New Substrates for Pauson-Khand Reaction

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the Degree of Doctor of Philosophy

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ABSTRACT

The Pauson-Khand reaction, a formal \([2+2+1]\) cycloaddition of an alkene \(\pi\) bond, an alkyne \(\pi\) bond and carbon monoxide to form a five-membered ring, was discovered in the early 1970's.

This thesis presents the work undertaken towards the synthesis of two new types of substrates for this reaction; namely silicon tethered enynes and silyl enol ethers.

Silicon-tethered enynes as substrates for PKR
The scope of silicon-tethered Pauson-Khand reactions of vinylsilane and allylsilane derived enynes was fully explored. The vinylsilane derived enynes yielded monocyclopentenone where the carbons bound to the silicon tether were reduced during the course of the reaction. The allylsilane derived enynes yielded the desired Pauson-Khand products in good to moderate yields. A series of allylsilane derived enynes with varying substituents at both alkyne and alkene moieties were synthesised and subjected to Pauson-Khand reaction.

Silyl enol ethers as substrates for PKR
Pauson-Khand reactions of the TMS and TIPS enol ethers of model substrates, derived from diethyl malonate, were investigated. The methodology developed for these silyl enol ethers was then applied to the synthesis of a model substrate for ingenol.

Synthesis of model substrate for Ingenol
Ingenol, is a highly oxygenated tetracyclic diterpene, isolated initially from the \textit{Euphorbia ingens} species of the \textit{Euphorbiaceae} plant family, by the Hecker group in 1968. It has attracted considerable interest from both the chemical and biological communities because of its unique structure and an array of biological properties. Ingenol has a \textit{trans}-intrabridgehead BC ring junction. We have investigated the possibility of using the PKR to synthesise the ring skeleton of ingenol in an atom efficient and stereospecific manner.
To my family
ACKNOWLEDGEMENTS

First and foremost I would like to thank Allah Almighty for his many blessings.

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Finally, I want to express my love to Ilyas, whose encouragement and belief in me kept me going throughout this PhD. Thank you for your love, patience, support and for warming my feet!
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>acac</td>
<td>Acetylacetonyl</td>
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<tr>
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<td>Argon</td>
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<td>'Pr</td>
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</tr>
<tr>
<td>rt</td>
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<td>Thin layer chromatography</td>
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<td>Ru$<em>3$(CO)$</em>{12}$</td>
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<td>Ts</td>
<td>$para$-Toluenesulfonyl</td>
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1 Introduction

1.1 The Pauson-Khand reaction

The synthesis of organic carbocyclic and heterocyclic systems from acyclic building blocks is usually achieved by either condensation or cycloaddition processes. Organic cycloaddition reactions allow the synthesis of a variety of systems especially ones containing 3- to 7-membered rings. These cycloaddition processes can involve reaction of two or more components. Transition metals have been known to induce a wide variety of organic reactions including cycloaddition reactions. As a fuller understanding of transition metal mediated reactions has evolved, the rational development of new and more selective transformations has begun to take place. This introduction chapter deals with cycloaddition of alkynes, alkenes and carbon monoxide to form cyclopentenones, the Pauson-Khand reaction. Several reviews of Pauson-Khand reaction have appeared in the literature.\(^1,2,3,4,5,6,7\)

The Pauson-Khand reaction, a formal [2+2+1] cycloaddition of an alkene \(\pi\) bond, an alkyne \(\pi\) bond and carbon monoxide to form a five-membered ring, was discovered in the early 1970's and is summarised in Scheme 1.

\[
\begin{align*}
\text{CO}_2(\text{CO})_8 & \rightarrow \text{C}_5\text{H}_8\text{O} \\
\text{CO}_2(\text{CO})_8 & \rightarrow \text{C}_5\text{H}_8\text{O}
\end{align*}
\]

Scheme 1

The reaction was discovered accidentally in a study aimed at the preparation and characterisation of alkyne complexes derived from dicobalt octacarbonyl, metal-free compounds containing a cyclopentenone were also isolated.

In the original procedure, the alkyne was allowed to react with a stoichiometric amount of dicobalt octacarbonyl at room temperature over several hours in hydrocarbon or ethereal solvent to generate a dicobalt hexacarbonyl complex of the alkyne, which then reacted with an alkene upon heating to generate a cyclopentenone.\(^1\) Scheme 2 illustrates two of the earlier examples of intermolecular Pauson-Khand cyclisation.\(^9,10\)
While this reaction represented a dramatic increase in molecular complexity from starting materials to product, the reaction was somewhat limited in its application to synthesis of complex molecules. For instance, unless strained alkenes were used, the efficiency of the cycloaddition was typically low and the use of unsymmetrical alkenes led to mixtures of cyclopentenone regioisomers. The reaction was also sensitive to steric and electronic effects of the substituents introduced into either the alkene or the alkyne precursors. Finally, the conditions required to effect the cycloaddition (high temperatures and long reaction times) led in many cases to decomposition of starting materials and/or products.  

Making the reaction intramolecular by attaching the alkene and alkyne through a carbon tether increased the synthetic utility of the reaction; strained olefins were also no longer required and the reaction became regioselective with respect to the olefin.  

Major methodological improvements appeared in late 1980s and in the early 1990s, which increased the scope of the reaction further. These included adsorption of the enyne onto a chromatographic support, and addition of one of a number of 'promoters'. More recently, catalytic and stereoselective version of the Pauson-Khand reaction have been developed, as have similar reactions employing metals other than cobalt. These
advances in the Pauson-Khand reaction methodology as well as mechanism of this reaction will be reviewed in the following sections.

1.2 **Mechanism of the Pauson-Khand reaction**

Beyond the fact that a dicobalt hexacarbonyl alkyne complex is involved, little is actually known about the mechanism of the Pauson-Khand cycloaddition. Magnus originally proposed the currently accepted mechanistic pathway in 1985\(^2\). Direct studies on the mechanism have been limited by the fact that attempts to observe intermediates of the reaction pathway beyond the alkyne complexation stage have been unsuccessful, final products being the only detectable species during the course of the reaction.\(^1\)

It is generally assumed that the rate-limiting step occurs early in the sequence preventing the build up of any subsequent intermediates to observable levels. The current understanding of the mechanism of the Pauson-Khand reaction has been inferred from the regio- and stereochemistry observed in the products. These observations include characterisation of isolable alkyne dicobalt hexacarbonyl complexes, an isolable pentacarbonyl complex stabilised by chelation of a bishomopropargylic-sulfide group\(^13\) and an intercepted intermediate\(^14\).

