: a. KOAc, Ac₂O, reflux, 16 h; b. H₂O, reflux, 4 h; c. HNO₃, H₂SO₄, 65 °C, 2 h; POCl₃, PCl₅, reflux, 2 h; e. copper dust, DMF, 140 °C, 90 min; f. SeO₂, dioxane, reflux, 3 h; g. Ag₂O, NaOH, EtOH, H₂O, 10 °C, 20 min then NaOH, 40 °C, 2 h; h. H₂, 5% Pd/C, MeOH, 3 h.

The third CD-ring synthesis of streptonigrin 215 was presented by DeShong and coworkers, also based on a biaryl cross-coupling strategy. The synthesis started from known pyridone 309, which was converted into bromopyridine 310 after hydrolysis, decarboxylation, treatment with phosphorus oxybromide and methylation (Scheme 76). Formation of the N-oxide, Polonovski rearrangement and subsequent hydrolysis of the acetate, methylation and nitration delivered 311. DeShong found that oxidation at the C-2 position of the pyridine to the carboxylate ester was crucial before biaryl cross coupling, as the same transformation could not be achieved with the D-ring in place. Thus, removal of the methyl group from 311 was effected using boron trichloride in quantitative yield, followed by oxidation and esterification to give 312. Suzuki cross-coupling with boronic acid 313 was accomplished in 68% yield.
Treatment of the biaryl product with phosphorus tribromide revealed the pyridone, which was converted into the corresponding pyridyl triflate 314. A second biaryl cross-coupling of 314 with an AB-ring precursor has yet to be achieved.

Scheme 76. Reagents and conditions: a. 2 M NaOH, reflux, 2 h then HCl, rt, 12 h; b. POBr₃, DMF, 110 °C, 45 min; c. Mel, Ag₂CO₃, CHCl₃, 50 °C, 24 h; d. 30% H₂O₂, AcOH, 60 °C, 3 d; e. Ac₂O, 120 °C, 2 h; f. K₂CO₃, MeOH; g. Ag₂O, Mel, THF, reflux, 4 d; h. HNO₃, H₂SO₄, rt, 2 d; i. BCl₃, CH₂Cl₂, 0 °C to rt, 16 h; j. KMnO₄, NaOH, H₂O, rt, 24 h; k. H₂SO₄, MeOH, reflux, 16 h; l. Pd(PPh₃)₄, CsF, DME, 75 °C, 24 h; m. PBr₃, DCE, reflux, 12 h; n. Tf₂O, DMAP, CH₂Cl₂, 0 °C to rt, 12 h.
3.4 Retrosynthetic Analysis

Our current retrosynthetic analysis of streptonigrin 215 begins with a change in oxidation levels and functional group transformations which lead to the advanced intermediate 298 previously obtained by Kende and Boger (Scheme 77). The synthesis of this compound will therefore constitute a formal total synthesis of streptonigrin 215.

Scheme 77.
Compound 298 is anticipated to arise from the cyclic ether 315 via oxidation of the pyran ring to the lactone, followed by hydrolysis, protection of the phenol and Curtius rearrangement. Disconnection of the pyridine ring of 315 reveals 316 as a likely precursor. In the forward sense an intramolecular hetero-Diels-Alder reaction between the acetylene and 1-azadiene units followed by selective oxidation of the pyridine C-2 methyl group will generate the desired heterocycle. Rapid construction of IMDA substrate 316 was expected from AB-ring precursor 317, D-ring 318 and phosphonate 319 through Sonogashira cross-coupling and Wadsworth-Emmons reaction.

3.5 Model Intramolecular Hetero-Diels-Alder Reactions

In order to ascertain whether an intramolecular hetero-Diels-Alder route was a viable strategy for the synthesis of the pyridine core of streptonigrin 215, a series of model systems were prepared and their IMDA cycloadditions evaluated.\textsuperscript{132}

The required substrates for hetero-Diels-Alder reaction were prepared in three steps from commercially available starting materials. First, alkylation of salicylaldehyde 320 and 3-methylsalicylaldehyde 321 with propargyl chloride proceeded in excellent yield to provide the aryl propargyl ethers 322-323 (Scheme 78, Table 32).\textsuperscript{59} Next, the Wadsworth-Emmons reaction was examined. Treatment of the required β-ketophosphonates 319 and 324-325, obtained either from commercial sources or by acylation of the phosphonate-derived carbanion by known or modified procedures,\textsuperscript{133} with sodium hydride or potassium \textit{tert}-butoxide in 1,2-dimethoxyethane (DME) or toluene, followed by addition of the aldehyde gave the desired α,β-unsaturated ketones 326-329 as single (\textit{E})-geometric isomers in good to excellent yields.
Treatment of related α,β-unsaturated ketones (vide infra) with N,N-dimethylhydrazine led to a complex mixture of products due to the competing formation of Michael adducts. Thus, further functionalisation to the 1-aza-1,3-butadiene moiety was readily achieved by conversion of 326-329 into the O-methyl oximes 330-333 on heating with methoxylamine hydrochloride and sodium acetate trihydrate in aqueous ethanol in almost quantitative yield, without the need for further purification by column chromatography.

\[
\begin{align*}
\text{HO-CHO} & \xrightarrow{\text{a}} \text{CHO} \\
320-321 & \xrightarrow{86-100\%} 322-323 & \text{CHO} \xrightarrow{65-91\%} \text{EtO-P-0} \xrightarrow{\text{b}} 319, 324-325 \\
\text{R}^1 & \text{R}^1 \\
\text{R}^2 & \text{R}^2 \\
\text{R}^3 & \text{R}^3 \\
\text{OMe} & \text{N} \xrightarrow{72-98\%} \text{R}^1 \\
330-333 & \xrightarrow{\text{c}} 326-329
\end{align*}
\]

**Scheme 78.** **Reagents and conditions:** a. HC≡CCH\(_2\)Cl, K\(_2\)CO\(_3\), EtOH, reflux, 16 h; b. (RO)\(_2\)P(O)CHR\(^3\)COR\(^3\), NaH or KO'Bu, DME or toluene, rt, 16 h; c. MeONH\(_2\)-HCl, NaOAc·3H\(_2\)O, EtOH, H\(_2\)O, 60 °C, 16 h.
Table 32. Synthesis of IMDA substrates 330-333.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Ketone</th>
<th>Yield/%</th>
<th>Oxime</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>320</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>326</td>
<td>91</td>
<td>330</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>321</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>327</td>
<td>76</td>
<td>331</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>321</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>328</td>
<td>71</td>
<td>332</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>321</td>
<td>Me</td>
<td>Me</td>
<td>CH₂OMe</td>
<td>329</td>
<td>65</td>
<td>333</td>
<td>95</td>
</tr>
</tbody>
</table>

The key IMDA cycloadditions were then examined under simple heating (Scheme 79). Thus, heating oxime 330 to 180 °C in xylene in a sealed tube gave the desired [c]-annelated pyridine 334 in 30% yield after 16 h (Table 33, entry 1). A minor byproduct was isolated in 8% yield, which was identified as (3E)-4-(2H-chromen-8-yl)but-3-en-2-one O-methyloxime 338, that presumably arises through a [3,3]-sigmatropic rearrangement and [1,5]-hydrogen shift in analogous fashion to that previously reported for vinyl hydrazone dienes (Scheme 80).⁵⁹

Scheme 79. Reagents and conditions: a. xylene, 180 °C, sealed tube, 16 h.

Table 33. IMDA cycloaddition of α,β-unsaturated O-methyl oximes 330-333.

<table>
<thead>
<tr>
<th>Entry</th>
<th>IMDA Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>330</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>334</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>331</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>335</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>332</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>336</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>333</td>
<td>Me</td>
<td>Me</td>
<td>CH₂OMe</td>
<td>337</td>
<td>27</td>
</tr>
</tbody>
</table>
A blocking substituent in the form of a methyl group ortho to the propargylic ether moiety eliminates this competing rearrangement, and the desired pyridine 335 was isolated in 37% yield (Table 33, entry 2). Variations in the diene component were also tolerated. Indeed, IMDA reaction of substrates 332-333 (Table 33, entries 3-4) proceeded smoothly, albeit in modest yield, to provide the tetra-substituted pyridines 336-337.

Scheme 80. Formation of chromene byproduct 338 resulting from competing [3,3]-sigmatropic rearrangement of 330.

A range of substrates bearing a substituent at the terminus of the acetylenic dienophile were also prepared in order to examine their effect on the intramolecular hetero-Diels-Alder reaction. The IMDA substrate 340 was obtained by Sonogashira reaction between acetylene 327 and iodobenzene under standard conditions\textsuperscript{134} to give 339, followed by formation of the corresponding oxime as detailed above (Scheme 81).
Scheme 81. Reagents and conditions: a. Phl, Pd(PPh₃)₂Cl₂ (7 mol%), Cul, Et₃N, THF, 60 °C, 16 h.; b. MeONH₂·HCl, NaOAc·3H₂O, EtOH, H₂O, 60 °C, 16 h.

IMDA substrates 341-343 bearing a methyl ester, chloro or trimethylsilyl group at the alkyne terminus were prepared directly from oxime 331 via deprotonation of the acidic acetylenic proton with lithium hexamethyldisilazide (LiHMDS) and trapping with the appropriate electrophile (Scheme 82).

Scheme 82. Reagents and conditions: a. LiHMDS, electrophile, THF, -78 °C to rt, 16 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>R¹</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CICO₂Me</td>
<td>CO₂Me</td>
<td>341</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>NCS</td>
<td>Cl</td>
<td>342</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl</td>
<td>TMS</td>
<td>343</td>
<td>53</td>
</tr>
</tbody>
</table>
Once again, the key IMDA reactions were investigated under simple thermal heating. Introduction of an electron-withdrawing group at the terminus of the acetylene would be expected to facilitate the IMDA reaction on the basis of lowering the relevant LUMO of the dienophile, assuming that the α,β-unsaturated oximes participate in a normal electron-demand hetero-Diels-Alder reaction (HOMO<sub>diene</sub>/LUMO<sub>dienophile</sub>).

This indeed proved to be the case (Scheme 83); heating oxime 340 in xylene in a sealed tube at 180 °C gave the desired tetra-substituted pyridine 344 in 62% yield (Table 35, entry 1). The reaction still proceeded at 140 °C, unlike the terminal acetylenes, although a slight drop in yield was noticed (Table 35, entry 2). IMDA reaction of oxime 341 also proceeded smoothly, with the expected product 345 isolated in 50% and 41% yield after 16 h at 180 °C and 140 °C respectively (Table 35, entries 3-4).

![Scheme 83. Reagents and conditions: a. xylene, 140-180 °C, sealed tube, 16 h.](image-url)
Table 35. IMDA reactions of α,β-unsaturated oximes 340-343.

<table>
<thead>
<tr>
<th>Entry</th>
<th>IMDA Substrate</th>
<th>R¹</th>
<th>Product</th>
<th>Temp/°C</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>340</td>
<td>Ph</td>
<td>344</td>
<td>180</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>Ph</td>
<td>344</td>
<td>140</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>341</td>
<td>CO₂Me</td>
<td>345</td>
<td>180</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>341</td>
<td>CO₂Me</td>
<td>345</td>
<td>140</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>342</td>
<td>Cl</td>
<td>346</td>
<td>180</td>
<td>16⁹</td>
</tr>
<tr>
<td>6</td>
<td>343</td>
<td>TMS</td>
<td>335</td>
<td>200</td>
<td>12⁶</td>
</tr>
</tbody>
</table>

⁹ Also isolated was pyridine 335 in 30% yield.

⁶ Also isolated was recovered starting material 343 in 69% yield.

However, IMDA reaction of oxime 342 gave only small amounts of the expected 2-chloropyridine 346 (Table 35, entry 5), with the main isolated product being pyridine 335 that arises through formal loss of the chlorine atom, although it is not yet clear at which stage this loss occurs. As may be expected, introduction of a bulky TMS group into the dienophile greatly retarded the IMDA reaction (Table 35, entry 6), such that even after prolonged heating 69% of the unreacted starting material was recovered, with only 12% of the desilylated pyridine 335 being isolated.

It was also envisioned that direct conversion of the α,β-unsaturated ketones 327 and 339 to the aromatic products would also be possible through a one-pot oxime formation/hetero-Diels-Alder reaction (Scheme 84). Pleasingly, treatment of ketones 327 and 339 with methoxylamine hydrochloride and triethylamine in xylene in a sealed tube and heating to 180 °C for 16 h gave the desired pyridines 335 and 344 in 29% and 37% yield respectively (Table 36, entries 1 and 2).
Scheme 84. Reagents and conditions: a. MeONH₂·HCl, Et₃N, xylene, 180 °C, sealed tube, 16 h.

Table 36. One pot oxime formation/hetero-Diels-Alder reaction of α,β-unsaturated ketones 327-339.

<table>
<thead>
<tr>
<th>Entry</th>
<th>IMDA Substrate</th>
<th>R¹</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>327</td>
<td>H</td>
<td>335</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>339</td>
<td>Ph</td>
<td>344</td>
<td>37</td>
</tr>
</tbody>
</table>

Having successfully demonstrated that the intramolecular hetero-Diels-Alder reaction of vinyl oxime ethers with acetylenes represents a rapid and versatile route to a range of [c]-annelated pyridines, attention was turned to the preparation of the required hetero-Diels-Alder substrate for the formal synthesis of streptonigrin 215.

3.6 Synthesis of the Model CD-rings

First, IMDA substrates 350-351 bearing the correct CD-ring substitution pattern for streptonigrin 215 were prepared using the above methodology. The required 3,4-dimethoxysalicaldehyde 279 was readily obtained in multigram quantities from 2,3,4-trimethoxybenzaldehyde 347 by selective demethylation (controlled by the presence of the proximal aldehyde moiety) using aluminium trichloride in benzene (Scheme 85). Alkylation of 279 with propargyl chloride⁵⁹ and Wadsworth-Emmons
reaction\textsuperscript{133} delivered $\alpha,\beta$-unsaturated ketones 348-349. Synthesis of the corresponding hydrazones was attempted on treatment with $N,N$-dimethylhydrazine under a range of dehydrating conditions. However formation of Michael adducts precluded isolation of the desired product. In contrast, oxime formation\textsuperscript{139} proceeded without incident and in excellent yield to provide IMDA substrates 350-351. As expected, intramolecular cycloaddition proceeded smoothly to provide the chromeno[c]pyridines 352-353 in 45\% and 48\% yield respectively (Table 37, entries 1-2). Direct conversion of ketones 348 and 349 to pyridines 352 and 353 was also achieved in one pot on heating with methoxylamine hydrochloride and triethylamine in xylene in 54\% and 56\% yield.\textsuperscript{132}

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{scheme85.png}
\end{center}
\end{figure}

Scheme 85. Reagents and conditions: a. AlCl$_3$, benzene, reflux, 6 h; b. HC=CH$_2$Cl, K$_2$CO$_3$, EtOH, reflux, 18 h; c. (EtO)$_2$P(O)CHCOMe, NaH or KO'Bu, DME, rt, 16 h; d. MeONH$_2$·HCl, NaOAc·3H$_2$O, EtOH, H$_2$O, 60 °C, 16 h; e. xylene, 180 °C, sealed tube, 16 h.
Table 37. Synthesis of model pyridines 352-353.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ketone</th>
<th>Yield/%</th>
<th>Oxime</th>
<th>Yield/%</th>
<th>Pyridine</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>348</td>
<td>75</td>
<td>350</td>
<td>100</td>
<td>352</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>349</td>
<td>81</td>
<td>351</td>
<td>100</td>
<td>353</td>
<td>48</td>
</tr>
</tbody>
</table>

3.7 Synthesis of the Quinoline AB-Ring Fragment

Next, attention was turned to the synthesis of the quinoline AB-ring fragment. In the event, 2-iodo-6-methoxy-5-nitroquinoline 317 was prepared in multigram quantities following literature procedure.\textsuperscript{140} Commercially available 6-methoxyquinoline 299 was first converted into its N-oxide 354 on heating with hydrogen peroxide in acetic acid (Scheme 86). Treatment of 354 with a large excess of phosphorus oxychloride gave a 1:1 mixture of the 2- and 4-chloroquinoline regioisomers, which were separable by flash chromatography, allowing the desired 2-chloro-6-methoxyquinoline 355 to be isolated in 50\% yield. Conversion into the iodide 356 was then accomplished on treatment of 355 with sodium iodide in excellent yield. Selective nitration afforded the desired 2-iodo-6-methoxy-5-nitroquinoline 317.
New Developments in the 1-Aza-Diels-Alder Reaction

Scheme 86. Reagents and conditions: a. H_2O_2, AcOH, 80 °C, 6 h; b. POCl_3, 100 °C, 1 h; c. NaI, 5 M HCl, MeCN, reflux, 16 h; d. HNO_3, H_2SO_4, 0 °C, 45 min.

3.8 Sonogashira Coupling of the AB- and D-ring fragments

The union of quinoline fragment 317 and the D-ring was first envisaged through a Sonogashira cross-coupling strategy. Initial attempts involved the coupling of a 3-carbon propargyl unit with iodoquinoline 317 (Scheme 87). A poor yield was obtained using propargyl alcohol 357, and no reaction was observed with the tosylate 358 under optimised reaction conditions. However, the tetrahydropyranyl (THP) ether of propargyl alcohol 359 gave an excellent yield of the coupled product 362.

Scheme 87. Reagents and conditions: a. PdCl_2(PPh_3)_2, Cul, Et_3N, 60 °C, 16 h.
Table 38. Sonogashira coupling of iodoquinoline 317 with acetylenes 357-359.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acetylene</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>357</td>
<td>OH</td>
<td>360</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>358</td>
<td>OTs</td>
<td>361</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>359</td>
<td>OTHP</td>
<td>362</td>
<td>87</td>
</tr>
</tbody>
</table>

Having successfully coupled the propargyl unit onto the AB-ring system of streptonigrin, addition of the D-ring was then envisaged through a simple alkylation strategy. Thus, deprotection of the THP group from 362 was carried out using para-toluenesulfonic acid in ethanol in 73% yield (Scheme 88). Tosylation of propargylic alcohol 360 was then achieved in good yield under standard conditions.<sup>141</sup> Unfortunately, attempted alkylation of phenol 279 with tosylate 361 using potassium carbonate in ethanol led only to decomposition of the starting materials. Mitsunobu coupling was also attempted between propargyl alcohol 360 and phenol 279, but only starting material was recovered.<sup>143</sup>
Sonogashira reaction using an O-propargyl aryl ether as the acetylenic partner was next examined. Initially, the sensitive aldehyde moiety in 318 was protected as its cyclic acetal 364 in excellent yield on treatment with 1,3-propanediol and catalytic para-toluenesulfonic acid under Dean-Stark conditions, followed by Sonogashira coupling with iodoquinoline 317 in 83% yield under previously optimised conditions (Scheme 89). Deprotection of the acetal was accomplished in quantitative yield on heating 365 in a 9:1 acetic acid/water solvent mixture. The aldehyde was then elaborated into the \( \alpha,\beta \)-unsaturated ketone 366 using a Wadsworth-Emmons reaction as described above.
Scheme 89. Reagents and conditions: a. HO(CH$_2$)$_3$OH, p-TsOH, toluene, reflux, Dean-Stark, 18 h; b. 317, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, 60 °C, 16 h; c. AcOH, H$_2$O, 50 °C, 2 h; d. (EtO)$_2$P(O)CHMeCOMe 319, NaH, DME, rt, 16 h.

The synthesis was shortened by the discovery that ketone 366 could be prepared by direct cross-coupling of acetylene 349 with iodoquinoline 317, negating the need for aldehyde protection and deprotection (Scheme 90). The 1-aza-1,3-butadiene unit was installed using conditions developed for the model systems, again in excellent yield. IMDA cycloaddition was induced on heating 316 under reflux in xylene for 16 hours, giving the desired penta-substituted pyridine 367 in 68% yield. Thus, synthesis of the complete carbon skeleton of streptonigrin 215 was achieved in just 9 steps (6 steps longest linear sequence).
Oxidation of the benzylic ether and the pyridine methyl group to the corresponding lactone and carboxylic acid were next investigated (Scheme 91). Oxidation of simple benzopyrans and 2-methylpyridines have been reported using a variety of oxidants, most commonly chromium based reagents such as pyridinium chlorochromate\(^\text{146-148}\) (PCC) and pyridinium dichromate\(^\text{149}\) (PDC), or selenium reagents including selenium dioxide\(^\text{130, 140, 150-152}\) and selenious acid.\(^\text{153}\) Unfortunately, treatment of pyridine 367 with a large range of oxidants, including chromium reagents\(^\text{146-149, 154-158}\) (Table 39, entries 1-6), selenium reagents\(^\text{130, 140, 150-153}\) (Table 39, entries 7-9), cerium ammonium nitrate\(^\text{159}\) and cerium triflate\(^\text{160}\) (Table 39, entries 10-11), potassium permanganate\(^\text{161}\) (Table 39, entry 12) and manganese dioxide\(^\text{162, 163}\) (Table 39, entry 13). In most cases,
unreacted starting material was recovered, except when using PDC as the oxidant at high temperature under microwave heating, which lead to decomposition (Table 39, entry 3). Attempted oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) also led to decomposition of the starting material, presumably through the electron-rich D-ring (Table 39, entry 14). Treatment of 367 with isoamyl nitrite and hydrochloric acid under reflux in ethanol led to formation of the pyridine hydrochloride salt (Table 39, entry 15), which was converted back into the free base on washing with saturated sodium bicarbonate solution. Oxidation of benzylic ethers has also been reported using ruthenium tetroxide formed in situ from ruthenium chloride and sodium periodate. Once again, only starting material was recovered under these conditions (Table 39, entry 16). Functionalisation of the activated methylene and methyl groups through radical bromination and lithiation strategies also proved unsuccessful.

Scheme 91. Reagents and conditions: see table.
Table 39. Attempted oxidation of pyridine 367.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCC</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>16</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>PDC</td>
<td>DMF</td>
<td>30-70 °C</td>
<td>48</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>PDC</td>
<td>DMF</td>
<td>120-180 °C</td>
<td>6</td>
<td>decomp.</td>
</tr>
<tr>
<td></td>
<td>(MW)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Jones</td>
<td>acetone</td>
<td>rt</td>
<td>2</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>CrO₃</td>
<td>Ac₂O</td>
<td>0 °C</td>
<td>6</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>CrO₂Cl₂</td>
<td>CCl₄</td>
<td>reflux</td>
<td>18</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>SeO₂</td>
<td>xylene</td>
<td>reflux</td>
<td>16</td>
<td>SM</td>
</tr>
<tr>
<td>8</td>
<td>SeO₂</td>
<td>AcOH</td>
<td>reflux</td>
<td>16</td>
<td>SM</td>
</tr>
<tr>
<td>9</td>
<td>H₂SeO₃</td>
<td>Dioxane</td>
<td>reflux</td>
<td>20</td>
<td>SM</td>
</tr>
<tr>
<td>10</td>
<td>CAN</td>
<td>AcOH</td>
<td>100 °C</td>
<td>27</td>
<td>SM</td>
</tr>
<tr>
<td>11</td>
<td>Ce(OTf)₄</td>
<td>MeCN</td>
<td>rt</td>
<td>2</td>
<td>SM</td>
</tr>
<tr>
<td>12</td>
<td>KMnO₄</td>
<td>acetone</td>
<td>reflux</td>
<td>3</td>
<td>SM</td>
</tr>
<tr>
<td>13</td>
<td>MnO₂</td>
<td>dioxane</td>
<td>120-150 °C</td>
<td>6</td>
<td>SM</td>
</tr>
<tr>
<td></td>
<td>(MW)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>DDQ</td>
<td>toluene</td>
<td>reflux</td>
<td>20</td>
<td>decomp.</td>
</tr>
<tr>
<td>15</td>
<td>ISOamyl nitrite</td>
<td>EtOH, HCl</td>
<td>reflux</td>
<td>3</td>
<td>367-HCl salt</td>
</tr>
<tr>
<td>16</td>
<td>RuCl₃,H₂O</td>
<td>MeCN</td>
<td>rt</td>
<td>1</td>
<td>SM</td>
</tr>
<tr>
<td></td>
<td>NaIO₄</td>
<td>CCl₄, H₂O</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difficulties in oxidising the pyridine C-2 methyl group have been encountered by both Cheng and DeShong in their syntheses of the CD-rings of streptonigrin 215. Deshong found that oxidation at this position could not be realised whilst the D-ring was in place due to competing degradation,¹³¹ whilst Cheng and coworkers reported that a
strong electron-withdrawing group \textit{para} to the methyl group was required for oxidation to take place.\textsuperscript{130}

\section*{3.9 Synthesis of IMDA Substrates Bearing an Ester at C-2 of the 1-Azadiene}

Direct incorporation of an ester moiety into the 1-azadiene unit prior to cycloaddition was therefore attempted. Initial attempts centred on a Wittig reaction between an appropriately substituted benzylic phosphonium salt and an \(\alpha\)-oximino-\(\beta\)-ketoacetate.

Model Wittig reactions were carried out between the phosphorane derived from benzyltriphenylphosphonium bromide 369 and methyl methoximinoacetoacetate 235 (\textbf{Scheme 92}). The best yield previously reported for this reaction was 31\% using \(n\)-butyllithium as base in THF (\textbf{Table 40}, entry 1).\textsuperscript{167} However, simple modification of the base and solvent allowed the desired alkene 370 to be isolated in 81-85\% yield (\textbf{Table 40}, entries 2-3). The Wittig reaction between 369 and the TBDMS protected oxime 371 also proceeded smoothly with no loss of the silyl protecting group (\textbf{Table 40}, entries 4-5). In both cases potassium \textit{tert}-butoxide was shown to be the superior base, giving the desired alkenes in excellent yield.

\begin{center}
\textbf{Scheme 92.} Reagents and conditions: a. see table.
\end{center}
Table 40. Model Wittig reactions between benzytriophenylphosphonium bromide 369 and oximinoacetoacetates 235 and 370.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime</th>
<th>R</th>
<th>Method</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>235</td>
<td>OMe</td>
<td>n-BuLi, THF -78 °C to rt</td>
<td>371</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>235</td>
<td>OMe</td>
<td>NaH, DME 0 °C to rt</td>
<td>371</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>235</td>
<td>OMe</td>
<td>KOtBu, DME 0 °C to rt</td>
<td>371</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>370</td>
<td>OTBDMS</td>
<td>NaH, DME 0 °C to rt</td>
<td>372</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>370</td>
<td>OTBDMS</td>
<td>KOtBu, DME 0 °C to rt</td>
<td>372</td>
<td>81</td>
</tr>
</tbody>
</table>

Next, the fully substituted D-ring phosphonium salt 375 was prepared from aldehyde 318 in 3 steps (Scheme 93). Reduction of the aldehyde proceeded in quantitative yield on treatment with sodium borohydride in methanol to give the alcohol 373, which was converted into the chloride 374 in good yield using thionyl chloride and pyridine in ethanol. Formation of the phosphonium salt 375 was achieved on heating 374 with triphenylphosphine in toluene for 18 hours. Wittig reaction between 375 and oximinoacetates 235 and 370 was then attempted using the optimised conditions above. Unfortunately, a mixture of products containing only traces of the desired compound was observed by $^1$H NMR spectroscopic analysis of the crude reaction mixtures. One possible reason for this could be the presence of the acidic terminal acetylene moiety in 375.
Thus, formation of the phosphonium salt and subsequent Wittig reaction after Sonagashira coupling of the AB- and D-rings was next investigated. Direct reduction of the aldehyde function in 363 led to concomitant reduction of the aromatic nitro group to the corresponding amine. Thus, benzylic alcohol 373 was protected as the TBDMS ether 378 in excellent yield (Scheme 94).\(^{169}\) Once again, cross-coupling of 2-iodo-6-methoxy-5-nitroquinoline 317 with the terminal alkyne was carried out in good yield to afford 379. Deprotection of the silyl group was achieved on stirring with Dowex-50W\(^{TM}\) acidic resin in methanol.\(^{170}\) Conversion of the resulting alcohol into the chloride 380 was then accomplished using thionyl chloride and pyridine in ethanol.\(^{168}\) Attempted formation of the Wittig salt on heating 380 with triphenylphosphine led only to decomposition of the starting material, possibly due to the presence of the aromatic nitro group.
Scheme 94. Reagents and conditions: a. TBDMSI, imidazole, CH$_2$Cl$_2$, rt, 3 h; b. PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, 60 °C, 16 h; c. Dowex-50W$^{\text{TM}}$, MeOH, rt, 5 h; d. SOCl$_2$, pyridine, CH$_2$Cl$_2$, rt, 3 h.

Attention was next turned to installation of the ester group into the 1-aza-diene via a Wadsworth-Emmons reaction. The required β-oximinophosphonates 385 and 386 were prepared from methyl bromopyruvate 381 and α-bromo-2-ketobutyric acid methyl ester$^{171}$ 382 respectively in two steps on treatment with methoxylamine hydrochloride followed by Arbuzov reaction with trimethyl phosphite (Scheme 95).$^{172}$

Wadsworth-Emmons reaction using potassium tert-butoxide as base failed to afford any of the desired products, most likely due to the decreased acidity of the α-proton in 385-386 compared to the β-ketophosphonates used previously. Switching to n-butyllithium as a stronger base allowed formation of α,β-unsaturated oxime 387, although no reaction was still observed with more hindered phosphonate 386. The deactivating effect of the ester moiety on 1-azadiene 387 proved to be too great, as
intramolecular cycloaddition was not observed at temperatures up to 180 °C. This route was therefore abandoned.

Scheme 95. Reagents and conditions: a. MeO-NH₂·HCl, MeOH, 16 h; b. P(OEt)₃, reflux, 48 h; c. 318, n-BuLi, THF, -78 °C to rt, 16 h; d. xylene, 180 °C, sealed tube, 16 h.

Table 41. Synthesis of IMDA substrates bearing an ester at C-2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Oxime</th>
<th>Yield/%</th>
<th>Phosphonate</th>
<th>Yield/%</th>
<th>IMDA Substrate</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>383</td>
<td>90</td>
<td>385</td>
<td>59</td>
<td>387</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>384</td>
<td>87</td>
<td>386</td>
<td>23</td>
<td>388</td>
<td>-</td>
</tr>
</tbody>
</table>
3.10 Introduction of Oxygen Functionality into the Diene

In order to promote the oxidation of the pyridine C-2 methyl group without compromising 1-azadiene reactivity, oxygen functionality was introduced at an earlier stage in the synthesis (Scheme 96, Table 42). Thus, β-ketophosphonates 396-399 were prepared by acylation of the carbanion of diethyl ethylphosphonate133 391 with protected methyl glycolates 392-395, themselves obtained from methoxyacetic acid or glycolic acid.173-177 First, TBDMS protected phosphonate 396 was examined in the Wadsworth-Emmons reaction with 318. Unfortunately, loss of the protecting group was observed under the reaction conditions. Phosphonates 397-399 bearing the more hydrolytically stable allyl, methyl and PMB protecting groups however delivered the desired α,β-unsaturated ketones 401-403 in good yield. Elaboration of the terminal acetylenes via a Sonogashira reaction proceeded without incident to give 405-407, followed by formation of the corresponding oximes 409-411. Attempted IMDA cycloaddition of allyl protected substrate 405 led to formation of a complex mixture of products on heating in xylene at 180 °C for 16 hours. However, the required penta-substituted pyridines 414 and 415 were obtained from 410 and 411, albeit in modest yield, under the same conditions.
Scheme 96. Reagents and conditions: a. 391, n-BuLi, THF, -78 °C, 1 h then 392-395, THF, -78 °C to rt, 16 h; b. 318, KO'Bu, toluene, rt, 16 h; c. 317, PdCl₂(PPh₃)₂, CuI, Et₃N, 60 °C, 16 h; d. MeONH₂·HCl, NaOAc·3H₂O, EtOH, H₂O, 60 °C, 16 h; e. xylene, 180 °C, sealed tube, 16 h.
Table 42. Synthesis of functionalised pyridines 412-415.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ketone</th>
<th>Yield/%</th>
<th>Ketone</th>
<th>Yield/%</th>
<th>Pyridine</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTBDMS</td>
<td>400</td>
<td>-</td>
<td>404</td>
<td>-</td>
<td>412</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>OAllyl</td>
<td>401</td>
<td>38</td>
<td>405</td>
<td>82</td>
<td>413</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>402</td>
<td>64</td>
<td>406</td>
<td>74</td>
<td>414</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>OPMB</td>
<td>403</td>
<td>75</td>
<td>407</td>
<td>94</td>
<td>415</td>
<td>38</td>
</tr>
</tbody>
</table>

Removal of the protecting groups was then investigated. Demethylation from methoxymethylpyridine 414 was attempted under a range of conditions, including boron trichloride,\(^{131}\) boron tribromide and *in situ* generated trimethyliodosilane. Unfortunately, unreacted starting material was recovered in each case. However, removal of the PMB group from 415 was readily effected on treatment with trifluoroacetic acid in the presence of anisole in excellent yield (Scheme 97).\(^{178}\)

Although oxidation of the hydroxymethyl group to the aldehyde 417 was accomplished using various reagents including activated manganese dioxide in chloroform,\(^{179}\) as evidenced by NMR spectroscopic analysis of the crude reaction mixture, further oxidation to the desired carboxylic acid 418 could not be achieved under a range of conditions, such as sodium chlorite\(^{180}\) and silver nitrate. Direct conversion of 416 to the carboxylic acid was also unsuccessful.
Scheme 97. Reagents and conditions: a. TFA, anisole, CH₂Cl₂, rt, 2 h; b. MnO₂, CHCl₃, rt, 2 h.

3.11 Synthesis and IMDA Reactions of Model Propiolate Esters

Cheng and coworkers have previously observed that oxidation of a pyridine C-2 methyl group could not be achieved in their synthesis of the CD-rings of streptonigrin 215 unless a strong electron-withdrawing group was present in the para-position.¹³⁰ Synthesis and intramolecular hetero-Diels-Alder reaction of substrates containing a propiolate ester linker was therefore examined. The ester moiety would have the twin function of introducing the required lactone carbonyl group prior to cycloaddition,
obviating the need for later oxidation, as well as promoting oxidation of the para methyl group.

In order to determine whether this was a viable strategy, a suitable model system was constructed. The hydroxyl function in 3-methylsalicaldehyde 321 was first protected as its allyl ether 419, followed by Wadsworth-Emmons reaction and oxime formation to introduce the 1-azadiene unit 420 (Scheme 98). The allyl group was removed on treatment with catalytic palladium(II) acetate, triphenylphosphine and morpholine to reveal phenol 421. The propiolate ester 422 was then obtained in almost quantitative yield via coupling of 421 with phenylpropiolic acid chloride, formed in situ from the free acid using thionyl chloride in dichloromethane. Pleasingly, intramolecular cycloaddition proceeded without incident on heating at 180 °C in xylene for 24 hours in a sealed tube to provide the penta-substituted pyridine 423 in 48% yield.
Scheme 98. Reagents and conditions: a. H₂C=CCCH₂Br, K₂CO₃, EtOH, reflux, 16 h; b. (MeO)₃P(O)CH₂COMe, KO'Bu, DME, rt, 16 h; c. MeONH₂·HCl, NaOAc·3H₂O, EtOH, H₂O, 60 °C, 16 h; d. Pd(OAc)₂, PPh₃, morpholine, THF, rt, 16 h; e. PhC≡CCO₂H, SOCl₂, CH₂Cl₂, 40 °C, 16 h then 421, K₂CO₃, DMF, rt, 16 h; f. xylene, 180 °C, sealed tube, 24 h.

Next, the key methyl group oxidation was attempted. In the event, oxidation of 423 to carboxylic acid 424 was achieved in a single step and in quantitative yield on treatment with selenium dioxide under reflux in pyridine (Scheme 99).¹⁴⁰ Subsequent steps to prove that the lactone could be opened to a diacid related to that necessary for the formal synthesis of streptonigrin 215 were then examined. Lactone 424 proved resistant to hydrolysis under mild conditions such as lithium hydroxide in aqueous THF at room temperature. More forcing conditions therefore need to be examined to effect the required transformation, although this has yet to be achieved.¹⁸²
Having proved that oxidation of the pyridine C-2 methyl group was possible when activated by a suitable electron-withdrawing group, the same sequence of reactions was used to prepare a substrate bearing the correct D-ring substitution and the extra methyl group present on the pyridine ring. This was to ascertain whether competing oxidation of the pyridine C-3 methyl group or oxidative degradation of the electron-rich D-ring would interfere with the desired transformation.