The mechanism is illustrated schematically in **Scheme 3**.
The initial step involves complexation of the alkyne triple bond with dicobalt octacarbonyl to form dicobalt hexacarbonyl complex 7. The reaction involves five main steps from this initial complex 7: (i) decarbonylation of 7, (ii) coordination of an olefin onto a coordinatively unsaturated cobalt centre in 8, (iii) insertion of the Ti-complexed olefin into a Co-C bond (11), (iv) insertion of CO into a Co-C sp³ bond (12), and (v) reductive elimination and subsequent loss of a dicobalt carbonyl fragment to give the final cyclopentenone 14.
1.2.1 Regiochemistry of cycloaddition

The principal interactions that control the regio and stereochemistry of the Pauson-Khand reactions appear to be steric in nature. It is usually assumed that complexation of the alkene to one cobalt atom takes place via a dissociative mechanism involving loss of CO. This process is thought to be reversible. In the amine-N-oxide promoted reaction, CO$_2$ is liberated in the first step and the first step becomes irreversible. Subsequently irreversible insertion of the complexed face of the alkene $\pi$-bond into one of the formal cobalt-carbon bonds of the alkyne complex occurs. This step is probably both rate and product determining and is followed by addition of CO to the coordinatively unsaturated cobalt atom. The metallocycle that forms may proceed to product by a standard sequence of steps beginning with migratory insertion of a cobalt bound CO, addition of a ligand and reductive elimination of the Co(CO)$_3$ moiety. The Co$_2$(CO)$_6$ fragment of the final enone leads to the product via the loss of Co$_2$(CO)$_6$ fragment.$^1$

Regiochemistry with respect to both alkyne and alkene is determined during the insertion in the cobalt carbon bond$^1$. The incipient carbon-carbon bond is most susceptible to steric crowding. If the alkyne is unsymmetrical, insertion and carbon-carbon bond formation proceed exclusively at the alkyne carbon possessing the smaller substituent.

Alkene regiochemistry in the Pauson-Khand reaction is less readily predicted, as it is dependent on the nature of both the alkene and the alkyne. Upon reaction with ethyne or terminal alkynes, terminal alkenes typically display minimum regioselectivity, which may vary with reaction conditions, although the incorporation of alkyne remains totally regioselective as shown in Scheme 4. Alkyne regiocontrol stays high in the reactions with ethene, even though steric interactions are rather small (Scheme 5).
Reactions of monosubstituted alkenes with internal alkynes lead to the 2,3,5-trisubstituted isomer as the major product. It is assumed that the isomer of pseudooctahedral cobalt (26), that leads to insertion of alkene contains the alkene complexed trans to the bond between the cobalt and the substituted alkyne carbon, avoiding a steric interaction with the latter (Scheme 6). Insertion can therefore only occur into other cobalt-carbon bond, fixing the alkyne regiochemistry.

Scheme 4

Scheme 5
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With most terminal alkynes, there is little preference between the two possible con conformations about the cobalt-alkene bond, resulting in no regioselectivity in the alkene insertion. However if the \( R_1 \) group on alkenes is sufficiently large, conformation (2) is preferred as shown in Scheme 6, placing the large group onto the cobalt–carbon bond away from \( R_2 \) of the alkyne. This results in a preference for the 5-substituted cyclopentenone (32) as shown in Scheme 6. Pauson-Khand reaction illustrated in Scheme 7 demonstrates this point. Reaction of alkene 33 with dicobalt hexacarbonyl complex of acetylene led to 5-substituted cyclopentenone 34 as major product.
New Substrates for PKR

Introduction

Scheme 6
Krafft has provided support for this picture by observation of greatly increased alkene regioselectivity in Pauson-Khand cycloaddition with internal alkynes as shown in Scheme 8. 2,3,5-Substituted cyclopentenone 38 was the major product in this reaction\(^\text{15}\).

The site of co-ordination of the alkene determines alkyne regioselectivity, while the conformation of the coordinated alkene prior to insertion contributes to alkene regioselectivity. The presence of groups larger than hydrogen on both alkyne carbons introduces unavoidable steric interactions that lead to preference for conformation (2) in Scheme 6.

Initial support for the proposed mechanism cited steric control of the regiochemical outcome of the intermolecular reactions. However electronics have also been shown to have an effect on the regiochemical product mixture.
Cycloadditions of conjugated alkynones and alkynoate esters proceed exclusively to give cyclopentenones in which the ketone or ester function is located at C-3 (Scheme 9)\textsuperscript{16}. While this result is consistent with steric origin (i.e. tetrahedral carbon being larger than trigonal carbonyl carbon), the complete regioselectivity is surprising considering the rather small size differential involved. It is suggested that an electronic component is involved and that bond formation between the more electron rich $\alpha$-carbon of the triple bond and an alkene carbon is favoured.

\[ \text{Et} + \text{Me} \xrightarrow{(\text{OC})_3\text{Co}} \text{Toluene, 71 °C} \xrightarrow{78\%} \text{O} \text{Me} \]

Scheme 9

1.2.2 Evidence in support of the proposed mechanism

1.2.2.1 Interrupted PKR

Krafft has successfully interrupted the intramolecular cycloaddition process by exposing the reaction mixture to an oxygen-containing atmosphere as shown in Scheme 10. Monocyclic products of type 44 were isolated, in which oxygen had been incorporated instead of carbon monoxide insertion and the cyclisation to form the second ring had not proceeded in the normal fashion\textsuperscript{14}.

\[ \text{R Air, 90 °C} \xrightarrow{(\text{OC})_3\text{Co}} \text{Co(CO)_3} \xrightarrow{\text{O} \text{ R}} \]

Scheme 10
Although, the actual role of molecular oxygen in interrupting the normal Pauson-Khand reaction is unclear, Krafft has suggested that both the enone product 44 and the expected cyclopentenone product 49 can arise from a common intermediate 47 in the proposed mechanism as shown in Scheme 11. The interception of 47 by molecular oxygen, perhaps at the metal centre, could inhibit carbon monoxide insertion, and therefore be responsible for driving the reaction towards the observed enone 44.14

**Scheme 11**

1.2.2.2 Isolation of a pentacarbonyl intermediate

Krafft has found that the rate of cycloaddition of 1,6-enynes is accelerated by the presence of sulfur, nitrogen or oxygen in the homopropargylic or bishomopropargylic position13. Upon heating, the heteroatom-substituted substrates, especially sulfur substituted substrates, reacted faster than their corresponding analogues, without the coordinating heteroatoms. During the course of their studies of 4-methylmorpholine-N-
oxide promoted reactions with complexes of sulfur-substituted substrates, they isolated a new intermediate 50 which represents a trapped form of pentacarbonyl intermediate in the proposed mechanism for the Pauson-Khand reaction (Figure 1). They also isolated a similar, more stable intermediate 51. The NMR spectra of both 50 and 51 showed absence of alkene coordination and indicated the presence of coordinated sulfur (shift of the protons adjacent to sulfur and a nonequivalence of the methylene protons on the tether between the alkyne and the sulfide).