Thus, starting from 3,4-dimethoxy salicaldehyde 279, protection of the phenol, Wadsworth-Emmons reaction, formation of the oxime and removal of the allyl group delivered phenol 427 in 63% yield over 4 steps (Scheme 100). Formation of phenylpropiolate ester 428 was carried out using identical conditions to those used above. Intramolecular hetero-Diels-Alder reaction generated the pyridine 429 in 46% yield. Unfortunately, attempted methyl group oxidation using selenium dioxide in pyridine led to decomposition of the starting material, presumably due to the electron-rich D-ring. One possible solution to this problem would be formation of the corresponding N-oxide and treatment with acetic anhydride to provide the 2-acetoxy methylpyridine which could be further oxidised to the carboxylic acid, although this has yet to be achieved.
Scheme 100. Reagents and conditions: a. H$_2$C=CH$_2$Br, K$_2$CO$_3$, EtOH, reflux, 16 h; b. \((\text{MeO})_2\text{P}(\text{O})\text{CHMeCOMe}, \text{KO'Bu}, \text{DME}, \text{rt, 16 h}; c. \text{MeONH}_2\cdot\text{HCl}, \text{NaOAc} \cdot 3\text{H}_2\text{O}, \text{EtOH, H}_2\text{O, 60 °C, 16 h}; d. \text{Pd(OAc)}_2, \text{PPh}_3, \text{morpholine, THF, rt, 16 h}; e. \text{PhC}=\text{CCO}_2\text{H}, \text{SOCl}_2, \text{CH}_2\text{Cl}_2, 40 ^\circ\text{C, 16 h then 427, K}_2\text{CO}_3, \text{DMF, rt, 16 h}; f. \text{xylene, 180 °C, sealed tube, 24 h.}

3.12 Propiolate Ester Synthesis

In order to prepare a propiolate ester bearing the quinoline AB-ring necessary for streptonigrin 215, the appropriately substituted propiolic acid 431 was required. Only a handful of examples of Sonogashira reactions using propiolate esters as the acetylenic partner have been reported.\textsuperscript{183-191} However, cross-coupling of iodoquinoline 317 with methyl propiolate 228 proceeded without incident to provide 430 in 59% yield (Scheme 101). Reoptimisation of the reaction conditions led to an improved yield of 92% using DIPEA as the base. Hydrolysis of the ester was achieved in
quantitative yield under basic conditions using lithium hydroxide in aqueous THF.\textsuperscript{189, 192}

Attention was next turned to formation of the required propiolate ester 432. Initial attempts involved formation of the acid chloride in analogous fashion to the model systems prepared above. Unfortunately, treatment of 431 with an excess of thionyl chloride in dichloromethane followed by phenol 421 and potassium carbonate in DMF led to recovery of the starting phenol (Table 43, entry 1).\textsuperscript{181} More forcing conditions, including heating 431 in neat oxalyl chloride or thionyl chloride followed by addition of phenol 421 and base once again led to recovery of the starting material (Table 43, entries 2-3). Formation of the acid chloride via the carboxylate salt initially proved unsuccessful, most likely due to insolubility of the free acid in the reaction solvents (Table 43, entries 4-5).\textsuperscript{193} The carboxylate salt was eventually obtained directly from the more soluble methyl ester on treatment with potassium trimethylsilanolate in THF. Analysis of the product by infrared (IR) spectroscopy showed a large shift for the carbonyl peak from 1730 cm\textsuperscript{-1} to 1600 cm\textsuperscript{-1}, which is indicative for the formation of the carboxylate salt. Conversion to the acid chloride was achieved on stirring with oxalyl chloride in dichloromethane, again evidenced by shift of the carbonyl peak in the IR spectrum (1600 cm\textsuperscript{-1} to 1750 cm\textsuperscript{-1}). Unfortunately, only a trace of the desired product was observed after reaction with phenol 427 under basic conditions (Table 43, entry 6). Esterification via the mixed anhydride (Table 43, entry 7) and acyl imidazolium salt (Table 43, entry 8), or under Corey-Nicolaou\textsuperscript{194} and Mukaiyama macrolactonisation conditions (Table 43, entries 9-10) all failed to give any of the desired product.
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Scheme 101. **Reagents and conditions:** a. PdCl2(PPh3)2, CuI, DIPEA, THF, 50 °C, 3 h; b. LiOH·H2O, THF, H2O, rt, 3 h.
Table 43. Attempted formation of propiolate esters 432-433.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Conditions</th>
<th>Product</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1. SOCl₂, CH₂Cl₂, 40 °C</td>
<td>432</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. 421, K₂CO₃, DMF</td>
<td></td>
<td>421</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1. (COCl)₂, reflux, x h</td>
<td>432</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. 421, K₂CO₃, DMF</td>
<td></td>
<td>421</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1. SOCl₂, reflux, x h</td>
<td>432</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. 421, K₂CO₃, DMF</td>
<td></td>
<td>421</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1. NaOMe, MeOH</td>
<td>432</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. (COCl)₂, PhH</td>
<td></td>
<td>421</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. 421, K₂CO₃, DMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1. NaH, THF</td>
<td>432</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. (COCl)₂, PhH</td>
<td></td>
<td>421</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. 421, K₂CO₃, DMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1. KOTMS, THF</td>
<td>432</td>
<td>trace 432</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. (COCl)₂, CH₂Cl₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. 421, K₂CO₃, DMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>1. 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 110 °C</td>
<td>433</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. 427, DMAP, THF</td>
<td></td>
<td>427</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>1. CDI, CH₂Cl₂, reflux</td>
<td>433</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. 427, DMAP (cat.)</td>
<td></td>
<td>427</td>
</tr>
<tr>
<td>9</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>427, Py2S2, PPh₃</td>
<td>433</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>xylene, reflux</td>
<td></td>
<td>427</td>
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<tr>
<td>10</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>427, 1-methyl-2-</td>
<td>433</td>
<td>recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>chloropyridinium iodide, Et₃N,</td>
<td></td>
<td>427</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CH₂Cl₂, reflux</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In an attempt to verify 431 as the correct structure, several attempts to grow crystals were made using both vapour- and solvent-diffusion techniques and in a wide variety of solvents. Unfortunately, crystallisation provided only thin needles that were unsuitable for X-ray analysis. In order to determine whether the failure of 431 to undergo esterification was due to some property inherent in that particular system, two
derivatives were synthesised. Thus, reduction of the nitro group in 317 was achieved in 94% yield on heating in ethanol in the presence of iron powder and acetic acid (Scheme 102). Oxidation with Fremy’s salt delivered quinone 435. Aniline 434 was also protected as its benzyl carbamate 436.

Scheme 102. Reagents and conditions: a. Fe (powder), AcOH, EtOH, reflux, 4 h; b. Fremy’s salt, NaH2PO4 (0.3 M in H2O), acetone, rt, 12 h; c. benzyl chloroformate, DIPEA, THF, rt, 16 h.

Sonogashira cross-coupling of 435 or 436 with methyl propiolate 228 was then examined. Although quinone 435 failed to give any of the desired coupled product under the standard conditions, 437 was obtained from iodoquinoline 436 in good yield (Scheme 103). Hydrolysis of the ester was carried out as before to afford propiolic acid 438. As was observed for nitroquinoline 431, several attempts to form the desired ester 439 using a variety of conditions, including via the acid chloride, mixed anhydride and DCC activated ester, resulted in recovery of the starting phenol 427.
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Scheme 103. Reagents and conditions: a. PdCl$_2$(PPh$_3$)$_2$, Cul, DIPEA, 50 °C, 3 h; b. LiOH·H$_2$O, THF, H$_2$O, rt, 1 h.

Direct Sonogashira coupling of activated propiolate esters$^{196}$ 440-442 with iodoquinoline 317 was also attempted. However recovery of the iodide and degradation of the acetylene was observed in each case (Scheme 104).

Scheme 104. Reagents and conditions: a. PdCl$_2$(PPh$_3$)$_2$, Cul, Et$_3$N, 60 °C, 16 h.
Sonogashira coupling of D-ring phenyl propiolate ester 448 was next investigated. First, formation of the activated ester of propiolic acid 446 was achieved using dicyclohexylcarbodiimide (DCC) and catalytic 4-dimethylaminopyridine (DMAP), followed by coupling with salicaldehyde 279 in good yield to give 447 (Scheme 105). Protection of the aldehyde as the 6-membered cyclic acetal under Dean-Stark conditions provided acetylene 448, which underwent smooth palladium-catalysed cross-coupling with iodoquinoline 317 to afford 449. Acidic hydrolysis delivered aldehyde 450 ready for elaboration into the α,β-unsaturated ketone via a Wadsworth-Emmons reaction. Unfortunately, cleavage of the labile phenolate ester moiety was observed on treatment with the carbanion derived from β-ketophosphonate 319, leading to recovery of salicaldehyde 279.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activated Ester</th>
<th>R</th>
<th>Product</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>440</td>
<td>Bt</td>
<td>443</td>
<td>recovered 317</td>
</tr>
<tr>
<td>2</td>
<td>441</td>
<td>OPFP</td>
<td>444</td>
<td>recovered 317</td>
</tr>
<tr>
<td>3</td>
<td>442</td>
<td>OC₆H₅(p-NO₂)</td>
<td>445</td>
<td>recovered 317</td>
</tr>
</tbody>
</table>
New Developments in the 1-Aza-Diels-Alder Reaction

Due to the difficulties previously encountered in trying to prepare IMDA substrates 432–433, an esterification/Sonogashira strategy was next envisaged. First, coupling of propiolic acid 446 with phenol 427 was attempted via the activated ester (Scheme 106). Treatment of 446 and 427 with DCC in the presence of catalytic DMAP led to a complex mixture of products, due to the formation of Michael adducts competing with the desired transformation (Table 45, entry 1). Similar results were obtained using acyl benzotriazole196 440, pentafluorophenyl (PFP) ester 441 and para-nitrophenyl ester 442 (Table 45, entries 2–4). Propiolic acid chloride 451 has previously been synthesised by treating propiolic acid 446 with phosphorus pentachloride, though isolation must be carried out at low temperature (-135 °C) and under an inert atmosphere as 451 has been reported to spontaneously ignite in air, possibly due to
traces of monochloroacetylenes formed under the reaction conditions. Schirok and coworkers however have reported the *in situ* generation of propiolic acid chloride \( 451 \) under mild conditions using Ghosez’s reagent. Esterification using this method was attempted, but once again a complex mixture of inseparable products was obtained (Table 45, entry 5).

![Scheme 106. Reagents and conditions: a. See table.](image)

**Table 45.** Attempted coupling of phenol 427 with activated esters 440-442, 446 and 451.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activated Ester</th>
<th>R</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>446</td>
<td>OH</td>
<td>DCC, DMAP (cat.) CH(_2)Cl(_2)</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>440</td>
<td>Bt</td>
<td>DMAP, THF       (65^\circ\text{C} \text{ (MW)})</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>441</td>
<td>OPFP</td>
<td>DMAP, THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>442</td>
<td>(\text{OC}_6\text{H}_5(p-\text{NO}_2))</td>
<td>DMAP, THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>451</td>
<td>Cl</td>
<td>Ghosez’s reagent (\text{CH}_2\text{Cl}_2)</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

A blocking substituent in the form of a TMS group at the alkyne terminus allowed formation of the required esters 454-455 in 85-92% yield via the known
trimethylsilylpropionic acid chloride (Scheme 107, Table 46). Attempted removal of the silicon group from 454 under basic conditions using potassium carbonate in methanol led to cleavage of the labile ester group and recovery of phenol 421. Degradation of the starting material was also observed on treatment with tetrabutylammonium fluoride (TBAF). Unreacted started material however was recovered using hydrogen fluoride triethylamine complex as the fluoride source. Desilylation was also attempted under acidic conditions, but starting material was once again recovered in each case.

\[
\begin{align*}
\text{Scheme 107. Reagents and conditions: a. } & 453, (\text{COCl})_2, \text{ DMF, rt, 30 min then } 421 \text{ or } 427, \\
& \text{DMAP, THF, rt, 18 h.}
\end{align*}
\]

Table 46. Synthesis of trimethylsilylpropionate esters 454-455.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>421</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>454</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>427</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>455</td>
<td>82</td>
</tr>
</tbody>
</table>

Finally, IMDA reaction of trimethylsilylpropionate ester 455 was attempted to ascertain whether the 2-trimethylsilylpyridine could be prepared for further functionalisation. In the event, heating 455 under reflux in xylene or in a sealed tube at
180 °C for 16 hours led to recovery of the starting material (Scheme 108). Switching to the higher boiling solvent o-dichlorobenzene and increasing the temperature to 220 °C was necessary to induce intramolecular cycloaddition. Loss of the trimethylsilyl group was observed during this process to afford pyridine 456 in 38% yield. Oxidation of the C-2 methyl group, opening of the lactone and functionalisation of the C-6 position with a halogen or metal atom would deliver the fully functionalised CD-rings of streptonigrin 215 suitable for cross-coupling with AB-ring fragment 317, although this has yet to be realised.

Scheme 108. Reagents and conditions: a. o-dichlorobenzene, 220 °C, sealed tube, 16 h.
3.13 Conclusions and Future Work

In conclusion, the intramolecular 1-aza-Diels-Alder reaction has been presented as a versatile method for the synthesis of a variety of \([c]\)-annelated pyridines. First, a series of model IMDA substrates were rapidly prepared from commercially available salicaldehydes, and then subsequently shown to undergo thermally induced cycloaddition in moderate to good yield.

This methodology was subsequently utilised in the synthesis of the penta-substituted pyridine core of the naturally occurring antibiotic streptonigrin. However, difficulties were encountered on attempted oxidation of the pyridine C-2 methyl group to the carboxylic acid present in the natural product. Activation of this methyl group by virtue of introducing an electron-withdrawing substituent in the \(para\)-position allowed this oxidation to be carried out in nearly quantitative yield in a related model system. Unfortunately, synthesis of the propiolate ester required for the synthesis of streptonigrin could not be achieved. However, the appropriately substituted trimethylsilylpropiolate ester was prepared in good yield, and subsequent intramolecular cycloaddition delivered a tetra-substituted pyridine which may be suitable for further elaboration into the natural product.
Chapter 4

Experimental
4.1 General Information

Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000-600 cm⁻¹ using a Nicolet Magna 550 or Bruker Tensor 27 spectrometer. ¹H and ¹³C NMR spectra were recorded using a Bruker DRX500, AV400 or AM300 spectrometer operating at 500 MHz, 400 MHz and 300 MHz respectively (¹H frequency, corresponding ¹³C frequencies are 125 MHz, 100 MHz and 75 MHz). In the ¹³C NMR spectra, signals corresponding to CH, CH₂, or Me groups are assigned from DEPT. High and low-resolution mass spectra were recorded on a Thermoquest AS 2000 spectrometer (EI) or Bruker microTOF spectrometer (ESI). Microwave reactions were carried out in a CEM Discover™ mono-mode focused microwave reactor using an IR temperature probe.
4.2 General Procedures

General Procedure 1 - silylation of α-ketoximes

To a stirred solution of the α-ketoxime (5.0 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise diisopropylethylamine (1.68 g, 13.0 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (3.30 g, 12.5 mmol). Stirring was continued at 0 °C for 2-4 h, and the solvent evaporated. The residue was diluted with n-pentane (25 mL), stirred at 0 °C for 1 h, then filtered and evaporated to afford the title compound, which was used without further purification.

General Procedure 2 - preparation of α-ketohydrazones

To a stirred solution of 2,3-butanedione (0.861 g, 10.0 mmol) in ethanol (10 mL) at 0 °C was added the hydrazine (11.0 mmol) dropwise. Stirring was continued at 0 °C until the reaction was judged to be complete by TLC. The solution was then dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound.

General Procedure 3 - silylation of α-ketohydrazones

To a stirred solution of the α-ketohydrazone (10.0 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise diisopropylethylamine (1.68 g, 13.0 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (3.30 g, 12.5 mmol). Stirring was continued at 0 °C for 2 h, and the solvent evaporated. The residue was diluted with n-pentane (25 mL), stirred at 0 °C for 1 h, then filtered and evaporated to afford the title compound, which was used without further purification.
General procedure 4 - intermolecular hetero-Diels-Alder reactions under microwave irradiation

A solution of the 1-aza-1,3-butadiene (1.0 mmol) and the dienophile (1.0-2.0 mmol) in toluene (2 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 150 °C for the time indicated. The resulting mixture was concentrated in vacuo, and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound.

General procedure 5 - intermolecular hetero-Diels-Alder reactions under microwave irradiation

A solution of the 1-aza-1,3-butadiene (1.0 mmol) and the dienophile (1.0-2.0 mmol, 1.0-2.0 equiv) in toluene (2 mL) and THF (0.25 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 180 °C for the time indicated. The resulting mixture was concentrated in vacuo, and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound.

General procedure 6 - alkylation of salicaldehydes

To a solution of the salicaldehyde (10.0 mmol) in ethanol (60 mL) was added potassium carbonate (2.07 g, 15.0 mmol, 1.5 equiv) and propargyl chloride (3.62 mL, 50.0 mmol, 5.0 equiv). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and the solvent removed in vacuo. The residue was partitioned between sodium hydroxide solution (2 M; 150 mL) and ether (3 × 150 mL). The combined organic extracts were washed with water (150 mL), dried over MgSO₄ and
concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound.

**General Procedure 7 - Wadsworth-Emmons reactions**
To a solution of sodium hydride (0.360 g, 9.00 mmol, 1.5 equiv) or potassium tert-butoxide (1.01 g, 9.00 mmol, 1.5 equiv) in 1,2-dimethoxyethane (10 mL) was added the phosphonate (9.00 mmol, 1.5 equiv) in 1,2-dimethoxyethane (5 mL) dropwise over 30 min. The reaction mixture was stirred for 30 min, followed by dropwise addition of the aldehyde (6.00 mmol) in 1,2-dimethoxyethane (5 mL) over 30 min. The resulting mixture was stirred at room temperature for 16 h and partitioned between saturated ammonium chloride (75 mL) and ethyl acetate (3 x 75 mL). The combined organic extracts were washed with water (75 mL) and saturated brine (75 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9), to afford the title compound.

**General Procedure 8 - Sonagashira reactions**
To a solution of the aryl iodide (3.33 mmol), bis(triphenylphosphine)palladium (II) chloride (0.164 g, 0.233 mmol, 7 mol%) and copper (I) iodide (0.190 g, 1.00 mmol, 0.3 equiv) in THF (35 mL) was added triethylamine (0.70 mL, 5.00 mmol, 1.5 equiv), followed by the alkyne (5.00 mmol, 1.5 equiv) in THF (15 mL). The reaction mixture was heated at 60 °C for 18 h, then partitioned between saturated ammonium chloride (75 mL) and ethyl acetate (3 x 75 mL). The combined organics were washed with saturated ammonium chloride (2 x 75 mL) and saturated brine (75 mL), dried over
MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:3) to afford the title compound.

**General Procedure 9 - preparation of O-methyl oximes**

A solution of the ketone (4.00 mmol), methoxylamine hydrochloride (0.418 g, 5.00 mmol, 1.25 equiv) and sodium acetate trihydrate (0.455 g, 4.20 mmol, 1.05 equiv) in ethanol (28 mL) and water (3.5 mL) was heated to 60 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The resulting residue was partitioned between water (65 mL) and ethyl acetate (3 × 65 mL). The combined organic extracts were washed with water (2 × 65 mL) and saturated brine (65 mL), dried over MgSO$_4$ and concentrated *in vacuo* to afford the title compound which was used without further purification.

**General Procedure 10 - functionalisation of terminal alkynes**

To a solution of the O-methyl oxime (4.00 mmol) in THF (10 mL) at -78 °C was added lithium hexamethyldisilazide (1 M in THF; 4.20 mL, 4.20 mmol, 1.05 equiv) dropwise over 20 min. The reaction mixture was stirred at -78 °C for 1 h, then the electrophile (6.00 mmol, 1.5 equiv) added dropwise over 15 min. The resulting mixture was then stirred for a further 1 h at -78 °C, allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by addition of saturated ammonium chloride (75 mL), and the aqueous phase extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with water (75 mL), dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound.
General Procedure 11 - intramolecular hetero-Diels-Alder reactions

A solution of the α,β-unsaturated oxime (0.50 mmol) in dry xylene (10 mL) was placed in a sealed tube and heated to the required temperature for the time indicated. The reaction mixture was then cooled to room temperature, concentrated in vacuo and the crude product purified by flash chromatography on silica gel to afford the title compound.

General Procedure 12 - one-pot oxime formation/intramolecular hetero-Diels-Alder reaction

A solution of the α,β-unsaturated oxime (0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol, 2.00 equiv) and triethylamine (0.139 mL, 1.00 mmol, 2.00 equiv) in xylene (10 mL) in a sealed tube was heated at 180 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound.

General Procedure 13 - acylation of diethyl ethylphosphonate

To a stirred solution of n-butyllithium (2.5 M in hexanes; 26.5 mL, 66.2 mmol, 1.10 equiv) in THF (50 mL) at -78 °C was added diethyl ethylphosphonate (10.0 g, 60.2 mmol) in THF (15 mL) dropwise over 30 min. Stirring was continued at -78 °C for 1 h. The electrophile (66.2 mmol, 1.10 equiv) in THF (15 mL) was added dropwise over 10 min. After a further 1 h at -78 °C, the reaction mixture was allowed to warm slowly to room temperature and stirred for 16 h. The reaction was quenched by the addition of citric acid (10%, 150 mL) and the aqueous phase was then extracted with dichloromethane (2 × 250 mL). The combined organics were washed with saturated
brine (100 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:1 to 4:1) to afford the title compound.

**Methyl oximinoacetoacetate**

To a stirred solution of methyl acetoacetate (11.60 g, 0.100 mol) in acetic acid (14.3 mL) at -5 °C was added sodium nitrite (7.72 g, 0.112 mol) in water (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Water (60 mL) was added and stirring continued for 2.5 h. The reaction mixture was then extracted with ether (3 × 40 mL) and the combined organics washed with water (20 mL), saturated sodium hydrogen carbonate solution (4 × 20 mL) and water (20 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless oil (13.20 g, 91%); νmax (CHCl₃)/cm⁻¹ 3363 (O-H), 3034 (O-H), 1748 (C=O), 1694 (C=O), 1627 (C=N); δH (300 MHz; CDCl₃) 9.55 (1 H, br s, OH), 3.90 (3 H, s, OMe), 2.42 (3 H, s, Me); δC (75 MHz; CDCl₃) 195.0 (C), 162.9 (C), 151.3 (C), 55.4 (OMe), 25.7 (Me).
2,3-Butanedione mono(O-methyl-oxime)\(^{200}\) \(\text{234}\)

To 2,3-butanedione monoxime (2.02 g, 20.0 mmol) was added 10% sodium hydroxide (8.8 mL, 22.0 mmol). Dimethyl sulfate (3.03 g, 24.0 mmol) was added dropwise, during which the temperature increased to ca. 40 °C. The reaction mixture was stirred for 30 min, then refluxed for 5 min. The reaction mixture was then separated and the aqueous phase extracted with ether (2 \(\times\) 20 mL). The combined organics were dried over MgSO\(_4\) and concentrated \textit{in vacuo} to afford the title compound as a colourless oil (1.79 g, 78%), which may be distilled to purity \textit{in vacuo} (0.807 g, 35%); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1694 (C=O), 1609 (C=N); \(\delta_H\) (300 MHz; CDCl\(_3\)) 4.06 (3 H, s, OMe), 2.37 (3 H, s, Me), 1.91 (3 H, s, Me); \(\delta_C\) (75 MHz; CDCl\(_3\)) 197.0 (C), 155.8 (C), 63.4 (OMe), 25.2 (Me), 8.8 (Me).

2-(Methoxyimino)-3-oxo-butanoic acid methyl ester\(^{201}\) \(\text{235}\)

To a stirred suspension of methyl oximinoacetoacetate (1.45 g, 10.0 mmol) and potassium carbonate (2.07 g, 15.0 mmol) in acetone (15 mL) at 10 °C was added dropwise dimethyl sulfate (1.26 g, 10.0 mmol). The reaction mixture was stirred at 4 °C for 24 h, poured into water (50 mL) and extracted with CH\(_2\)Cl\(_2\) (4 \(\times\) 50 mL). The combined organics were dried over MgSO\(_4\) and concentrated \textit{in vacuo} to afford the title compound as a colourless oil (1.41 g, 89%), which was used without further
purification; (Found: $M^+$, 159.0519. C$_6$H$_9$NOC requires 159.0532); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1748 (C=O), 1602 (C=N); $\delta_H$ (300 MHz; CDCl$_3$) 4.11 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.41 (3 H, s, Me); m/z (EI) 172 (9%), 158 (7), 149 (11), 144 (26), 116 (49), 113 (18), 86 (78), 59 (100).

3-(tert-Butyldimethylsilyloxy)-but-3-en-2-one O-methyl-oxime 236

Following general procedure 1, the title compound was obtained from 2,3-butanedione mono-(O-methyl oxime) 234 (0.576 g. 5.00 mmol), then purified by flash chromatography on silica gel to afford the title compound as a colourless oil (0.950 g, 83%), containing 1,3-di-tert-butyl-1,1,3,3-tetramethyl-disiloxane (0.130 g); (Molecular ion not found. C$_{11}$H$_{23}$NOC$_2$Si requires 229.1498); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1619 (C=C), 1254 (Si-Me), 1059 (Si-O); $\delta_H$ (300 MHz; CDCl$_3$) 4.78 (1 H, d, $J = 1.1$ Hz, C=CH), 4.50 (1 H, d, $J = 1.1$ Hz, C=CH), 3.92 (3 H, s, OMe), 1.92 (3 H, s, Me), 0.95 (9 H, s, CMe$_3$), 0.17 (6 H, s, SiMe$_2$); $\delta_C$ (75 MHz; CDCl$_3$) 153.7 (C), 153.4 (C), 96.7 (CH$_2$), 62.3 (OMe), 26.1 (Me), 18.7 (CMe$_3$), 11.5 (Me), -2.6 (SiMe$_2$). m/z (EI) 285 (23%), 266 (22), 190 (40), 172 (43), 147 (11), 127 (8), 121 (100), 115 (25), 113 (15), 89 (12), 84 (18), 72 (30), 69 (96), 58 (30).
3-(tert-Butyldimethylsilyloxy)-2-(methoxyimino)-but-3-enoic acid methyl ester

To a stirred solution of 2-(methoxyimino)-3-oxo-butanoic acid methyl ester 235 (1.20 g, 7.34 mmol) in dry CH$_2$Cl$_2$ (30 mL) at 0 °C was added dropwise diisopropylethylamine (1.27 g, 9.80 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (2.49 g, 9.43 mmol). Stirring was continued at 0 °C for 2.5 h, then further base (0.508 g, 4.90 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.25 g, 4.72 mmol) added. Stirring was continued for 3 h then further base (0.508 g, 4.90 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.25 g, 4.72 mmol) added. Stirring was continued for 1.5 h and the solvent evaporated. The residue was diluted with n-pentane (50 mL), stirred at 0 °C for 1.5 h, then filtered and evaporated. The crude material was purified by flash chromatography on silica gel, eluting with dichloromethane to afford the title compound as a colourless oil (1.11 g, 54%); (Found: MH$^+$, 274.1476. C$_{12}$H$_{23}$N$_2$O$_4$Si $+$ H requires 274.1474); $\nu_{max}$ (film)/cm$^{-1}$ 1748 (C=O), 1614 (C=C), 1259 (Si-Me), 1047 (Si-O); $\delta$H (300 MHz; CDCl$_3$) 4.67 (2 H, s, CH$_2$), 3.95 (3 H, s, OMe), 3.85 (3 H, s, OMe), 0.94 (9 H, s, CMe$_3$), 0.19 (6 H, s, SiMe$_2$); $\delta$C (75 MHz; CDCl$_3$) 163.8 (C), 149.8 (C), 148.9 (C), 100.0 (CH$_2$), 63.5 (OMe), 52.8 (OMe), 26.0 (Me), 18.6 (CMe$_3$), -3.2 (SiMe$_2$); $m/z$ (El) 232 (10%), 218 (100), 216 (54), 200 (28), 188 (12), 172 (13), 158 (23), 146 (40), 129 (15), 116 (18), 100 (22), 86 (53), 84 (60), 73 (91), 59 (96).
2-Methyl-1,3-bis(tert-butyldimethylsiloxy)-1-aza-1,3-butadiene 238

Following general procedure 1, the title compound was obtained from 2,3-butanedione monoxime (0.435 g, 5.0 mmol) as a colourless oil (1.44 g, 87%); (Found: MH+, 330.2281. C_{16}H_{33}NO_{2}Si_{2} + H requires 330.2284); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1615 (C=C), 1254 (Si-Me), 1030 (Si-O); \( \delta_{H} \) (300 MHz; CDCl\(_3\)) 4.78 (1 H, d, \( J = 1.1 \) Hz, C=CH), 4.48 (1 H, d, \( J = 1.1 \) Hz, C=CH), 1.96 (3 H, s, Me), 0.94 (9 H, s, CMe\(_3\)), 0.92 (9 H, s, CMe\(_3\)), 0.16 (6 H, s, SiMe\(_2\)), 0.14 (6 H, s, SiMe\(_2\)); \( \delta_{C} \) (75 MHz; CDCl\(_3\)) 158.2 (C), 154.1 (C), 96.6 (CH\(_2\)), 26.5 (Me), 26.1 (Me), 18.6 (CMe\(_3\)), 18.4 (CMe\(_3\)), 11.6 (Me), -4.1 (SiMe\(_2\)), -4.3 (SiMe\(_2\)); \( m/z \) (Cl) 358 (15%), 330 (MH+, 90), 314 (100), 272 (85), 231 (37), 216 (13), 200 (18), 189 (30), 156 (12), 115 (21).

2-Methoxycarbonyl-1,3-bis(tert-butyldimethylsiloxy)-1-aza-1,3-butadiene 239

Following general procedure 1, the title compound was obtained from 233 (0.716 g, 5.0 mmol) as a colourless oil (1.73 g, 93%); (Found: MH+, 374.2182. C_{17}H_{35}NO_{4}Si_{2} + H requires 374.2183); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1751 (C=O), 1614 (C=C), 1254 (Si-Me), 1102 (Si-O); \( \delta_{H} \) (300 MHz; CDCl\(_3\)) 4.68 (1 H, d, \( J = 2.1 \) Hz, C=CH), 4.64 (1 H, d, \( J = 2.1 \) Hz, C=CH), 3.83 (3 H, s, OMe), 0.94 (9 H, s, CMe\(_3\)), 0.89 (9 H, s, CMe\(_3\)), 0.16 (12 H, s, 2 x SiMe\(_2\)); \( \delta_{C} \) (75 MHz; CDCl\(_3\)) 164.3 (C), 155.2 (C), 149.1 (C), 100.3 (CH\(_2\)), 52.4
(Me), 26.1 (Me), 26.0 (Me), 18.5 (CMe3), 18.3 (CMe3), -4.3 (SiMe2), -5.0 (SiMe2);

\[ m/z \text{ (CI) } 402 \text{ (8\%), } 374 \text{ (MH}^+\text{, 32), } 358 \text{ (50), } 316 \text{ (60), } 286 \text{ (10), } 247 \text{ (18), } 231 \text{ (90), } 200 \text{ (10), } 189 \text{ (100), } 184 \text{ (20), } 157 \text{ (40), } 147 \text{ (50), } 115 \text{ (70), } 86 \text{ (100), } 73 \text{ (28)}. \]

2,3-Butanedi-one mono(dimethylhydrazone)\(^{50}\) 248

![Diagram of 2,3-Butanedi-one mono(dimethylhydrazone) with structures 242, 243, and 248]

Following general procedure 2, the title compound was obtained from 2,3-butanedi-one 242 (8.61 g, 0.100 mol) as a yellow oil (9.17 g, 72\%); \( \nu_{\text{max}} \text{ (CHCl}_3\text{/cm}^-1 \) 1672 (C=O); \( \delta_\text{H} \) (300 MHz; CDCl\(_3\)) 2.96 (6 H, s, NMe\(_2\)), 2.32 (3 H, s, Me), 2.01 (3 H, s, Me); \( \delta_\text{C} \) (75 MHz; CDCl\(_3\)) 199.4 (C), 147.6 (C), 47.3 (NMe\(_2\)), 24.8 (Me), 13.2 (Me).

3-(Piperidin-1-ylimino)-butan-2-one 249

![Diagram of 3-(Piperidin-1-ylimino)-butan-2-one with structures 242, 244, and 249]

Following general procedure 2, the title compound was obtained from 1-aminopiperidine (1.10 g, 11.0 mmol) as a colourless oil (1.02 g, 62\%); (Found: MH\(^+\), 169.1363. C\(_9\)H\(_{16}\)N\(_2\)O + H requires 169.1341); \( \nu_{\text{max}} \text{ (film)/cm}^-1 \) 1687 (C=O); \( \delta_\text{H} \) (300 MHz; CDCl\(_3\)) 3.12 - 3.08 (4 H, m, 2 x CH\(_2\)), 2.35 (3 H, s, Me), 1.98 (3 H, s, Me), 1.74 - 1.67 (4 H, m, 2 x CH\(_2\)), 1.59 - 1.54 (2 H, m, CH\(_2\)); \( \delta_\text{C} \) (75 MHz; CDCl\(_3\)) 199.7 (C), 152.4 (C), 55.9 (CH\(_2\)), 25.7 (CH\(_2\)), 24.9 (Me), 24.4 (CH\(_2\)), 13.6 (Me); \( m/z \text{ (CI) } 197 \text{ (8\%), } 169 \text{ (MH}^+\text{, 100), } 84 \text{ (15)}. \)
N-Methyl-hydrazinecarboxylic acid tert-butyl ester 245

![Chemical structure of N-Methyl-hydrazinecarboxylic acid tert-butyl ester 245](image)

To a stirred solution of methyl hydrazine (0.461 g, 10.0 mmol) and DMAP (37.0 mg, 0.300 mmol) in acetonitrile (10 mL) was added dropwise di-tert-butyl dicarbonate (2.40 g, 11.0 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate/light petroleum (1:3) to afford the title compound as a colourless oil (1.34 g, 92%); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3334 (NH$_2$), 3221 (NH$_2$), 1694 (C=O); $\delta$$_{H}$ (300 MHz; CDCl$_3$) 4.10 (2 H, br s, NH$_2$), 3.06 (3 H, s, Me), 1.48 (9 H, s, CMe$_3$); $\delta$$_{C}$ (75 MHz; CDCl$_3$) 80.8 (CMe$_3$), 38.6 (Me), 28.8 (Me).

N-Methyl-N'-[1-methyl-2-oxo-propylidene]-hydrazinecarboxylic acid tert-butyl ester 250

![Chemical structure of N-Methyl-N'-[1-methyl-2-oxo-propylidene]-hydrazinecarboxylic acid tert-butyl ester 250](image)

Following general procedure 2, the title compound was obtained from 2,3-butanedione 242 (0.430 g, 5.00 mmol) and N-methyl-hydrazinecarboxylic acid tert-butyl ester 245 (0.805 g, 5.50 mmol) as a colourless oil (1.03 g, 96%); (Found: MH$^+$, 215.1388, C$_{10}$H$_{18}$N$_2$O$_3$ + H requires 215.1395); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1699 (C=O), 1610 (C=N); $\delta$$_{H}$ (300 MHz; CDCl$_3$) 3.29 (3 H, s, NMe), 2.44 (3 H, s, Me), 1.95 (3 H, s, Me), 1.50 (9 H,
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s, CMe₃); δC (75 MHz; CDCl₃) 199.4 (C), 163.7 (C), 152.5 (C), 82.1 (CMe₃), 39.4 (Me), 28.7 (Me), 25.5 (Me), 14.6 (Me); m/z (Cl) 215 (MH⁺, 20%), 187 (30), 159 (100), 143 (15), 115 (92).

1-Benzylxocarbonyl-1-methyl-hydrazine ²⁰³ ²⁴⁶

\[
\begin{align*}
\text{NH}_2 & \quad \text{Me}^+ \\
\text{Me}^{-} & \quad \text{NH} \\
& \quad \text{O} \quad \text{Bn}
\end{align*}
\]

To a stirred solution of methylhydrazine (0.461 g, 10.0 mmol) in dry dichloromethane (20 mL) at 0 °C was added triethylamine (1.21 g, 12.0 mmol) and benzyl chloroformate (1.88 g, 11.0 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h. Water (15 mL) was added, and the organic layer separated. The aqueous layer was further extracted with dichloromethane (3 × 25 mL). The combined organics were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:1) to afford the title compound as a colourless oil (1.04 g, 58%);

νmax (CHCl₃)/cm⁻¹ 3026 (NH₂), 1697 (C=O), 1627 (C=C), 1498 (C=C); δH (300 MHz; CDCl₃) 7.38 - 7.31 (5 H, m, ArH), 5.15 (2 H, s, CH₂), 3.82 (2 H, br s, NH₂), 3.14 (3 H, s, Me); δC (75 MHz; CDCl₃) 136.8 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 68.1 (CH₂), 38.8 (Me).
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N-Benzylxocarbonyl-N-methyl butane-2,3-dione monohydrazone 251

\[
\begin{align*}
\text{242} & \quad + \quad \text{246} \\
\text{251}
\end{align*}
\]

Following general procedure 2, the title compound was obtained from 1-methyl-1-benzylxocarbonylhydrazine 246 (0.991 g, 5.5 mmol) as a colourless solid (0.963 g, 78%), mp 64-65 °C (from light petroleum); (Found: MH\(^+\), 249.1236. C\(_{13}\)H\(_{16}\)N\(_2\)O\(_3\) + H requires 249.1239); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1703 (C=O), 1613 (C=N), 1469 (C=C); \(\delta\)\(_{H}\) (300 MHz; CDCl\(_3\)) 7.39 - 7.32 (5 H, m, ArH), 5.21 (2 H, s, CH\(_2\)), 3.35 (3 H, s, NMe), 2.44 (3 H, s, Me), 1.95 (3 H, s, Me); \(\delta\)\(_{C}\) (75 MHz; CDCl\(_3\)) 199.2 (C), 164.8 (C), 153.6 (C), 136.3 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 68.5 (CH\(_2\)), 39.3 (Me), 25.6 (Me), 14.6 (Me); \text{mlz} (CI) 339 (30%), 249 (MH\(^+\), 100), 205 (25), 181 (10), 137 (10), 91 (48).

N-Phthaloyl butane-2,3-dione monohydrazone\(^93\) 252

\[
\begin{align*}
\text{242} & \quad + \quad \text{247} \\
\text{252}
\end{align*}
\]

To a stirred solution of 2,3-butanedione 242 (8.61 g, 0.100 mol) in chloroform (200 mL) was added N-aminophthalimide 247 (17.8 g, 0.110 mol). The reaction mixture was heated under reflux for 3 d, allowed to cool to room temperature, filtered and concentrated \textit{in vacuo} to afford the title compound as a colourless solid (20.1 g, 87%), mp 157-158 °C (from chloroform), (lit., mp 165 °C), which was used without further...
purification; $\delta_H$ (300 MHz; CDCl$_3$) 7.95 - 7.92 (2 H, m, ArH), 7.82 - 7.79 (2 H, m, ArH), 2.60 (3 H, s, Me), 2.11 (3 H, s, Me); $\delta_C$ (75 MHz; CDCl$_3$) 198.0 (C), 172.1 (C), 163.6 (C), 135.1 (CH), 131.4 (C), 124.4 (CH), 26.0 (Me), 16.1 (Me).

3-(tert-Butyldimethylsiloxy)-2-methyl-1-(dimethylamino)-1-aza-1,3-butadiene$^{50}$ 53

Following general procedure 3, the title compound was obtained from 2,3-butanedione mono(dimethylhydrazone) 248 (1.92 g, 15.0 mmol) as a colourless oil (3.47 g, 95%); $\nu_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 1616 (C=N), 1593 (C=C), 1254 (Si-Me), 1228 (NMe$_2$), 1204 (NMe$_2$); $\delta_H$ (400 MHz; CDCl$_3$) 4.87 (1 H, d, $J$ = 1.2 Hz, C=CH), 4.51 (1 H, d, $J$ = 1.2 Hz, C=CH), 2.55 (6 H, s, N(CH$_3$)$_3$), 2.05 (3 H, s, CH$_3$), 0.96 (9 H, s, C(CH$_3$)$_3$), 0.18 (6 H, s, Si(CH$_3$)$_3$); $\delta_C$ (100 MHz; CDCl$_3$) 157.7 (C), 153.6 (C), 94.2 (CH$_2$), 45.1 (NMe$_2$), 23.6 (CMe$_3$), 16.3 (CMe$_3$), 12.2 (Me).

3-(tert-Butyldimethylsiloxy)-2-methyl-1-(piperidinyl)-1-aza-1,3-butadiene 253

Following general procedure 3, the title compound was obtained from 3-(piperidin-1-ylimino)-butan-2-one 249 (0.504 g, 3.0 mmol) as a colourless oil (0.715 g, 84%); (Found: MH$^+$, 283.2205. C$_{15}$H$_{30}$N$_2$OSi + H requires 283.2205); $\nu_{\text{max}}$ (CHCl$_3$/cm$^{-1}$)
1615 (C=N), 1593 (C=C), 1253 (Si-Me); δH (300 MHz; CDCl3) 4.86 (1 H, d, J = 0.9 Hz, C=CH), 4.52 (1 H, d, J = 0.9 Hz, C=CH), 2.75 - 2.71 (4 H, m, 2 × CH2), 2.04 (3 H, s, Me), 1.72-1.65 (4 H, m, 2 × CH2), 1.48-1.44 (2 H, m, CH2), 0.96 (9 H, s, CMe3), 0.17 (6 H, s, SiMe2); δC (75 MHz; CDCl3) 160.4 (C), 156.2 (C), 96.9 (CH2), 56.5 (CH2), 26.2 (CH2), 25.7 (CH2), 24.3 (CH2), 18.8 (CMe3), 14.8 (Me), -2.5 (SiMe2); m/z 311 (8%), 283 (MH+, 100), 267 (45), 225 (30), 200 (5), 169 (10), 159 (5).

1-(Benzyloxy carbonylmethylamino)-3-(tert-butyl dimethylsiloxy)-2-methyl-1-aza-1,3-butadiene 255

Following general procedure 3, the title compound was obtained from N-benzyloxy carbonyl-N-methyl butane-2,3-dione monohydrazone 251 (0.745 g, 3.0 mmol) as a colourless oil (1.01 g, 93%); (Found: MH+, 363.2097. C19H30N2O3Si + H requires 363.2104); νmax (CHCl3)/cm⁻¹ 1698 (C=O), 1620 (C=N), 1595 (C=C), 1498 (C=C), 1472 (C=C), 1256 (Si-Me); δH (300 MHz; CDCl3) 7.35 - 7.32 (5 H, m, ArH), 5.15 (2 H, s, CH2), 5.04 (1 H, d, J = 1.3 Hz, C=CH), 4.60 (1 H, d, J = 1.3 Hz, C=CH), 3.20 (3 H, s, NMe), 1.93 (3 H, s, Me), 0.95 (9 H, s, CMe3), 0.16 (6 H, s, SiMe2); δC (75 MHz; CDCl3) 178.0 (C), 163.5 (C), 154.7 (C), 136.8 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 98.7 (CH2), 67.9 (CH2), 38.1 (Me), 26.1 (Me), 16.0 (CMe3), 14.5 (Me), -2.5 (SiMe2); m/z (Cl) 453 (8%), 363 (MH+, 25), 339 (8), 311 (10), 283 (80), 271 (22), 249 (12), 221 (20), 193 (57), 181 (25), 149 (27), 137 (18), 91 (100).
3-(tert-Butyldimethylsiloxy)-2-methyl-1-(phthalimido)-1-aza-1,3-butadiene 256

Following general procedure 3, the title compound was obtained from N-phthaloyl butane-2,3-dione monohydrazone 252 (1.15 g, 5.0 mmol) as a colourless solid (1.38 g, 79%), mp 106-107 ºC (from ethanol); (Found: MH+, 345.1632. C_{18}H_{24}N_{2}O_{3}Si + H requires 345.1634); \( \nu_{\text{max}} \) (CHCl\textsubscript{3})/cm\textsuperscript{-1} 1717 (C=O), 1618 (C=N), 1596 (C=C), 1467 (C=C), 1256 (Si-Me); \( \delta_{H} \) (300 MHz; CDCl\textsubscript{3}) 7.89 - 7.86 (2 H, m, ArH), 7.76 - 7.73 (2 H, m, ArH), 5.30 (1 H, d, \( J = 1.3 \) Hz, C=CH), 4.75 (1 H, d, \( J = 1.3 \) Hz, C=CH), 2.07 (3 H, s, Me), 1.00 (9 H, s, CMe\textsubscript{3}), 0.23 (6 H, s, SiMe\textsubscript{2}); \( \delta_{C} \) (75 MHz; CDCl\textsubscript{3}) 174.0 (C), 164.3 (C), 153.8 (C), 134.6 (CH), 131.6 (C), 124.0 (CH), 100.3 (CH\textsubscript{2}), 26.1 (Me), 18.7 (CMe\textsubscript{3}), 17.5 (Me), - 4.7 (SiMe\textsubscript{2}); m/z (Cl) 373 (10%), 345 (MH\textsuperscript{+}, 95), 287 (50), 200 (32), 148 (100).

Dimethyl 5-(tert-butyldimethylsiloxy)-6-methylpyridine-2,3-dicarboxylate 240

a) Following general procedure 4 from 238 (0.330 g, 1.0 mmol) and DMAD 136 (0.284 g, 2.0 mmol), the title compound was obtained in 6 h as a colourless oil (0.190 g, 56%); (Found: M\textsuperscript{+}, 339.1507. C_{16}H_{25}NO_{3}Si requires 339.1502); \( \nu_{\text{max}} \) (film)/cm\textsuperscript{-1} 1732 (C=O), 1588 (C=C), 1558 (C=C), 1461 (C=C), 1258 (Si-Me); \( \delta_{H} \) (300 MHz;
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CDCl$_3$ 7.35 (1 H, s, H-4), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.52 (3 H, s, Me), 1.00 (9 H, s, CMe$_3$), 0.25 (6 H, s, SiMe$_2$); $\delta$ (75 MHz; CDCl$_3$) 167.1 (C), 166.5 (C), 155.0 (C), 151.8 (C), 142.0 (C), 126.4 (C), 125.0 ( CH), 53.4 (Me), 53.3 (Me), 26.2 (Me), 20.5 (Me), 18.6 (CMe$_3$), -3.9 (SiMe$_2$); $m/z$ (EI) 339 (M$^+$, 12%), 308 (8), 282 (36), 250 (100), 222 (18), 192 (28), 164 (20).

b) Following general procedure 4 from 238 (0.330 g, 1.0 mmol) and DMAD (0.142 g, 1.0 mmol), the title compound was obtained in 8 h as a colourless oil (0.170 g, 50%); data as above.

c) Following general procedure 5 from 238 (0.330 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 2 h as a colourless oil (0.190 g, 56%); data as above.

d) Following general procedure 5 from 238 (0.330 g, 1.0 mmol) and DMAD (0.142 g, 1.0 mmol), the title compound was obtained in 3 h as a colourless oil (0.170 g, 50%); data as above.

e) A solution of 1-azadiene 238 (0.330 g, 1.0 mmol) and DMAD (5, 0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed tube was heated to 150 °C for 6 h. The resulting mixture was concentrated in vacuo and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound as a colourless oil (0.194 g, 57%); data as above.
f) Following general procedure 4 from 53 (0.242 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 2 h as a colourless oil (0.176 g, 52%); data as above.

g) Following general procedure 5 from 53 (0.242 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 45 min as a colourless oil (0.150 g, 44%); data as above.

h) A solution of 1-azadiene 53 (0.242 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed tube was heated to 150 °C for 2 h. The resulting mixture was concentrated in vacuo and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound as a colourless oil (0.157 g, 46%); data as above.

i) Following general procedure 4 from 253 (0.283 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 2 h as a colourless oil (0.160 g, 47%); data as above.
j) Following general procedure 4 from 255 (0.363 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 4 h as a colourless oil (0.157 g, 46%); data as above.

k) Following general procedure 5 from 256 (0.344 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 3 h as a colourless oil (0.197 g, 58%); data as above.

l) Following general procedure 5 from 256 (0.344 g, 1.0 mmol) and DMAD (0.142 g, 1.0 mmol), the title compound was obtained in 4 h as a colourless oil (0.183 g, 54%); data as above.
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Trimethyl 5-(tert-butyldimethylsiloxy)pyridine-2,3,6-tricarboxylate 241

\[
\begin{array}{c}
\text{TBDMSO} \quad \begin{array}{c}
\text{N} \\
\text{MeO}_2C \\
\text{OTBDMS}
\end{array} \\
\text{239}
\end{array} + \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{136}
\end{array} \rightarrow \begin{array}{c}
\text{TBDMSO} \\
\text{CO}_2\text{Me} \\
\text{241}
\end{array}
\]

a) Following general procedure 4 from 239 (0.374 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 10 h as a colourless oil (0.121 g, 32%); (Found: M⁺, 384.1473. C₁₇H₂₅NO₃Si + H requires 384.1478); νmax (CHCl₃)/cm⁻¹ 1742 (C=O), 1589 (C=C), 1555 (C=C), 1253 (Si-Me); δH (300 MHz; CDCl₃) 7.48 (1 H, s, H-4), 3.92 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 0.96 (9 H, s, CMe₃), 0.25 (6 H, s, SiMe₂); δC (75 MHz; CDCl₃) 165.9 (C), 165.7 (C), 164.7 (C), 152.7 (C), 144.0 (C), 141.4 (C), 131.3 (C), 128.7 (CH), 53.6 (Me), 53.5 (Me), 53.2 (Me), 25.7 (Me), 18.6 (CMe₃), - 3.8 (SiMe₂); m/z (Cl) 384 (MH⁺, 6%), 270 (100), 238 (23).

b) Following general procedure 5 from 239 (0.374 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 6 h as a colourless oil (0.119 g, 31%); data as above.

Methyl 3-(tert-butyldimethylsiloxy)-2-methylpyridine-6-carboxylate 258

\[
\begin{array}{c}
\text{TBDMSO} \quad \begin{array}{c}
\text{N} \\
\text{NMe₂}
\end{array} \\
\text{53}
\end{array} + \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{228}
\end{array} \rightarrow \begin{array}{c}
\text{TBDMSO} \\
\text{CO}_2\text{Me} \\
\text{258}
\end{array}
\]

Following general procedure 5 from 53 (0.242 g, 1.0 mmol) and methyl propiolate 228 (0.168 g, 2.0 mmol), the title compound was obtained in 6 h as a colourless oil (0.082 g, 29%); (Found: M⁺, 282.1526. C₁₄H₂₃NO₃Si requires 282.1525); νmax (film)/cm⁻¹ 1719 (C=O), 1574 (C=C), 1463 (C=C), 1258 (Si-Me); δH (300 MHz; CDCl₃) 7.88 (1
H, d, J = 8.3 Hz, ArH), 7.06 (1 H, d, J = 8.3 Hz, ArH), 3.92 (3 H, s, OMe), 3.51 (3 H, s, Me), 0.98 (9 H, s, CMe3), 0.22 (6 H, s, SiMe2); δC (75 MHz; CDCl3) 168.3 (C), 156.0 (C), 154.4 (C), 142.1 (C), 127.2 (CH), 127.0 (CH), 55.5 (Me), 28.2 (Me), 22.8 (Me), 20.8 (CMe3), -1.3 (SiMe2); m/z (Cl) 282 (M⁺, 100%).

6-Acetyl-3-(tert-butyldimethylsiloxy)-2-methylpyridine 259

Following general procedure 5 from 53 (0.242 g, 1.0 mmol) and 3-butyn-2-one 229 (0.136 g, 2.0 mmol), the title compound was obtained in 6 h as a colourless oil (0.073 g, 28%); (Found: MH⁺, 266.1585. C₁₄H₂₃NO₂Si requires 266.1576); νmax (CHCl₃)/cm⁻¹ 1684 (C=O), 1596 (C=C), 1569 (C=C), 1508 (C=C), 1256 (Si-Me); δH (300 MHz; CDCl₃) 7.83 (1 H, d, J = 8.3 Hz, ArH), 7.07 (1 H, d, J = 8.3 Hz, ArH), 2.66 (3 H, s, Me), 2.49 (3 H, s, Me), 1.02 (9 H, s, CMe3), 0.25 (6 H, s, SiMe2); δC (75 MHz; CDCl₃) 199.9 (C), 153.8 (C), 150.7 (C), 146.6 (C), 124.7 (CH), 121.5 (CH), 26.0 (Me), 20.5 (Me), 18.6 (CMe3), -3.5 (SiMe2); m/z (Cl) 266 (M⁺, 100%), 152 (5).

Toluene-4-sulfonic acid but-3-ynyl ester² 265

A solution of para-toluenesulfonyl chloride (42.6 g, 0.222 mol) in warm pyridine (21 mL) was cooled rapidly to form crystals. 3-Butyn-1-ol (14.0 g, 0.200 mol) was then added dropwise with cooling. The reaction mixture was warmed to room temperature and stirred overnight, then cooled to 0 °C and diluted with water (30 mL). The
resulting suspension was then poured into water (45 mL) and extracted with ether (4 × 50 mL). The combined organics were washed with sulphuric acid (2 M; 4 × 100 mL), saturated sodium hydrogen carbonate (3 × 100 mL) and brine (100 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless oil (32.4 g, 72%); νmax (film)/cm⁻¹ 3292 (alkyne C-H), 2125 (C≡C), 1598 (C=C), 1496 (C=C), 1464 (C=C), 1360 (S=O); δH (300 MHz; CDCl₃) 7.81 (2 H, d, J = 8.3 Hz, ArH), 7.36 (2 H, d, J = 8.3 Hz, ArH), 4.11 (2 H, t, J = 7.0 Hz, OCH₂), 2.56 (2 H, dt, J = 7.0, 2.6 Hz, CH₂), 2.46 (3 H, s, Me), 1.97 (1 H, t, J = 2.6 Hz, C=CH); δC (75 MHz; CDCl₃) 145.5 (C), 133.2 (C), 130.3 (CH), 128.4 (CH), 78.8 (C≡CH), 71.2 (C≡CH), 67.8 (CH₂), 22.1 (Me), 19.8 (CH₂).

4-Iodobut-1-yne

To a stirred solution of toluene-4-sulfonic acid but-3-ynyl ester (15.0 g, 66.9 mmol) in acetone (50 mL) was added sodium iodide (10.0 g, 66.7 mmol). The reaction mixture was stirred for 3 d and the solvent boiled off at atmospheric pressure. The crude product was distilled at room temperature in vacuo to afford the title compound as a colourless oil (5.58 g, 46%); νmax (film)/cm⁻¹ 3293 (alkyne C-H), 2119 (C≡C), 1175 (C-I); δH (300 MHz; CDCl₃) 3.24 (2 H, t, J = 7.4 Hz, CH₂I), 2.80 (2 H, dt, J = 7.4, 2.5 Hz, CH₂), 2.17 (1 H, t, J = 2.5 Hz, C≡CH); δC (75 MHz; CDCl₃) 81.9 (C≡CH), 69.4 (C≡CH), 22.8 (CH₂), 0.0 (CH₂I).
Following general procedure 2, the title compound was obtained from 2,3-butanedione \( 242 \) (1.72 g, 20.0 mmol) and methylhydrazine (1.01 g, 22.0 mmol) as a colourless oil (1.37 g, 60%); \( \nu_{\text{max}} \) (CHCl\(_3\))/cm\(^{-1} \) 3298 (NH), 1726 (C=O), 1651 (C=N); \( \delta_H \) (300 MHz; CDCl\(_3\)) 5.75 (1 H, br s, NH), 3.24 (3 H, s, NMe), 2.36 (3 H, s, Me), 1.79 (3 H, s, Me); \( \delta_C \) (75 MHz; CDCl\(_3\)) 197.6 (C), 140.3 (C), 38.4 (NMe), 24.1 (Me), 7.42 (Me).

**Hydrazine carboxylic acid benzyl ester**

To a stirred solution of hydrazine monohydrate (5.01 g, 0.100 mol) in CH\(_2\)Cl\(_2\) (100 mL) at 0 °C was added triethylamine (12.1 g, 0.120 mol) and benzyl chloroformate (18.8 g, 0.110 mol). Stirring was continued at 0 °C for 4.5 h, and the reaction mixture was then diluted with water (75 mL), separated, and the aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organics were washed with brine (25 mL), dried over MgSO\(_4\) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate followed by methanol to afford the title compound as a colourless solid (3.55 g, 21%); (Found: MH\(^+\), 167.0840. C\(_8\)H\(_{10}\)N\(_2\)O\(_2\) + H requires 167.0820); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1} \) 3331 (NH\(_2\)), 3212 (NH\(_2\)), 1690 (C=O), 1650 (C=C), 1520 (C=C), 1465 (C=C); \( \delta_H \) (300 MHz; CDCl\(_3\)) 7.43 - 7.29 (5 H, m, ArH), 6.02 (1 H, br s, NH), 5.15 (2 H, s, CH\(_2\)), 3.75 (2 H, br s, NH\(_2\)) ; \( \delta_C \) (75
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MHz; CDCl₃ 159.1 (C), 136.4 (C), 129.0 (CH), 128.8 (CH), 128.6 (CH), 67.7 (CH₂); m/z (Cl) 423 (8%), 257 (85), 213 (30), 167 (15), 123 (17), 119 (10), 91 (100).

N’-(1-Methyl-2-oxo-propylidene)-hydrazinecarboxylic acid benzyl ester 269

\[
\begin{align*}
\text{NH}_2 & \\
\text{Cbz}^+ & \quad \text{Me} \\
\text{NH} & \\
\text{Me} & \\
\text{Cbz}^- & \quad \text{Me} \\
\end{align*}
\]

Following general procedure 2, the title compound was obtained from 2,3-butanedione 242 (0.430 g, 5.00 mmol) and hydrazine carboxylic acid benzyl ester (0.914 g, 5.50 mmol) as a colourless solid (1.01 g, 86%), mp 131-133 °C (from dichloromethane-hexane); (Found: MH⁺, 235.1078. C₁₂H₁₄N₂O₃ + H requires 235.1082); \( \nu_{\text{max}} \) (KBr)/cm⁻¹ 3454 (NH), 1711 (C=O), 1683 (C=O), 1605 (C=C), 1485 (C=C); δH (300 MHz; CDCl₃) 7.97 (1 H, br s, NH), 7.45 - 7.36 (5 H, m, ArH), 5.30 (2 H, s, CH₂), 2.47 (3 H, s, Me), 1.92 (3 H, s, Me); δC (75 MHz; CDCl₃) 198.1 (C), 135.6 (C), 129.1 (CH), 128.9 (CH), 68.7 (CH₂), 24.9 (Me), 8.7 (Me); m/z (Cl) 325 (35%), 263 (5), 235 (MH⁺, 55), 191 (12), 91 (100).

N-methylpent-4-ynehydrazide²⁹ 273

\[
\begin{align*}
\text{HO}_2C & \\
\text{Me} & \\
\end{align*}
\]

A solution of 4-pentynoic acid (5.00 g, 51.0 mmol) in freshly distilled thionyl chloride (3.71 mL, 51.0 mmol) was heated under reflux for 45 min. The reaction mixture was cooled to room temperature, diluted with dichloromethane (14 mL) and added dropwise to a solution of methylhydrazine (9.21 g, 200 mmol) in dichloromethane (50
mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and the solid filtered off. The filtrate was concentrated *in vacuo*, and the crude product purified by flash chromatography on silica gel, eluting with methanol-ethyl acetate (0:1 to 1:19) to afford the title compound as a pale yellow solid (3.30 g, 51%), mp 57-59 °C (from dichloromethane-hexane) (lit.,29 52-54 °C); δ_H (400 MHz; CDCl₃) two rotomers, 3.87 (2 H, br s, NH₂), 3.24 and 3.20 (3 H, s, NMe), 2.88 (1 H, t, J = 7.2 Hz, CH₂), 2.58-2.49 (3 H, m, CH₂ + CH₂), 1.99 and 1.96 (1 H, t, J = 2.8 Hz, C=CH); δ_C (100 MHz; CDCl₃) two rotomers, 68.9 (C=CH), 68.3 (C=CH), 38.7 and 38.5 (NMe), 31.9 and 31.8 (CH₂), 15.51 and 15.5 (CH₂).

(E)-N-Methyl-N'-(3-oxobutan-2-ylidene)pent-4-yneyhydradize 274

![Formula](image)

To a solution of 2,3-butanedione 242 (0.861 g, 10.0 mmol) in ethanol (3 mL) at 0 °C was added hydrazide 273 (1.39 g, 11.0 mmol) in ethanol (7 mL) dropwise over 15 min. The reaction mixture was stirred at 0 °C for 3.5 h, then allowed to warm to room temperature and stirred for a further 18 h. The resulting solution was dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:5) to afford the *title compound* as a colourless solid (1.83 g, 94%), mp 90-92 °C (from dichloromethane-hexane); ν_max (CHCl₃)/cm⁻¹ 3308 (alkyne C-H), 2121 (C=C), 1690 (C=O), 1606 (C=N); (Found: MH⁺, 195.1125. C₁₀H₁₄N₂O₂ + H requires 195.1128); δ_H (400 MHz; CDCl₃) 3.45 (3 H, s, NMe), 3.0-2.96 (2 H, m, CH₂), 2.60-2.56 (2 H, m,
CH₂), 2.44 (3 H, s, Me), 2.19 (3 H, s, Me), 1.98 (1 H, t, J = 2.8 Hz, C≡CH); δC (100 MHz; CDCl₃) 198.3 (C), 174.5 (C), 83.3 (C≡CH), 68.7 (C≡CH), 35.3 (NMe), 33.3 (CH₂), 25.2 (Me), 14.3 (CH₂), 14.0 (Me); m/z (ESI) 217 (MNa⁺, 100%), 195 (11).

(E)-N'-[(3-(tert-Butyldimethylsilyloxy)but-3-en-2-ylidene)-N-methylpent-4-ynehydrazide 275

Following general procedure 3, the title compound was obtained from α-ketohydrazide 274 (0.777 g, 4.00 mmol) as a pale orange oil (1.24 g, 100%); (Found: MH⁺, 309.1979. C₁₆H₂₈N₂O₂Si + H requires 309.1993); νmax (CHCl₃)/cm⁻¹ 3308 (alkyne CH), 2121 (C=C), 1718 (C=O), 1664 (C=O), 1606 (C=C); δH (400 MHz; CDCl₃) 5.10 (1 H, d, J = 1.6 Hz, C=CH), 4.62 (1 H, d, J = 1.6 Hz, C=CH), 3.15 (3 H, s, NMe), 2.61-2.58 (2 H, m, CH₂), 2.54-2.51 (2 H, m, CH₂), 2.05 (3 H, s, Me), 1.95 (1 H, t, J = 1.5 Hz, C≡CH), 0.98 (9 H, s, CMe₃), 0.11 (6 H, s, SiMe₂); δC (100 MHz; CDCl₃) 172.3 (C), 167.2 (C), 154.1 (C), 97.8 (CH₂), 83.6 (C≡CH), 68.4 (C≡CH), 35.6 (NMe), 32.7 (CH₂), 25.4 (CMe₃), 18.2 (CMe₃), 16.0 (Me), 14.0 (CH₂), -4.7 (SiMe₂); m/z (ESI) 331 (MNa⁺, 100%), 309 (MH⁺, 87).
2-(Prop-2-ynyloxy)benzaldehyde\textsuperscript{9} 322

Following general procedure 6, the title compound was obtained from salicaldehyde \textbf{320} (0.305 g, 2.50 mmol), potassium carbonate (0.518 g, 3.75 mmol) and propargyl chloride (0.90 mL, 12.5 mmol) as a colourless oil (0.400 g, 100%); $\nu_{\text{max}}$ (CHCl\textsubscript{3})/cm\textsuperscript{-1} 3307 (alkyne C-H), 2127 (C≡C), 1690 (C=O), 1601 (C=C), 1483 (C=C), 1460 (C=C), 1023 (C-O); $\delta$\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 10.47 (1 H, s, CHO), 7.85 (1 H, d, $J$ = 7.6 Hz, ArH), 7.55 (1 H, t, $J$ = 7.6 Hz, ArH), 7.12 - 7.05 (2 H, m, ArH), 4.82 (2 H, d, $J$ = 2.4 Hz, CH\textsubscript{2}), 2.58 (1 H, t, $J$ = 2.4 Hz, C≡CH); $\delta$\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 189.5 (CHO), 159.8 (C), 135.7 (CH), 128.5 (CH), 125.5 (C), 121.7 (CH), 77.7 (C≡CH), 76.5 (C≡CH), 56.4 (CH\textsubscript{2});

3-Methyl-2-(prop-2-ynyloxy)benzaldehyde 323

Following general procedure 6, the title compound was obtained from 3-methylsalicaldehyde \textbf{321} (0.340 g, 2.50 mmol), potassium carbonate (0.518 g, 3.75 mmol) and propargyl chloride (0.90 mL, 12.5 mmol) as a colourless oil (0.375 g, 86%); (Found: MH\textsuperscript{+}, 175.0758. C\textsubscript{11}H\textsubscript{10}O\textsubscript{2} + H requires 175.0754); $\nu_{\text{max}}$ (CHCl\textsubscript{3})/cm\textsuperscript{-1} 3306 (alkyne C-H), 2126 (C≡C), 1693 (C=O), 1588 (C=C), 1469 (C=C), 1249 (C-O), 1086 (C-O); $\delta$\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 10.42 (1 H, s, CHO), 7.71 (1 H, d, $J$ = 7.6 Hz, H-6), 7.45 (1 H, d, $J$ = 7.6 Hz, H-4), 7.17 (1 H, t, $J$ = 7.6 Hz, H-5), 4.68 (2 H, d, $J$ = 2.0 Hz, CH\textsubscript{2}).
Hz, CH₂), 2.54 (1 H, t, J = 2.0 Hz, C=CH), 2.36 (3 H, s, Me); δC (100 MHz; CDCl₃) 190.6 (CH), 158.9 (C), 137.5 (CH), 132.4 (C), 130.2 (C), 126.5 (CH), 125.0 (CH), 77.9 (C), 76.8 (CH), 62.1 (CH₂), 15.9 (Me); m/z (ESI) 197 (MNa⁺, 100%), 175 (MH⁺, 37), 147 (66).

(E)-4-(2-(Prop-2-ynyloxy)phenyl)but-3-en-2-one

Following general procedure 7, the title compound was obtained from 2-(prop-2-ynyloxy)benzaldehyde 322 (0.288 g, 1.80 mmol), sodium hydride (0.108 g, 2.70 mmol) and dimethyl 2-oxopropylphosphonate 324 (0.448 g, 2.70 mmol) as a colourless oil (0.329 g, 91%); δH (400 MHz; CDCl₃) 7.88 (1 H, d, J = 16.4 Hz, C=CH), 7.56 (1 H, d, J = 7.6 Hz, H-10), 7.37 (1 H, t, J = 7.6 Hz, H-9), 7.05 (1 H, d, J = 7.6 Hz, H-7), 7.02 (1 H, t, J = 7.6 Hz, H-8), 6.73 (1 H, d, J = 16.4 Hz, C=CH), 4.78 (2 H, d, J = 1.2 Hz, CH₂), 2.55 (1 H, t, J = 1.2 Hz, C≡CH), 2.38 (3 H, s, Me); δC (100 MHz; CDCl₃) 199.0 (C), 156.1 (C), 138.4 (CH), 131.6 (CH), 128.3 (CH), 128.1 (CH), 124.0 (C), 121.8 (CH), 112.8 (CH), 78.1 (C), 76.1 (CH), 56.2 (CH₂), 27.2 (Me).
(E)-4-(3-Methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one 327

Following general procedure 7, the *title compound* was obtained from 3-methyl-2-(prop-2-ynyloxy)benzaldehyde 323 (0.314 g, 1.80 mmol), sodium hydride (0.108 g, 2.70 mmol) and dimethyl 2-oxopropylphosphonate 324 (0.448 g, 2.70 mmol) as a colourless oil (0.340 g, 88%); (Found: MH\(^+\), 215.1077. C\(_{14}\)H\(_{14}\)O\(_2\) + H requires 215.1066); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 3307 (alkyne C-H), 2127 (C=C), 1669 (C=O), 1644 (C=C), 1623 (C=C), 1607 (C=C), 1462 (C=C), 1259 (C=O), 1090 (C=O); \(\delta_H\) (400 MHz; CDCl\(_3\)) 7.94 (1 H, d, \(J = 16.4\) Hz, C=CH), 7.44 (1 H, d, \(J = 7.6\) Hz, H-10), 7.24 (1 H, d, \(J = 7.6\) Hz, H-8), 7.08 (1 H, t, \(J = 7.6\) Hz, H-9), 6.69 (1 H, d, \(J = 16.4\) Hz, C=CH), 4.55 (2 H, d, \(J = 1.2\) Hz, CH\(_2\)), 2.55 (1 H, t, \(J = 1.2\) Hz, C=CH), 2.41 (3 H, s, Me), 2.34 (3 H, s, Me); \(\delta_C\) (100 MHz; CDCl\(_3\)) 198.9 (C), 156.0 (C), 139.0 (CH), 133.6 (CH), 132.1 (C), 128.5 (CH), 128.4 (C), 125.2 (CH), 125.0 (CH), 78.6 (C), 76.1 (CH), 61.4 (CH\(_2\)), 27.0 (Me), 16.4 (Me); \(m/z\) (ESI) 237 (MNa\(^+\), 61%), 215 (MH\(^+\), 100).

(E)-3-Methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one 328

Following general procedure 7, the *title compound* was obtained from 3-methyl-2-(prop-2-ynyloxy)benzaldehyde 323 (0.401 g, 2.30 mmol), potassium tert-butoxide
(0.387 g, 3.45 mmol) and diethyl 1-methyl-2-oxopropylphosphonate 319 (0.718 g, 3.45 mmol) as a colourless oil (0.420 g, 82%); (Found: MH⁺, 229.1227. C₁₅H₁₆O₂ + H requires 229.1223); \( \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} \) 3307 (alkyne C-H), 2128 (C=C), 1665 (C=O), 1623 (C=C), 1586 (C=C), 1461 (C=C), 1263 (C-O), 1089 (C-O); \( \delta_H \) (400 MHz; CDCl₃) 7.78 (1 H, s, C=CH), 7.23-7.20 (2 H, m, ArH), 7.10 (1 H, t, \( J = 7.6 \) Hz, H-9), 4.50 (2 H, d, \( J = 1.3 \) Hz, CH₂), 2.52 (1 H, t, \( J = 1.3 \) Hz, C=CH), 2.51 (3 H, s, Me), 2.37 (3 H, s, Me), 2.01 (3 H, s, Me); \( \delta_C \) (100 MHz; CDCl₃) 200.5 (C), 155.2 (C), 138.6 (C), 136.0 (CH), 131.8 (CH), 131.7 (C), 129.5 (C), 128.2 (CH), 124.3 (CH), 78.9 (C), 75.6 (CH), 61.0 (CH₂), 26.0 (Me), 16.4 (Me), 13.0 (Me); \( m/z \) (ESI) 251 (MNa⁺, 75%), 229 (MH⁺, 100).

\((E)-1\text{-Methoxy-3-methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one} 329\)

To a solution of potassium tert-butoxide (0.421 g, 3.75 mmol) in toluene (4 mL) was added diethyl 4-methoxy-3-oxobutan-2-ylphosphonate 325 (0.893 g, 3.75 mmol) in toluene (3 mL) dropwise over 15 min. The reaction mixture was stirred for 30 min, followed by dropwise addition of 3-methyl-2-(prop-2-ynyloxy)benzaldehyde 323 (0.436 g, 2.50 mmol) in toluene (3 mL) over 15 min. The resulting mixture was stirred at room temperature for 16 h and partitioned between saturated ammonium chloride (45 mL) and ethyl acetate (3 × 45 mL). The combined organic extracts were washed with water (45 mL) and saturated brine (45 mL), dried over MgSO₄ and concentrated.
in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9), to afford the title compound as a colourless oil (0.487 g, 75%); (Found: MH$^+$, 259.1336. C$_{16}$H$_{18}$O$_3$ + H requires 259.1329); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3307 (alkyne C-H), 2127 (C=C), 1683 (C=O), 1627 (C=C), 1586 (C=C), 1461 (C=C), 1261 (C-O), 1090 (C-O), 1056 (C-O); $\delta_H$ (400 MHz; CDCl$_3$) 7.70 (1 H, s, C=CH), 7.23-7.20 (2 H, m, ArH), 7.09 (1 H, t, $J$ = 7.6 Hz, H-9), 4.61 (2 H, s, CH$_2$), 4.49 (2 H, d, $J$ = 1.2 Hz, CH$_2$), 3.49 (3 H, s, OMe), 2.53 (1 H, t, $J$ = 1.2 Hz, C=CH), 2.35 (3 H, s, Me), 2.03 (3 H, s, Me); $\delta_C$ (100 MHz; CDCl$_3$) 197.9 (C), 155.2 (C), 136.1 (C), 135.2 (CH), 132.1 (CH), 131.8 (C), 129.1 (C), 128.1 (CH), 124.4 (CH), 78.9 (C), 75.7 (CH), 74.8 (CH$_2$), 61.1 (CH$_2$), 59.4 (Me), 16.4 (Me), 13.1 (Me); $m/z$ (ESI) 281 (MNa$^+$, 100%), 259 (MH$^+$, 42), 241 (72).