Figure 1

Krafft has rationalised these results within the context of the proposed mechanistic pathway. Their rationale is illustrated in Scheme 12.
Scheme 12
Three steps in the proposed mechanism, 52 to 53, 54 to 55, and 55 to 56, necessarily generate a vacant coordination site. Judicious placement of a coordinating ligand can be expected to lead to a stabilisation of coordinatively unsaturated complex by heteroatom complexation to the metal centre. Stabilisation of the pentacarbonyl complex 53 by formation of a coordinatively saturated complex 50 may be considered as rate decelerating with increasing stability of 50. Transformations 54 to 55 and 55 to 56 may be driven by heteroatom coordination to provide complexes 55' or 56', respectively. This acceleration may be a result of insertion of CO in complex 55' occurring faster than in 55 as a result of heteroatom coordination. Alternatively, decarbonylation of 56 may be inhibited due to coordination of the heteroatom in 56'. The bishomopropargylic ligand would be expected to provide a more stable complex (six-membered chelate ring) than the homopropargylic cases (five-membered chelate ring) due to the strain in a five membered chelate ring caused by the bond angle at the carbon bound to cobalt. Interaction of the coordinating ligand in 55 or 56 could be viewed as a rate-accelerating role which can compensate for the decrease in rate caused by the formation of complex 50. Krafft postulates that these findings and new intermediates, isolated during the course of the reaction, support the dissociative loss of CO from the initial dicobalt hexacarbonyl complex to form dicobalt pentacarbonyl complex which in turn leads to complexation and insertion of alkene. Pericas and coworkers have also isolated similar sulfur chelated dicobalt pentacarbonyl intermediates which support this dissociative loss of CO from dicobalt hexacarbonyl complex17,18,19.

1.2.2.3 Theoretical studies

Several theoretical studies support this generally accepted mechanism. Pericas has studied both the initial complexation and then the insertion of alkene into pentacarbonyl dicobalt intermediate using density functional studies20. The author has shown the importance of facilitating CO dissociation from the dicobalt hexacarbonyl complex but points out that this is not a sufficient condition for the reaction and the energy of olefin complexation and insertion is also very important. This is the reason why strained olefins react so well as in this step strain of the cyclic olefins is liberated, favouring the process17,18,19.

Other authors including Nakamura21 and Milet and Gimbert22 have performed high level theoretical calculations on the cobaltacycle formation step. These studies suggest that
the insertion of the olefin is the critical stereo- and regiochemical determining step of the Pauson-Khand reaction. Nakamura points out that while the bond forming events occur on one metal atom, the other metal atom acts as an anchor and also exerts electronic influences on the other through the metal-metal bond.

Further study is required to firmly establish the mechanism aspects of the Pauson-Khand reaction. This is especially true with the development of reaction variations including the use of alternative metals and catalytic processes.

1.3 Stoichiometric Pauson-Khand reaction

The main drawbacks of the Pauson-Khand reaction as originally described were its relatively narrow scope and, in many cases, poor conversions. Over the past few years there has been a remarkable increase in the scope and applicability of the reaction due to the development of new reaction conditions such as the use of ‘promoters’ or ‘additives’ to accelerate and/or increase the yields of reactions. Several metals other than cobalt have also been employed in carrying out stoichiometric Pauson-Khand reactions. This section discusses these methods.

1.3.1 Polar Solvents

Polar solvents such as acetonitrile (CH$_3$CN), dimethyl sulfoxide (DMSO) and methanol (MeOH) have been shown by Pauson and coworkers to promote both inter- and intramolecular Pauson-Khand reaction$^{23}$. The effect of DMSO and other polar solvents on intramolecular Pauson-Khand cyclisation of allyl propargyl malonate was studied by Pauson and co-workers and some of the results are shown in Scheme 13 and Table 1.
New Substrates for PKR

Scheme 13

Table 1. Effect of DMSO on PKR of 59

<table>
<thead>
<tr>
<th>Entry</th>
<th>Promoter</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield % 61</th>
<th>Yield % 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>36</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>DMSO (1eq)</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>85</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>DMSO (3 eq)</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DMSO (3 eq)</td>
<td>C₆H₆</td>
<td>40</td>
<td>24</td>
<td>92</td>
<td>0</td>
</tr>
</tbody>
</table>

In the absence of DMSO (entry 1), yield of both 61 and 62 was poor whereas in the presence of 1 or 3 equivalents of DMSO (entries 2 & 3) yield of 61 improves dramatically. Formation of the saturated ketone byproduct 62 is avoided by replacing dichloromethane (CH₂Cl₂) as solvent with benzene (C₆H₆) (entry 4). The latter also gives better yields, albeit with longer reaction times.

DMSO has also been shown to promote intermolecular Pauson-Khand reaction. Results show successful use of unprotected allyl alcohol 19 in the DMSO promoted reaction as shown in Scheme 14. Protection of alcohol had previously been found to be necessary under higher temperature conditions²⁴.
The effect of a series of polar solvents including CH$_2$Cl$_2$, MeOH, CH$_3$CN, THF and Et$_2$O was studied on the Pauson-Khand reaction depicted in Scheme 15. All were shown to have a promoting effect on the Pauson-Khand reaction (Table 2). Both CH$_3$CN (entry 2) and MeOH (entry 6), while requiring slightly longer reaction times gave comparable and slightly better yields. These conclusions relate primarily to CH$_2$Cl$_2$ solutions of the promoters; when in place of this, chloroform (CHCl$_3$) was used as the solvent, the reaction yielded variable but substantial amounts of the corresponding saturated ketone byproduct 66 (entries 3 & 7).
1.3.2 Amine-N-Oxides

In the early 1990s, Schreiber\textsuperscript{25} and Jeong\textsuperscript{26} independently reported the promotion of Pauson-Khand reaction at room temperature using 4-methylmorpholine-N-oxide (NMO) and trimethylamine-N-oxide (TMANO) respectively.