(E)-4-(2-(3-Phenylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one 339

Following general procedure 8, the title compound was obtained from iodobenzene (0.67 mL, 6.00 mmol) and alkyne 327 (0.857 g, 4.00 mmol as a colourless oil (0.768 g, 66%); (Found: MH$^+$, 291.1382. C$_{20}$H$_{18}$O$_2$ + H requires 291.1380); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 2233 (C=C), 1669 (C=C), 1644 (C=C), 1622 (C=C), 1606 (C=C), 1588 (C=C), 1491 (C=C), 1461 (C=C), 1443 (C=C), 1260 (C-O), 1090 (C-O); $\delta_H$ (400 MHz; CDCl$_3$) 8.05 (1 H, d, $J$ = 16.5 Hz, C=CH), 7.49 (1 H, d, $J$ = 7.6 Hz, H-10), 7.40-7.38 (2 H, m, ArH), 7.35-7.32 (3 H, m, ArH), 7.28 (1 H, d, $J$ = 7.2 Hz, H-8), 7.12 (1 H, t, $J$ = 7.6 Hz, H-9), 6.72 (1 H, d, $J$ = 16.5 Hz, C=CH), 4.81 (2 H, s, CH$_2$), 2.41 (3 H, s, Me), 2.34 (3
(3E)-4-(2-(Prop-2-ynyloxy)phenyl)but-3-en-2-one O-methyloxime 330

Following general procedure 9, the title compound was obtained from ketone 326 (0.280 g, 1.40 mmol), methoxylamine hydrochloride (0.146 g, 1.75 mmol) and sodium acetate (0.200 g, 1.47 mmol) as a colourless oil (0.314 g, 98%); (Found: M\text{H}^+, 230.1192. \text{C}_{14}\text{H}_{15}\text{N} \text{O}_2 + \text{H} \text{ requires } 230.1181); \nu_{\max} (\text{CHCl}_3)/\text{cm}^{-1} 3308 (\text{alkyne C-H}), 2125 (\text{C=C}), 1600 (\text{C=C}), 1487 (\text{C=C}), 1457 (\text{C=C}), 1240 (\text{C-O}), 1055 (\text{C-O}); \delta_{\text{H}} (400 \text{ MHz}; \text{CDCl}_3) 7.57 (1 \text{ H, d, } J = 7.6 \text{ Hz, H-10}), 7.35 - 7.24 (2 \text{ H, m, ArH } + \text{C=CH}), 7.04 - 6.86 (2 \text{ H, m, ArH}), 6.85 (1 \text{ H, d, } J = 16.4 \text{ Hz, C=CH}), 4.77 (2 \text{ H, d, } J = 1.2 \text{ Hz, CH}_2), 3.96 (3 \text{ H, s, OMe}), 2.54 (1 \text{ H, t, } J = 1.2 \text{ Hz, C=CH}), 2.10 (3 \text{ H, s, Me}); \delta_{\text{C}} (100 \text{ MHz}; \text{CDCl}_3) 156.3 (\text{C}), 154.9 (\text{C}), 145.8 (\text{C}), 129.2 (\text{CH}), 127.3 (\text{CH}), 126.6 (\text{CH}), 126.4 (\text{CH}), 121.8 (\text{CH}), 112.8 (\text{CH}), 78.5 (\text{C}), 75.8 (\text{CH}), 61.8 (\text{Me}), 56.3 (\text{CH}_2), 10.2 (\text{Me}); m/z (ESI) 252 (MNa\text{\textsuperscript{+}}, 11\%), 230 (M\text{H}^+, 100).
(3E)-4-(3-Methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one O-methyloxime 331

Following general procedure 9, the *title compound* was obtained from ketone 327 (0.300 g, 1.40 mmol), methoxylamine hydrochloride (0.146 g, 1.75 mmol) and sodium acetate (0.200 g, 1.47 mmol) as a colourless oil (0.333 g, 98%); (Found: MH⁺, 244.1346, C₁₅H₁₇NO₂ + H requires 244.1332); νmax (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 2127 (C=C), 1619 (C=C), 1586 (C=C), 1462 (C=C), 1240 (C-O), 1056 (C-O); δH (400 MHz; CDCl₃) 7.43 (1 H, d, J = 6.8 Hz, H-10), 7.29 (1 H, d, J = 16.8 Hz, C=CH), 7.13 (1 H, d, J = 7.2 Hz, H-8), 7.05 (1 H, t, J = 7.2 Hz, H-9), 6.81 (1 H, d, J = 16.8 Hz, C=CH), 4.51 (2 H, d, J = 1.2 Hz, CH₂), 3.96 (3 H, s, OMe), 2.54 (1 H, t, J = 1.2 Hz, C=CH), 2.34 (3 H, s, Me), 2.12 (3 H, s, Me); δc (100 MHz; CDCl₃) 156.1 (C), 154.8 (C), 131.9 (C), 131.2 (CH), 130.2 (C), 127.9 (CH), 126.9 (CH), 124.9 (CH), 124.0 (CH), 79.0 (C), 75.6 (CH), 61.9 (Me), 61.1 (CH₂), 16.4 (Me), 10.2 (Me); m/z (ESI) 266 (MNa⁺, 22%), 244 (MH⁺, 100).
(3E)-3-Methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one O-methyl oxime 332

Following general procedure 9, the title compound was obtained from ketone 328 (0.297 g, 1.30 mmol), methoxylamine hydrochloride (0.136 g, 1.63 mmol) and sodium acetate trihydrate (0.186 g, 1.37 mmol) as a colourless oil (0.242 g, 72%); (Found: MH^+, 258.1497. C_{16}H_{19}N_{2}O_{2} + H requires 258.1489); ν_{max} (CHCl_{3})/cm^{-1} 3308 (alkyne C-H), 2128 (C≡C), 1586 (C≡C), 1461 (C=C), 1253 (C-O), 1055 (C-O); δ_{H} (400 MHz; CDCl_{3}) 7.14 - 7.13 (2 H, m, ArH), 7.06 (1 H, d, J = 7.6 Hz, H-8), 7.01 (1 H, s, C≡CH), 4.47 (2 H, d, J = 1.2 Hz, CH_{2}), 3.97 (3 H, s, OMe), 2.48 (1 H, t, J = 1.2 Hz, C≡CH), 2.36 (3 H, s, Me), 2.15 (3 H, s, Me), 2.06 (3 H, s, Me); δ_{C} (100 MHz; CDCl_{3}) 156.9 (C), 155.0 (C), 135.7 (C), 131.5 (C), 130.7 (C), 130.3 (CH), 128.6 (CH), 126.5 (CH), 124.0 (CH), 79.3 (C), 75.0 (CH), 61.8 (Me), 60.5 (CH_{2}), 16.5 (Me), 14.4 (Me), 10.8 (Me); m/z (ESI) 280 (MNa^+, 32%), 258 (MH^+, 100).
(3E)-1-Methoxy-3-methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one

O-methyloxime 333

Following general procedure 9, the title compound was obtained from ketone 329 (0.387 g, 1.50 mmol), methoxylamine hydrochloride (0.157 g, 1.88 mmol) and sodium acetate trihydrate (0.214 g, 1.58 mmol) as a colourless oil (0.410 g, 95%); (Found: MH+, 288.1603. C17H21NO3 + H requires 288.1594); v_max (CHCl3)/cm⁻¹ 3308 (alkyne C-H), 2127 (C≡C), 1596 (C=C), 1461 (C=C), 1254 (C-O), 1051 (C-O); δ_H (400 MHz; CDCl3) 7.18-7.13 (2 H, m, ArH), 7.06 (1 H, d, J = 7.4 Hz, H-8), 4.52 (2 H, d, J = 1.2 Hz, CH₂), 4.51 (2 H, s, CH₂), 3.99 (3 H, s, OMe), 3.43 (3 H, s, OMe), 2.50 (1 H, t, J = 1.2 Hz, C≡CH), 2.49 (3 H, s, Me), 2.03 (3 H, s, Me); δ_C (100 MHz; CDCl3) 156.7 (C), 154.8 (C), 133.3 (C), 131.6 (C), 130.6 (C), 130.5 (CH), 128.6 (CH), 127.8 (CH), 123.9 (CH), 79.4 (C), 75.0 (CH), 62.3 (CH₂), 62.0 (Me), 60.4 (CH₂), 58.6 (Me), 16.6 (Me), 14.6 (Me); m/z (ESI) 310 (MNa⁺, 67%), 288 (MH⁺, 100).
(3E)-4-(2-(3-Phenylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one O-methyl oxime 340

Following general procedure 9, the title compound was obtained from ketone 339 (0.667 g, 2.30 mmol), methoxylamine hydrochloride (0.240 g, 2.88 mmol) and sodium acetate trihydrate (0.329 g, 2.42 mmol) as a colourless oil (0.690 g, 94%); (Found: MH$^+$, 320.1661. C$_{21}$H$_{21}$N0$_2$ + H requires 320.1645); $\nu$$_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 2235 (C=C), 1599 (C=C), 1491 (C=C), 1462 (C=C), 1443 (C=C), 1244 (C-O), 1056 (C-O); $\delta$$_{\text{H}}$ (400 MHz; CDCl$_3$) 7.49-7.31 (7 H, m, 6 $\times$ ArH + C=CH), 7.17 (1 H, d, $J$ = 7.4 Hz, H-8), 7.08 (1 H, t, $J$ = 7.4 Hz, H-9), 6.86 (1 H, d, $J$ = 16.6 Hz, C=CH), 4.77 (2 H, s, CH$_2$), 3.97 (3 H, s, OMe), 2.41 (3 H, s, Me), 2.08 (3 H, s, Me); $\delta$$_{\text{C}}$ (100 MHz; CDCl$_3$) 156.2 (C), 155.0 (C), 131.9 (CH), 131.8 (C), 131.2 (CH), 130.3 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 126.7 (CH), 124.8 (CH), 124.0 (CH), 122.3 (C), 87.4 (C=CPh), 84.3 (C=CPh), 62.0 (CH$_2$), 61.9 (OMe), 16.5 (Me), 10.2 (Me); $m/z$ (ESI) 342 (MNa$^+$, 42%), 320 (MH$^+$, 100), 288 (30).
(3E)-4-(2-(3-Methoxycarbonylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one

*O*-methyl oxime 341

Following general procedure 10, the *title compound* was obtained from *O*-methyl oxime 331 (0.973 g, 4.00 mmol) and methyl chloroformate (0.46 mL, 6.00 mmol) as a colourless oil (0.495 g, 41%); (Found: MH⁺, 302.1388. C₁₇H₁₉NO₄ + H requires 302.1387); νmax (CHCl₃)/cm⁻¹ 2245 (C≡C), 1717 (C=O), 1585 (C=C), 1462 (C=C), 1436 (C=C), 1266 (C-O), 1056 (C-O); δH (400 MHz; CDCl₃) 7.43 (1 H, d, J = 7.6 Hz, H-10), 7.23 (1 H, d, J = 16.5 Hz, C=CH), 7.14 (1 H, d, J = 7.6 Hz, H-8), 7.07 (1 H, t, J = 7.6 Hz, H-9), 6.82 (1 H, d, J = 16.5 Hz, C=CH), 4.65 (2 H, s, CH₂), 3.86 (3 H, s, OMe), 3.77 (3 H, s, OMe), 2.34 (3 H, s, Me), 2.11 (3 H, s, Me); δC (100 MHz; CDCl₃) 156.1 (C), 154.5 (C), 153.3 (C), 131.6 (C), 131.3 (CH), 130.2 (C), 127.5 (CH), 127.4 (CH), 125.2 (CH), 124.3 (CH), 82.6 (C), 78.6 (C), 61.9 (Me), 60.6 (CH₂), 52.8 (Me), 16.4 (Me), 10.2 (Me); m/z (ESI) 324 (MNa⁺, 100%), 302 (MH⁺, 17).
Following general procedure 10, the title compound was obtained from O-methyl oxime 331 (0.973 g, 4.00 mmol) and N-chlorosuccinimide (0.801 g, 6.00 mmol) as a colourless oil (0.546 g, 49%); (Found: MH⁺, 278.0947. C₁₅H₁₆ClNO₂ + H requires 278.0942); νₓ max (CHCl₃/cm⁻¹ 2245 (C=Ć), 1627 (C=C), 1586 (C=C), 1463 (C=C), 1056 (C-O); δₜ (400 MHz; CDCl₃) 7.44 (1 H, d, J = 7.6 Hz, H-8), 7.28 (1 H, d, J = 16.6 Hz, C=CH), 7.13 (1 H, d, J = 7.6 Hz, H-10), 7.06 (1 H, t, J = 7.6 Hz, H-9), 6.82 (1 H, d, J = 16.6 Hz, C=CH), 4.52 (2 H, s, CH₂), 3.97 (3 H, s, OMe), 2.33 (3 H, s, Me), 2.13 (3 H, s, Me); δₓ (100 MHz; CDCl₃) 156.1 (C), 154.7 (C), 131.7 (C), 131.3 (CH), 130.3 (C), 127.8 (CH), 126.8 (CH), 125.0 (CH), 124.0 (CH), 66.0 (C), 64.9 (C), 61.9 (Me), 61.5 (CH₂), 16.3 (Me), 10.2 (Me); m/z (ESI) m/z (ESI) 280/278 (MH⁺, 36/100%), 246 (30).
(3E)-4-(2-(3-Trimethylsilylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one  O-methyl oxime 343

Following general procedure 10, the *title compound* was obtained from O-methyl oxime 331 (0.973 g, 4.00 mmol) and chlorotrimethylsilane (0.77 mL, 6.00 mmol) as a colourless oil (0.664 g, 53%); (Found: MH⁺, 316.1724. C₁₈H₂₅NO₂Si + H requires 316.1727); ν_max (CHCl₃)/cm⁻¹ 2181 (C=O), 1625 (C=C), 1586 (C=C), 1462 (C=C), 1056 (C-O), 848 (C-Si); δ_H (400 MHz; CDCl₃) 7.44 (1 H, d, J = 7.6 Hz, H-10), 7.30 (1 H, d, J = 16.5 Hz, C=CH), 7.13 (1 H, d, J = 7.6 Hz, H-8), 7.05 (1 H, t, J = 7.6 Hz, H-9), 6.82 (1 H, d, J = 16.5 Hz, C=CH), 4.53 (2 H, s, CH₂), 3.98 (3 H, s, OMe), 2.35 (3 H, s, Me), 2.14 (3 H, s, Me), 0.18 (9 H, s, SiMe₃); δ_C (100 MHz; CDCl₃) 156.5 (C), 155.2 (C), 132.1 (C), 131.5 (CH), 130.5 (C), 128.4 (CH), 127.0 (CH), 125.1 (CH), 124.2 (CH), 100.8 (C), 93.0 (C), 62.2 (CH₂), 61.9 (OMe), 16.8 (Me), 10.6 (Me), 0.0 (SiMe₃); m/z (ESI) 338 (MNa⁺, 18%), 316 (MH⁺, 100).
2-Methyl-5H-chromeno[3,4-c]pyridine

Following general procedure 11, the title compound was obtained from O-methyl oxime (0.115 g, 0.50 mmol) after 16 h at 180 °C as a yellow oil (0.030 g, 30%); $\nu_{max}$ (CHCl$_3$/cm$^{-1}$) 1610 (C=C), 1588 (C=C), 1553 (C=C), 1499 (C=C), 1485 (C=C), 1457 (C=C); $\delta$$_H$ (400 MHz; CDCl$_3$) 8.30 (1 H, s, H-4), 7.73 (1 H, d, $J$ = 8.0 Hz, H-10), 7.41 (1 H, s, H-1), 7.33 (1 H, t, $J$ = 8.0 Hz, H-9), 7.08 (1 H, t, $J$ = 8.0 Hz, H-8), 7.01 (1 H, d, $J$ = 8.0 Hz, H-7), 5.13 (2 H, s, CH$_2$), 2.61 (3 H, s, Me); $\delta$$_C$ (100 MHz; CDCl$_3$) 158.7 (C), 155.8 (C), 145.0 (CH), 137.9 (C), 131.6 (CH), 123.9 (CH), 123.2 (C), 122.3 (CH), 120.6 (C), 117.8 (CH), 115.4 (CH), 65.8 (CH$_2$), 24.5 (Me).

2,7-Dimethyl-5H-chromeno[3,4-c]pyridine

(a) Following general procedure 11, the title compound was obtained from O-methyl oxime (0.122 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.039 g, 37%), mp 107-109 °C (from ethyl acetate-hexane); (Found: MH$^+$, 212.1079. C$_{14}$H$_{13}$NO + H requires 212.1079); $\nu_{max}$ (CHCl$_3$/cm$^{-1}$) 1610 (C=C), 1599 (C=C), 1561 (C=C), 1465 (C=C), 1021 (C-O); $\delta$$_H$ (400 MHz; CDCl$_3$) 8.30 (1 H, s, H-4), 7.57 (1 H,
d, $J = 7.7$ Hz, H-10), 7.38 (1 H, s, H-1), 7.21 (1 H, d, $J = 7.4$ Hz, H-8), 6.97 (1 H, dd, $J = 7.4$ and 7.7 Hz, H-9), 5.13 (2 H, s, CH$_2$), 2.60 (3 H, s, Me), 2.27 (3 H, s, Me); $\delta_C$ (100 MHz; CDCl$_3$) 158.6 (C), 153.9 (C), 144.9 (CH), 138.3 (C), 132.8 (CH), 127.2 (C), 123.2 (C), 121.6 (CH), 121.5 (CH), 120.1 (C), 115.5 (CH), 65.8 (CH$_2$), 24.6 (Me), 15.9 (Me); $m/z$ (ESI) 212 (MH$^+$, 100%).

(b) Following general procedure 11, the title compound was obtained from O-methyl oxime 343 (0.158 g, 0.50 mmol) after 120 h at 180-200 °C as a colourless solid (0.013 g, 12%); data as above.

(c) Following general procedure 12, the title compound was obtained from ketone 327 (0.107 g, 0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) as a colourless solid (0.031 g, 29%); data as above.
1,2,7-Trimethyl-5H-chromeno[3,4-c]pyridine 336

Following general procedure 11, the title compound was obtained from O-methyl oxime 332 (0.129 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.026 g, 26%), mp 74-76 °C (from ethyl acetate-hexane); (Found: MH+, 226.1232. C15H16NO + H requires 226.1226); νmax (CHCl3)/cm⁻¹ 1590 (C=C), 1556 (C=C), 1464 (C=C), 1066 (C-O); δH (400 MHz; CDCl3) 8.18 (1 H, s, H-4), 7.59 (1 H, d, J = 8.0 Hz, H-10), 7.20 (1 H, d, J = 7.2 Hz-8), 7.02 (1 H, t, J = 7.2 Hz, H-9), 4.95 (2 H, s, CH2), 2.60 (3 H, s, Me), 2.53 (3 H, s, Me), 2.31 (3 H, s, Me); δC (100 MHz; CDCl3) 158.6 (C), 155.7 (C), 141.7 (CH), 137.2 (C), 131.8 (CH), 127.2 (C), 126.9 (C), 126.6 (C), 126.4 (CH), 122.1 (C), 120.8 (CH), 66.9 (CH2), 23.9 (Me), 17.7 (Me), 16.0 (Me); m/z (ESI) m/z (ESI) 226 (MH+, 100%).

2-Methoxymethyl-1,7-dimethyl-5H-chromeno[3,4-c]pyridine 337

Following general procedure 11, the title compound was obtained from O-methyl oxime 333 (0.144 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.035 g, 27%), mp 50-52 °C (from ethyl acetate-hexane); (Found: MH+, 256.1346. C16H17NO2
New Developments in the 1-Aza-Diels-Alder Reaction

Timothy E. Hurst

+ H requires 256.1332; \( \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} \) 1588 (C=C), 1556 (C=C), 1464 (C=C), 1094 (C-O); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 8.30 (1 H, s, H-4), 7.65 (1 H, d, \( J = 7.9 \) Hz, H-10), 7.23 (1 H, d, \( J = 7.6 \) Hz, H-8), 7.04 (1 H, dd, \( J = 7.6 \) and 7.9 Hz, H-9), 5.00 (2 H, s, CH\(_2\)), 4.72 (2 H, s, CH\(_2\)), 3.48 (3 H, s, OMe), 2.64 (3 H, s, Me), 2.33 (3 H, s, Me); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 157.1 (C), 155.6 (C), 142.0 (CH), 138.1 (C), 132.1 (CH), 128.4 (C), 128.0 (C), 127.2 (C), 126.5 (CH), 121.9 (C), 120.9 (CH), 75.6 (CH\(_2\)), 66.8 (CH\(_2\)), 58.5 (Me), 16.8 (Me), 16.0 (Me); \( m/z \) (ESI) 270 (32%), 256 (MH\(^+\), 100%).

2,7-Dimethyl-4-phenyl-5H-chromeno[3,4-c]pyridine 344

(\( a \)) Following general procedure 11, the **title compound** was obtained from O-methyl oxime 340 (0.160 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.089 g, 62%), mp 148-150 °C (from ethyl acetate-hexane); (Found: MH\(^+\), 288.1396. C\(_{20}\)H\(_{17}\)NO + H requires 288.1383); \( \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} \) 1595 (C=C), 1579 (C=C), 1560 (C=C), 1498 (C=C), 1471 (C=C), 1450 (C=C), 1420 (C=C), 1021 (C-O); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 7.64 (1 H, d, \( J = 7.6 \) Hz, H-10), 7.51-7.44 (5 H, m, ArH), 7.42 (1 H, s, H-3), 7.22 (1 H, d, \( J = 7.5 \) Hz, H-8), 7.02 (1 H, dd, \( J = 7.5 \) and 7.6 Hz, H-9), 5.18 (2 H, s, CH\(_2\)), 2.69 (3 H, s, Me), 2.27 (3 H, s, Me); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 157.7 (C), 155.2 (C), 153.9 (C), 139.2 (C), 139.0 (C), 132.6 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.0 (C), 121.8 (CH), 121.7(CH), 121.3 (C), 120.8 (C), 114.9 (CH), 65.5 (CH\(_2\)), 24.8 (Me), 15.8 (Me); \( m/z \) (ESI) 288 (MH\(^+\), 100%).
(b) Following general procedure 11, the title compound was obtained from O-methyl oxime 340 (0.151 g, 0.50 mmol) after 16 h at 140 °C as a colourless solid (0.055 g, 41%); data as above.

Methyl 2,7-dimethyl-5H-chromeno[3,4-c]pyridine-4-carboxylate 345

(a) Following general procedure 11, the title compound was obtained from O-methyl oxime 341 (0.090 g, 0.30 mmol) after 16 h at 180 °C as a colourless solid (0.040 g, 50%), mp 47-49 °C (from ethyl acetate-hexane); (Found: MH⁺, 270.1129. C₁₆H₁₅N₂O₃ + H requires 270.1125); νmax (CHCl₃)/cm⁻¹ 1719 (C=O), 1597 (C=C), 1556 (C=C), 1472 (C=C), 1438 (C=C) 1087 (C-O); δH (400 MHz; CDCl₃) 7.56-7.55 (2 H, m, ArH), 7.21 (1 H, d, J = 7.3 Hz, H-8), 6.97 (1 H, dd, J = 7.3 and 8.1 Hz, H-9), 5.52 (2 H, s, CH₂), 4.01 (3 H, s, OMe), 2.67 (3 H, s, Me), 2.28 (3 H, s, Me); δC (100 MHz; CDCl₃)
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165.0 (C), 156.7 (C), 152.9 (C), 142.4 (C), 139.1 (C), 132.1 (CH), 126.1 (C), 125.7 (C), 120.6 (CH), 120.5 (CH), 118.4 (C), 117.8 (CH), 63.9 (CH₂), 51.9 (Me), 23.6 (Me), 14.6 (Me); m/z (ESI) 292 (MNa⁺, 28%), 284 (41), 270 (MH⁺, 100).

(b) Following general procedure 11, the title compound was obtained from O-methyl oxime 341 (0.151 g, 0.50 mmol) after 16 h at 140 °C as a colourless solid (0.055 g, 41%); data as above.

4-Chloro-2,7-dimethyl-5H-chromeno[3,4-c]pyridine 346

Following general procedure 11, the title compound was obtained from O-methyl oxime 342 (0.139 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.020 g, 16%), mp 110-112 °C (from ethyl acetate-hexane); (Found: MH⁺, 246.0683. C₁₄H₁₂ClNO + H requires 246.0680); νmax (CHCl₃)/cm⁻¹ 1600 (C=C), 1548 (C=C), 1448 (C=C), 1056 (C-O); δH (400 MHz; CDCl₃) 7.54 (1 H, d, J = 7.7 Hz, H-10), 7.35 (1 H, s, H-1), 7.23 (1 H, d, J = 7.7 Hz, H-8), 6.99 (1 H, t, J = 7.7 Hz, H-9), 5.26 (2 H, s, CH₂), 2.59 (3 H, s, Me), 2.28 (3 H, s, Me); δC (100 MHz; CDCl₃) 158.6 (C), 153.7 (C), 146.5 (C), 141.4 (C), 133.4 (CH), 127.3 (C), 121.8 (CH), 121.7 (CH), 121.4 (C), 119.2 (C), 115.0 (CH), 64.7 (CH₂), 24.3 (Me), 15.8 (Me); m/z (ESI) 248/246 (MH⁺, 30/100%). Also obtained was 2,7-dimethyl-5H-chromeno[3,4-c]pyridine 240 (30%).
2-Hydroxy-3,4-dimethoxybenzaldehyde\textsuperscript{138} 279

To a solution of 2,3,4-trimethoxybenzaldehyde 347 (75.0 g, 0.382 mol) in benzene (1000 mL) was added aluminium trichloride (53.5 g, 0.401 mol). The reaction mixture was heated at reflux for 6 h then cooled to room temperature. Ice/water (1000 mL) and concentrated hydrochloric acid (200 mL) were added and the reaction mixture stirred for 30 min. The organics was separated and the aqueous layer was extracted with ether (6 × 1000 mL). The combined organics were washed with water (2000 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (49.5 g, 71\%), mp 70 - 71 °C (lit.,\textsuperscript{138} mp 69 - 70 °C); \(\delta\)\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 11.2 (1 H, s, CHO), 9.7 (1 H, s, OH), 7.29 (1 H, d, \(J = 8.7\) Hz, ArH), 6.60 (1 H, d, \(J = 8.7\) Hz, ArH), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe); \(\delta\)\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 195.0 (CH), 159.4 (C), 155.7 (C), 136.1 (C), 130.3 (CH), 116.5 (C), 104.1 (CH), 60.7 (OMe), 56.2 (OMe).

3,4-Dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318

Following general procedure 6, the \textit{title compound} was obtained from 2-hydroxy-3,4-dimethoxybenzaldehyde 279 (36.4 g, 0.2200 mol), potassium carbonate (41.4 g, 0.300
mol) and propargyl chloride (71.6 mL, 1.00 mol) as a pale yellow solid (36.2 g, 82%), mp 106-107 °C (from ethanol); (Found: MH⁺, 221.0822. C₁₂H₁₂O₄ + H requires 221.0814); vₘₐₓ (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 2125 (C≡C), 1678 (C=O), 1592 (C=C), 1498 (C=C), 1460 (C=C); δ_H (400 MHz; CDCl₃) 10.3 (1 H, d, J = 0.7 Hz, CHO), 7.64 (1 H, d, J = 8.8 Hz, ArH), 6.81 (1 H, d, J = 8.8 Hz, ArH), 4.91 (2 H, d, J = 2.4 Hz, CH₂), 3.94 (3 H, s, OMe), 3.89 (3 H, s, OMe), 2.50 (1 H, t, J = 2.4 Hz, C≡CH); δ_C (75 MHz; CDCl₃) 189.2 (C), 159.0 (CH), 154.2 (C), 141.7 (C), 129.0 (C), 128.2 (C), 124.5 (C), 123.7 (CH), 108.3 (CH), 61.4 (OMe), 61.1 (OMe), 56.2 (CH₂); m/z (EI) 221 (MH⁺, 100%), 193 (37), 189 (80).

**Diethyl 1-methyl-2-oxopropylphosphonate**

![Chemical structure](image)

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate (10.0 g, 60.2 mmol) and ethyl acetate (5.83 g, 66.2 mmol) as a colourless oil (11.4 g, 91%); vₘₐₓ (CHCl₃)/cm⁻¹ 1714 (C=O), 1302 (P=O); δ_H (400 MHz; CDCl₃) 4.16 - 4.07 (4 H, m, 2 × CH₂), 3.25 - 3.13 (1 H, dq, J = 7.1 and 25.6 Hz, CH), 2.32 (3 H, s, CH₃), 1.37 - 1.29 (9 H, m, 3 × CH₃); δ_C (100 MHz; CDCl₃) 203.9 (d, ²J_C-P = 3.7 Hz, C=O), 62.6 (d, ²J_C-P = 6.7 Hz, CH₂), 62.5 (d, ²J_C-P = 6.7 Hz, CH₂), 47.5 (d, ¹J_C-P = 126.9 Hz, CH), 30.4 (Me), 16.4 (Me), 16.3 (Me), 10.8 (d, ²J_C-P = 6.5 Hz, Me).
Following general procedure 7, the title compound was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318 (0.440 g, 2.00 mmol) and diethyl 2-oxopropylphosphonate (0.583 g, 3.00 mmol) as a colourless solid (0.478 g, 92%), mp 71-72 °C (from ethanol); (Found: MH\(^+\), 261.1122. C\(_{15}\)H\(_{16}\)O\(_4\) + H requires 261.1126); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 3306 (alkyne C-H), 2126 (C≡C), 1667 (C=O), 1642 (C=C), 1594 (C=C), 1496 (C=C), 1456 (C=C), 1096 (C-O); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 7.90 (1 H, d, \(J = 16.6 \text{ Hz}, \text{C}=\text{CH}\)), 7.35 (1 H, d, \(J = 8.8 \text{ Hz}, \text{ArH}\)), 6.76 (1 H, d, \(J = 8.8 \text{ Hz}, \text{ArH}\)), 6.64 (1 H, d, \(J = 16.6 \text{ Hz}, \text{C}=\text{CH}\)), 4.83 (2 H, d, \(J = 2.4 \text{ Hz}, \text{CH}_2\)), 3.91 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.51 (1 H, t, \(J = 2.4 \text{ Hz}, \text{C}=\text{CH}\)), 2.40 (3 H, s, Me); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 199.1 (C), 155.6 (C), 150.9 (C), 142.3 (C), 138.9 (CH), 126.6 (CH), 122.4 (CH), 122.2 (C), 108.5 (CH), 78.8 (C≡CH), 76.0 (C=C), 61.1 (CH\(_2\)), 61.0 (CH\(_3\)), 56.1 (CH\(_3\)), 26.7 (CH\(_3\)); m/z (ESI) 283 (MNa\(^+\), 71%), 261 (MH\(^+\), 100).
4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one 349

Following general procedure 7, the title compound was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318 (0.440 g, 2.00 mmol) and diethyl 1-methyl-2-oxopropylphosphonate 319 (0.625 g, 3.00 mmol) as a colourless oil (0.545 g, 99%);

(Found: MNa+, 297.1097. C_{16}H_{18}O_4 + Na requires 297.1097); v_{max} (CHCl_3)/\text{cm}^{-1} 3306 (alkyne C-H), 1659 (C=O), 1625 (C=C), 1595 (C=C), 1495 (C=C), 1455 (C=C), 1365 (N=O), 1099 (C-O); δ_{H} (400 MHz; CDCl_3) 7.83 (1 H, s, C=CH), 7.17 (1 H, d, J = 8.7 Hz, ArH), 6.76 (1 H, d, J = 8.7 Hz, ArH), 4.79 (2 H, d, J = 2.4 Hz, CH_2), 3.92 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.49 (3 H, s, Me), 2.01 (3 H, s, Me); δ_{C} (100 MHz; CDCl_3) 200.6 (C), 154.2 (C), 150.4 (C), 142.2 (C), 136.9 (C), 135.6 (CH), 125.0 (C), 123.5 (CH), 107.7 (CH), 79.1 (C=CH), 75.5 (C=CH), 61.0 (OMe), 56.1 (OMe), 29.7 (CH_2), 25.8 (Me), 12.9 (Me); m/z (ESI) 297 (MNa^+, 100%), 275 (MH^+, 79), 243 (22).
(3E)-4-(3,4-Dimethoxy-2-(prop-2-ynyl)oxy)phenyl)but-3-en-2-one O-methyl oxime

Following general procedure 9, the **title compound** was obtained from α,β-unsaturated ketone 348 (0.195 g, 0.75 mmol), methoxylamine hydrochloride (0.078 g, 0.938 mmol) and sodium acetate trihydrate (0.107 g, 0.788 mmol) as a colourless oil (0.217 g, 100%); (Found: MH⁺, 290.1382. C₁₆H₁₉NO₄ + H requires 290.1387); νmax (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 2126 (C≡C), 1598 (C=C), 1497 (C=C), 1457 (C=C), 1097 (C-O); δH (400 MHz; CDCl₃) 7.31 (1 H, d, J = 8.8 Hz, ArH), 7.27 (1 H, d, J = 16.4 Hz, C=CH), 6.72 (1 H, d, J = 16.4 Hz, C=CH), 6.71 (1 H, d, J = 8.8 Hz, ArH), 4.77 (2 H, d, J = 2.4 Hz, CH₂), 3.95 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.50 (1 H, t, J = 2.4 Hz, C=CH), 2.09 (3 H, s, Me); δC (100 MHz; CDCl₃) 156.3 (C), 153.7 (C), 149.7 (C), 142.3 (C), 127.5 (CH), 124.7 (CH), 124.3 (C), 120.4 (CH), 108.5 (CH), 79.1 (C=CH), 75.6 (C=CH), 61.8 (OMe), 61.1 (CH₂), 60.9 (OMe), 56.0 (OMe), 10.1 (Me); m/z (ESI) 312 (MNa⁺, 100%), 290 (MH⁺, 38).
(3E)-4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one  O-methyl oxime 351

Following general procedure 9, the title compound was obtained from α,β-unsaturated ketone 349 (0.206 g, 0.75 mmol), methoxylamine hydrochloride (0.078 g, 0.938 mmol) and sodium acetate trihydrate (0.107 g, 0.788 mmol) as a colourless oil (0.228 g, 100%); Found: MH⁺, 304.1530. C₁₇H₂₁NO₄ + H requires 304.1543; vₘₐₓ (CHCl₃)/cm⁻¹ 3308 (alkyne C-H), 2126 (C≡C), 1599 (C=C), 1495 (C=C), 1455 (C=C), 1097 (C-O); ¹H (400 MHz; CDCl₃) 7.03 (1 H, s, C=CH), 7.02 (1 H, d, J = 8.8 Hz, ArH), 6.72 (1 H, d, J = 8.8 Hz, ArH), 4.71 (2 H, d, J = 2.4 Hz, CH₂), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.47 (1 H, t, J = 2.4 Hz, C=CH), 2.13 (3 H, s, Me), 2.05 (3 H, s, Me); ¹C (100 MHz; CDCl₃) 157.2 (C), 152.9 (C), 150.0 (C), 142.2 (C), 134.4 (C), 125.9 (CH), 125.0 (CH), 124.8 (C), 107.5 (CH), 79.3 (C≡C), 75.1 (C=C), 61.8 (OMe), 61.0 (OMe), 60.4 (CH₂), 56.0 (OMe), 14.4 (Me), 10.8 (Me); m/z (ESI) 326 (MNa⁺, 100%), 304 (MH⁺, 26).
7,8-Dimethoxy-2-methyl-5H-chromeno[3,4-c]pyridine 352

a. Following general procedure 11, the *title compound* was obtained from 0-methyl oxime 349 (0.100 g, 0.346 mmol) as a colourless solid (0.040 g, 45%), mp 115-117 °C (from dichloromethane-hexane); (Found: MH\(^+\), 258.1124. C\(_{13}\)H\(_{15}\)NO\(_3\) + H requires 258.1125); \(\nu\)\(_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1607 (C=C), 1508 (C=C), 1488 (C=C), 1081 (C-O); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 8.30 (1 H, s, ArH), 7.46 (1 H, d, J = 8.8 Hz, ArH), 7.33 (1 H, s, ArH), 6.68 (1 H, d, J = 8.8 Hz, ArH), 5.17 (2 H, s, CH\(_2\)), 3.93 (3 H, s, OMe), 3.91 (3 H, s, OMe), 2.60 (Me); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 158.6 (C), 155.2 (C), 145.0 (CH), 138.0 (C), 122.3 (C), 119.0 (CH), 115.2 (C), 114.9 (CH), 106.0 (CH), 66.3 (CH\(_2\)), 61.2 (OMe), 56.1 (OMe), 24.6 (Me); \(m/z\) (ESI) 258 (MH\(^+\), 100%), 242 (16).

b. Following general procedure 12, the *title compound* was obtained from ketone 348 (0.052, 0.200 mmol), methoxylamine hydrochloride (0.033 g, 0.400 mmol) and triethylamine (0.040 g, 0.400 mmol) as a colourless solid (0.028 g, 54%); data as above.
7,8-Dimethoxy-1,2-dimethyl-5H-chromeno[3,4-c]pyridine 353

![Chemical structure image]

a) Following general procedure 11, the title compound was obtained from O-methyl oxime 351 (0.100 g, 0.330 mmol) as a colourless solid (0.043 g, 48%), mp 131-133 °C (from dichloromethane-hexane); (Found: MH⁺, 272.1272. C₁₆H₁₇NΟ₃ + H requires 272.1281); νmax (CHCl₃)/cm⁻¹ 1592 (C=C), 1552 (C=C), 1506 (C=C), 1467 (C=C), 1104 (C-O); δH (400 MHz; CDCl₃) 8.18 (1 H, s, ArH), 7.46 (1 H, d, J = 8.8 Hz, ArH), 6.69 (1 H, d, J = 8.8 Hz, ArH), 4.98 (2 H, s, CH₂), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.58 (3 H, s, Me), 2.50 (3 H, s, Me); δc (100 MHz; CDCl₃) 158.5 (C), 154.1 (C), 151.3 (C), 141.7 (CH), 138.3 (C), 136.9 (C), 126.0 (C), 125.9 (C), 123.9 (CH), 117.0 (C), 105.0 (CH), 67.5 (CH₂), 61.3 (OMe), 56.1 (OMe), 23.8 (Me), 17.7 (Me); m/z (ESI) 272 (MH⁺, 100%).

![Chemical structure image]

b. Following general procedure 12, the title compound was obtained from α,β-unsaturated ketone 349 (0.055, 0.200 mmol), methoxylamine hydrochloride (0.033 g,
0.400 mmol) and triethylamine (0.040 g, 0.400 mmol) as a colourless solid (0.030 g, 56%); data as above.

6-Methoxyquinoline-N-oxide 354

To a solution of 6-methoxyquinoline 299 (50.0 g, 314 mmol) in glacial acetic acid (315 mL) was added 30% hydrogen peroxide (50 mL). The reaction mixture was heated at 80 °C for 3 h, then further 30% hydrogen peroxide (50 mL) was added. Stirring was continued at 80 °C for 3 h. The reaction mixture was allowed to cool to room temperature, basified with sodium hydroxide (2 M) and extracted with dichloromethane (5 × 1000 mL). The combined organics were dried over Na₂SO₄ and concentrated in vacuo to afford the title compound as a colourless solid (47.2 g, 85%), mp 109 - 110 °C (lit., 140 mp 110 - 112 °C); δH (400 MHz; CDCl₃) 8.64 (1 H, d, J = 9.5 Hz, ArH), 8.39 (1 H, dd, J = 6.0 and 0.7 Hz, ArH), 7.62 (1 H, d, J = 8.5 Hz, ArH), 7.36 (1 H, dd, J = 9.5 and 2.6 Hz, ArH), 7.24 (1 H, dd, J = 8.5 and 6.0 Hz, ArH), 7.09 (1 H, d, J = 2.6 Hz, ArH); δC (100 MHz; CDCl₃) 159.4 (C), 137.1 (C), 133.8 (CH), 132.0 (C), 125.2 (CH), 122.8 (CH), 121.5 (CH), 121.4 (CH), 105.8 (CH), 55.7 (OMe).
2-Chloro-6-methoxyquinoline 355

6-Methoxyquinoline-\(N\)-oxide 354 (20.0 g, 114 mmol) was added portionwise to phosphorus oxychloride (100 mL) at 0 °C. The reaction mixture was heated at 100 °C for 1 h and cooled to room temperature. The reaction mixture was then poured into sodium hydroxide (5 M; 1500 mL). The resulting precipitate was filtered off and washed with dichloromethane (1000 mL). The filtrate was extracted with dichloromethane (5 x 1000 mL). The combined organics were washed with water (2000 mL), dried over \(\text{Na}_2\text{SO}_4\) and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (11.0 g, 50%), mp 105 - 106 °C (lit.,\textsuperscript{140} mp 106.5 - 107.5 °C); \(\delta_H\) (400 MHz; CDCl\textsubscript{3}) 7.85 (1 H, d, \(J=8.9\) Hz, ArH), 7.82 (1 H, d, \(J=9.5\) Hz, ArH), 7.29 (1 H, dd, \(J=2.6\) Hz and 9.2 Hz, ArH), 7.21 (1 H, d, \(J=8.5\) Hz, ArH), 6.93 (1 H, d, \(J=2.4\) Hz, ArH), 3.83 (3 H, s, OMe); \(\delta_C\) (100 MHz; CDCl\textsubscript{3}) 185.1 (C), 148.0 (C), 143.8 (C), 137.6 (CH), 129.9 (CH), 127.9 (C), 123.1 (CH), 122.5 (CH), 105.3 (CH), 55.6 (OMe).