A typical reaction protocol by Schreiber involves treating the cobalt complex of an enyne with six molar equivalents of NMO at room temperature followed by stirring at room temperature until completion of the reaction\textsuperscript{25}. The mild reaction conditions allow for the incorporation of various functional groups in the cyclization process; alcohols, ethers, silyl ethers, acetals and remote olefins remain intact during the reaction. The lower temperature of the reaction also leads to higher levels of stereoselectivity as compared to corresponding thermal conditions. For example, cyclisation of dicobalt

\[ \begin{align*}
\text{(OC)}_3\text{Co} + \text{Ph} &\quad \text{Promoter} \\
\text{(OC)}_3\text{Co} &\quad \text{reflux} \\
\text{63} &\quad \text{64}
\end{align*} \]
hexacarbonyl complex 67 occurs to give a 4 : 1 ratio of 68 and 69 under thermal conditions whereas use of NMO increased the ratio to 11 : 1. (Scheme 16, Table 3)\textsuperscript{25}

Scheme 16

Table 3. Comparison of NMO & CH\textsubscript{3}CN as promoters of PKR of 67

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Selectivity (68 : 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMO, CH\textsubscript{2}Cl\textsubscript{2}, rt</td>
<td>68</td>
<td>11 : 1</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{3}CN, 82 °C</td>
<td>75</td>
<td>4 : 1</td>
</tr>
<tr>
<td>3</td>
<td>CH\textsubscript{3}CN, 45 °C</td>
<td>45</td>
<td>3 : 1</td>
</tr>
</tbody>
</table>

Jeong has reported that for oxygen and nitrogen containing substrates (70 & 73 respectively) the presence of O\textsubscript{2} during the reaction is quite crucial. In the absence of O\textsubscript{2} ring opened products are formed from oxygen containing substrates (72) and saturated ketones from the nitrogen containing substrates (75) along with the desired products as shown in Scheme 17.\textsuperscript{26}
These results are quite contradictory to the "interrupted Pauson-Khand reaction" reported by Krafft. Thermal Pauson-Khand reaction of a range of cobalt complexed enynes in the presence of a controlled amount of oxygen led to monocyclic enones being isolated in addition to small quantities of expected Pauson-Khand enones. An example is illustrated in Scheme 18. The actual role of molecular oxygen in interrupting the normal Pauson-Khand reaction is unclear, however it is postulated that both the normal and interrupted Pauson-Khand products arise via a common metallacyclic intermediate (section 1.2.2.1, Scheme 11, p. 20).
Comparison of DMSO and TMANO as promoters of Pauson-Khand reaction showed that yields for the reaction illustrated in Scheme 19 are similar although DMSO requires longer reaction times (Table 4, entry 3).

Table 4. Comparison of DMSO and TMANO as promoters of PKR of 59

<table>
<thead>
<tr>
<th>Entry</th>
<th>Promoter</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMANO</td>
<td>CH₂Cl₂</td>
<td>20</td>
<td>3</td>
<td>90 61 62</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>36</td>
<td>25 2</td>
</tr>
<tr>
<td>3</td>
<td>DMSO (3eq)</td>
<td>C₆H₆</td>
<td>40</td>
<td>24</td>
<td>92 0</td>
</tr>
</tbody>
</table>

The TMANO method has also been shown to make possible the use of both allylic and propargylic alcohol components without OH protection (which had previously been found to be necessary under higher temperature conditions. Scheme 20 illustrates two of the examples where both unprotected propargylic and allylic alcohol have been used. Dicobalt hexacarbonyl of propargyl alcohol 79 reacts with norbornadiene 80 to
give the cycloadduct 81 in 62% yield. Dicobalt hexacarbonyl of propargyl alcohol 79 and allylic alcohol 19 react to give the cyclopentenones 82 and 83 in 64% yield.

Scheme 20

It seemed that the primary reason for requiring harsh reaction conditions (high temperature and pressure) for thermal Pauson-Khand reaction in its early stages was associated with the initial step of decarbonylation of dicobalt hexacarbonyl complex of the alkyne to generate a vacancy for the incoming alkene. It has been known that amine-\(N\)-oxides such as trimethylamine-\(N\)-oxide (TMANO) and 4-methylmorpholine-\(N\)-oxide (NMO) can help make the ligand more labile on the transition metal complex of the alkyne and in this case lead to oxidative removal of a carbon monoxide ligand, as carbon dioxide, from the cobalt and therefore create a vacancy for oxidative addition of alkene.
1.3.3 Primary Amines and Ammonia

Sugihara has reported the use of primary amines and ammonia in the rate enhancement of the Pauson-Khand reaction. According to this study, primary amines with moderately hindered secondary alkyl groups such as cyclohexylamine (CyNH$_2$) dramatically increase the rate of Pauson-Khand cycloaddition. In addition, use of aqueous ammonium hydroxide in a biphasic system was reported.

As can be seen from Table 5, both methods gave comparable results in terms of yields and rates for both inter- and intramolecular Pauson-Khand reaction (Scheme 21). In all the cases they studied, the reaction was complete in a short time (10-135 min) and afforded the desired cyclopentenones in moderate to good yields (45-100%).

Sugihara postulates that amines act as hard ligands which react with the dicobalt hexacarbonyl complex of alkyne and facilitate the substitution of a CO ligand by the olefin. This labilising effect may also make the coordinated alkyne more reactive and therefore promote the reaction.
**Scheme 21**

**Table 5. Cyclohexylamine and ammonia as promoters of PKR**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Condition A</th>
<th>Condition B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>t (min)</td>
<td>t (min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yield (%)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>63 + 40</td>
<td>84</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>86</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Condition A: 3.5 eq of CyNH₂ in 1,2-dichloroethane at 83 °C. Condition B: 1:3 mixture (v/v) of 1,4-dioxane and 2M aq. NH₄OH at 100 °C.

The drawback of using this method is the formation of highly reducible cobalt complexes during the reaction which in some cases, induce the cleavage of a carbon-heteroatom bond at the α-position of the complex (**Scheme 22**). When 87 was treated with cyclohexylamine in the presence of norbornene 40, benzyl alcohol 88 was produced via the reductive cleavage of the ether bond at the α position. The same result was observed when 89 was treated with cyclohexylamine. Also simple alkenes such as cyclopentene and cyclohexene do not react intermolecularly via this method.²⁹
1.3.4 Sulfides

As discussed in the introduction (section 1.2.2.2, p. 20), a suitably positioned sulfur moiety, tethered to the Pauson-Khand cyclisation precursor, increases the reaction efficiency. Sugihara and Yamaguchi have extended this to the use of various sulfides as promoters of Pauson-Khand reaction. Among aryl sulfides, sterically less hindered sulfides such as thioanisole are most efficient at promoting the reaction and sulfides which have electron-donating groups are more effective than those with electron-withdrawing groups. The same steric effect has been observed with dialkyl sulfides. Among these, ones having primary and secondary alkyl groups are more effective than those with tertiary alkyl groups. These observations have led to $n$-butyl methyl sulfide being selected as the promoter of choice. $n$-Butyl methyl sulfide was shown to promote both inter- and intramolecular Pauson-Khand reaction (Table 6). Substrates with ether group at the α position cyclised efficiently (entry 1). Substrates with all carbon tether also underwent sulfide promoted Pauson-Khand reaction (entry 2). The cyclisation with reactive alkenes such as norbornene 40 proceeded to give tricyclic compounds in excellent yields (entry 3). Since the sulfide promoted Pauson-Khand reaction proceeded even at 35 °C, the cyclisation of alkenes with low boiling points, such as cyclopentene 64 and cyclohexene 96 was also achieved (entries 4 & 5 respectively).
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Table 6. PKR in the presence of n-butyl methyl sulfide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate(s)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>81&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>94&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>99&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>75&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>nBu</td>
<td>nBu</td>
<td>68&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* All reactions were carried out in 0.1 M concentration of dicobalthexacarbonyl complex of substrates in 1,2-dichloroethane. <sup>b</sup> Reaction mixture was refluxed at 83 °C. <sup>c</sup> Reaction were carried out in 0.1 M concentration of dicobalthexacarbonyl complex of alkyne in 1,2-dichloroethane. <sup>d</sup> Reaction mixture was heated at 35 °C.

Direct comparison of this method with other Pauson-Khand cyclisation conditions showed it to be the milder method (Scheme 23).
As can be seen from Scheme 23, use of cyclohexylamine in the case of enyne 89 leads to a cleavage product 90 whereas the expected product 74 is formed in 79% yield when the sulfide is used as the promoter. Also there is no cleavage of the carbon-heteroatom bond at the α-position. The yield of cyclopentenone 99 is markedly improved to 85% in sulfide promoted reaction relative to 23% in the thermal cyclisation whereas NMO promoted reaction did not lead to any product.

1.3.5 Dry State Adsorption Conditions (DSAC)

In 1986, Smit and Caple discovered that the intramolecular Pauson-Khand reaction could be accelerated if it was carried out not in solution, but with the substrate adsorbed
onto a chromatographic adsorbent in the absence of solvents and in an atmosphere of oxygen. These conditions are referred to as ‘dry state adsorption conditions’ (DSAC). A typical procedure involves loading of the dicobalt hexacarbonyl complex of an enyne onto silica followed by removal of solvent then heating in an atmosphere of oxygen.

This method was applied to a series of allyl propargyl ethers containing substituents in various positions. Two examples are illustrated in Scheme 24 & 25. Various substrates undergo Pauson-Khand reaction using DSAC and the yields range from 43% to 92%. Use of an argon atmosphere in place of oxygen resulted in the reactant 100 being converted into a monocyclic product 101 and enyne 103 led to 104. Yields of the reaction under an argon atmosphere range from 40% to 73%.

\[
\begin{align*}
&100 \\
&i) \text{Co}_2(\text{CO})_8 \\
&ii) \text{Alumina, Ar, 45 °C} \\
&90% \\
&101 \\
&\text{O} \\
&\text{HO} \\
&\text{O} \\
&102 \\
&103 \\
&i) \text{Co}_2(\text{CO})_8 \\
&ii) \text{Silica, O}_2, 45 °C \\
&76%
\end{align*}
\]

Scheme 24
According to Smit and Caple’s studies, various types of silica gels produce comparable results and alumina can also be used as active support for this reaction, the effect being insensitive to the pH of the adsorbent. Silica gels containing about 30% water, dried up or containing 5% water, are rather inactive as media for the reaction and the optimum water content lies between 10 and 20%. The addition of a solvent, such as methanol or hexane, leads to a decrease in the rate and efficiency of the cyclisation.

The catalytic effects of adsorption are attributed to two factors: (i) the preferential stabilisation of the coiled conformation required for the formation of the cyclic intermediate via the interaction of the polar centres (e.g. ether centre) of the enyne with the surface hydroxy groups of the adsorbent. This effect, together with the repulsive interactions of the surface with the hydrophobic ends of the precursor would assist in the formation of the cyclic transition state leading to the bicyclic product, and (ii) the promotion of the ligand exchange arising from the interaction of the dicobalt hexacarbonyl complex fragment with the donor centres of the surface.
1.3.6 Molecular Sieves

Perez-Castells has reported promotion of intra- and intermolecular Pauson-Khand cyclisation by addition of molecular sieves.\textsuperscript{33} The study employed aromatic enynes, of general structure shown in Figure 2, as substrates for the cyclisation and it was hoped that the Pauson-Khand cycloaddition would lead to tricyclic products.\textsuperscript{34}

\[
\begin{array}{c}
  X \\
  m \\
  n \end{array}
\]
\[n = 1, 2\]
\[m = 1, 2\]
\[X = O, NH\]

Figure 2

Detailed studies on compound 106 in Scheme 26 showed that use of molecular sieves in refluxing toluene led to an increase in the yield of Pauson-Khand cycloaddition\textsuperscript{33}. These aromatic enynes yielded tricyclic enones as products and the major compound was the one where the emerging double bond has isomerised to be conjugated with the aromatic ring as shown in Scheme 26, Table 7.
**Scheme 26**

Table 7. Reaction of compound 106 in different conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Promoter</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>TMANO</td>
<td>-10</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>TMANO/4Å MS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-10</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>Benzene</td>
<td>TMANO</td>
<td>-10</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>TMANO</td>
<td>-10</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>TMANO/4Å MS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-10</td>
<td>90 &lt;5</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>4Å MS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>112</td>
<td>45 &lt;5</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>none</td>
<td>112</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>TMANO/4Å MS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-10</td>
<td>15 75</td>
</tr>
</tbody>
</table>

<sup>a</sup> Powdered molecular sieves preheated in an oven at 125 °C for 4 h and cooled under argon. No reaction was observed at lower temperatures. <sup>b</sup> Commercial powdered and activated 4Å molecular sieves (8-12 mesh).

Initial studies on compound 106 showed that (i) the more polar the solvent, the more depropargylation is observed. For example with acetonitrile, depropargylation is the major process observed (entry 1 and 2). With less polar solvents such as benzene (entry 3) or toluene (entry 4), no vinyl phenol 109 was observed and the best conversions were achieved with toluene. (ii) TMANO was the only promoter that led to high conversions (entry 5), (iii) raising the temperature to refluxing toluene showed that molecular sieves were able to promote the reaction on their own albeit with lower yield (entry 6), (iv) in the absence of zeolites, the thermal promotion of the reaction only yielded 15% of the compound 107 (entry 7) (v) in addition to favouring the reaction, molecular sieves also modify the double bond isomerisation process. Compound 108 is the major product when less water is present in the reaction mixture (entry 8). It can be considered as the
New Substrates for PKR

Introduction

Intermediate to compound 107 as when it is stirred with traces of acid or base or simply with dicobalt octacarbonyl, it isomerises quantitatively to compound 107.