2-Iodo-6-methoxyquinoline 356

To a solution of 2-chloro-6-methoxyquinoline 355 (22.0 g, 114 mmol) and sodium iodide (85.4 g, 570 mmol) in acetonitrile (450 mL) was added hydrochloric acid (5 M;
22 mL). The reaction mixture was heated under reflux for 17 h and concentrated in vacuo. Water (1000 mL) was added and the aqueous phase neutralised with saturated sodium hydrogen carbonate. The aqueous phase was then extracted with dichloromethane (4 × 1000 mL) and chloroform (4 × 1000 mL). The combined organics were dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the title compound as a colourless solid (29.2 g, 90%), mp 144 - 145 °C (lit., 140 mp 146 - 147 °C); δ_H (400 MHz; CDCl₃) 7.93 (1 H, d, J = 9.2 Hz, H-8), 7.66 (2 H, m, H-3/4), 7.34 (1 H, dd, J = 9.2 and 2.8 Hz, H-7), 7.02 (1 H, d, J = 2.8 Hz, H-5), 3.92 (3 H, s, OMe); δ_C (100 MHz; CDCl₃) 158.1 (C), 145.8 (C), 136.0 (CH), 132.1 (CH), 130.3 (CH), 128.3 (C), 105.3 (CH), 55.6 (OMe).

2-Iodo-6-methoxy-5-nitroquinoline 317

Three flasks were each charged with 2-iodo-6-methoxyquinoline 356 (9.25 g, 32.4 mmol) in concentrated sulfuric acid (35.5 mL) at 0 °C. To each reaction was added nitric acid (70%; 6.5 mL) dropwise over 30 min. Stirring was continued at 0 °C for 45 min. Each reaction mixture was poured onto ice (350 mL), basified with sodium hydroxide (2 M) and extracted with dichloromethane (3 × 500 mL) and chloroform (3 × 500 mL). The combined organics were washed with water (500 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was combined and filtered through a pad of silica gel, eluting with dichloromethane, to afford the title compound as a pale yellow solid (16.6 g, 52%), mp 173 - 174 °C (lit., 140 mp 171.5 - 173 °C); δ_H
(400 MHz; CDCl₃) 8.21 (1 H, d, J = 9.5 Hz, H-4), 7.83 (1 H, d, J = 8.9 Hz, H-8), 7.69 (1 H, d, J = 8.9 Hz, H-7), 7.57 (1 H, d, J = 9.5 Hz, H-3), 4.08 (3 H, s, OMe); δc (100 MHz; CDCl₃) 149.6 (C), 143.4 (C), 134.4 (CH), 133.5 (CH), 132.3 (C), 130.3 (CH), 120.6 (C), 117.5 (C), 117.0 (CH), 57.3 (OMe).

Prop-2-ynyl-4-methylbenzenesulfonate

To a solution of propargyl alcohol 357 (1.46 mL, 25.0 mmol) and para-toluenesulfonyl chloride (5.72 g, 30.0 mmol) in ether (100 mL) at -5 °C was added potassium hydroxide (14.0 g, 250 mmol) portionwise. Stirring was continued at -5 °C for 2 h. The reaction mixture was poured into water (100 mL) and extracted with ether (2 x 100 mL). The combined organics were washed with water (2 x 100 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4), to afford the title compound as a colourless oil (4.44 g, 84%); ν max (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 2135 (C≡C), 1598 (C≡C), 1494 (C≡C), 1452 (C≡C), 1368 (S=O), 1096 (S=O); δh (400 MHz; CDCl₃) 7.83 (2 H, d, J = 8.4 Hz, ArH), 7.36 (2 H, d, J = 8.4 Hz, ArH), 4.71 (2 H, d, J = 2.5 Hz, CH₂), 2.48 (1 H, t, J = 2.5 Hz, C≡CH), 2.47 (3 H, s, Me); δc (100 MHz; CDCl₃) 145.2 (C), 132.9 (C), 129.9 (CH), 128.1 (CH), 75.4 (C≡CH), 57.3 (CH₂), 21.7 (Me).
2-[(Prop-2-yn-1-yl)oxy]tetrahydropyran\(^{142}\) \(\text{359}\)

\[
\begin{array}{c}
\text{\(\text{357}\)} \\
\text{\(\rightarrow\)} \\
\text{\(\text{359}\)}
\end{array}
\]

To a solution of propargyl alcohol \(\text{357}\) (1.74 mL, 30.0 mmol) and \(2H\)-3,4-dihydropyran (3.28 mL, 36.0 mmol) in dichloromethane (75 mL) was added para-toluenesulfonic acid (0.050 g, 0.263 mmol). The reaction mixture was stirred for 20 h and poured into water (200 mL). The aqueous layer was separated and extracted with dichloromethane (150 mL). The combined organics were washed with water (200 mL) and saturated brine (200 mL), dried over MgSO\(_4\) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:49 to 1:19), to afford the title compound as a colourless oil (3.12 g, 74\%); \(v_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 3307 (alkyne C-H), 2122 (C=\(\equiv\)C), 1119 (C-O), 1077 (C-O), 1056 (C-O), 1042 (C-O); \(\delta_H\) (400 MHz; CDCl\(_3\)) 4.83 (1 H, t, \(J = 3.3\) Hz, CH), 4.30 (1 H, dd, \(J = 15.7\) and 2.4 Hz, CH), 4.24 (1 H, dd, \(J = 15.7\) and 2.4 Hz, CH), 3.88-3.82 (1 H, m, CH), 3.57-3.52 (1 H, m, CH), 2.42 (1 H, t, \(J = 2.4\) Hz, CH), 1.90-1.49 (6 H, m, 3\(\times\) CH\(_2\)); \(\delta_C\) (100 MHz; CDCl\(_3\)) 96.9 (CH), 79.8 (C\(\equiv\)CH), 74.0 (C\(\equiv\)CH), 62.0 (CH\(_2\)), 54.0 (CH\(_2\)), 30.2 (CH\(_2\)), 25.3 (CH\(_2\)), 19.0 (CH\(_2\)).

6-Methoxy-5-nitro-2-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)quinoline \(\text{362}\)

\[
\begin{array}{c}
\text{\(\text{317}\)} \\
+ \\
\text{\(\text{359}\)} \\
\rightarrow \\
\text{\(\text{362}\)}
\end{array}
\]

Following general procedure 12, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline \(\text{317}\) (1.10 g, 3.33 mmol) and 2-[(prop-2-yn-1-yl)oxy]tetrahydropyran \(\text{359}\) (0.700 g, 5.00 mmol) as a pale orange solid (0.912 g,
80%), mp 107-109 °C (from ethanol); (Found: MH+, 343.1281. C_{18}H_{18}N_{2}O_{2} + H requires 343.1299); \nu_{\text{max}} \text{(CHCl}_3)/\text{cm}^{-1} \ 1628 \ (C=C), 1595 \ (C=C), 1550 \ (N=O), 1494 \ (C=C), 1460 \ (C=C), 1356 \ (N=O), 1120 \ (C=O), 1078 \ (C=O); \delta_{H} \ (400 \text{ MHz; CDCl}_3)

8.15 \ (1 \text{ H, d, } J = 9.5 \text{ Hz, ArH}), 7.96 \ (1 \text{ H, d, } J = 8.8 \text{ Hz, ArH}), 7.55 \ (1 \text{ H, d, } J = 8.8 \text{ Hz, ArH}), 7.54 \ (1 \text{ H, d, } J = 9.5 \text{ Hz, ArH}), 4.87 \ (1 \text{ H, t, } J = 3.4 \text{ Hz, CH}), 4.55 \ (1 \text{ H, d, } J = 16.1 \text{ Hz, C=CCH}), 4.49 \ (1 \text{ H, d, } J = 16.1 \text{ Hz, C=CCH}), 4.03 \ (3 \text{ H, s, OMe}), 3.87-3.81 \ (1 \text{ H, m, CH}), 3.56-3.51 \ (1 \text{ H, m, CH}), 1.82-1.52 \ (6 \text{ H, m, } 3 \times \text{ CH}_2); \delta_{C} \ (100 \text{ MHz; CDCl}_3) \ 149.7 \ (C), 142.2 \ (C), 142.0 \ (C), 134.4 \ (C), 133.9 \ (CH), 129.4 \ (CH), 126.6 \ (CH), 120.2 \ (C), 116.8 \ (CH), 97.2 \ (CH), 87.3 \ (C), 84.8 \ (C), 62.0 \ (CH_2), 57.2 \ (CH_2), 54.5 \ (CH_2), 30.2 \ (CH_2), 25.3 \ (CH_2), 18.9 \ (CH_2); m/z \ (ESI) 365 \ (20\%), 343 \ (MH^+, 100), 241 \ (21).

3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-yn-1-ol 360

To a solution of 6-methoxy-5-nitro-2-(3-(tetrahydro-2H-pyran-2-ylxyloxy)prop-1-ynyl)quinoline 362 (0.850 g, 2.48 mmol) in ethanol (35 mL) was added para-toluenesulfonic acid (0.095 g, 0.496 mmol) in one portion. The reaction mixture was stirred at room temperature for 4 h and concentrated in vacuo. The residue was partitioned between water (100 mL) and chloroform (3 × 250 mL). The combined organics were washed with saturated sodium hydrogen carbonate (250 mL) and saturated brine (250 mL), dried over MgSO\textsubscript{4} and concentrated in vacuo to afford the title compound as an orange solid (0.626 g, 98%), mp 223-225 °C with decomposition
(from ethanol); (Found: MH⁺, 259.0707. C₁₃H₁₀N₂O₄ + H requires 259.0724); νₛₐₐₓ
(CHCl₃)/cm⁻¹ 3696 (O-H), 3606 (O-H), 1628 (C=C), 1600 (C=C), 1494 (C=C), 1459
(C=C), 1356 (N=O), 1100 (C-O); δH (400 MHz; CDCl₃) 8.23 (1 H, d, J = 9.5 Hz,
ArH), 8.07 (1 H, d, J = 9.4 Hz, ArH), 7.95 (1 H, d, J = 9.6 Hz, ArH), 7.69 (1 H, d, J =
8.8 Hz, ArH), 5.51 (1 H, br s, OH), 4.39 (2 H, s, CH₂), 4.08 (3 H, s, OMe); δC (100
MHz; CDCl₃) 149.4 (C), 141.7 (C), 141.5 (C), 133.6 (CH), 129.3 (CH), 126.6 (CH),
119.2 (C), 118.3 (CH), 96.6 (C), 91.2 (C), 83.3 (C), 57.5 (Me), 49.3 (CH₂); m/z (ESI)
365 (17%), 343 (76), 281 (19), 279 (28), 259 (MH⁺, 100), 241 (19).

3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-yny1 4-methylbenzenesulfonate 361

![Chemical structure](image)

To a suspension of sodium hydride (0.010 g, 0.260 mmol) in THF (3 mL) at 0 °C was
added 3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-yn-1-ol 360 (0.052 g, 0.200 mmol) in
one portion. The reaction mixture was allowed to warm to room temperature, stirred
for 30 min then cooled back to 0 °C. Para-toluenesulfonyl chloride (0.046 g, 0.240
mmol) was added, and the reaction mixture was allowed to warm to room temperature
and stirred for 2 h. The solvent was removed in vacuo, and the residue was dissolved
in ethyl acetate (50 mL) and washed with water (3 × 25 mL). The organic layer was
dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash
chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to
afford the title compound as a colourless solid (0.065 g, 79%), mp 138-140 °C (from
dichlormethane-hexane); (Found: MH⁺, 413.0798. C₂₀H₁₆N₂O₆S + H requires
413.0802); δH (400 MHz; CDCl₃) 8.23 (1 H, d, J = 9.2 Hz, ArH), 8.03 (1 H, d, J = 8.0
Hz, ArH), 7.89 (2 H, d, J = 6.8 Hz, ArH), 7.62 (1 H, d, J = 9.2 Hz, ArH), 7.42 (1 H, d, 
J = 8.8 Hz, ArH), 7.35 (2 H, d, J = 8.0 Hz, ArH), 5.01 (2 H, s, CH₂), 4.10 (3 H, s, 
OMe), 2.40 (3 H, s, Me); δc (100 MHz; CDCl₃) 150.1 (C), 145.4 (C), 141.9 (C), 140.9 
(C), 134.3 (C), 134.0 (CH), 132.9 (C), 130.0 (CH), 129.5 (CH), 128.2 (CH), 126.3 
(CH), 120.5 (C), 117.2 (CH), 87.4 (C≡C), 82.0 (C≡C), 57.8 (CH₂), 57.3 (OMe), 21.7 
(Me); m/z (ESI) 435 (MNa⁺, 100%), 413 (MH⁺, 76).

2-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-1,3-dioxane 364

![Diagram]

To a solution of 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318 (34.1 g, 155 
mmol) and para-toluenesulfonic acid (250 mg) in toluene (750 mL) was added 1,3-
propanediol (17.7 g, 233 mmol). The reaction mixture was heated under reflux in a 
Dean-Stark apparatus for 42 h. The solvent was removed in vacuo and the crude 
product purified by flash chromatography on silica gel, eluting with ethyl acetate-light 
petroleum (1:4) to afford the title compound as a colourless solid (39.0 g, 90%), mp 
59-60 °C (from ethanol); (Found: MH⁺, 279.1220. C₁₃H₁₈O₅ + H requires 279.1232); 
νmax (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 1605 (C=C), 1500 (C=C), 1462 (C=C), 1096 
(C-O), 1053 (C-O); δH (400 MHz; CDCl₃) 7.32 (1 H, d, J = 8.7 Hz, ArH), 6.74 (1 H, d, 
J = 8.7 Hz, ArH), 5.84 (1 H, s, CH), 4.76 (2 H, d, J = 2.4 Hz, CH₂), 4.27 -4.23 (2 H, 
m, CH₂), 4.06 - 3.99 (2 H, m, CH₂), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.53 (1 H, 
t, J = 2.4 Hz, C≡CH), 2.29 - 2.27 (1 H, m, CH), 1.46 - 1.41 (1 H, m, CH); δc (100
New Developments in the 1-Aza-Diels-Alder Reaction

Timothy E. Hurst

MHz; CDCl$_3$ 154.0 (C), 149.2 (C), 141.8 (C), 125.8 (C), 121.5 (CH), 108.3 (CH), 97.5 (CH), 79.3 (C=CH), 75.1 (C=CH), 67.6 (CH$_2$), 61.2 (CH$_2$), 61.0 (CH$_3$), 56.1 (CH$_3$), 25.8 (CH$_3$); $m/z$ (ESI) 301 (MNa$^+$, 34%), 279 (MH$^+$, 100).

(3-(6-(1,3-Dioxan-2-yl)-2,3-dimethoxyphenoxy)prop-1-ynyl)-6-methoxy-5-nitroquinoline 365

Following general procedure 12, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (4.50 g, 13.6 mmol) and alkyne 364 (5.68 g, 20.4 mmol) as a colourless solid (5.44 g, 83%), mp 146-147 °C (from ethanol); (Found: MH$^+$, 481.1602. C$_{23}$H$_{24}$N$_2$O$_8$ + H requires 481.1610); $\nu$ max (CHCl$_3$)/cm$^{-1}$ 1627 (C=C), 1596 (C=C), 1494 (C=C), 1461 (C=C), 1358 (N=O), 1107 (C-O), 1097 (C-O); $\delta_H$ (400 MHz; CDCl$_3$) 8.23 (1 H, d, $J$ = 9.4 Hz, ArH), 8.02 (1 H, d, $J$ = 8.8 Hz, ArH), 7.60 (1 H, d, $J$ = 8.8 Hz, ArH), 7.59 (1 H, d, $J$ = 9.6 Hz, ArH), 7.35 (1 H, d, $J$ = 8.7 Hz, ArH), 6.77 (1 H, d, $J$ = 8.7 Hz, ArH), 5.93 (1 H, s, CH), 5.07 (2 H, s, CH$_2$), 4.22 - 4.18 (2 H, m, CH$_2$), 4.08 (3 H, s, OMe), 4.03 - 3.97 (2 H, m, CH$_2$), 3.90 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.27 - 2.15 (1 H, m, CH), 1.42 - 1.38 (1 H, m, CH); $\delta_C$ (100 MHz; CDCl$_3$) 154.0 (C), 149.8 (C), 149.0 (C), 142.2 (C), 142.1 (C), 141.8 (C), 134.0 (CH), 129.4 (CH), 126.7 (CH), 126.0 (C), 121.7 (CH), 120.4 (C), 116.8 (CH), 108.5 (CH), 97.6 (CH), 86.8 (C), 86.0 (C), 67.6 (CH$_2$), 61.6 (CH$_2$), 61.1 (Me), 57.2 (Me), 56.1 (Me), 25.8 (CH$_2$); $m/z$ (ESI) 503 (MNa$^+$, 20%), 481 (MH$^+$, 100).
2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxybenzaldehyde

![](image)

A solution of the acetal 365 (11.0 g, 22.9 mmol) in acetic acid (300 mL) and water (35 mL) was heated to 50 °C for 2 h. The reaction mixture was allowed to cool to room temperature, poured into saturated sodium hydrogen carbonate solution (3000 mL) and extracted with ethyl acetate (5 × 1000 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (1000 mL) and water (1000 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a brown solid (9.67 g, 100%), which was used without further purification, mp 146-147 °C (from ethanol); (Found: MH⁺, 423.1189. C₂₂H₁₈N₂O₇ + H requires 423.1192); νₘₐₓ (CHCl₃)/cm⁻¹ 1679 (C=O), 1627 (C=C), 1592 (C=C), 1495 (C=C), 1460 (C=C), 1357 (N=O), 1093 (C-O); δH (400 MHz; CDCl₃) 10.4 (1 H, s, CHO), 8.21 (1 H, d, J = 9.5 Hz, ArH), 8.02 (1 H, d, J = 8.8 Hz, ArH), 7.68 (1 H, d, J = 8.8 Hz, ArH), 7.59 (1 H, d, J = 9.5 Hz, ArH), 7.48 (1 H, d, J = 8.8 Hz, ArH), 6.84 (1 H, d, J = 8.8 Hz, ArH), 5.21 (2 H, s, CH₂), 4.08 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.95 (3 H, s, OMe); δC (100 MHz; CDCl₃) 189.0 (C), 159.1 (C), 154.2 (C), 149.9 (C), 142.1 (C), 141.9 (C), 141.6 (C), 134.0 (CH), 129.7 (CH), 126.4 (CH), 124.5 (C), 123.9 (CH), 120.5 (C), 116.9 (CH), 108.5 (CH), 87.4 (C≡C), 85.3 (C≡C), 62.1 (CH₂), 61.2 (OMe), 57.2 (OMe), 56.3 (OMe); m/z (ESI) 445 (MNa⁺, 49%), 423 (MH⁺, 100).
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4-(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one 366

[Chemical structure image]

a) Following general procedure 7, the title compound was obtained from diethyl 1-methyl-2-oxopropylphosphonate\textsuperscript{133} 319 (0.368 g, 1.77 mmol) and the aldehyde (0.500 g, 1.18 mmol) as a colourless solid (0.542 g, 96%), mp 118-120 °C (from ethanol);

(Found: MH\textsuperscript{+}, 477.1669. C\textsubscript{26}H\textsubscript{24}N\textsubscript{2}O\textsubscript{7} + H requires 477.1662); \(\nu\)\textsubscript{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 1659 (C=O), 1627 (C=C), 1597 (C=C), 1494 (C=C), 1455 (C=C), 1357 (N=O), 1099 (C-O);

\(\delta\)\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 8.20 (1 H, d, \(J\) = 9.5 Hz, ArH), 8.02 (1 H, d, \(J\) = 8.8 Hz, ArH), 7.92 (1 H, s, C=CH), 7.60 (1 H, d, \(J\) = 9.5 Hz, ArH), 7.46 (1 H, d, \(J\) = 8.8 Hz, ArH), 7.19 (1 H, d, \(J\) = 8.7 Hz, ArH), 6.79 (1 H, d, \(J\) = 8.7 Hz, ArH), 5.09 (2 H, s, CH\textsubscript{2}), 4.09 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.93 (3 H, s, OMe), 2.49 (3 H, s, Me), 1.98 (3 H, d, \(J\) = 1.3 Hz, Me); \(\delta\)\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 200.5 (C), 154.3 (C), 150.5 (C), 149.9 (C), 142.2 (C), 141.7 (C), 136.9 (C), 135.4 (CH), 134.0 (CH), 129.5 (CH), 126.3 (CH), 125.1 (CH), 123.7 (C), 120.4 (C), 117.0 (CH), 107.9 (CH), 86.4 (C), 86.2 (C), 61.6 (CH\textsubscript{2}), 61.1 (OMe), 57.2 (OMe), 56.1 (OMe), 25.9 (Me), 13.0 (Me); \(m/z\) (ESI) 499 (MNa\textsuperscript{+}, 41%), 477 (MH\textsuperscript{+}, 100).
b) Following general procedure 12, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (0.050 g, 0.151 mmol) and alkyne 349 (0.062 g, 0.227 mmol) as a colourless solid (0.072 g, 100%); data as above.

\[
(3E)-4-(3,4\text{-dimethoxy}-2-(3\text{-}(6\text{-methoxy-5-nitroquinolin-2-yl})prop-2\text{-ynyloxy})phenyl)-3\text{-methylbut-3-en-2-one O-methyl oxime 316}
\]

Following general procedure 9, the title compound was obtained from ketone 366 (1.50 g, 3.15 mmol), methoxylamine hydrochloride (0.329 g, 3.94 mmol) and sodium acetate trihydrate (0.450 g, 3.31 mmol) as a pale yellow solid (1.56 g, 98%), mp 98-100 °C (from dichloromethane-hexane); (Found: C, 63.98; H, 5.37; N, 8.15. C\text{27}H\text{27}N\text{3}O\text{7} requires C, 64.15; H, 5.38; N, 8.31%); (Found: MH\text{+}, 506.1912. C\text{27}H\text{27}N\text{3}O\text{7} + H requires 506.1922); \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1628 (\text{C=C}), 1596 (\text{C=C}), 1532 (\text{C=C}), 1495 (\text{C=C}), 1463 (\text{C=)}, 1357 (\text{N=O}), 1096 (\text{C-O}), 1056 (\text{C-O}); \delta_{\text{H}} (400 \text{MHz}; \text{CDCl}_3) 8.21 (1 \text{ H, d, } J = 9.6 \text{ Hz, ArH}), 8.00 (1 \text{ H, d, } J = 8.8 \text{ Hz, ArH}), 7.58 (1 \text{ H, d, } J = 9.6 \text{ Hz, ArH}), 7.49 (1 \text{ H, d, } J = 8.8 \text{ Hz, ArH}), 7.10 (1 \text{ H, s, C=CH}), 7.04 (1 \text{ H, ...
d, $J = 8.8$ Hz, ArH), 6.74 (1 H, d, $J = 8.8$ Hz, ArH), 5.01 (2 H, s, CH$_2$), 4.08 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.10 (3 H, s, Me), 2.01 (3 H, s, Me); $\delta_c$ (100 MHz, CDCl$_3$) 157.1 (C), 153.0 (C), 150.0 (C), 149.8 (C), 142.3 (C), 142.1 (C), 142.0 (C), 134.4 (C), 134.0 (CH), 129.4 (CH), 126.6 (CH), 125.9 (CH), 125.1 (CH), 120.3 (C), 116.8 (CH), 107.8 (CH), 86.7 (C=C), 86.0 (C=C), 61.7 (OMe), 61.3 (CH$_2$), 61.1 (OMe), 57.2 (OMe), 56.1 (OMe), 14.4 (Me), 10.9 (Me); $m/z$ (ESI) 528 (MNa$^+$, 100%), 506 (MH$^+$, 61).

7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-1,2-dimethyl-5H-chromeno[3,4-c]pyridine 367

Following general procedure 11, the *title compound* was obtained from O-methyl oxime 316 (1.00 g, 1.98 mmol) after 18 h at 140 °C as a pale yellow solid (0.637 g, 68%), mp 211-212 °C (from dichloromethane-hexane); (Found: MH$^+$, 474.1662. C$_{26}$H$_{23}$N$_3$O$_6$ + H requires 474.1660); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1629 (C=C), 1601 (C=C), 1572 (C=C), 1551 (C=C), 1531 (C=C), 1498 (C=C), 1357 (N=O), 1103 (C-O), 1080 (C-O); $\delta_H$ (400 MHz; CDCl$_3$) 8.54 (1 H, d, $J = 9.0$ Hz, ArH), 8.23 (1 H, d, $J = 9.4$ Hz, ArH), 8.19 (1 H, d, $J = 9.0$ Hz, ArH), 7.58 (1 H, d, $J = 9.4$ Hz, ArH), 7.44 (1 H, d, $J = 8.8$ Hz, ArH), 6.73 (1 H, d, $J = 8.8$ Hz, ArH), 5.61 (2 H, s, CH$_2$), 4.10 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.94 (3 H, s, OMe), 2.70 (3 H, s, Me), 2.60 (3 H, s, Me); $\delta_c$ (100
New Developments in the 1-Aza-Diels-Alder Reaction

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MHz; CDCl₃ 157.2 (C), 156.9 (C), 153.8 (C), 151.3 (C), 149.3 (C), 147.9 (C), 141.1 (C), 138.5 (C), 138.0 (C), 134.8 (C), 134.0 (CH), 129.5 (CH), 127.4 (C), 126.7 (C), 124.1 (CH), 123.8 (CH), 120.3 (C), 117.3 (C), 116.0 (CH), 104.9 (CH), 67.5 (CH₂), 61.3 (OMe), 57.1 (OMe), 56.0 (OMe), 24.0 (Me), 18.0 (Me); m/z (ESI) 474 (MH⁺, 100%), 151 (16), 130 (20).

Methyl oximinoacetoacetate-O-tert-butylidimethylsilyl ether 370

\[
\text{Me} \quad \begin{array}{c}
\equiv \\
\text{O} \\
\text{N} \quad \text{OH}
\end{array} \quad \begin{array}{c}
\equiv \\
\text{O} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OTBDMS}
\end{array}
\]

To a solution of methyl oximinoacetoacetate (3.63 g, 25.0 mmol) in dichloromethane (30 mL) at 0 °C was added diisopropylethylamine (5.62 mL, 32.5 mmol) and tert-butlydimethylsilyl trifluoromethanesulfonate (7.18 mL, 31.3 mmol) dropwise. Stirring was continued at 0 °C for 2 h. The solvent was removed in vacuo, and the resulting residue diluted with n-pentane (20 mL). The suspension was stirred at 0 °C for 1 h. The solid was filtered off, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the title compound as a colourless oil (5.75 g, 89%); (Found: MNa⁺, 282.1136. C₁₁H₂₁N₀₄Si + Na requires 282.1138); v max (CHCl₃)/cm⁻¹ 1747 (C=O), 1693 (C=O); δH (400 MHz; CDCl₃) 3.85 (3 H, s, OMe), 2.39 (3 H, s, Me), 0.93 (9 H, s, CMe₃), 0.25 (6 H, s, SiMe₂); δC (100 MHz; CDCl₃) 193.4 (C), 162.0 (C), 155.2 (C), 52.3 (OMe), 25.6 (CMe₃), 25.3 (Me), 18.1 (CMe₃), -5.5 (SiMe₂); m/z (ESI) 541 (19%), 374 (19), 282 (MNa⁺, 100), 260 (MH⁺, 7%).
Methyl 2-methoxyimino-3-methyl-4-phenylbut-3-enoate

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

\[\text{235} \rightarrow \text{371}\]

a) To a stirred suspension of sodium hydride (0.054 g, 1.35 mmol) in DME (3 mL) at 0 °C was added benzyltriphenylphosphonium chloride (0.506 g, 1.30 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 30 min, and cooled back to 0 °C. Methyl methoxyiminoacetoacetate (0.145 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.187 g, 81%); \(v_{\text{max}}\) (CHCl₃)/cm\(^{-1}\) 1738 (C=O), 1600 (C=C), 1490 (C=C), 1460 (C=C), 1082 (C-O), 1045 (C-O); \(\delta_{\text{H}}\) (400 MHz; CDCl₃) 7.39-7.28 (5 H, m, ArH), 6.56 (1 H, s, CH), 3.99 (3 H, s, OMe), 3.94 (3 H, s, OMe), 2.12 (3 H, d, \(J = 1.3\) Hz, Me); \(\delta_{\text{C}}\) (100 MHz; CDCl₃) 164.7 (C), 154.6 (C), 136.1 (C), 134.5 (CH), 129.9 (CH), 129.4 (CH), 128.3 (CH), 127.7 (CH), 62.9 (Me), 52.3 (Me), 13.5 (Me).

b) To a stirred solution of benzyltriphenylphosphonium chloride (0.583 g, 1.50 mmol) in DME (3 mL) at 0 °C was added potassium tert-butoxide (0.174 g, 1.55 mmol) portionwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then cooled back to 0 °C. Methyl methoxyiminoacetoacetate (0.145 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction was quenched with saturated ammonium chloride (10 mL), and extracted.
with ethyl acetate (3 × 20 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.197 g, 85%); data as above.

**Methyl 2-tert-butylidimethylsiloxyimino-3-methyl-4-phenylbut-3-enoate 372**

![Chemical Structure](image)

a) To a stirred suspension of sodium hydride (0.054 g, 1.35 mmol) in DME (3 mL) at 0 °C was added benzyltriphenylphosphonium chloride (0.506 g, 1.30 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then cooled back to 0 °C. Methyl oximinoacetoacetate tert-butylidimethylsilyl ether 370 (0.259 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9), to afford the *title compound* as a colourless oil (0.220 g, 66%); (Found: MH⁺, 334.1828. C₁₈H₂₆N₂O₅Si + H requires 334.1833); νₘₐₓ (CHCl₃)/cm⁻¹ 1739 (C=O), 1601 (C=C), 1490 (C=C), 1462 (C=C), 1079 (C-O); δH (400 MHz; CDCl₃) 7.39 - 7.26 (5 H, m, ArH), 6.59 (1 H, s, CH), 3.91 (3 H, s, OMe), 2.12 (3 H, d, J = 1.3 Hz, Me), 0.96 (9 H, s, CMes₃), 0.22 (6 H, s, SiMe₂); δC (100 MHz; CDCl₃) 165.1 (C), 159.4 (C), 136.2 (C), 134.4 (CH), 130.2 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 52.0 (OMe), 25.9
(CMe₃), 18.1 (CMe₃), 13.5 (Me), -5.4 (Me); m/z (ESI) 356 (MNa⁺, 24%), 334 (MH⁺, 100), 279 (11).

b) To a stirred solution of benzyltriphenylphosphonium chloride (0.506 g, 1.30 mmol) in DME (3 mL) at 0 °C was added potassium tert-butoxide (0.152 g, 1.35 mmol) portionwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then cooled back to 0 °C. Methyl methoxyiminoacetoacetate 370 (0.145 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction was quenched with saturated ammonium chloride (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.270 g, 81%); data as above.

1-(Hydroxymethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 373

![diagram]

To a solution of 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318 (1.50 g, 6.81 mmol) in methanol (150 mL) at 0 °C was added sodium borohydride (0.386 g, 10.2 mmol) portionwise. Stirring was continued at 0 °C for 1 h. The solvent was removed in vacuo and the residue partitioned between water (50 mL) and dichloromethane (3 × 50 mL). The combined organics were washed with water (50 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a pale yellow solid (1.51 g,
100%), mp 53-54 °C (from ethyl acetate-hexane); (Found: C, 64.45; H, 6.29. \(\text{C}_{12}\text{H}_{14}\text{O}_4\) requires C, 64.85; H, 6.35%); (Found: M\(\text{Na}^+\), 245.0784. \(\text{C}_{12}\text{H}_{14}\text{O}_4 + \text{Na}\) requires 245.0784); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 3606 (O-H), 3306 (alkyne C-H), 2123 (C≡C), 1602 (C≡C), 1496 (C≡C), 1461 (C≡C), 1308 (C-O), 1278 (C-O), 1097 (C-O); \(\delta_H\) (400 MHz; CDCl\(_3\)) 7.03 (1 H, d, \(J = 8.5\) Hz, ArH), 6.69 (1 H, d, \(J = 8.5\) Hz, ArH), 4.87 (2 H, d, \(J = 2.4\) Hz, C≡CCH\(_2\)), 4.67 (2 H, d, \(J = 6.0\) Hz, ArCH\(_2\)), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.51 (1 H, t, \(J = 2.4\) Hz, C≡CH), 2.17 (1 H, t, \(J = 6.2\) Hz, OH); \(\delta_C\) (100 MHz; CDCl\(_3\)) 153.6 (C), 149.5 (C), 141.9 (C), 127.7 (C), 123.7 (CH), 107.8 (CH), 79.4 (C≡CH), 75.6 (C≡CH), 61.4 (CH\(_2\)), 60.9 (Me), 60.6 (CH\(_2\)), 56.0 (Me); \(m/z\) (ESI) 245 (M\(\text{Na}^+\), 41), 205 (M-OH, 100), 174 (14).

1-(Chloromethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 374

![Diagram of 1-(Chloromethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene](image)

To a solution of 1-(hydroxymethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 373 (1.01 g, 4.57 mmol) and pyridine (0.55 mL, 6.86 mmol) in dichloromethane (15 mL) was added thionyl chloride (0.67 g, 9.14 mmol). The reaction mixture was stirred at room temperature for 3 h, then poured onto water (20 mL). The aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organics were washed with hydrochloric acid (2 M; 2 x 25 mL) and saturated brine (25 mL), dried over MgSO\(_4\) and concentrated in vacuo to afford the title compound as a brown solid (1.01 g, 86%), mp 36-38 °C (from ethanol); (Found: [M-Cl]\(^+\), 205.0861. C\(_{12}\)H\(_{13}\)ClO\(_3\) - Cl 205.0859); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 3307 (alkyne C-H), 2125 (C≡C), 1601 (C≡C), 1496
New Developments in the 1-Aza-Diels-Alder Reaction

Timothy E. Hurst

(C≡C), 1462 (C≡C), 1096 (C-O); δH (400 MHz; CDCl₃) 7.09 (1 H, d, J = 8.6 Hz, ArH), 6.71 (1 H, d, J = 8.6 Hz, ArH), 4.85 (2 H, d, J = 2.4 Hz, C≡CCH₂), 4.68 (2 H, s, ArCH₂), 3.88 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.51 (1 H, t, J = 2.4 Hz, C≡CH); δC (100 MHz; CDCl₃) 154.2 (C), 149.7 (C), 142.2 (C), 125.0 (CH), 124.5 (C), 108.1 (CH), 79.1 (C≡CH), 75.5 (C≡CH), 60.9 (Me), 60.8 (CH₂), 56.0 (Me), 41.8 (CH₂); m/z (ESI) 259 (16%), 205 ([M-Cl]+, 100), 174 (12).

1-(Triphenylphosphinomethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 375

To a solution of 1-(chloromethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 374 (0.478 g, 1.86 mmol) in toluene (2 mL) was added triphenylphosphine (0.488 g, 1.86 mmol) in toluene (3 mL). The reaction mixture was heated at 60 °C for 18 h. The solid was filtered off, washed with ether and dried in vacuo at 40 °C to afford the title compound as a colourless solid (0.776 g, 83%), mp 208-209 °C (from toluene); (Found: [M-Cl]+, 467.1772. C₃₀H₂₈ClO₃P - Cl requires 467.1771); νmax (CHCl₃)/cm⁻¹ 3305 (alkyne C-H), 1601 (C≡C), 1495 (C≡C), 1462 (C≡C), 1110 (C-O), 1096 (C-O), 1041 (C-O); δH (400 MHz; CDCl₃) 7.78-7.60 (15 H, m, ArH), 7.21 (1 H, dd, J = 2.9 and 8.7 Hz, H-5), 6.57 (1 H, d, J = 8.7 Hz, H-4), 5.35 (2 H, d, J = 13.5 Hz, ArCH₂), 4.39 (2 H, d, J = 2.4 Hz, C≡CCH₂), 3.79 (3 H, s, OMe), 3.57 (3 H, s, OMe), 2.61 (1 H, t, J = 2.4 Hz, C≡CH); δC (100 MHz; CDCl₃) 134.8 (CH), 134.7 (C), 134.4 (CH), 134.3 (CH), 130.1 (CH), 130.0 (CH), 127.2 (CH), 127.1 (C), 118.7 (C), 117.9 (C), 108.4
New Developments in the 1-Aza-Diels-Alder Reaction

Timothy E. Hurst

(\text{CH}), 79.0 (C=\text{CH}), 76.3 (C=\text{CH}), 60.6 (\text{Me}), 60.4 (\text{CH}_2), 56.0 (\text{Me}); m/z (ESI) 467 ([M-Cl]^+, 100%).

1-(\text{tert}-\text{Butyldimethylsilyl})\text{oxymethyl})-2-(\text{prop-2-ynyloxy})-3,4\text{-dimethoxybenzene}

To a solution of 1-(\text{hydroxymethyl})-3,4\text{-dimethoxy}-2-(\text{prop-2-ynyloxy})\text{benzene} 373 (0.445 g, 2.00 mmol) and \text{tert}-\text{butyldimethylchlorosilane} (0.377 g, 2.50 mmol) in dichloromethane (2 mL) was added imidazole (0.204 g, 3.00 mmol) in dichloromethane (3 mL). Stirring was continued for 3 h. The crude reaction mixture was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the title compound as a colourless oil (0.588 g, 94%); (Found: MNa^+, 359.1650. C_{18}H_{28}O_4Si + Na requires 359.1649); \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3307 (alkyne C-H), 2124 (C≡C), 1603 (C≡C), 1495 (C≡C), 1461 (C=C), 1094 (C=O), 1041 (Si-O), 1004 (C-O); \delta_\text{H} (400 MHz; CDCl_3) 7.13 (1 H, d, J = 8.6 Hz, ArH), 6.72 (1 H, d, J = 8.6 Hz, ArH), 4.79 (2 H, s, ArCH_2), 4.78 (2 H, d, J = 2.4 Hz, C≡CCH_2), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.47 (1 H, t, J = 2.4 Hz, C≡CH), 0.96 (9 H, s, CMe_3), 0.12 (6 H, s, SiMe_2); \delta_\text{C} (100 MHz; CDCl_3) 152.6 (C), 148.4 (C), 141.8 (C), 128.1 (C), 121.9 (CH), 107.8 (CH), 79.6 (C≡CH), 75.0 (C≡CH), 60.9 (Me), 60.4 (CH_2), 60.3, 56.0 (Me), 26.0 (CMe_3), 18.4 (CMe_3), -5.3 (Me); m/z (ESI) 359 (MNa^+, 57%), 205 (M-OTBDMS, 100), 174 (17).
2-{3-[6-(tert-Butyldimethylsilyloxymethyl)-2,3-dimethoxy-phenoxy]-prop-1-ynyl}-6-methoxy-5-nitroquinoline 379

Following general procedure 12, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (0.500 g, 1.51 mmol) and alkyne 378 (0.712 g, 2.27 mmol) as a colourless oil (0.570 g, 70%); (Found: MH\(^+\), 539.2221. C\(_{28}\)H\(_{34}\)N\(_2\)O\(_7\)Si + H requires 539.2208); \(v_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1628 (C=C), 1595 (C=C), 1550 (C=C), 1494 (C=C), 1461 (C=C), 1358 (N=O), 1094 (C-O), 1080 (C-O), 1033 (Si-O), 992 (C-O); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 8.21 (1 H, dd, \(J = 0.6\) and 9.4 Hz, ArH), 8.00 (1 H, dd, \(J = 0.6\) and 8.8 Hz, ArH), 7.58 (1 H, d, \(J = 9.5\) Hz, ArH), 7.53 (1 H, d, \(J = 8.8\) Hz, ArH), 7.14 (1 H, d, \(J = 8.6\) Hz, ArH), 6.73 (1 H, d, \(J = 8.6\) Hz, ArH), 5.06 (2 H, s, CH\(_2\)), 4.84 (2 H, s, CH\(_2\)), 4.07 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.86 (3 H, s, OMe), 0.92 (9 H, s, CMe\(_3\)), 0.09 (6 H, s, SiMe\(_2\)); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 152.7 (C), 149.8 (C), 148.5 (C), 142.1 (C), 141.9 (C), 134.5 (C), 134.0 (CH), 129.4 (CH), 128.1 (C), 126.6 (CH), 122.1 (CH), 120.3 (C), 116.9 (CH), 108.0 (CH), 86.9 (C=O), 85.8 (C=C), 61.0 (OMe), 60.9 (CH\(_2\)), 60.4 (CH\(_2\)), 57.2 (OMe), 56.0 (OMe), 26.0 (CMe\(_3\)), 18.4 (CMe\(_3\)), -5.3 (SiMe\(_2\)); m/z (ESI) 561 (MNa\(^+\), 25%), 539 (MH\(^+\), 32), 407 (100).
(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)methanol

To a solution of quinoline 379 (0.500 g, 0.928 mmol) in methanol (15 mL) was added Dowex-50W™ acidic resin (0.150 g). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed in vacuo, and the residue diluted with chloroform (150 mL) and filtered. The filtrate was concentrated in vacuo to afford the title compound as a colourless solid (0.373 g, 95%), mp 161-162 °C from (dichloromethane-hexane); (Found: MNa⁺, 447.1165. C₂₂H₂₀N₂O₇ + Na requires 447.1174); ν max (CHCl₃)/cm⁻¹ 1628 (C=C), 1596 (C=C), 1495 (C=C), 1536 (C=C), 1496 (C=C), 1459 (C=C), 1356 (N=O), 1096 (C-O), 1006 (C-O); δH (400 MHz; CDCl₃) 8.19 (1 H, d, J = 9.5 ArH), 8.00 (1 H, d, J = 8.8 Hz, ArH), 7.57 (1 H, d, J = 9.5 Hz, ArH), 7.50 (1 H, d, J = 8.8 Hz, ArH), 7.19 (1 H, d, J = 8.6 Hz, ArH), 6.75 (1 H, d, J = 8.6 Hz, ArH), 5.12 (2 H, s, CH₂), 4.83 (2 H, s, CH₂), 4.08 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.87 (3 H, s, OMe); δC (100 MHz; CDCl₃) 153.2 (C), 60.9 (CH₂), 149.9 (C), 60.2 (CH₂), 142.0 (C), 57.2 (OMe), 141.8 (C), 56.1 (OMe), 141.7 (C), 133.7 (CH), 129.8 (CH), 128.8 (C), 126.0 (CH), 123.8 (CH), 120.4 (C), 117.0 (CH), 108.5 (CH), 87.0 (C=C), 86.6 (C=C), 61.0 (OMe); m/z (ESI) 447 (MNa⁺, 35%), 425 (MH⁺, 23), 407 (100).
2-(3-(6-(Chloromethyl)-2,3-dimethoxyphenoxy)prop-1-ynyl)-6-methoxy-5-nitroquinoline 380

To a solution of the benzyl alcohol (0.210 g, 0.495 mmol) in dichloromethane (5 mL) was added pyridine (0.060 mL, 0.743 mmol) and thionyl chloride (0.072 mL, 0.990 mmol). The reaction mixture was stirred at room temperature for 3 h, poured into water (15 mL) and extracted into dichloromethane (2 × 15 mL). The combined organics were washed with hydrochloric acid (2 M; 2 × 15 mL) and saturated brine (15 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless solid (0.219 g, 100%); Found: MH⁺, 443.1001. C₂₂H₁₉ClN₂O₆ + H requires 443.1004; νmax (CHCl₃)/cm⁻¹ 1627 (C≡C), 1603 (C=C), 1532 (C≡C), 1500 (C=C), 1463 (C=C), 1366 (N=O); δH (400 MHz; CDCl₃) 8.22 (1 H, d, J = 9.2 Hz, ArH), 8.02 (1 H, d, J = 8.8 Hz, ArH), 7.59 (1 H, d, J = 9.2 Hz, ArH), 7.57 (1 H, d, J = 8.8 Hz, ArH), 7.12 (1 H, d, J = 8.8 Hz, ArH), 6.73 (1 H, d, J = 8.8 Hz, ArH), 5.16 (2 H, s, CH₂), 4.75 (2 H, s, CH₂), 4.07 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.87 (3 H, s, OMe); δC (100 MHz; CDCl₃) 153.2 (C), 148.8 (C), 148.7 (C), 141.2 (C), 141.0 (C), 140.9 (C), 133.0 (CH), 128.5 (CH), 125.6 (CH), 124.1 (CH), 123.2 (C), 119.3 (C), 115.8 (CH), 107.2 (CH), 85.4 (C≡C), 85.1 (C≡C), 60.3 (CH₂), 60.0 (OMe), 56.2 (OMe), 55.0 (OMe), 40.7 (CH₂); m/z (ESI) 522 (100%), 443 (MH⁺, 51), 366 (27), 338 (25), 301 (37).
New Developments in the 1-Aza-Diels-Alder Reaction

Timothy E. Hurst

2-Ketobutanoic acid methyl ester

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

To a solution of 2-ketobutanoic acid (3.06 g, 30.0 mmol) in methanol (12 mL) and acetone dimethylacetal (48 mL) was added chlorotrimethylsilane (0.38 mL, 3.00 mmol). The reaction mixture was stirred at room temperature for 19 h and concentrated in vacuo to afford the title compound as a colourless oil (2.51 g, 72%); \( \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1732 (\text{C}=\text{O}); \delta_\text{H} (400 \text{ MHz; CDCl}_3) 3.81 (3 \text{ H, s, OMe}), 2.82 (2 \text{ H, q, } J = 7.2 \text{ Hz, CH}_2), 1.07 (3 \text{ H, t, } J = 7.2 \text{ Hz, Me}); \delta_\text{C} (100 \text{ MHz; CDCl}_3) 194.7 (\text{C}), 161.5 (\text{C}), 52.8 (\text{OMe}), 32.8 (\text{CH}_2), 6.9 (\text{Me}).
\]

\(a\)-Bromo-2-ketobutanoic acid methyl ester

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Me} & \quad \text{Br}\quad \text{CO}_2\text{Me}
\end{align*}
\]

Bromine (0.88 mL, 17.2 mmol) was added dropwise over 30 min to 2-ketobutanoic acid methyl ester (2.00 g, 17.2 mmol) at 0 °C. Stirring was continued at 0 °C for 20 min. The reaction was then quenched by the careful addition of saturated sodium hydrogen carbonate (20 mL). The aqueous layer was extracted with ether (2 \times 35 mL), and the combined organics washed with saturated sodium hydrogen carbonate (2 \times 35 mL), water (35 mL) and saturated brine (35 mL), dried over MgSO\(_4\) and concentrated in vacuo to afford the title compound as a colourless oil (2.12 g, 63%); \( \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1784 (\text{C}=\text{O}), 1733 (\text{C}=\text{O}); \delta_\text{H} (400 \text{ MHz; CDCl}_3) 5.17 (1 \text{ H, q, } J = 6.8 \text{ Hz, CH}), 3.93 (3 \text{ H, s, OMe}), 1.81 (3 \text{ H, d, } J = 6.8 \text{ Hz, Me}); \delta_\text{C} (100 \text{ MHz; CDCl}_3) \)
162.0 (C), 150.1 (C), 64.0 (OMe), 52.8 (OMe), 33.2 (CH), 21.9 (Me); δC (100 MHz; CDCl₃) 186.9 (C), 161.0 (C), 53.5 (OMe), 42.3 (CH), 18.5 (Me).

**Methyl 3-bromo-2-(methoxyimino)propanoate**

To a solution of methyl bromopyruvate 381 (3.62 g, 20.0 mmol) in methanol (60 mL) was added methoxylamine hydrochloride (2.51 g, 30.0 mmol) in one portion. The reaction mixture was stirred at room temperature for 22 h and the solvent removed in vacuo. The residue was partitioned between water (50 mL) and ether (3 × 75 mL). The combined organics were washed with water (2 × 75 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless oil (3.76 g, 90%), which was used without further purification; νmax (CHCl₃)/cm⁻¹ 1736 (C=O), 1599 (C=N); δH (400 MHz; CDCl₃) 4.37 (2 H, s, CH₂), 4.18 (3 H, s, OMe), 3.92 (3 H, s, OMe); δC (100 MHz; CDCl₃) 162.3 (C), 146.9 (C), 64.3 (OMe), 53.2 (OMe), 30.9 (CH₂).

**Methyl 3-bromo-2-(methoxyimino)butanoate**

To a solution of methyl 3-bromo-2-oxobutanoate 382 (1.00 g, 5.13 mmol) in methanol (20 mL) was added methoxylamine hydrochloride (2.14 g, 25.7 mmol) and magnesium sulfate (2.00 g). The reaction mixture was stirred at room temperature for
16 h, filtered and concentrated in vacuo. The residue was partitioned between water (75 mL) and ethyl acetate (3 × 75 mL). The combined organics were washed with water (3 × 75 mL) and saturated brine (75 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless oil (0.995 g, 87%), which was used without further purification; (Found: MH⁺, 254.0786. C₈H₁₆NO₅P + H requires 254.0788); \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1736 (C=O), 1586 (C=N); \( \delta_H \) (360 MHz; CDCl₃) 5.39 (1 H, q, J = 7.1 Hz, CH), 4.12 (3 H, s, OMe), 3.88 (3 H, s, OMe), 1.93 (3 H, d, J = 7.1 Hz, Me); \( \delta_C \) (100 MHz; CDCl₃) 162.0 (C), 150.1 (C), 64.0 (OMe), 52.8 (OMe), 33.2 (CH), 21.9 (Me); m/z (ESI) 276 (MNa⁺, 100%), 254 (MH⁺, 8).

Methyl 3-(dimethoxyphosphino)-2-(methoxyimino)propanoate¹⁷² ³⁸⁵

\[
\text{Br-}N^\text{OMe} \quad \rightarrow \quad \text{MeO-P} - N^\text{OMe}
\]

A solution of (E)-methyl 3-bromo-2-(methoxyimino)propanoate ³⁸³ (3.76 g, 17.9 mmol) in trimethyl phosphite (2.96 g, 25.0 mmol) was heated under reflux for 48 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (3:1) to afford the title compound as a colourless oil (2.54 g, 59%); \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1736 (C=O), 1242 (P=O), 1031 (P-O); \( \delta_H \) (400 MHz; CDCl₃) 4.06 (3 H, s, OMe), 3.82 (3 H, s, OMe), 7.72 (3 H, d, J = 4.8 Hz, POMe), 3.68 (3 H, d, J = 4.8 Hz, POMe), 3.27 (2 H, d, J = 23.6 Hz, CH₂); \( \delta_C \) (100 MHz; CDCl₃) 163.0 (d, \( J_{C-P} = 8.0 \) Hz, C), 143.4 (d, \( J_{C-P} = 12.0 \) Hz, C), 63.6 (OMe), 53.0 (OMe, d, \( J_{C-P} = 6.0 \) Hz), 52.9 (OMe, d, \( J_{C-P} = 6.0 \) Hz), 23.3 (CH₂, d, \( J_{C-P} = 136.2 \) Hz).
Methyl 3-(dimethoxyphosphoryl)-2-(methoxyimino)butanoate 386

![Chemical Structure](image)

A solution of (E)-methyl 3-bromo-2-(methoxyimino)butanoate 384 (0.650 g, 2.90 mmol) in triethylphosphite (0.48 mL, 4.06 mmol) was heated under reflux for 38 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (3:1) to afford the title compound as a colourless oil (0.171 g, 23%); ν_max (CHCl₃) cm⁻¹ 1733 (C=O), 1256 (P=O), 1093 (P-O); δ_H (400 MHz; CDCl₃) 4.05 (3 H, s, OMe), 3.93 (1 H, dq, J = 31.2 and 6.0 Hz, PCH), 3.82 (3 H, s, OMe), 3.72 (3 H, d, J = 6.4 Hz, POMe), 3.69 (3 H, d, J = 6.4 Hz, POMe), 1.45 (3 H, dd, J = 17.5 and 8.5 Hz, Me); δ_C (100 MHz; CDCl₃) 163.0 (d, 3J_C-P = 3.0 Hz, C), 148.0 (d, 2J_C-P = 5.0 Hz, C), 63.6 (OMe), 53.4 (d, J = 6.0 Hz, POMe), 52.9 (d, J = 6.0 Hz, POMe), 52.2 (OMe), 30.2 (d, J = 114.1 Hz, CH), 11.9 (d, 2J_C-P = 5.0 Hz, Me).

(3E)-methyl 4-(3,4-dimethoxy-2-(prop-2-ynyloxy)phenyl)-2-(methoxyimino)but-3-enoate 387

![Chemical Structure](image)

To a solution of (E)-methyl 3-(dimethoxyphosphino)-2-(methoxyimino)propanoate 385 (0.957 g, 4.00 mmol) in THF (8 mL) at -78 °C was added n-butyllithium (2.5 M in
hexanes; 1.60 mL, 4.00 mmol) dropwise over 20 min. The reaction mixture was stirred at -78 °C for 1 h. A solution of 3,4-dimethoxy-2-(prop-2-ynyl)benzaldehyde 318 (0.440 g, 2.00 mmol) in THF (12 mL) was added dropwise over 20 min. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. Saturated ammonium chloride (50 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the title compound as a colourless solid (0.331 g, 50%), mp 87-88 °C (from dichloromethane-hexane); (Found: C, 61.25; H, 5.75; N, 4.06. C₁₇H₁₉NO₆ requires C, 61.25; H, 5.75; N, 4.20%); (Found: MH⁺, 334.1272. C₁₇H₁₉NO₆ + H requires 334.1285); vₘₐₓ (CHCl₃)/cm⁻¹ 3308 (alkyne C-H), 2126 (C≡C), 1733 (C=O), 1596 (C=C), 1593 (C=C), 1497 (C=C), 1097 (C-O); δH (500 MHz; CDCl₃) 7.92 (1 H, d, J = 17.0 Hz, C=CH), 7.36 (1 H, d, J = 9.0 Hz, ArH), 7.13 (1 H, d, J = 17.0 Hz, C=CH), 6.73 (1 H, d, J = 9.0 Hz, ArH), 4.78 (2 H, d, J = 2.5 Hz, CH₂), 4.12 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.93 (3 H, s, OMe), 2.50 (1 H, t, J = 2.5 Hz, C=CH), 2.18 (3 H, s, Me); 163.8 (C), 154.7 (C), 150.5 (C), 147.9 (C), 142.3 (C), 135.1 (CH), 124.0 (C), 121.5 (CH), 112.7 (CH), 110.0 (C), 108.3 (CH), 78.9 (C≡C), 75.7 (C=C), 63.5 (OMe), 61.0 (CH₂), 56.1 (OMe), 52.8 (OMe); m/z (ESI) 356 (MNa⁺, 100%), 334 (MH⁺, 34).

Methyl Glycolate174

\[
\text{HO}_2C\text{OH} \rightarrow \text{MeO}_2\text{C}\text{OH}
\]

To a solution of glycolic acid (22.8 g, 300 mmol) in methanol (300 mL) was added boric acid (1.85 g, 30.0 mmol). The reaction mixture was stirred at room temperature
for 15 h then concentrated \textit{in vacuo}. The crude product was purified by distillation (40 °C at 20 mm Hg) to afford the title compound as a colourless oil (15.1 g, 56%); $\nu_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 3547 (O-H), 1746 (C=O); $\delta_H$ (500 MHz; CDCl$_3$) 4.12 (2 H, s, CH$_2$), 3.73 (3 H, s, OMe); $\delta_C$ (125 MHz; CDCl$_3$) 173.9 (C), 60.4 (CH$_2$), 52.2 (Me).

**Methyl 2-(\textit{tert}-butyldimethylsilyloxy)acetate**$^{175}$ 392

\[
\begin{align*}
\text{MeO}_2\text{C}_\text{\underline{\text{O}}}_\text{H} & \quad \rightarrow \quad \text{MeO}_2\text{C}_\text{\underline{\text{O}}}_\text{TBDMSC} \\
392
\end{align*}
\]

To a solution of methyl glycolate (0.568 g, 6.31 mmol) in THF (15 mL) was added \textit{tert}-butyldimethylchlorosilane (1.14 g, 7.57 mmol) and imidazole (1.29 g, 18.9 mmol). The reaction mixture was stirred at room temperature for 2 h then partitioned between water (50 mL) and dichloromethane (3 $\times$ 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over MgSO$_4$ and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.475 g, 37%); $\nu_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 1757 (C=O); $\delta_H$ (400 MHz; CDCl$_3$) 4.24 (2 H, s, CH$_2$), 3.73 (3 H, s, OMe), 0.90 (9 H, s, CMe$_3$), 0.10 (6 H, s, SiMe$_2$); $\delta_C$ (100 MHz; CDCl$_3$) 172.1 (C), 61.7 (CH$_2$), 57.7 (OMe), 25.6 (CMe$_3$), 14.2 (CMe$_3$), -5.5 (SiMe$_2$).

**Methyl 2-(allyloxy)acetate**$^{204}$ 393

\[
\begin{align*}
\text{MeO}_2\text{C}_\text{\underline{\text{O}}}_\text{H} & \quad \rightarrow \quad \text{MeO}_2\text{C}_\text{\underline{\text{O}}}_\text{CHCH} \\
393
\end{align*}
\]

Methyl glycolate (5.00 g, 55.5 mmol) was added to a solution of sodium hydride (2.44 g, 61.1 mmol) in DMF (100 mL). The reaction mixture was stirred at room temperature for 19 h and quenched by careful addition of saturated ammonium
chloride (250 mL). The aqueous layer was extracted with ether (4 × 250 mL) and the combined organic extracts washed with water (4 × 250 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (2.94 g, 41%); ν max (CHCl₃)/cm⁻¹ 1750 (C=O), 1602 (C=C); δ H (400 MHz; CDCl₃) 5.96-5.89 (1 H, m, CH₂=CH), 5.30 (1 H, ddt, J = 17.2, 1.6 and 1.5 Hz, CH₂=CH), 5.23 (1 H, ddt, J = 10.4, 1.6 and 1.2 Hz, CH₂=CH), 4.11 (2 H, m, CH₂), 4.10 (2 H, s, CH₂), 3.76 (3 H, s, OMe); δ C (100 MHz; CDCl₃) 170.8 (C), 133.7 (CH), 118.3 (CH₂), 72.4 (CH₂), 67.1 (CH₂), 51.8 (OMe).

**Methyl 2-methoxyacetate 394**

\[
\text{HO}_2C\underset{\text{OMe}}{\text{O}} \longrightarrow \text{MeO}_2C\underset{\text{OMe}}{\text{O}}
\]

To a solution of methoxyacetic acid (5.40 g, 60.0 mmol) in dry methanol (24 mL) and acetone dimethylacetal (96 mL) was added chlorotrimethylsilane (0.77 mL, 6.00 mmol) dropwise over 10 min. The reaction mixture was stirred for 16 h and concentrated in vacuo to afford the title compound as a colourless oil (3.72 g, 59%); ν max (CHCl₃)/cm⁻¹ 1754 (C=O); δ H (500 MHz; CDCl₃) 4.05 (2 H, s, CH₂), 3.77 (3 H, s, OMe), 3.46 (3 H, s, OMe); δ C (125 MHz; CDCl₃) 170.7 (C), 69.7 (CH₂), 59.3 (OMe), 51.8 (OMe).

**Methyl 2-(4-methoxybenzyl)oxyacetate 395**

\[
\text{MeO}_2C\underset{\text{OH}}{\text{O}} \longrightarrow \text{MeO}_2C\underset{\text{OPMB}}{\text{O}}
\]

To a suspension of sodium hydride (3.12 g, 78.0 mmol) and para-methoxybenzyl chloride (12.2 g, 78.0 mmol) in DMF (100 mL) at 0 °C was added methyl glycolate
(7.03 g, 78.0 mmol) dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h, then partitioned between water (100 mL) and ether (4 × 100 mL). The combined organics were washed with water (4 × 100 mL) and saturated brine (100 mL), dried over MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (7.81 g, 48%); $\nu_{\text{max}}$ (CHCl3)/cm$^{-1}$ 1752 (C=O), 1613 (C=C), 1587 (C=C), 1514 (C=C); $\delta_{\text{H}}$ (500 MHz; CDC13) 7.29 (2 H, d, $J = 8.5$ Hz, ArH), 6.89 (2 H, d, $J = 8.5$ Hz, ArH), 4.57 (2 H, s, CH2), 4.08 (2 H, s, CH2), 3.81 (3 H, s, OMe), 3.77 (3 H, s, OMe); $\delta_{\text{C}}$ (125 MHz; CDC13) 170.9 (C), 159.6 (C), 129.8 (CH), 129.1 (C), 113.9 (CH), 73.0 (CH2), 66.8 (CH2), 55.3 (OMe), 51.9 (OMe);

**Diethyl 4-(tert-butyldimethylsilyloxy)-3-oxobutan-2-ylphosphonate 396**

Following general procedure 13, the title compound was obtained from diethyl ethyl phosphonate 391 (0.233 g, 1.40 mmol) and methyl 2-(tert-butyldimethylsilyloxy)acetate 392 (0.315 g, 1.54 mmol) as a colourless oil (0.295 g, 62%); (Found: MH+, 339.1732. C14H32O3PSi + H requires C14H32O3PSi); $\nu_{\text{max}}$ (CHCl3)/cm$^{-1}$ 1735 (C=O), 1253 (P=O), 1026 (P-O); $\delta_{\text{H}}$ (400 MHz; CDC13) 4.49 (1 H, d, $J = 17.9$ Hz, CH2), 4.31 (1 H, d, $J = 17.9$ Hz, CH2), 4.19-4.09 (4 H, m, 2 × POC2H), 3.51 (1 H, dq, $J = 24.6$ Hz and 7.1 Hz, PCH), 1.32-1.29 (6 H, m, 2 × POCH2Me), 0.90 (9 H, s, CMe3), 0.08 (6 H, s, SiMe2); $\delta_{\text{C}}$ (100 MHz; CDC13) 205.1 (d, $^2J_{\text{C-P}} = 4.4$ Hz, C), 69.5 (CH2), 62.7 (d, $^2J_{\text{C-P}} = 6.7$ Hz, POCH2), 62.5 (d, $^2J_{\text{C-P}} = 6.7$ Hz, POCH2), 41.3
(d, $^1J_{C-P} = 128.7$ Hz, PCH), 25.8 (CMe$_3$), 18.4 (CMe$_3$), 16.4 (d, $^2J_{C-P} = 6.5$ Hz, POCH$_2$Me), 16.3 (d, $^2J_{C-P} = 6.5$ Hz, POCH$_2$Me), -5.5 (SiMe$_2$); $m/z$ (ESI) 361 (MN$_{a+}$, 100%), 339 (MH$^+$, 89).

### Diethyl 4-(allyloxy)-3-oxobutan-2-ylphosphonate 397

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate 391 (2.99 g, 18.0 mmol) and methyl 2-(allyloxy)acetate 393 (2.58 g, 19.8 mmol) as a colourless oil (2.94 g, 62%). Found: MH$^+$, 265.1190. C$_{11}$H$_{21}$O$_5$P + H requires 265.1199; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1721 (C=O), 1241 (P=O), 1026 (P-O); $\delta_H$ (400 MHz; CDCl$_3$) 5.96-5.86 (1 H, m, CH=CH$_2$), 5.30 (1 H, ddt, $J = 17.2$, 1.6 and 1.5, CH=CH$_2$), 5.23 (1 H, ddt, $J = 10.4$, 1.6 and 1.5, CH=CH$_2$), 4.36 (1 H, d, $J = 17.2$ Hz, CH$_2$), 4.19 (1 H, d, $J = 17.2$ Hz, CH$_2$), 4.15-4.10 (4 H, m, 2 x CH$_2$), 4.08-4.06 (2 H, m, CHCH$_2$), 3.43 (1 H, dq, $J = 25.2$ and 6.8 Hz, PCH), 1.39-1.29 (9 H, m, 3 x Me); $\delta_C$ (100 MHz; CDCl$_3$) 203.6 (d, $^2J_{C-P} = 4.4$ Hz, C), 133.8 (CH), 118.4 (CH$_2$), 74.9 (CH$_2$), 72.3 (CH$_2$), 63.3 (d, $^2J_{C-P} = 6.9$ Hz, CH$_2$), 63.0 (d, $^2J_{C-P} = 6.9$ Hz, CH$_2$), 42.8 (d, $^1J_{C-P} = 127.0$ Hz, PCH), 16.7 (d, $^3J_{C-P} = 5.9$ Hz, 2 x Me), 10.9 (d, $^2J_{C-P} = 6.6$ Hz, Me); $m/z$ (ESI) 287 (MN$_{a+}$, 100%), 265 (MH$^+$, 23).
Diethyl 4-methoxy-3-oxobutan-2-ylphosphonate 398

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate 391 (9.97 g, 60.0 mmol) and methyl 2-methoxyacetate 394 (6.87 g, 66.0 mmol) as a colourless oil (12.1 g, 85%); υ_{max} (CHCl₃)/cm⁻¹ 1731 (C=O), 1241 (P=O); δ_H (400 MHz; CDCl₃) 4.34 (1 H, d, J = 17.2 Hz, CH₂), 4.18-4.10 (5 H, m, 2 × CH₂ + CH₃), 3.43 (3 H, s, OMe), 3.41 (1 H, dq, J = 25.2 and 7.2 Hz, PCH), 1.36-1.32 (9 H, m, 3 × Me); δ_C (100 MHz; CDCl₃) 203.5 (d, $^{2}J_{C-P}$ = 4.2 Hz, C), 77.4 (CH₂), 62.9 (d, $^{2}J_{C-P}$ = 6.6 Hz, CH₂), 62.8 (d, $^{2}J_{C-P}$ = 6.6 Hz, CH₂), 59.2 (OMe), 42.5 (d, $^{1}J_{C-P}$ = 127.0 Hz, CH), 16.8 (d, $^{3}J_{C-P}$ = 5.8 Hz, 2 × Me), 10.9 (d, $^{2}J_{C-P}$ = 6.5 Hz, Me).

Diethyl 4-(4-methoxybenzylxylo)-3-oxobutan-2-ylphosphonate 399

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate 391 (4.98 g, 30.0 mmol) and methyl 2-(4-methoxybenzylxylo)acetate 395 (6.94 g, 33.0 mmol) as a colourless oil (7.98 g, 77%); (Found: MH⁺, 345.1451. C₁₆H₂₅O₆P + H requires 345.1462); υ_{max} (CHCl₃)/cm⁻¹ 1730 (C=O), 1612 (C=C), 1586 (C=C), 1514 (C=C), 1240 (P=O), 1024 (P-O); δ_H (400 MHz; CDCl₃) 7.30 (2 H, d, J = 8.7 Hz, ArH), 6.88 (2 H, d, J = 8.7 Hz, ArH), 4.54 (2 H, s, CH₂), 4.37 (1 H, d, J = 17.2 Hz, CH₃), 4.20 (1 H, d, J = 17.2 Hz, CH₂), 4.16-4.06 (4 H, m, 2 × POCH₂), 3.81 (3 H, s, OMe), 3.44 (1 H, dq, J = 25.1 and 7.1 Hz, CH), 1.37-1.24 (11 H, m, 3 × Me); δ_C
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(100 MHz; CDCl₃) 203.7 (d, ^2J_{C-P} = 4.4 Hz, C), 159.5 (C), 129.7 (CH), 129.3 (C), 113.9 (CH), 74.7 (CH₂), 73.1 (CH₂), 62.7 (d, ^2J_{C-P} = 6.8 Hz, POCH₂), 62.6 (d, ^2J_{C-P} = 6.8 Hz, POCH₂), 55.3 (OMe), 42.5 (d, ^1J_{C-P} = 127.7 Hz, PCH), 16.4 (2 × Me), 10.5 (d, ^2J_{C-P} = 6.6 Hz, Me); m/z (ESI) 367 (MNa^+, 100%), 345 (MH^+, 1).

(E)-1-(Allyloxy)-4-(3,4-dimethoxy-2-(prop-2-nyloxy)phenyl)-3-methylbut-3-en-2-one 401

Following general procedure 7, the title compound was obtained from 3,4-dimethoxy-2-(prop-2-nyloxy)benzaldehyde 318 (1.46 g, 6.63 mmol), potassium tert-butoxide (1.12 g, 9.95 mmol) and diethyl 4-(allyloxy)-3-oxobutan-2-ylphosphonate 397 (2.63 g, 9.95 mmol) as a colourless oil (0.840 g, 38%); (Found: MH^+, 331.1522. C_{19}H_{22}O_5 + H requires 331.1540); ν_{max} (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 2126 (C≡C), 1719 (C=O), 1623 (C=C), 1596 (C=C), 1497 (C=C), 1097 (C-O); δ_H (400 MHz; CDCl₃) 7.73 (1 H, s, C=CH), 7.17 (1 H, d, J = 8.8 Hz, ArH), 6.76 (1 H, d, J = 8.8 Hz, ArH), 6.02-5.93 (1 H, m, CH=CH₂), 5.34 (1 H, ddt, J = 17.2, 1.6 and 1.5 Hz, CH=CH₂), 5.24 (1 H, ddt, J = 10.4, 1.6 and 1.2 Hz, CH=CH₂), 4.77 (2 H, d, J = 2.4 Hz, CH₂), 4.66 (2 H, s, CH₂), 4.15-4.13 (2 H, m, CHCH₂), 3.89 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.48 (1 H, t, J = 2.4 Hz, C≡CH), 2.04 (3 H, s, Me); δ_C (100 MHz; CDCl₃) 197.9 (C), 154.4 (C), 150.4 (C), 142.2 (C), 134.6 (CH), 134.5 (C), 134.3 (CH), 125.1 (CH), 123.1 (C), 117.9
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(CH₂), 107.7 (CH), 79.1 (C=C), 75.6 (C=C), 72.4 (CH₂), 71.9 (CH₂), 61.0 (CH₂), 60.9 (OMe), 56.1 (OMe), 13.0 (Me); m/z (ESI) 353 (MNa⁺, 100%), 331 (MH⁺, 8).