Yields of molecular sieve promoted Pauson-Khand reaction are always good when the alkene moiety is unsubstituted (44-90%), although slightly lower when non-terminal alkynes are used (50-55%). Extension of this reaction to the trisubstituted alkene resulted in failure to obtain Pauson-Khand products; use of TMANO and molecular sieves at -10 °C led to depargylation, whereas use of molecular sieves in refluxing toluene gave interrupted Pauson-Khand products 111 and 113 (Scheme 27). Obtention of these interrupted Pauson-Khand products was attributed to the steric hindrance caused by the substitution in the alkene moiety which prevents carbon monoxide incorporation and led directly to the decomplexation of the cobalt.

\[
i) \text{Co}_2\text{(CO)}_8 \quad \text{ii) 4Å MS, Toluene reflux}
\]

\[
n = 1, 110 \quad n = 2, 112
\]

\[
n = 1, 111, 30\% \quad n = 2, 113, 20\%
\]

Scheme 27

Only one example of intermolecular reaction was reported and is illustrated in Scheme 28.

\[
\text{Et TMANO/4Å MS, Toluene} \quad \text{Et reflux}
\]

\[
\text{Et} \quad \text{4Å MS, Toluene reflux}
\]

\[
\text{Et} \quad \text{H}
\]

\[
\text{Et} \quad \text{H}
\]

\[
n = 1, 110 \quad n = 2, 112
\]

\[
n = 1, 111, 30\% \quad n = 2, 113, 20\%
\]

Scheme 28
It was suggested that molecular sieves in this process may act to adsorb the enyne and stabilise a pre-transition state or they may promote ligand exchange.\textsuperscript{34}

1.3.7 Aqueous Phase Thermal Pauson-Khand reaction

Krafft has reported the first protocol for stoichiometric thermal Pauson-Khand reaction in water as the only solvent, and in the presence of surfactants as additives, to circumvent the sluggishness of the reaction in water alone.\textsuperscript{35}

Preliminary experiments on several enynes led to optimised reaction conditions. An example is shown in Scheme 29. The protocol involves heating a dicobalt hexacarbonyl complex of an enyne in water at 70 °C with a small amount of Celite\textsuperscript{®} and 0.6 equivalent of cetyltrimethylammonium bromide (CTAB, a surfactant) under nitrogen. Most reactions went to completion after 18 h of heating. Various other surfactants were tested but the highest yields were obtained with CTAB and cetyltrimethylammonium hydrogen sulfate (CTAHS).

\begin{center}
\begin{tabular}{c}
\textbf{EtO}_2\textbf{C} \hspace{1cm} & \hspace{1cm} \textbf{i) Co}_2\textbf{(CO)}_8 \\
\textbf{EtO}_2\textbf{C} \hspace{1cm} & \hspace{1cm} \textbf{ii) H}_2\textbf{O}, \textbf{CTAB}, \textbf{Celite}, \textbf{70 °C} \\
& \hspace{1cm} \textbf{EtO}_2\textbf{C} \hspace{1cm} \xrightarrow{83\%} \\
& \hspace{1cm} \textbf{O} \\
\end{tabular}
\end{center}

Scheme 29

A variety of substrates were screened via the above method to verify the generality of this method. A few examples are illustrated in Table 8.

As can be seen from Table 8, there was a marginal decrease in the yield from the cyclisation of the enyne with one ester group in the tether (entry 2, 78%) compared to enyne with two ester groups in the tether (entry 1, 83%). A dihydroxylated enyne \textbf{120} cyclised to give a good yield of enone \textbf{121} (entry 3, 65%). Reaction of enyne \textbf{122} bearing the ketal functionality gave moderate yields of the enone \textbf{123} (entry 4, 40%). Use of CTAHS as surfactant for the cyclisation of ketal bearing enyne \textbf{122} led to loss of the ketal functionality in the resulting enone and \textbf{121} was obtained in 62% yield.
**Table 8. Aqueous Pauson-Khand reactions with CTAB**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
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<td>EtO₂C</td>
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<td>117</td>
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<tr>
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<td>EtO₂C</td>
<td>EtO₂C</td>
<td>78</td>
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<tr>
<td></td>
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<td>H</td>
<td></td>
</tr>
<tr>
<td>118</td>
<td></td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>HO-</td>
<td>HO-</td>
<td>65</td>
</tr>
<tr>
<td></td>
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<td>HO-</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>O-</td>
<td>O-</td>
<td>40</td>
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<tr>
<td></td>
<td>O</td>
<td>O-</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td></td>
<td>123</td>
<td></td>
</tr>
</tbody>
</table>

One example of intermolecular Pauson-Khand reaction was reported, where the dicobalt hexacarbonyl complex of phenylacetylene \( \text{63} \) and norbornene \( \text{40} \) cyclised in a H₂O-CTAB medium to provide enone \( \text{84} \) in 62% yield (Scheme 30).

![Scheme 30](image)

In the same paper it was also reported that cyclisations using tetracobalt dodecacarbonyl \( \text{Co₄(CO)₁₂} \) provided variable results. In the case of terminal alkynes reductive Pauson-
Khand products were obtained whereas internal alkyne substrates (which are less prone to reductive Pauson-Khand reaction) were not efficiently converted to their corresponding enones.35

1.3.8 Pauson-Khand reaction with metals other than Cobalt

Other metals apart from cobalt can mediate Pauson-Khand-type reactions. Although these have found best use in catalytic version, as will be discussed later, the stoichiometric reaction has been performed with zirconium36 iron37 molybdenum and tungsten38 palladium39 and with varying degrees of success.

Negishi has reported a zirconium promoted intramolecular variation of the Pauson-Khand reaction involving a zirconacycle intermediate 125 (Scheme 31).36 Carbonylation occurs under an atmosphere of CO to afford cyclopentenone as shown in Scheme 31.

\[
\begin{align*}
R' & \quad \text{Cp}_2\text{ZrCl}_2 \quad \text{2 n-BuLi} \quad -78^\circ\text{C, THF} \quad \text{R} \\
& \quad \text{R'} \quad \text{ZrCp}_2 \quad \text{CO} \quad \text{O} \\
124 & \quad 125 & \quad 126 
\end{align*}
\]

Scheme 31

When an isocyanide is used instead of CO, the reaction gives an iminocyclopentene, which can be hydrolysed to a bicyclic enone.

Tamao40 has used bis(cyclooctadienyl)-nickel in the presence of an isocyanide 128, a carbon monoxide equivalent, to convert enynes of type 127 to bicyclic iminocyclopentenes 129 which can be hydrolysed to the corresponding cyclopentenones 130, as shown in Scheme 32.
New Substrates for PKR

M(CO)$_6$ (M = Mo, W) has been used in the presence of excess DMSO to yield cyclopentenones.$^{38}$ The Pauson-Khand reaction of enyne 59 under these conditions yielded cyclopentenone 61 in 76% yield (Scheme 33). Intermolecular reactions were not as effective as the intramolecular version.