(E)-4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-1-methoxy-3-methylbut-3-en-2-one 402

Following general procedure 7, the title compound was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318 (1.10 g, 5.00 mmol), potassium tert-butoxide (0.842 g, 7.50 mmol) and diethyl 4-methoxy-3-oxobutan-2-ylphosphonate 398 (1.79 g, 7.50 mmol) as a colourless oil (0.970 g, 64%); (Found: MH⁺, 305.1379. C₁₇H₂₀O₅ + H requires 305.1384); νₘₐₓ (CHCl₃)/cm⁻¹ 3307 (alkyne C-H), 1678 (C=O), 1623 (C=C), 1596 (C=C), 1496 (C=C), 1455 (C=C), 1098 (C-O); δH (500 MHz; CDCl₃) 7.72 (1 H, s, C=CH), 7.17 (1 H, d, J = 8.7 Hz, ArH), 6.75 (1 H, d, J = 8.7 Hz, ArH), 4.78 (2 H, d, J = 2.4 Hz, CH₂), 4.62 (2 H, s, CH₂), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.49 (3 H, s, OMe), 2.49 (1 H, t, J = 2.4 Hz, C≡CH), 2.04 (3 H, s, Me); δC (125 MHz; CDCl₃) 197.8 (C), 154.5 (C), 150.5 (C), 142.2 (C), 134.6 (CH), 134.5 (C), 125.1 (CH), 123.1 (C), 107.8 (C), 107.7 (CH), 79.1 (C≡CH), 75.7 (CH₂), 74.6 (C=CH), 61.1 (CH₂), 61.0 (OMe), 59.4 (OMe), 56.1 (OMe), 13.0 (Me); m/z (ESI) 327 (MNa⁺, 100%), 305 (MH⁺, 7%).
(E)-1-(4-Methoxybenzyloxy)-4-(3,4-dimethoxy-2-(prop-2-nyloxy)phenyl)-3-
methylbut-3-en-2-one 403

Following general procedure 7, the title compound was obtained from 3,4-dimethoxy-
2-(prop-2-nyloxy)benzaldehyde 318 (2.98 g, 13.6 mmol), potassium tert-butoxide (2.29 g, 20.4 mmol) and diethyl 4-(4-methoxybenzyloxy)-3-oxobutan-2-
ylphosphonate 399 (7.02 g, 20.4 mmol) as a colourless oil (4.19 g, 75%); (Found:
MH⁺, 411.1788. C₂₄H₂₆O₄ + H requires 411.1802); νmax (CHCl₃)/cm⁻¹ 3307 (alkyne C-
H), 1678 (C=O), 1612 (C=C), 1596 (C=C), 1514 (C=C), 1497 (C=C), 1098 (C-O); δH
(400 MHz; CDCl₃) 7.70 (1 H, s, C=CH), 7.34 (2 H, d, J = 8.8 Hz, ArH), 7.15 (1 H, d, J = 8.8 Hz, ArH), 6.89 (2 H, d, J = 8.8 Hz, ArH), 6.75 (1 H, d, J = 8.8 Hz, ArH), 4.73
(2 H, d, J = 2.4 Hz, CH₂), 4.64 (2 H, s, CH₂), 4.61 (2 H, s, CH₂), 3.89 (3 H, s, OMe),
3.78 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.36 (1 H, t, J = 2.4 Hz, C≡CH), 2.03 (3 H, s, Me); δC (100 MHz; CDCl₃) 198.0 (C), 159.4 (C), 154.4 (C), 150.5 (C), 142.2 (C),
134.7 (CH), 134.5 (C), 129.7 (CH), 125.1 (CH), 123.1 (C), 113.9 (CH), 107.7 (CH),
79.1 (C≡CH), 75.7 (C≡CH), 72.9 (CH₂), 71.6 (CH₂), 61.1 (CH₂), 61.0 (OMe), 56.1
(OMe), 55.3 (OMe), 13.0 (Me); m/z (ESI) m/z (ESI) 433 (MNa⁺, 100%), 411 (MH⁺, 2).
(E)-1-(Allyloxy)-4-(3,4-dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyl)phenyl)-3-methylbut-3-en-2-one 405

Following general procedure 8, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (0.505 g, 1.53 mmol) and alkyne 401 (0.758 g, 2.30 mmol) as a colourless solid (0.668 g, 82%), mp 133-135 °C (from dichloromethane-hexane); (Found: MH+, 533.1921. C29H28N2O8 + H requires 533.1918); νmax (CHCl3)/cm⁻¹ 1678 (C=O), 1628 (C=C), 1595 (C=C), 1532 (C=C), 1496 (C=C), 1356, (NO2), 1097 (C-O); δH (400 MHz; CDCl3) 8.25 (1 H, d, J= 9.4 Hz, ArH), 8.03 (1 H, d, J= 8.8 Hz, ArH), 7.85 (1 H, s, C=CH), 7.61 (1 H, d, J= 9.4 Hz, ArH), 7.49 (1 H, d, J= 8.8 Hz, ArH), 7.21 (1 H, d, J= 8.8 Hz, ArH), 6.80 (1 H, d, J= 8.8 Hz, ArH), 5.93-5.84 (1 H, m, C=CH), 5.24 (1 H, ddt, J= 17.2, 1.6, and 1.5 Hz, C=CH2), 5.14 (1 H, ddt, J= 10.4, 1.6 and 1.2 Hz, C=CH2), 5.10 (2 H, s, CH2), 4.74 (2 H, s, CH2), 4.10 (3 H, s, OMe), 4.06-4.04 (2 H, m, CH2), 3.95 (3 H, s, OMe), 3.94 (3 H, s, OMe), 1.59 (3 H, s, Me); δC (100 MHz; CDCl3) 198.0 (C), 154.5 (C), 150.5 (C), 149.9 (C), 142.3 (C), 142.2 (C), 141.7 (C), 134.6 (C), 134.4 (CH), 134.2 (CH), 134.1 (CH), 129.6 (CH), 126.4 (CH), 125.2 (CH), 123.3 (C), 120.4 (C), 117.7 (CH2), 117.0 (CH), 107.9 (CH), 99.3 (C), 86.5 (C=C), 86.1 (C=C), 72.3 (CH2), 72.1 (CH2), 61.6 (CH2), 61.1 (OMe), 57.2 (OMe), 56.1 (OMe), 13.1 (Me); m/z (ESI) 555 (MNa+, 100%), 533 (MH+, 36).
(E)-4-(3,4-Dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-1-methoxy-3-methylbut-3-en-2-one 406

Following general procedure 8, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (0.660 g, 2.00 mmol) and alkyne 402 (0.913 g, 3.00 mmol) as a colourless solid (0.754 g, 74%), mp 148-150 °C (from dichloromethane-hexane); (Found: C, 63.93; H, 5.17; N, 5.43. C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub> requires C, 64.02; H, 5.17; N, 5.53); (Found: MH<sup>+</sup>, 507.1764. C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub> + H requires 507.1762); ν<sub>max</sub> (CHCl<sub>3</sub>)<sup>cm</sup><sup>-1</sup> 1677 (C=O), 1628 (C=C), 1595 (C=C), 1532 (C=C), 1495 (C=C), 1461 (C=C), 1356 (NO<sub>2</sub>), 1096 (C-O); δ<sub>1H</sub> (400 MHz; CDCl<sub>3</sub>) 8.23 (1 H, d, J = 9.6 Hz, ArH), 8.01 (1 H, d, J = 8.8 Hz, ArH), 7.84 (1 H, s, C=CH), 7.60 (1 H, d, J = 9.6 Hz, ArH), 7.48 (1 H, d, J = 8.8 Hz, ArH), 7.20 (1 H, d, J = 8.8 Hz, ArH), 6.79 (1 H, d, J = 8.8 Hz, ArH), 5.09 (2 H, s, CH<sub>2</sub>), 4.69 (2 H, s, CH<sub>2</sub>), 4.09 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.37 (3 H, s, OMe), 2.02 (3 H, s, Me); δ<sub>13C</sub> (100 MHz; CDCl<sub>3</sub>) 197.8 (C), 154.5 (C), 150.5 (C), 149.9 (C), 142.2 (C), 141.7 (C), 134.5 (C), 134.4 (CH), 134.1 (CH), 129.6 (CH), 126.3 (CH), 125.2 (CH), 123.3 (C), 120.4 (C), 117.0 (CH), 108.0 (CH), 86.5 (C=C), 86.1 (C=C), 74.7 (CH<sub>2</sub>), 61.6 (CH<sub>2</sub>), 61.1 (OMe), 59.3 (OMe), 57.2 (OMe), 56.1 (OMe), 13.1 (Me); m/z (ESI) 529 (MNa<sup>+</sup>, 100%), 507 (MH<sup>+</sup>, 46).
(E)-4-((2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)-1-(4-methoxybenzyloxy)-3-methylbut-3-en-2-one 407

Following general procedure 8, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (1.40 g, 4.24 mmol) and alkyne 403 (2.61 g, 6.36 mmol) as a colourless solid (2.45 g, 94%), mp 125-126 °C (from dichloromethane-hexane); (Found: C, 66.37; H, 5.18; N 4.40. C₃₄H₃₂N₂O₉ requires C, 66.66; H, 5.26; N, 4.57%); (Found: MH⁺, 613.2165. C₃₄H₃₂N₂O₉ + H requires 613.2181); \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1677 (C=O), 1628 (C=C), 1613 (C=C), 1595 (C=C), 1531 (C=C), 1514 (C=C), 1496 (C=C), 1096 (C-O); \( \delta_H \) (400 MHz; CDCl₃) 8.18 (1 H, d, \( J = 9.6 \) Hz, ArH), 7.98 (1 H, d, \( J = 8.8 \) Hz, ArH), 7.84 (1 H, s, C=CH), 7.52 (1 H, d, \( J = 9.6 \) Hz, ArH), 7.44 (1 H, d, \( J = 8.8 \) Hz, ArH), 7.22 (2 H, d, \( J = 8.4 \) Hz, ArH), 7.18 (1 H, d, \( J = 8.8 \) Hz, ArH), 6.81 (2 H, d, \( J = 8.4 \) Hz, ArH), 6.78 (1 H, d, \( J = 8.8 \) Hz, ArH), 5.06 (2 H, s, CH₂), 4.73 (2 H, s, CH₂), 4.48 (2 H, s, CH₂), 4.06 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.77 (3 H, s, OMe), 2.01 (3 H, s, Me); \( \delta_C \) (100 MHz; CDCl₃) 198.2 (C), 159.3 (C), 154.5 (C), 150.5 (C), 149.9 (C), 142.2 (C), 141.7 (C), 134.7 (C), 57.2 (OMe), 134.5 (CH), 134.2 (CH), 129.7 (C), 129.6 (CH), 126.3 (CH), 125.2 (CH), 123.3 (C), 120.3 (C), 117.1 (CH), 116.9 (CH), 113.7 (CH), 107.9 (CH), 72.9 (CH₂), 72.0 (CH₂), 61.6 (CH₂), 61.1 (OMe), 56.1 (OMe), 55.2 (OMe), 13.1 (Me); m/z (ESI) 635 (MNa⁺, 100%), 613 (MH⁺, 36).
(E)-1-(Allyloxy)-4-(3,4-dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one O-methyl oxime

Following general procedure 9, the title compound was prepared from ketone 405 (0.400 g, 0.751 mmol), methoxylamine hydrochloride (0.078 g, 0.939 mmol) and sodium acetate trihydrate (0.107 g, 0.789 mmol) as an orange solid (0.422 g, 100%), mp 78-80 °C (from dichloromethane-hexane); (Found: MH\(^+\), 562.2171. C\(_{30}\)H\(_{31}\)N\(_3\)O\(_8\) + H requires 562.2184); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1628 (C=C), 1597 (C=C), 1531 (C=C), 1495 (C=C), 1462 (C=C), 1357 (N=O), 1097 (C-O); \(\delta_H\) (400 MHz; CDCl\(_3\)) 8.18 (1 H, d, \(J = 9.5\) Hz, ArH), 7.97 (1 H, d, \(J = 8.8\) Hz, ArH), 7.56 (1 H, d, \(J = 9.5\) Hz, ArH), 7.51 (1 H, d, \(J = 8.8\) Hz, ArH), 7.23 (1 H, s, C=CH), 7.03 (1 H, d, \(J = 8.7\) Hz, ArH), 6.72 (1 H, d, \(J = 8.7\) Hz, ArH), 5.95-5.83 (1 H, m, CH=CH\(_2\)), 5.25 (1 H, ddt, \(J = 17.2, 1.6\) and 1.5 Hz, CH=CH\(_2\)), 5.12 (1 H, ddt, \(J = 17.2, 1.6\) and 1.2 Hz, CH=CH\(_2\)), 5.00 (2 H, s, CH\(_2\)), 4.51 (2 H, s, CH\(_2\)), 4.05 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.88 (3 H, s, CH\(_2\)), 3.87 (3 H, s, CH\(_2\)), 3.88 (3 H, s, CH\(_2\)), 3.87 (3 H, s, CH\(_2\)); \(\delta_C\) (100 MHz; CDCl\(_3\)) 157.1 (C), 153.0 (C), 149.9 (C), 149.7 (C), 142.3 (C), 142.1 (C), 142.0 (C), 134.6 (CH), 134.0 (CH), 132.3 (C), 129.4 (C), 129.3 (CH), 127.2 (CH), 126.7 (CH), 126.6 (C), 125.1 (CH), 120.3 (C), 117.4 (CH\(_2\)), 116.8 (CH), 107.6 (CH), 86.9 (C≡C), 85.9 (C≡C), 71.9 (CH\(_2\)), 62.1 (OMe), 61.2 (OMe), 61.1 (CH\(_2\)), 60.0 (CH\(_2\)), 57.2 (OMe), 56.0 (OMe), 14.6 (Me); \(m/z\) (ESI) 584 (MNa\(^+\), 96%), 562 (MH\(^+\), 100).
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Timothy E. Hurst

(E)-4-(3,4-Dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-1-methoxy-3-methylbut-3-en-2-one O-methyl oxime

Following general procedure 9, the title compound was obtained from ketone 406 (0.600 g, 1.18 mmol), methoxylamine hydrochloride (0.123 g, 1.48 mmol) and sodium acetate trihydrate (0.169 g, 1.24 mmol) as a colourless solid (0.376 g, 59%), mp 73-75 °C (from dichloromethane-hexane); (Found: MH\(^+\), 536.2019. C\(_{28}\)H\(_{30}\)N\(_3\)O\(_8\) + H requires 536.2027); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 2253 (C=\(\equiv\)C), 1628 (C=\(\equiv\)C), 1596 (C=\(\equiv\)C), 1531 (C=\(\equiv\)C), 1495 (C=\(\equiv\)C), 1463 (C=\(\equiv\)C), 1357 (N=O), 1097 (C-O); \(\delta_\text{H}\) (500 MHz; CDCl\(_3\)) 8.18 (1 H, d, \(J = 9.5\) Hz, ArH), 7.98 (1 H, d, \(J = 8.8\) Hz, ArH), 7.56 (1 H, d, \(J = 9.5\) Hz, ArH), 7.51 (1 H, d, \(J = 8.8\) Hz, ArH), 7.21 (1 H, s, C=CH), 7.05 (1 H, d, \(J = 8.7\) Hz, ArH), 6.72 (1 H, d, \(J = 8.7\) Hz, ArH), 5.00 (2 H, s, CH\(_2\)), 4.46 (2 H, s, CH\(_2\)), 4.07 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.34 (3 H, s, OMe), 2.01 (3 H, s, Me); \(\delta_\text{C}\) (125 MHz; CDCl\(_3\)) 157.0 (C), 153.1 (C), 150.0 (C), 149.8 (C), 142.4 (C), 142.2 (C), 134.0 (CH), 132.3 (C), 129.4 (CH), 127.1 (CH), 126.7 (CH), 125.1 (CH), 124.8 (C), 120.3 (C), 116.8 (CH), 107.7 (CH), 86.9 (C=CH), 86.0 (C=CH), 62.5 (CH\(_2\)), 62.2 (OMe), 61.2 (OMe), 61.1 (CH\(_2\)), 58.7 (OMe), 57.3 (OMe), 56.1 (OMe), 14.6 (Me); \(m/z\) (ESI) 558 (MNa\(^+\), 100%), 536 (MH\(^+\), 94).
New Developments in the 1-Aza-Diels-Alder Reaction

(Timothy E. Hurst)

\[(E)-4-(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-
\quad \text{dimethoxyphenyl)-1-(4-methoxybenzylxoy)-3-methylbut-3-en-2-one} \quad \text{O-methyl oxime 411} \]

Following general procedure 9, the \textit{title compound} was obtained from ketone 407 (2.30 g, 3.75 mmol), methoxylamine hydrochloride (0.392 g, 4.69 mmol) and sodium acetate trihydrate (0.536 g, 3.94 mmol) as a colourless solid (2.30 g, 84%), mp 76-78 °C (from dichloromethane-hexane); (Found: MH\(^+\), 642.2447. \(\text{C}_{35}\text{H}_{35}\text{N}_{3}\text{O}_{9} + \text{H requires} 642.2446\)); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1677 (C=O), 1628 (C=C), 1613 (C=C), 1595 (C=C), 1531 (C=C), 1514 (C=C), 1496 (C=C), 1096 (C-O); \(\delta_H\) (400 MHz; CDCl\(_3\)) 8.16 (1 H, d, \(J = 9.6\) Hz, ArH), 7.91 (1 H, d, \(J = 8.8\) Hz, ArH), 7.55 (1 H, d, \(J = 9.6\) Hz, ArH), 7.45 (1 H, d, \(J = 8.8\) Hz, ArH), 7.25 (1 H, s, C=CH), 7.24 (2 H, d, \(J = 8.4\) Hz, ArH), 7.05 (1 H, d, \(J = 8.8\) Hz, ArH), 6.81 (2 H, d, \(J = 8.4\) Hz, ArH), 6.74 (1 H, d, \(J = 8.8\) Hz, ArH), 4.98 (2 H, s, CH\(_2\)), 4.54 (2 H, s, CH\(_2\)), 4.47 (2 H, s, CH\(_2\)), 4.07 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.75 (3 H, s, OMe), 2.02 (3 H, s, Me); \(\delta_C\) (100 MHz; CDCl\(_3\)) 159.1 (C), 157.3 (C), 153.0 (C), 150.0 (C), 149.7 (C), 142.4 (C), 142.1 (C), 142.0 (C), 134.0 (CH), 130.2 (C), 129.5 (CH), 129.3 (CH), 127.3 (CH), 126.7 (CH), 125.1 (CH), 124.9 (C), 120.3 (C), 116.7 (CH), 113.6 (CH), 107.7 (CH), 86.9 (C=C), 86.0 (C=C), 72.5 (CH\(_2\)), 62.1 (OMe), 61.2 (OMe), 61.1 (CH\(_2\)), 60.0 (CH\(_2\)), 57.2 (OMe), 56.1 (OMe), 55.2 (OMe), 53.4 (OMe), 14.7 (Me); \(m/z\) (ESI) 664 (MNa\(^+\), 99%), 642 (MH\(^+\), 100).
7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-2-(methoxymethyl)-1-methyl-
5H-chromeno[3,4-c]pyridine 414

Following general procedure 11, the title compound was obtained from oxime 410
(0.300 g, 0.560 mmol) after 16 h at reflux in xylene as a colourless solid (0.115 g,
41%), mp 205-207 °C (from dichloromethane-hexane); (Found: MH⁺, 504.1759.
C₂₇H₂₅N₃O₇ + H requires 504.1765); ν max (CHCl₃)/cm⁻¹ 1629 (C=C), 1600 (C=C),
1551 (C=C), 1531 (C=C), 1499 (C=C), 1463 (C=C), 1355 (N=O), 1105 (C-O); δH
(400 MHz; CDCl₃) 8.57 (1 H, d, J = 9.2 Hz, ArH), 8.24 (1 H, d, J = 9.6 Hz, ArH), 8.19
(1 H, d, J = 8.8 Hz, ArH), 7.59 (1 H, d, J = 9.6 Hz, ArH), 7.49 (1 H, d, J = 8.8 Hz,
ArH), 6.75 (1 H, d, J = 8.8 Hz, ArH), 5.65 (2 H, s, CH₂), 4.80 (2 H, s, CH₂), 4.09 (3 H,
s, OMe), 3.97 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.51 (3 H, s, OMe), 2.70 (3 H, s,
Me); δC (100 MHz; CDCl₃) 156.8 (C), 155.7 (C), 154.1 (C), 149.5 (C), 141.2 (C),
138.1 (C), 134.1 (CH), 129.6 (CH), 129.3 (C), 128.5 (C), 124.3 (CH), 124.1 (CH),
120.5 (C), 117.1 (C), 116.2 (CH), 105.5 (CH), 76.0 (CH₂), 67.5 (CH₂), 61.4 (OMe),
58.5 (OMe), 57.2 (OMe), 56.1 (OMe), 17.3 (Me); m/z (ESI) 526 (MNa⁺, 19%), 504
(MH⁺, 100).
7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-2-((4-
methoxybenzyloxy)methyl)-1-methyl-5H-chromeno[3,4-c]pyridine 415

Following general procedure 11, the *title compound* was obtained from ketone 411 (0.250 g, 0.408 mmol), methoxylamine hydrochloride (0.068 g, 0.816 mmol) and triethylamine (0.113 mL, 0.816 mmol) after 16 h at reflux in xylene as a colourless solid (0.094 g, 38%), mp 199-201 °C (from dichloromethane-hexane); (Found: MH⁺, 610.2168. C₃₄H₃₁N₃O₈ + H requires 610.2184); νₘₐₓ (CHCl₃)/cm⁻¹ 1629 (C=C), 1601 (C=C), 1571 (C=C), 1550 (C=C), 1531 (C=C), 1513 (C=C), 1499 (C=C), 1464 (C=C), 1355 (N=O), 1105 (C-O); δₓ (400 MHz; CDCl₃) 8.58 (1 H, d, J = 9.2 Hz, ArH), 8.25 (1 H, d, J = 9.6 Hz, ArH), 8.21 (1 H, d, J = 9.2 Hz, ArH), 7.60 (1 H, d, J = 9.6 Hz, ArH), 7.49 (1 H, d, J = 8.8 Hz, ArH), 7.33 (2 H, d, J = 8.8 Hz, ArH), 6.90 (2 H, d, J = 8.8 Hz, ArH), 6.75 (1 H, d, J = 8.8 Hz, ArH), 5.66 (2 H, s, CH₂), 4.87 (2 H, s, CH₂), 4.60 (2 H, s, CH₂), 4.11 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.82 (3 H, s, OMe), 2.69 (3 H, s, Me); δₓ (100 MHz; CDCl₃) 159.4 (C), 155.0 (C), 154.7 (C), 154.5 (C), 151.5 (C), 149.9 (C), 146.8 (C), 141.3 (C), 134.7 (C), 134.2 (CH), 129.8 (CH), 129.6 (C), 129.3 (C), 124.4 (CH), 124.2 (CH), 120.7 (C), 116.6 (CH), 113.8 (CH), 105.3 (CH), 72.7 (CH₂), 71.9 (CH₂), 67.1 (CH₂), 61.4 (OMe), 57.3 (OMe), 56.1 (OMe), 55.3 (OMe), 17.5 (Me); m/z (ESI) 632 (MNa⁺, 39%), 610 (MH⁺, 90), 362 (13), 288 (16), 242 (100).
New Developments in the 1-Aza-Diels-Alder Reaction

(7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-1-methyl-5H-chromeno[3,4-c]pyridin-2-yl)methanol 416

To a solution of para-methoxybenzyl protected pyridine 415 (0.240 g, 0.394 mmol) in dichloromethane (2 mL) at 0 °C was added anisole (0.4 mL) and trifluoroacetic acid (2 mL). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed in vacuo, and the residue partitioned between water (20 mL) and dichloromethane (3 × 20 mL). The combined organics were washed with saturated brine (20 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (2:3) to afford the title compound as a colourless solid (0.168 g, 87%), mp 218-220 °C (from dichloromethane-hexane); (Found: MH⁺, 490.1595. C₂₆H₂₃N₃O₇ + H requires 490.1609); νmax (CHCl₃)/cm⁻¹ 3389 (O-H), 1628 (C=C), 1601 (C=C), 1579 (C=C), 1554 (C=C), 1531 (C=C), 1499 (C=C), 1463 (C=C), 1358 (N=O), 1105 (C-O); δH (500 MHz; CDCl₃) 8.50 (1 H, d, J = 9.5 Hz, ArH), 8.24 (1 H, d, J = 8.5 Hz, ArH), 8.22 (1 H, d, J = 8.5 Hz, ArH), 7.61 (1 H, d, J = 9.5 Hz, ArH), 5.66 (2 H, s, CH₂), 4.86 (2 H, s, CH₂), 4.12 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.95 (3 H, s, OMe), 2.50 (3 H, s, OMe); δC (100 MHz; CDCl₃) 156.1 (C), 155.8 (C), 154.3 (C), 151.5 (C), 149.7 (C), 147.0 (C), 141.2 (C), 139.6 (C), 138.1 (C), 134.8 (C), 134.2 (CH), 129.9 (CH), 128.6 (C), 124.8
(C), 124.0 (CH), 123.9 (CH), 120.6 (C), 116.7 (C), 116.4 (CH), 105.2 (CH), 67.5 (CH₂), 62.0 (CH₂), 61.4 (OMe), 57.3 (OMe), 56.1 (OMe), 15.3 (Me); m/z (ESI) 512 (MNa⁺, 31%), 490 (MH⁺, 95), 288 (16), 242 (100).

2-(Allyloxy)-3-methylbenzaldehyde⁹ 419

Following general procedure 6, the title compound was obtained from 3-methylsalicaldehyde 321 (8.17 g, 60.0 mmol), potassium carbonate (12.4 g, 90.0 mmol) and allyl bromide (26.0 mL, 300 mmol) as a colourless oil (10.6 g, 100%); νmax (CHCl₃)/cm⁻¹ 1678 (C=O), 1590 (C=C), 1471 (C=C), 1392 (C=C), 1086 (C-O); δH (400 MHz; CDCl₃) 10.38 (1 H, s, CHO), 7.69 (1 H, d, J = 7.6 Hz, ArH), 7.45 (1 H, d, J = 7.6 Hz, ArH), 7.14 (1 H, t, J = 7.6 Hz, ArH), 6.14 - 6.07 (1 H, m, CH), 5.43 (1 H, dd, J = 17.2 and 1.2 Hz, CH), 5.31 (1 H, dd, J = 10.4 and 1.2 Hz, CH), 4.47 (2 H, dd, J = 5.6 and 1.2 Hz, CH₂), 2.35 (3 H, s, Me); δc (100 MHz; CDCl₃) 190.5 (CHO), 160.4 (C), 137.5 (CH), 132.7 (CH), 132.5 (C), 129.5 (C), 126.4 (CH), 124.4 (CH), 118.7 (CH₂), 76.5 (CH₂), 15.9 (Me);
(E)-4-(2-(Allyloxy)-3-methylphenyl)but-3-en-2-one

![Chemical structure](image)

Following general procedure 7, the title compound was obtained from 2-(allyloxy)-3-methylbenzaldehyde 419 (6.17 g, 35.0 mmol), potassium tert-butoxide (5.89 g, 52.5 mmol) and dimethyl 2-oxopropylphosphonate 324 (8.72 g, 52.5 mmol) as a colourless oil (7.05 g, 93%); (Found: MNa⁺, 239.1043. C₁₄H₁₆O₂ + Na requires 239.1043); νmax (CHCl₃)/cm⁻¹ 1688 (C=O), 1644 (C=C), 1622 (C=C), 1606 (C=C), 1588 (C=C), 1464 (C=C), 1090 (C-O); δH (400 MHz; CDCl₃) 7.86 (1 H, d, J = 13.2 Hz, C=CH), 7.44 (1 H, d, J = 6.0 Hz, ArH), 7.25 (1 H, d, J = 6.0 Hz, ArH), 7.07 (1 H, t, J = 6.0 Hz, ArH), 6.71 (1 H, d, J = 13.2 Hz, C=CH), 6.15 - 6.09 (1 H, m, CH), 5.47 (1 H, dd, J = 13.6 and 1.3 Hz, CH=C₆H₅), 5.37 (1 H, dd, J = 10.4, and 1.3 Hz, CH=CH₂), 4.35 (2 H, m, CH₂), 2.39 (3 H, s, Me), 2.33 (3 H, s, Me); δC (100 MHz; CDCl₃) 198.9 (C), 156.8 (C), 139.0 (CH), 133.5 (CH), 133.4 (CH), 133.3 (C), 132.1 (C), 128.2 (CH), 128.1 (C), 125.2 (CH), 124.5 (CH), 117.8 (CH₂), 74.9 (CH₂), 27.0 (Me), 16.2 (Me); m/z (ESI) 239 (MNa⁺, 100%).
(3E)-4-(2-(Allyloxy)-3-methylphenyl)but-3-en-2-one O-methyl oxime 420

Following general procedure 9, the *title compound* was obtained from the ketone (9.00 g, 41.6 mmol), methoxylamine hydrochloride (4.34 g, 52.0 mmol) and sodium acetate trihydrate (5.94 g, 43.7 mmol) as a colourless oil (9.70 g, 95%); (Found: MH⁺, 246.1489. C₁₅H₁₉NO₂ + H requires 246.1489); νmax (CHCl₃)/cm⁻¹ 1647 (C=N), 1620 (C=C), 1587 (C=C), 1463 (C=C), 1089 (C-O); δH (400 MHz; CDCl₃) 7.44 (1 H, d, J = 7.6 Hz ArH), 7.22 (1 H, d, J = 16.4 Hz, C=CH), 7.13 (1 H, d, J = 7.6 Hz ArH), 7.03 (1 H, t, J = 7.6 Hz, ArH), 6.83 (1 H, d, J = 16.4 Hz, C=CH), 6.15 - 6.08 (1 H, m, CH=CH₂), 5.46 (1 H, dt, J = 16.8 and 1.2 Hz, CH=CH₂), 5.30 (1 H, dt, J = 10.4 and 1.2 Hz, C=CH₂), 4.33 (2 H, m, CH₂), 3.97 (3 H, s, OMe), 2.31 (3 H, s, Me), 2.08 (3 H, s, Me); δC (100 MHz; CDCl₃) 156.1 (CN), 155.5 (C), 133.7 (CH), 131.7 (C), 131.2 (CH), 130.2 (C), 127.9 (CH), 126.6 (CH), 124.3 (CH), 123.9 (CH), 117.4 (C=CH₂), 74.5 (CH₂), 61.9 (OMe), 16.2 (Me), 10.1 (Me); m/z (ESI) 268 (MNa⁺, 64%), 246 (MH⁺, 100%).
(E)-4-(2-hydroxy-3-methylphenyl)but-3-en-2-one O-methyl oxime 421

To a solution of oxime 420 (9.00 g, 36.7 mmol), palladium(II) acetate (0.823 g, 3.67 mmol) and triphenylphosphine (14.4 g, 55.1 mmol) in THF (150 mL) was added morpholine (3.86 mL, 44.0 mmol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the title compound as a colourless solid (6.18 g, 82%); 138-140 °C (from dichloromethane-hexane); (Found: C, 69.95; H, 7.38; N, 6.78. C12H15NO2 requires C, 70.22; H, 7.37; N, 6.82%); (Found: MH+, 206.1171. C12H15NO2 + H requires 206.1176); νmax (CHCl3)/cm−1 3606 (O-H), 1591 (C=C), 1465 (C=C), 1436 (C=C), 1057 (C-O); δH (400 MHz; CDCl3) 7.34 (1 H, d, J = 7.6 Hz, ArH), 7.20 (1 H, d, J = 16.5 C=CH), 7.07 (1 H, d, J = 7.6 Hz, ArH), 6.85 (1 H, t, J = 7.6 Hz, ArH), 6.83 (1 H, d, J = 16.5 Hz, C=CH), 5.02 (1 H, s, OH), 3.96 (3 H, s, OMe), 2.27 (3 H, s, Me), 2.10 (3 H, s, Me); δC (100 MHz; CDCl3) 156.2 (C), 151.6 (C), 130.7 (CH), 127.6 (CH), 126.7 (CH), 124.9 (CH), 123.6 (C), 123.5 (C), 120.8 (CH), 61.9 (OMe), 15.8 (Me), 10.2 (Me); m/z (ESI) 242 (63%), 228 (MNa+, 10), 206 (MH+, 100).
2-((1E)-3-(Methoxyimino)but-1-enyl)-6-methylphenyl 3-phenylpropiolate 422

To a solution of phenylpropiolic acid (1.50 g, 9.00 mmol) in dichloromethane (35 mL) was added thionyl chloride (1.97 mL, 27.0 mmol). The reaction mixture was heated to 40 °C for 18 h and then concentrated in vacuo. The crude acid chloride was dissolved in dry DMF (6 mL) and added to a suspension of phenol 421 (0.616 g, 3.00 mmol) and potassium carbonate (3.52 g, 25.5 mmol) in dry DMF (6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Water (75 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organics were washed with water (2 x 75 mL) and saturated brine (75 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19 to 1:9) to afford the title compound as a colourless solid (0.990 g, 99%), mp 103-105 °C (from dichloromethane-hexane); (Found: C, 75.43; H, 5.74; N, 3.93. C₂₁H₁₉N⁰₃ requires C, 75.66; H, 5.74; N, 4.20%); (Found: MH⁺, 334.1435. C₂₁H₁₉N⁰₃ + H requires 334.1438); νmax (CHCl₃)/cm⁻¹ 2235 (C=C), 1721 (C=O), 1612 (C=C), 1579 (C=C), 1491 (C=C), 1463 (C=C); δH (400 MHz; CDCl₃) 7.64 (2 H, d, J = 8.0 Hz, ArH), 7.53-7.50 (2 H, m, ArH), 7.42 (2 H, t, J = 8.0 Hz, ArH), 7.21-7.20 (2 H, m, ArH), 6.93 (1 H, d, J = 16.5 Hz, C=CH), 6.85 (1 H, d, J = 16.5 Hz, C=CH), 3.95 (3 H, s, OMe), 2.27 (3 H, s, Me), 2.06 (3 H, s, Me); δc (100 MHz; CDCl₃) 164.2 (C), 162.3 (C), 158.8 (C), 151.2 (C), 144.0 (C), 140.9 (C), 133.8 (C), 128.7 (CH), 128.0 (CH),
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127.2 (C), 124.0 (CH), 121.2 (CH), 116.0 (C), 113.5 (CH), 111.8 (C), 25.4 (Me), 15.8 (Me); m/z (ESI) 356 (MNa+, 100%), 334 (MH+, 32).

2,7-Dimethyl-4-phenyl-5H-chromeno[3,4-c]pyridin-5-one 423

A solution of oxime 422 (1.00 g, 3.00 mmol) in xylene (50 mL) was split into two equal portions and placed in two sealed reaction vessels. The reaction vessels were then heated to 180 °C for 24 h. The two reaction mixtures were then recombined and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the title compound as a colourless solid (0.434 g, 48%), mp 196-197 °C (from ethyl acetate-hexane); (Found: MH+, 302.1173. C20H15N02 + H requires 302.1176); νmax (CHCl3)/cm⁻¹ 1742 (C=O), 1615 (C=C), 1592 (C=C), 1579 (C=C), 1551 (C=C), 1497 (C=C); δH (400 MHz; CDCl3) 7.94 (1 H, d, J = 8.0 Hz, ArH), 7.80 (1 H, s, ArH), 7.57-7.54 (2 H, m, ArH), 7.49-7.46 (3 H, m, ArH), 7.45 (1 H, d, J = 8.0 Hz, ArH), 7.27 (1 H, t, J = 8.0 Hz, ArH), 2.78 (3 H, s, Me), 2.49 (3 H, s, Me); δC (100 MHz; CDCl3) 164.1 (C), 162.3 (C), 158.8 (C), 151.2 (C), 144.0 (C), 140.9 (C), 133.8 (CH), 128.6 (CH), 128.0 (CH), 127.1 (C), 124.0 (CH), 121.2 (CH), 115.9 (C), 113.5 (CH), 111.7 (C), 25.4 (Me), 15.8 (Me); m/z (ESI) 324 (MNa+, 82%), 302 (MH+, 100).
7-Methyl-5-oxo-4-phenyl-5H-chromeno[3,4-c]pyridine-2-carboxylic acid 424

To a solution of 423 (0.405 g, 1.34 mmol) in pyridine (10 mL) was added selenium dioxide (0.597 g, 5.38 mmol). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and filtered through celite. The filter cake was washed with chloroform (20 mL) and the combined organics concentrated in vacuo. The crude product was dissolved in ethyl acetate (100 mL), washed with water (100 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a pale orange solid (0.424 g, 95%), mp 222-224 °C (from dichloromethane-hexane); (Found: C, 72.01; H, 4.00; N, 4.09. C₂₀H₁₃N₀₄ requires C, 72.50; H, 3.95; N, 4.23%); (Found: [M-H]⁺, 330.0770. C₂₀H₁₃N₀₄ - H requires 330.0772); ν max (CHCl₃)/cm⁻¹ 1768 (C=O), 1747 (C=O), 1553 (C=C), 1492 (C=C); δH (400 MHz; DMSO) 8.73 (1 H, s, ArH), 8.33 (1 H, d, J = 8.0 Hz, ArH), 7.59-7.55 (3 H, m, ArH), 7.48-7.42 (3 H, m, ArH), 7.33 (1 H, t, J = 8.0 Hz, ArH), 2.37 (3 H, s, Me); δC (100 MHz; DMSO) 165.8 (C), 162.7 (C), 157.6 (C), 150.5 (C), 144.5 (C), 140.5 (C), 134.2 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 125.7 (C), 124.3 (CH), 122.5 (CH), 115.7 (C), 115.4 (CH), 15.2 (Me); m/z (ESI) 330 (M-H⁺, 17%), 286 ([M-CO₂]⁺, 100).
2-(Allyloxy)-3,4-dimethoxybenzaldehyde

Following general procedure 6, the title compound was obtained from 3,4-dimethoxy salicylaldehyde 279 (5.25 g, 28.8 mmol), potassium carbonate (5.97 g, 43.2 mmol) and allyl bromide (12.5 mL, 144 mmol) as a colourless oil (5.62 g, 88%); (Found: MNa+, 245.0778. C_{12}H_{14}O_{4} + Na requires 245.0784); ν_{max} (CHCl_{3})/cm^{-1} 1675 (C=O), 1591 (C=C), 1497 (C=C), 1463 (C=C), 1098 (C-O); δ_{H} (500 MHz; CDCl_{3}) 10.27 (1 H, s, CHO), 7.59 (1 H, d, J = 8.5 Hz, ArH), 6.75 (1 H, d, J = 8.5 Hz, ArH), 6.07 (1 H, ddt, J = 17.1, 10.3 and 6.0 Hz, CH_{2}=CH), 5.37 (1 H, ddt, J = 17.1, 1.5 and 1.5 Hz, CH_{2}=CH), 5.28 (1 H, ddt, J = 10.3, 1.5 and 1.5 Hz, CH_{2}=CH), 4.69 (2 H, dt, J = 6.0 and 1.5 Hz, CH_{2}), 3.92 (3 H, s, OMe), 3.87 (3 H, s, OMe); δ_{C} (125 MHz; CDCl_{3}) 189.1 (CHO), 159.3 (C), 155.6 (C), 141.8 (C), 133.2 (CH), 124.1 (CH), 123.8 (C), 118.9 (CH_{2}), 107.6 (CH), 75.4 (CH_{2}), 61.0 (OMe), 56.2 (OMe); m/z (ESI) 467 (21%), 245 (MNa^{+}, 100%).

(E)-4-(2-(Allyloxy)-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one 426

Following general procedure 7, the title compound was prepared from 2-(allyloxy)-3,4-dimethoxybenzaldehyde (5.00 g, 22.5 mmol), potassium tert-butoxide (4.13 g,
33.8 mmol) and diethyl 1-methyl-2-oxopropylphosphonate 319 (7.03 g, 33.8 mmol) as a colourless oil (5.79 g, 93%); (Found: MH\(^+\), 277.1423. C\(_{16}\)H\(_{20}\)O\(_4\) + H requires 277.1434); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1660 (C=O), 1625 (C=C), 1595 (C=C), 1496 (C=C), 1463 (C=C), 1100 (C-O); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 7.72 (1 H, s, CH), 7.15 (1 H, d, \(J = 8.5\) Hz, ArH), 6.73 (1 H, d, \(J = 8.5\) Hz, ArH), 6.07 (1 H, m, CH\(_2\)=CH), 5.40 (1 H, dd, \(J = 17.0\) and 1.5 Hz, CH\(_2\)=CH), 5.25 (1 H, dd, \(J = 9.0\) and 1.5 Hz, CH\(_2\)=CH), 4.56 (2 H, m, CH\(_2\)), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.45 (3 H, s, Me), 2.01 (3 H, s, Me); \(\delta\)\(_C\) (125 MHz; CDCl\(_3\)) 200.5 (C), 154.4 (C), 151.5 (C), 142.3 (C), 136.7 (C), 135.5 (CH), 133.9 (CH), 125.0 (CH), 123.2 (C), 117.9 (CH\(_2\)), 107.1 (CH), 74.8 (CH\(_2\)), 61.0 (OMe), 56.1 (OMe), 25.8 (Me), 13.0 (Me); \(m/z\) (ESI) 299 (MNa\(^+\), 100%), 277 (12).

(3E)-4-(2-(Allyloxy)-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one O-methyl oxime

Following general procedure 9, the title compound was obtained from ketone 426 (5.53 g, 20.0 mmol), methoxylamine hydrochloride (2.09 g, 25.0 mmol) and sodium acetate trihydrate (2.86 g, 21.0 mmol) as a colourless oil (5.85 g, 96%); (Found: MH\(^+\), 306.1691. C\(_{17}\)H\(_{23}\)NO\(_4\) + H requires 306.1700); \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1598 (C=C), 1494 (C=C), 1464 (C=C), 1097 (C-O); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 7.00 (1 H, d, \(J = 8.8\) Hz, ArH), 6.93 (1 H, s, C=CH), 6.69 (1 H, d, \(J = 8.8\) Hz, ArH), 6.10-6.01 (1 H, m, CH=CH\(_2\)), 5.35 (1 H, ddt, \(J = 17.2, 1.6\) and 1.5 Hz, CH=CH\(_2\)), 5.20 (1 H, m,
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CH=CH₂, 4.49 (2 H, dt, J = 5.8 and 1.5 Hz, CH₂), 3.95 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.09 (3 H, s, Me), 2.04 (3 H, s, Me); δC (100 MHz; CDCl₃) 157.1 (C), 153.0 (C), 151.0 (C), 142.3 (C), 134.2 (CH), 134.1 (C), 126.0 (CH), 124.9 (CH), 124.6 (C), 117.5 (CH₂), 107.0 (CH), 74.4 (CH₂), 61.8 (OMe), 61.0 (OMe), 56.0 (OMe), 14.4 (Me), 10.7 (Me); m/z (ESI) 328 (MNa⁺, 100%), 306 (MH⁺, 60), 287 (16).

(E)-4-(2-Hydroxy-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one O-methyl oxime

To a solution of the oxime (5.75 g, 18.8 mmol), palladium(II) acetate (0.423 g, 1.88 mmol) and triphenylphosphine (7.40 g, 28.2 mmol) in THF (130 mL) was added morpholine (1.97 mL, 22.6 mmol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the title compound as a colourless solid (4.00 g, 80%), mp 75-76 °C (from dichloromethane-hexane); (Found: C, 63.24; H, 7.19; N, 5.26. C₁₄H₁₉NO₄ requires C, 63.38; H, 7.22; N, 5.28%); (Found: MH⁺, 266.1385. C₁₄H₁₉NO₄ + H requires 266.1387); νmax (CHCl₃)/cm⁻¹ 3518 (O-H), 1615 (C=C), 1582 (C=C), 1508 (C=C), 1460 (C-O); δH (400 MHz; CDCl₃) 6.98 (1 H, d, J = 8.8 Hz, ArH), 6.90 (1 H, s, C=CH), 6.50 (1 H, d, J = 8.8 Hz, ArH), 6.00 (1 H, s, ArOH), 3.95 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.89 (3 H, s, OMe), 2.12 (3 H, s, Me),
2.05 (3 H, s, Me); δc (100 MHz; CDCl₃) 157.2 (C), 151.5 (C), 147.5 (C), 135.3 (C), 134.3 (C), 125.1 (CH), 124.7 (CH), 117.5 (C), 103.3 (CH), 61.8 (OMe), 61.0 (OMe), 55.8 (OMe), 14.5 (Me), 10.9 (Me); m/z (ESI) 288 (MNa⁺, 100%), 266 (MH⁺, 40).

2,3-dimethoxy-6-((1E)-3-(methoxyimino)-2-methylbut-1-enyl)phenyl

3-phenylpropiolate 428

To a solution of phenylpropionic acid (0.997 g, 6.00 mmol) in dichloromethane (20 mL) was added thionyl chloride (1.31 mL, 18.0 mmol). The reaction mixture was heated to 40 °C for 18 h and then concentrated in vacuo. The crude acid chloride was dissolved in dry DMF (5 mL) and added to a suspension of phenol 427 (0.531 g, 2.00 mmol) and potassium carbonate (2.35 g, 17.0 mmol) in dry DMF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Water (75 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organics were washed with water (2 × 75 mL) and saturated brine (75 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19 to 1:9) to afford the title compound as a colourless solid (0.708 g, 90%), mp 138-139 °C (from ethyl acetate-hexane); (Found: C, 69.43; H, 5.90; N, 3.47. C₂₃H₂₃NOS requires C, 70.21; H, 5.89; N, 3.56%); (Found: MH⁺, 394.1636. C₂₃H₂₄NO₅ + H requires 394.1649); νmax (CHCl₃)/cm⁻¹ 2226 (C≡C), 1727 (C=O),
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1608 (C=C), 1577 (C=C), 1500 (C=C), 1463 (C=C), 1086 (C-O); δ H (400 MHz; CDCl₃) 7.62 (2 H, d, J = 7.2 Hz, ArH), 7.47 (1 H, t, J = 7.2 Hz, ArH), 7.40 (2 H, t, J = 7.2 Hz, ArH), 7.05 (1 H, d, J = 8.6 Hz, ArH), 6.88 (1 H, d, J = 8.6 Hz, ArH), 3.94 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.91 (3 H, s, OMe), 2.08 (3 H, s, Me), 2.02 (3 H, s, OMe); δ C (100 MHz; CDCl₃) 156.6 (C), 152.8 (C), 151.7 (C), 141.8 (C), 141.3 (C), 136.7 (C), 133.3 (CH), 131.1 (CH), 128.7 (CH), 127.4 (C), 124.8 (CH), 123.9 (CH), 119.3 (C), 110.1 (CH), 88.8 (C-C), 79.9 (C-C), 61.9 (OMe), 61.0 (OMe), 56.2 (OMe), 14.4 (Me), 10.8 (Me); m/z (ESI) 452 (26%), 416 (MNa⁺, 100), 394 (MH⁺, 25).

To a solution of phenol 427 (0.531 g, 2.00 mmol) and DMAP (0.489 g, 4.00 mmol) in THF (4 mL) at 0 °C was added the acid chloride in THF (4 mL) dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Water (50 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and saturated brine (50 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound as a colourless solid (0.663 g, 85%); data as above.
7,8-Dimethoxy-1,2-dimethyl-4-phenyl-5H-chromeno[3,4-c]pyridin-5-one 429

Following general procedure 11, the title compound was obtained from oxime 428 (0.500 g, 1.27 mmol) after 24 h at 180 °C as a colourless solid (0.212 g, 46%), mp 175-177 °C (from dichloromethane-hexane); (Found: MH⁺, 362.1378. C₂₂H₁₉NO₄ + H requires 362.1387); v_max (CHCl₃)/cm⁻¹ 1742 (C=O), 1610 (C=C), 1544 (C=C), 1511 (C=C); δ_H (400 MHz; CDCl₃) 7.89 (1 H, d, J = 9.2 Hz, ArH), 7.54-7.51 (2 H, m, ArH), 7.46-7.42 (3 H, ArH), 6.92 (1 H, d, J = 9.2 Hz, ArH), 3.99 (3 H, s, OMe), 3.98 (3 H, s, OMe), 2.76 (3 H, s, Me), 2.74 (3 H, s, Me); δ_C (100 MHz; CDCl₃) 162.3 (C), 160.7 (C), 159.0 (C), 154.8 (C), 146.9 (C), 142.8 (C), 141.4 (C), 136.5 (C), 128.7 (CH), 128.4 (CH), 128.0 (CH), 124.5 (C), 123.7 (CH), 112.3 (C), 107.3 (CH), 61.6 (OMe), 56.3 (OMe), 24.9 (Me), 19.3 (Me); m/z (ESI) 384 (MNa⁺, 55%), 362 (MH⁺, 100%).

Methyl 3-(6-methoxy-5-nitroquinolin-2-yl)propiolate 430

To a solution of 2-iodo-6-methoxy-5-nitroquinoline 317 (2.00 g, 6.06 mmol), bis(triphenylphosphine)palladium(II) chloride (0.304 g, 0.433 mmol) and copper(I)
iodide (0.346 g, 1.82 mmol) in THF (40 mL) was added methyl propiolate (1.35 mL, 15.2 mmol) and diisopropylethylamine (1.58 mL, 9.09 mmol). The reaction mixture was heated to 50 °C for 3 h, then cooled to room temperature and partitioned between saturated ammonium chloride (200 mL) and ethyl acetate (3 × 200 mL). The combined organics were washed with saturated ammonium chloride (200 mL) and saturated brine (200 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (1.60 g, 92%), mp 209-211 °C (from dichloromethane-hexane); (Found: C, 58.43; H, 3.46; N 9.56. C₁₄H₁₀N₂O₅ requires C, 58.74; H, 3.52; N, 9.79%); (Found: MH⁺, 287.0660. C₁₄H₁₀N₂O₅ + H requires 287.0662); νₘₐₓ (CHCl₃)/cm⁻¹ 2230 (C=C), 1717 (C=O), 1628 (C=C), 1593 (C=C), 1533 (C=C), 1498 (C=C), 1347 (N=O), 1079 (C-O); δₜ (400 MHz; CDCl₃) 8.60 (1 H, d, J = 9.2 Hz, ArH), 8.11 (1 H, d, J = 8.8 Hz, ArH), 7.72 (1 H, d, J = 8.8 Hz, ArH), 7.67 (1 H, d, J = 9.2 Hz, ArH), 4.12 (3 H, s, OMe), 3.89 (3 H, s, OMe); δₜ (100 MHz; CDCl₃) 153.9 (C), 150.6 (C), 142.0 (C), 139.7 (C), 134.4 (CH), 129.9 (CH), 126.8 (CH), 121.0 (C), 117.4 (CH), 83.6 (C=C), 79.7 (C=C), 57.3 (OMe), 53.2 (OMe); m/z (ESI) 309 (MNa⁺, 76%), 287 (MH⁺, 100).

3-(6-Methoxy-5-nitroquinolin-2-yl)propioic acid 431

To a solution of methyl ester 430 (0.500 g, 1.75 mmol) in THF (30 mL) was added lithium hydroxide monohydrate (0.376 g, 8.75 mmol) in water (6 mL). The reaction
mixture was stirred at room temperature for 3 h, acidified with hydrochloric acid (2 M) and extracted into ethyl acetate (3 × 50 mL). The combined organics were washed with water (2 × 50 mL) and saturated brine (50 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a pale yellow solid (0.467 g, 98%), mp 220-224 °C with decomp. (from ethyl acetate-hexane); (Found: MH⁺, 273.0280. C₁₃H₈N₂O₅ + H requires 273.0506; νmax (CHCl₃)/cm⁻¹ 2220 (C=C), 1725 (C=O), 1623 (C=C), 1588 (C=C), 1515 (C=C), 1493 (C=C), 1356 (N=O), 1076 (C-O); δH (400 MHz; CDCl₃) 8.35 (1 H, d, J = 9.6 Hz, ArH), 8.21 (1 H, d, J = 8.8 Hz, ArH), 8.05 (1 H, d, J = 9.6 Hz, ArH), 7.91 (1 H, d, J = 8.8 Hz, ArH), 4.12 (3 H, s, OMe); δC (100 MHz; CDCl₃) 153.7 (C), 150.2 (C), 141.5 (C), 139.1 (C), 134.1 (CH), 133.3 (C), 129.9 (CH), 127.1 (CH), 120.0 (C), 118.9 (CH), 82.1 (C=C), 80.7 (C=C), 57.6 (OMe); m/z (ESI) 273 (MH⁺, 100%), 242 (74).

5-Amino-2-iodo-6-methoxyquinoline 434

To a suspension of 317 (1.65 g, 5.00 mmol) and iron powder (1.50 g) in ethanol (30 mL) was added glacial acetic acid (2.00 mL, 35.0 mmol). The reaction mixture was heated under reflux for 4 h, then cooled to room temperature and partitioned between water (100 mL) and chloroform (3 × 100 mL). The combined organics were washed with water (2 × 100 mL) and saturated brine (100 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound (1.41 g, 94%). The crude product was used without further purification, mp 138-140 °C (ethyl acetate-hexane); (Found: C, 40.20; H, 3.02; N 9.34. C₁₀H₉IN₂O requires C, 40.02; H, 3.02; N, 9.33%); (Found:
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MH\(^+\), 300.9824. C\(_{10}\)H\(_9\)IN\(_2\)O + H requires 300.9832); \(\nu\)\(_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 3477 (NH), 3392 (NH), 1616 (C=\(\equiv\)C), 1609 (C=\(\equiv\)C), 1570 (C=\(\equiv\)C), 1561 (C=\(\equiv\)C), 1561 (NH), 1499 (C=\(\equiv\)C), 1465 (C=\(\equiv\)C); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 7.5 (1 H, d, \(J = 8.8\) Hz, ArH), 7.57 (1 H, d, \(J = 8.8\) Hz, ArH), 7.50 (1 H, d, \(J = 9.2\) Hz, ArH), 7.37 (1 H, d, \(J = 9.2\) Hz, ArH), 4.27 (2 H, br s, NH\(_2\)), 3.97 (3 H, s, OMe); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 145.3 (C), 143.1 (C), 130.4 (CH), 130.0 (CH), 129.9 (C), 118.9 (CH), 117.4 (C), 116.6 (CH), 116.2 (C), 56.5 (OMe); \(m/z\) (ESI) 322 (MNa\(^+\), 4%), 300 (MH\(^+\), 100%).

2-Iodo-6-methoxyquinoline-5,8-dione 435

\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
\begin{array}{c}
\text{434} \quad \xrightarrow{\text{Fremy's salt}} \quad \text{MeO} \\
\end{array} \\
\begin{array}{c}
\text{435} \\
\end{array}
\end{align*}
\]

To a solution of 5-amino-2-iodo-6-methoxyquinoline 434 (1.00 g, 3.33 mmol) in acetone (125 mL) was added Fremy's salt (3.58 g, 13.3 mmol) in sodium dihydrogenphosphate buffer solution (0.3 M in H\(_2\)O; 125 mL) over 5 min. The reaction mixture was stirred at room temperature for 12 h and the acetone removed \textit{in vacuo}. The resulting aqueous residue was extracted with dichloromethane (3 × 100 mL) and the combined organics washed with saturated brine (100 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel, eluting with ether-dichloromethane (0:1 to 1:49) to afford the \textit{title compound} as a pale yellow solid (0.930 g, 89%), mp 241-243 °C (from dichloromethane-hexane); (Found: C, 38.33; H, 1.79; N, 4.13. C\(_{10}\)H\(_6\)IN\(_2\)O requires C, 38.12; H, 1.92; N, 4.45); (Found: MH\(^+\), 315.9464. C\(_{10}\)H\(_6\)IN\(_2\)O + H requires 315.9465); \(\nu\)\(_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1690 (C=O), 1667 (C=O), 1609 (C=\(\equiv\)C), 1564 (C=\(\equiv\)C), 1499 (C=\(\equiv\)C), 1465 (C=\(\equiv\)C), 130.4 (CH), 130.0 (CH), 129.9 (C), 118.9 (CH), 117.4 (C), 116.6 (CH), 116.2 (C), 56.5 (OMe); \(m/z\) (ESI) 322 (MNa\(^+\), 4%), 300 (MH\(^+\), 100%).
1499 (C=C), 1096 (C-O); $\delta_H$ (400 MHz; CDCl$_3$) 8.12 (1 H, d, $J = 8.0$ Hz, ArH), 8.02 (1 H, d, $J = 8.0$ Hz, ArH), 6.34 (1 H, s, ArH), 3.95 (3 H, s, OMe); $\delta_C$ (100 MHz; CDCl$_3$) 181.5 (C), 179.4 (C), 160.0 (C), 147.8 (C), 139.2 (CH), 135.3 (CH), 127.1 (C), 125.9 (C), 110.3 (CH), 56.8 (OMe); $m/z$ (ESI) 337 (MNa$^+$, 100%), 315 (MH$^+$, 21).

**Benzyl 2-iodo-6-methoxyquinolin-5-ylcarbamate 436**

![Diagram]

To a solution of aminoquinoline 434 (0.300 g, 1.00 mmol) in THF (5 mL) was added benzyl chloroformate (0.214 mL, 1.50 mmol) and diisopropylethylamine (0.348 mL, 2.00 mmol). The reaction mixture was stirred at room temperature for 16 h, diluted with water (25 mL) and extracted into dichloromethane (3 × 25 mL). The combined organic extracts were washed with water (25 mL) and saturated brine (25 mL), dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (2:3) to afford the title compound as a colourless solid (0.397 g, 91%), mp 204-205 °C (from dichloromethane-hexane); (Found: C, 49.95; H, 3.48; N 6.49. C$_{18}$H$_{15}$IN$_2$O$_3$ requires C, 49.79; H, 3.48; N, 6.45%); (Found: MH$^+$, 435.0197. C$_{18}$H$_{15}$IN$_2$O$_3$ + H requires 435.0200); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3414 (NH), 1733 (C=O), 1619 (C=C), 1581 (C=C), 1560 (NH), 1506 (C=C), 1483 (C=C); $\delta_H$ (400 MHz; CDCl$_3$) 7.98 (1 H, d, $J = 9.3$ Hz, ArH), 7.79 (1 H, d, $J = 8.8$ Hz, ArH), 7.65 (1 H, d, $J = 8.8$ Hz, ArH), 7.45 (1 H, d, $J = 9.3$ Hz, ArH), 7.42-7.34 (5 H, m, ArH), 6.63 (1 H, br s, NH), 5.22 (2 H, s, CH$_2$), 3.95 (3 H, s, OMe); $\delta_C$ (100 MHz; CDCl$_3$) 155.3 (C), 151.5 (C), 144.8 (C), 136.0 (C), 133.0 (CH), 132.0 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 125.1 (C), 118.9...
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(C), 116.5 (C), 116.2 (CH), 67.6 (CH$_2$), 56.4 (OMe); $m/z$ (ESI) 457 (MNa$^+$, 100%), 435 (MH$^+$, 53).

3-(5-(Benzyloxycarbonylamino)-6-methoxyquinolin-2-yl)propiolic acid methyl ester 437

![Diagram](image)

To a solution of iodoquinoline 436 (0.250 g, 0.576 mmol), bis(triphenylphosphine)palladium(II) chloride (0.029 g, 0.041 mmol) and copper(I) iodide (0.033 g, 0.173 mmol) in THF (10 mL) was added methyl propiolate (0.128 mL, 1.44 mmol) and diisopropylethylamine (0.151 mL, 0.864 mmol). The reaction mixture was stirred at 50 °C for 3 h, cooled to room temperature and partitioned between water (25 mL) and ethyl acetate (3 × 25 mL). The combined organics were washed with water (25 mL) and saturated brine (25 mL), dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (0.198 g, 88%), mp 194-196 °C (from dichloromethane-hexane); (Found: C, 67.13; H, 4.60; N, 6.95. C$_{22}$H$_{18}$N$_2$O$_5$ requires C, 67.69; H, 4.65; N, 7.18%); (Found: MH$^+$, 391.1282. C$_{22}$H$_{18}$N$_2$O$_5$ + H requires 391.1288); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3414 (NH), 2229 (C=O), 1715 (C=O), 1619 (C=C), 1593 (C=C), 1557 (NH), 1501 (C=C), 1463 (C=C); $\delta$$_H$ (400 MHz; CDCl$_3$) 8.22 (1 H, d, $J$ = 8.8 Hz, ArH), 8.09 (1 H, d, $J$ = 9.4 Hz, ArH), 7.57 (1 H, d, $J$ = 8.8 Hz, ArH), 7.55 (1 H, d, $J$ = 9.4 Hz, ArH), 7.45-7.32 (5 H, m, ArH), 6.60 (1 H, br s, NH), 5.23 (2 H, s, CH$_2$), 3.98 (3 H, s, OMe), 3.87 (3 H,
New Developments in the 1-Aza-Diels-Alder Reaction

Timothy E. Hurst

s, OMe); δC (100 MHz; CDCl3) 155.3 (C), 154.0 (C), 143.6 (C), 138.3 (C), 136.0 (C), 132.2 (CH), 130.1 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 124.6 (CH), 118.3 (C), 116.7 (CH), 84.8 (C≡C), 78.8 (C≡C), 67.7 (CH2), 56.4 (OMe), 53.0 (OMe); m/z (ESI) 413 (MNa⁺, 100%), 391 (MH⁺, 77), 312 (53).

3-(5-(Benzyloxycarbonylamino)-6-methoxyquinolin-2-yl)propionic acid 438

To a solution of propiolate ester 437 (0.150 g, 0.384 mmol) in THF (10 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.081 g, 1.92 mmol). The reaction mixture was stirred at room temperature for 1 h and acidified with hydrochloric acid (2 M). The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organics washed with water (20 mL) and saturated brine (20 mL), dried over MgSO4 and concentrated in vacuo to afford the title compound as a colourless solid (0.145 g, 100%), mp 147-149 °C (from dichloromethane-hexane); (Found: MNa⁺, 399.0953. C21H16N2O5 + Na requires 399.0957); νmax (CHCl3)/cm⁻¹ 3415 (NH), 3289 (OH), 2223 (C≡C), 1702 (C=O), 1613 (C≡C), 1550 (NH), 1498 (C=C); δH (400 MHz; DMSO) 9.16 (1 H, br s, NH), 8.26 (1 H, d, J = 8.8 Hz, ArH), 8.04 (1 H, d, J = 9.4 Hz, ArH), 7.85 (1 H, d, J = 9.4 Hz, ArH), 7.74 (1 H, d, J = 8.8 Hz, ArH), 7.46-7.36 (5 H, m, ArH), 5.13 (2 H, s, CH2), 3.95 (3 H, s, OMe); δC (100 MHz; DMSO) 154.9 (C), 153.9 (C), 143.0 (C), 137.6 (C), 136.8 (C), 131.9 (CH), 129.2 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 126.3 (C), 124.7 (CH), 118.7 (C), 118.6 (CH), 83.0 (C≡C), 80.0 (C≡C), 65.9 (CH2), 56.5 (OMe); m/z (ESI) 399 (MNa⁺, 12%), 331 (M-CO₂H, 100).
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1-(1H-1,2,3-Benzotriazol-1-yl)-2-propyn-1-one

To a solution of benzotriazole (4.76 g, 40.0 mmol) in dichloromethane (50 mL) was added thionyl chloride (0.73 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 30 min and propiolic acid 446 (0.62 mL, 10.0 mmol) was added. The reaction was stirred for a further 2 h, the colourless solid was filtered off and washed with dichloromethane (2 x 50 mL). The combined organics were washed with saturated sodium hydrogen carbonate (2 x 50 mL) and saturated brine (50 mL), dried over MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (0.800 g, 47%), mp 105-106 °C (from dichloromethane-hexane) (lit., 99 °C); δ(400 MHz; CDCl3) 8.18 (1 H, d, J = 8.4 Hz, ArH), 8.11 (1 H, d, J = 8.0 Hz, ArH), 7.66 (1 H, td, J = 8.4 and 1.2 Hz, ArH), 7.52 (1 H, td, J = 8.0 and 1.2 Hz, ArH), 3.77 (1 H, s, C=CH); δc (100 MHz; CDCl3) 149.2 (C), 146.2 (C), 130.9 (CH), 130.6 (C), 126.9 (CH), 120.5 (CH), 114.2 (CH), 84.2 (C=CH), 74.5 (C=CH).

4-Nitrophenyl propiolate

To a solution of propiolic acid 446 (0.246 mL, 4.00 mmol), 4-nitrophenol (0.556 g, 4.00 mmol) and DMAP (0.024 g, 0.200 mmol) in dichloromethane (15 mL) at 0 °C was added DCC (1 M in dichloromethane; 5.00 mL, 5.00 mmol) dropwise over 5 min.
The reaction mixture was allowed to warm to room temperature, stirred for 2 h and filtered. The solid was washed with dichloromethane (15 mL), and the combined filtrate concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (0.497 g, 65%), mp 135-136 °C (from dichloromethane-hexane) (lit., 132 °C); δ_H (400 MHz; CDCl_3) 8.31 (2 H, d, J = 9.2 Hz, ArH), 7.37 (2 H, d, J = 9.2 Hz, ArH), 3.19 (1 H, s, C=CH); δ_C (100 MHz; CDCl_3) 154.2 (C), 149.7 (C), 145.9 (C), 125.4 (CH), 122.3 (CH), 78.1 (C=CH), 73.6 (C=CH).

6-Formyl-2,3-dimethoxyphenyl propiolate 447

![Chemical Structure](image)

To a solution of propiolic acid 446 (3.69 mL, 60.0 mmol), 2-hydroxy-3,4-dimethoxybenzaldehyde 279 (5.47 g, 30.0 mmol) and DMAP (0.367 g, 3.00 mmol) in dichloromethane (50 mL) at 0 °C was added DCC (1 M in dichloromethane; 60.0 mL, 60.0 mmol) dropwise over 45 min. The reaction mixture was allowed to warm to room temperature, stirred for 17 h and filtered. The solid was washed with dichloromethane (3 x 75 mL) and the combined filtrate concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (5.76 g, 82%), mp 85-86 °C (from ethyl acetate-hexane); (Found: C, 61.40; H, 4.45. C_{12}H_{10}O_{5} requires C, 61.54; H, 4.30 %); (Found: MH\(^+\), 235.0603. C_{12}H_{10}O_{5} + H requires 235.0601); \nu_{\text{max}} (CHCl_3)/\text{cm}^{-1} 3298 (alkyne C-H), 2130 (C= C), 1742 (C=O), 1694 (C=O), 1601 (C= C),
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1577 (C=C), 1503 (C=C); \( \delta_H \) (400 MHz; CDCl\(_3\)) 9.92 (1 H, s, CHO), 7.58 (1 H, d, \( J = 8.8 \) Hz, ArH), 6.94 (1 H, d, \( J = 8.8 \) Hz, ArH), 3.93 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.25 (1 H, s, C\( \equiv \)CH); \( \delta_C \) (100 MHz; CDCl\(_3\)) 187.3 (C), 158.8 (C), 150.1 (C), 143.9 (C), 141.1 (C), 127.2 (CH), 122.0 (C), 110.2 (CH), 78.1 (C\( \equiv \)CH), 73.6 (C\( \equiv \)CH), 61.0 (OMe), 56.4 (OMe); \( m/z \) (ESI) 257 (MNa\(^+\), 100%), 235 (MH\(^+\), 51), 207 (58), 183 (47).

6-(1,3-Dioxan-2-yl)-2,3-dimethoxyphenyl propiolate 448

\[
\begin{align*}
\text{CHO} & \quad \leftrightarrow \\
\text{MeO} & \quad \text{OMe}
\end{align*}
\]

To a solution of 6-formyl-2,3-dimethoxyphenyl propiolate 447 (2.81 g, 12.0 mmol) and para-toluenesulfonic acid (0.060 g) in toluene (180 mL) was added 1,3-propanediol (4.34 mL, 60.0 mmol). The reaction mixture was heated under reflux under Dean-Stark apparatus for 22 h, then cooled to room temperature and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (2.11 g, 60%), mp 65-66 °C (from ethyl acetate-hexane); (Found: C, 61.49; H, 5.49. C\(_{15}\)H\(_{16}\)O\(_6\) requires C, 61.64; H, 5.52%); (Found: MH\(^+\), 293.1001. C\(_{15}\)H\(_{16}\)O\(_6\) + H requires 293.1020); \( \nu_{\text{max}} \) (CHCl\(_3\))/cm\(^{-1}\) 3299 (alkyne C-H), 2128 (C=C), 1740 (C=O), 1616 (C=C), 1506 (C=C), 1464 (C=C), 1086 (C-O); \( \delta_H \) (400 MHz; CDCl\(_3\)) 7.32 (1 H, d, \( J = 8.8 \) Hz, ArH), 6.86 (1 H, d, \( J = 8.8 \) Hz, ArH), 5.54 (1 H, s, CH), 4.27-4.23 (1 H, m, CH\(_2\)), 3.96 (2 H, td, \( J = 12.4 \) and 2.4 Hz, CH\(_2\)), 3.89 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.07 (1 H, s, C\( \equiv \)CH), 2.27-2.17 (1 H, m CH), 1.45-1.41 (1
H, m, CH); δc (100 MHz; CDCl₃) 153.9 (C), 150.3 (C), 141.1 (C), 140.9 (C), 124.0 (C), 121.6 (CH), 110.3 (CH), 97.9 (CH), 74.1 (C=CH), 67.4 (CH₂), 60.8 (OMe), 56.1 (OMe), 25.6 (CH₂); m/z (ESI) 315 (MNa⁺, 100%), 293 (MH⁺, 39).

6-(1,3-Dioxan-2-yl)-2,3-dimethoxyphenyl 3-(6-methoxy-5-nitroquinolin-2-yl)propiolate 449

Following general procedure 8, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline 317 (0.975 g, 2.95 mmol) and 6-(1,3-dioxan-2-yl)-2,3-dimethoxyphenyl propiolate 448 (1.29 g, 4.43 mmol) as a colourless solid (0.438 g, 30%), mp 201-202 °C (from ethyl acetate-hexane); (Found: MH⁺, 495.1398. C₂₅H₂₂N₂O₉ + H requires 495.1398); νmax (CHCl₃)/cm⁻¹ 2229 (C=O), 1737 (C=O), 1628 (C=C), 1593 (C=C), 1533 (C=C), 1496 (C=C), 1463 (C=C), 1347 (N=O), 1084 (C-O); δH (400 MHz; CDCl₃) 8.34 (1 H, d, J = 9.6 Hz, ArH), 8.15 (1 H, d, J = 8.8 Hz, ArH), 7.80 (1 H, d, J = 8.8 Hz, ArH), 7.69 (1 H, d, J = 9.6 Hz, ArH), 7.36 (1 H, d, J = 8.8 Hz, ArH), 6.88 (1 H, d, J = 8.8 Hz, ArH), 5.61 (1 H, s, CH), 4.29-4.15 (2 H, m, CH₂), 4.13 (3 H, s, OMe), 4.00 (2 H, td, J = 12.0 and 2.0 Hz, CH₂), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.30-2.18 (1 H, m, CH), 1.45-1.42 (1 H, m, CH); δc (100 MHz; CDCl₃) 153.9 (C=O), 134.5 (CH), 129.9 (CH), 127.1 (CH), 124.1 (C), 121.6 (CH), 117.4 (CH), 110.4 (CH), 97.7 (CH), 67.5 (CH₂), 60.9 (OMe), 57.3 (OMe), 56.1 (OMe), 25.7 (Me); m/z (ESI) 517 (MNa⁺, 100%), 495 (MH⁺, 37), 388 (24), 312 (27).
6-Formyl-2,3-dimethoxyphenyl 3-(6-methoxy-5-nitroquinolin-2-yl)propionate 450

A solution of acetal 449 (0.225 g, 0.455 mmol) in glacial acetic acid (5 mL) and water (0.5 mL) was heated at 50 °C for 3 h, cooled to room temperature and poured into saturated sodium hydrogen carbonate (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL) and the combined organics washed with saturated sodium hydrogen carbonate (100 mL) and water (100 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless solid (0.199 g, 100%) which was used without further purification, mp 179-180 °C (from ethyl acetate-hexane); (Found: MH⁺, 437.0981. C₂₂H₁₆N₂O₈ + H requires 437.0979); νmax (CHCl₃)/cm⁻¹ 2228 (C≡C), 1738 (C=O), 1694 (C=O), 1628 (C=C), 1600 (C=C), 1578 (C=C), 1533 (C=C), 1501 (C=C), 1461 (C=C), 1346 (N=O), 1082 (C-O); δH (400 MHz; CDCl₃) 10.06 (1 H, s, CHO), 8.34 (1 H, d, J = 9.6 Hz, ArH), 8.17 (1 H, d, J = 8.8 Hz, ArH), 7.84 (1 H, d, J = 8.8 Hz, ArH), 7.69 (1 H, d, J = 9.6 Hz, ArH), 7.68 (1 H, d, J = 8.8 Hz, ArH), 7.50 (1 H, d, J = 8.8 Hz, ArH), 4.13 (3 H, s, OMe), 4.00 (3 H, s, OMe), 3.93 (3 H, s, OMe); δC (100 MHz; CDCl₃) 187.2 (C), 158.8 (C), 150.8 (C), 150.6 (C), 144.2 (C), 142.3 (C), 141.2 (C), 139.2 (C), 134.5 (CH), 129.9 (CH), 127.0 (CH), 126.8 (CH), 122.2 (C), 121.2 (C), 117.6 (CH), 110.2 (CH), 86.0 (C≡C), 78.7 (C=C), 61.1 (OMe), 57.3 (OMe), 56.4 (OMe); m/z (ESI) 459 (MNa⁺, 100%), 437 (24), 312 (65).
To a solution of 3-(trimethylsilyl)propioic acid (0.711 g, 5.00 mmol) in freshly distilled oxalyl chloride (0.47 mL, 5.50 mmol) was added DMF (15.0 μL, 0.200 mmol). Vigorous bubbling was observed. The reaction mixture was stirred for 30 min, and the crude product distilled under reduced pressure to give 3-(trimethylsilyl)propioic acid chloride (bp 62 °C at 20 mm Hg) which was used without further purification.

To a solution of phenol 421 (0.411 g, 2.00 mmol) in THF (4 mL) at 0 °C was added DMAP (0.489 g, 4.00 mmol) in one portion, followed by the acid chloride in THF (4 mL) dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, stirred for 18 h and partitioned between water (50 mL) and ethyl acetate (3 × 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless solid (0.743 g, 92%), mp 68-70 °C (from dichloromethane-hexane); (Found: MH⁺, 334.1435. C₂₁H₁₉NO₃ + H requires 334.1438); ν max (CHCl₃)/cm⁻¹ 2181 (C=O), 1625 (C=C), 1586 (C=C), 1462 (C=C); δ H (400 MHz; CDCl₃) 7.64 (2 H, d, J = 8.0 Hz, ArH), 7.53-7.50 (2 H, m,
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ArH), 7.42 (2 H, t, J = 8.0 Hz, ArH), 7.21-7.20 (2 H, m, ArH), 6.93 (1 H, d, J = 16.5 Hz, C=CH), 6.85 (1 H, d, J = 16.5 Hz, C=CH), 3.95 (3 H, s, OMe), 2.27 (3 H, s, Me), 2.06 (3 H, s, Me); δC (100 MHz; CDCl₃) 164.2 (C), 162.3 (C), 158.8 (C), 151.2 (C), 144.0 (C), 140.9 (C), 133.8 (C), 128.7 (CH), 128.0 (CH), 127.2 (C), 124.0 (CH), 121.2 (CH), 116.0 (C), 113.5 (CH), 111.8 (C), 25.4 (Me), 15.8 (Me); m/z (ESI) 356 (MNa⁺, 100%), 334 (MH⁺, 32).

2,3-dimethoxy-6-((1E)-3-(methoxyimino)-2-methylbut-1-enyl)phenyl

3-(trimethylsilyl)propionate 455

\[
\begin{align*}
\text{OMe} & \quad \text{N} & \quad \text{Me} \\ 
\text{OMe} & \quad \text{Me} & \quad \text{TMS} & \quad \text{Me} \\
\text{MeO} & \quad \text{Me} & \quad \text{O} & \quad \text{HO} \\
427 & \quad & \rightarrow & \quad 455
\end{align*}
\]

To a solution of 3-(trimethylsilyl)propionic acid (0.711 g, 5.00 mmol) in freshly distilled oxalyl chloride (0.47 mL, 5.50 mmol) was added DMF (15.0 μL, 0.200 mmol). Vigorous bubbling was observed. The reaction mixture was stirred for 30 min, and the crude product distilled under reduced pressure to give 3-(trimethylsilyl)propionic acid chloride (bp 62 °C at 20 mm Hg) which was used without further purification.

To a solution of phenol 427 (0.531 g, 2.00 mmol) in THF (4 mL) at 0 °C was added DMAP (0.489 g, 4.00 mmol) in one portion, followed by the acid chloride in THF (4 mL) dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, stirred for 18 h and partitioned between water (50 mL) and ethyl acetate.
(3 x 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a pale yellow solid (0.663 g, 85%), mp 76-77 °C (from dichloromethane-hexane); (Found: MH⁺, 390.1708. C₂₀H₂₇NO₅Si + H requires 390.1731); νmax (CHCl₃)/cm⁻¹ 2180 (C≡C), 1728 (C=O), 1607 (C=C), 1501 (C=C), 1086 (C-O); δH (400 MHz; CDCl₃) 7.02 (1 H, d, J = 8.6 Hz, ArH), 6.84 (1 H, d, J = 8.6 Hz, ArH), 6.63 (1 H, s, C=CH), 3.95 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.08 (3 H, s, Me), 1.99 (3 H, s, Me), 0.27 (9 H, s, SiMe₃); δC (100 MHz; CDCl₃) 157.5 (C), 153.6 (C), 151.6 (C), 142.6 (C), 142.2 (C), 137.6 (C), 125.6 (CH), 124.7 (CH), 124.6 (C), 110.9 (CH), 97.9 (C=C), 94.5 (C=C), 62.8 (OMe), 61.8 (OMe), 57.0 (OMe), 15.3 (Me), 11.7 (Me), 0.0 (SiMe₃); m/z (ESI) 412 (MNa⁺, 100%), 390 (MH⁺, 56), 340 (81).

7,8-Dimethoxy-1,2-dimethyl-5H-chromeno[3,4-c]pyridin-5-one 456

A solution of 455 (0.568 g, 1.46 mmol) in o-DCB (15 mL) was placed in a sealed tube and heated to 220 °C for 16 h. The reaction mixture was cooled to room temperature and extracted with hydrochloric acid (2 M; 3 x 20 mL). The combined aqueous layers were concentrated in vacuo to afford the crude product as the hydrochloride salt. The residue was taken up in chloroform (25 mL), washed with sodium hydrogen carbonate
(25 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a pale orange solid (0.158 g, 38%); (Found: MH⁺, 286.1068. C₁₆H₁₅NO₄ + H requires 286.1074); νₘₐₓ (CHCl₃)/cm⁻¹ : δ₁H (400 MHz; CDCl₃) 9.30 (1 H, s, ArH), 7.97 (1 H, d, J = 9.2 Hz, ArH), 6.93 (1 H, d, J = 9.2 Hz, ArH), 4.00 (3 H, s, OMe), 3.99 (3 H, s, OMe), 2.75 (3 H, s, Me), 2.73 (3 H, s, Me); δ₁C (100 MHz; CDCl₃) 164.0 (C), 160.4 (C), 155.0 (C), 149.6 (CH), 147.1 (C), 140.3 (C), 137.0 (C), 125.6 (C), 123.5 (CH), 114.4 (C), 112.1 (C), 107.7 (CH), 61.6 (OMe), 56.3 (OMe), 25.0 (Me), 19.2 (Me); m/z (ESI) 308 (MNa⁺, 49%), 268 (MH⁺, 100).
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