**Scheme 32**

1.4 Catalytic Pauson-Khand reaction

Only catalytic Pauson-Khand reaction fulfils the criterion of atom economy. The use of stoichiometric amounts of the transition metal is not acceptable commercially. It is not surprising therefore, that several research groups have more recently focused on developing catalytic variants.$^{5}$ Although the catalytic Pauson-Khand reaction was reported as early as 1973, it was confined to strained reactive alkenes e.g. norbornene and norbornadiene, and required an excess of alkyne compound.$^{8a}$ Early work with gaseous alkynes suggested that the process could be carried out in a catalytic fashion by stirring a mixture of alkene and ca. 10 mol% Co$_2$(CO)$_8$ in an inert solvent under a 1:1 alkyne/CO atmosphere. The success of these attempts depended on a continuous supply of excess alkyne being able to trap and recycle reactive cobalt-containing fragments.$^{8a}$
NEW SUBSTRATES FOR PKR

INTRODUCTION

There has been a marked increase in interest to develop catalytic Pauson-Khand reaction by several groups working in this area, especially during the 1990s. Nowadays the catalytic variations have been successful in various examples of inter- and intramolecular Pauson-Khand reactions.

Methods that have been developed for the catalytic Pauson-Khand reaction are typically based on a combination of one or more of the following premises: i) in situ generation of the active cobalt carbonyl species, ii) preservation of the active cobalt carbonyl species, iii) preservation of the intermediate complexes, and iv) facilitation of decarbonylation, hence increased alkene complexation rate. Furthermore, catalysis in the Pauson-Khand reaction is best achieved in reactions that are carried out under an atmosphere of carbon monoxide so that regeneration of the active catalyst is possible.41

The catalytic Pauson-Khand reactions reported to date involve i) the use of carbon monoxide atmosphere, ii) modified cobalt complexes, iii) light induction, or iv) complexes of other metals such as titanium, ruthenium or rhodium.

1.4.1 Use of a carbon monoxide (CO) atmosphere

Rautenstrauch et al.42 showed in their 1990 synthesis of the dihydrojasmonate precursor 132 that catalytic Pauson-Khand reactions are possible if high CO pressure and high temperature are used.

\[
\begin{align*}
\text{C}_5\text{H}_{11} & + \text{CO (310-360 bar)} \\
0.22 \text{ mol\% Co}_2(\text{CO})_8 & \rightarrow \text{O} \\
\text{150 °C, 16 h, 48\%} & \rightarrow \text{C}_5\text{H}_{11}
\end{align*}
\]

Scheme 34

Modifications to the reaction conditions and/or the cobalt metal catalyst have proven to be effective in increasing the yields in catalytic Pauson-Khand cycloadditions.
In 1997 Jeong$^{43}$ reported the use of supercritical CO$_2$ fluid in catalytic Pauson-Khand reaction. The reactions were performed in supercritical CO$_2$ by charging a cylindrical stainless steel reactor with a catalyst and enyne followed by pressurising with CO and CO$_2$. According to their study, high reaction temperature (90-100 °C) and high CO pressure (15-30 atm) were required. The reaction was effective in inter- and intramolecular reactions, however there were only 4 intra- and 2 intermolecular examples and thorough studies are required. An intramolecular reaction of enyne 59 is illustrated in Scheme 35.

\[
\begin{align*}
\text{EtO}_2\text{C} & \xrightarrow{2.5 \text{ mol}\% \text{ Co}_2(\text{CO})_8} \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} & \xrightarrow{P_{\text{CO}} = 30 \text{ atm}} \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} & \xrightarrow{P_{\text{CO}_2} = 112 \text{ atm}} \text{EtO}_2\text{C} \\
59 & \implies \text{O} \\
\text{Scheme 35}
\end{align*}
\]

Chung and coworkers$^{44}$ have reasoned that the problem with catalytic thermal Pauson-Khand reaction may be the formation of Co$_4$(CO)$_{12}$ during the reaction which may cause a dead end. They suggested that at high pressure of CO and at high temperature most cobalt carbonyls exist as Co$_2$(CO)$_8$ instead of Co$_4$(CO)$_{12}$. They carried out the Pauson-Khand reaction using Co$_2$(CO)$_8$ and Co$_4$(CO)$_{12}$ under a high pressure of CO and at high temperature. The optimum conditions were for a reaction at 150 °C under 10 atm of CO. In general at less than 5 atm of CO the reaction did not proceed well for most substrates in the study. The practical lower limit of temperature seemed to be about 60-79 °C. The scope of the reaction was examined in both inter- and intramolecular fashion. The reaction of compound 59 using 1 mol% of Co$_4$(CO)$_{12}$ yielded 92% of the product 61. An intermolecular example is shown in Scheme 36.
New Substrates for PKR

**Introduction**

Scheme 36

This catalytic system has been shown to be quite effective for terminal alkynes having aryl, alkyl, alkyl chloride, alcohol and alkenes as substituents. Compared to intermolecular reactions, intramolecular reactions need more Co₄(CO)₁₂ (1 mol% compared to 0.5 mol%) and longer reaction times.

Sugihara has reported that both the inter- and intramolecular catalytic Pauson-Khand cycloaddition can be promoted using "hard" Lewis bases. He reasoned that "hard" Lewis bases on low-valent organotransition metal complexes labilise the existing ligand. This effect facilitates the ligand substitution reaction and sometimes makes the coordinating ligands reactive. In the case of alkyne or enyne dicobalt hexacarbonyl complexes, this labilising effect would lead to more facile co-ordination of the alkene onto a vacant site on cobalt.

Initial studies on compound 135 (Scheme 37) showed that cyclohexylamine, which was the best promoter for stoichiometric Pauson-Khand reaction, was not effective under catalytic conditions. On the contrary, secondary and tertiary amines allowed catalytic cyclisation and N,N-diisopropylethylamine was the most effective among investigated amines. These studies showed that a sterically bulky or less electron-donating "hard" Lewis base can activate dicobalt octacarbonyl without decomposition. Lewis bases such as N,N-diisopropylethylamine, benzyl alcohol, 1,4-dioxane, 1,2-dimethoxyethane (DME), and water catalysed the cyclisation of 135 in good yields. DME and water gave comparable results. Among these activators, DME and water seemed to be the most effective. DME can act as the activator of dicobalt octacarbonyl in a narrow range of temperature (60-70 °C) without decomposing the catalyst. The amount of additive is critical and a pressure of CO of about 7 atm is also necessary for efficient catalysis. This method is effective for both inter- and intramolecular reactions and example of each is shown in Scheme 37.
A proposed mechanistic hypothesis for this catalysis\textsuperscript{45} is shown in Scheme 38.
Under the original conditions, coordinatively unsaturated cobalt carbonyl complex 141 is produced after the cyclisation. When the reaction is carried out under CO atmosphere, the complex 141 may transform into Co₂(CO)₈ or in the presence of alkyne to dicobalt hexacarbonyl complex of alkyne 139, therefore a catalytic amount of Co₂(CO)₈ is theoretically required to complete the cyclisation. However the turnover number of the reactions carried out in this fashion have not been satisfactory. The reasons are
considered as follows: (i) feasibility in transformation of the coordinatively unsaturated
dicobalt carbonyl complex 141 into Co₄(CO)₁₂ which is considered as inactive in the
catalytic PKR, (ii) retardation in formation of complex 139 and coordination of an
alkene to 139 under CO atmosphere, and (iii) inefficiency of the PKR under the original
conditions. When the reaction is carried out in the presence of “hard” Lewis bases
Co₄(CO)₁₂ may be transformed into Co₂(CO)₈ or the coordinatively unsaturated cobalt
complexes 143 and 144. Complexes 143 and 144, are responsible for the catalytic action
in this reaction. The electron-donating effect of “hard” Lewis bases may stabilise these
 coordinatively unsaturated complexes. In addition once complex 145 is produced, the
cyclisation may be facilitated as seen in the primary amine promoted stoichiometric
Pauson-Khand reaction.

Sugihara in this paper postulated that the course of reaction differed for stoichiometric
and catalytic Pauson-Khand reaction, based on two findings in this study. Firstly that
cyclohexylamine is an efficient promoter of stoichiometric Pauson-Khand reaction but
it does not promote catalytic Pauson-Khand reaction at all and secondly that water does
not promote stoichiometric Pauson-Khand reaction, however it effectively catalysed the
catalytic Pauson-Khand reaction.

Livinghouse determined that the cobalt catalysed intramolecular Pauson-Khand reaction
could be promoted thermally under 1 atm of CO pressure. Cyclisation studies showed
that a very narrow thermal window (60-70 °C) exists for the efficient catalysis. Typical
conditions involve stirring the enyne of interest in degassed 1,2-DME in the presence of
high purity 5 mol% Co₂(CO)₈ at 60 °C under 1 atm of CO for 12-15 hours. Reaction
yields were high and ranged from 77-86%. Example of an intramolecular reaction is
shown in Scheme 39. In some cases (e.g., disubstituted alkenes) 7.5 to 10 mol% 
Co₂(CO)₈ was required.
New substrates for PKR

**Scheme 39**

Krafft has reported a modification of the Livinghouse procedure in which further purification of Co$_2$(CO)$_8$ is not necessary. They reported that when carefully base washed glassware was used, the catalytic reaction proceeded to completion in most cases using 10 mol% of unpurified Co$_2$(CO)$_8$ in 1,2-DME under a blanket of CO.

They also reported limitations of the Livinghouse procedure when internal or sterically hindered alkynes were used. In order for these to cyclise 30-60 mol% of the catalyst was required. Krafft used cyclohexylamine in their catalytic variation of Livinghouse process to obtain enhanced yields in most cases. A typical procedure involved using 5-10 mol% of Co$_2$(CO)$_8$ and 20 mol% of CyNH$_2$ with heating at 70 °C. Lower yields of products were obtained in THF or toluene compared to 1,2-DME.

The examples in **Scheme 40** illustrate that when a terminal alkyne (R = H, 148) is used, 5 mol% of the catalyst and 20 mol% of CyNH$_2$ are required whereas when an internal alkyne (R = "Pr, 150) is used 30 mol% of the catalyst and 60 mol% of CyNH$_2$ are required.

**Scheme 40**
Krafft\(^{49}\) has also reported that a catalytic amount of tetracobalt dodecacarbonyl \(\text{Co}_4(\text{CO})_{12}\) could be used in conjunction with cyclohexylamine to catalyse Pauson-Khand reaction at 1 atmosphere pressure of CO. Reactions were typically carried out at a substrate concentration of 0.05 M in DME using 10 mol% of \(\text{Co}_4(\text{CO})_{12}\) and 60 mol% of \(\text{CyNH}_2\) under a CO atmosphere at 70 °C. Two examples are illustrated in Scheme 41.

![Scheme 41](image)

Lower yields were obtained with enynes containing disubstituted alkenes (e.g. 152). Also enynes bearing internal alkynes or which are sterically hindered need a higher catalyst loading of approximately 30 mol% (e.g. 154). An intermolecular version was also reported as shown in Scheme 42.

![Scheme 42](image)
Krafft and coworkers\textsuperscript{49} have discounted the assumption that Co\textsubscript{4}(CO)\textsubscript{12} is inactive towards the Pauson-Khand reaction under mild conditions such as 1 atmosphere of CO and 70 °C. Krafft has postulated that Co\textsubscript{4}(CO)\textsubscript{12} under these conditions undergoes disproportionation into Co\textsubscript{2}(CO)\textsubscript{8} or a similar catalytically active cobalt species. They presume that CyNH\textsubscript{2} encourages disproportionation and promotes preservation of catalytically active cobalt species.

Recently Perez-Castells and co-workers\textsuperscript{50} have reported a new protocol for the catalytic Pauson-Khand reaction induced by molecular sieves which had been pretreated with CO. Enyne 59 was submitted to three reactions in air atmosphere with 10 % dicobalt octacarbonyl: blank reaction, addition of molecular sieves, and addition of molecular sieves which had been heated to 200 °C and cooled under carbon monoxide (Scheme 43).

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad 10 \text{ mol}\% \text{ Co}_2(\text{CO})_8 \quad \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} & \quad \text{Toluene, air} \quad \text{EtO}_2\text{C} \\
59 & \quad 65 \text{ °C} \\
\text{O} & \\
\text{59} & \quad 61 \\
\end{align*}
\]

Without MS: 15%  
With MS: 30%  
With MS pretreated with CO: 65%

\textbf{Scheme 43}

The results show a significant increase in yield with sieves, reaching 65 % with pretreated zeolites. After optimisation studies, the best results were obtained when reaction was carried out in toluene with molecular sieves (preheated to 125 °C for 4 h and cooled under argon), under carbon monoxide atmosphere and 10 mol% dicobalt octacarbonyl. The results for some of the substrates are shown in Table 9.
### Table 9. Catalytic PKR in the presence of molecular sieves

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO EtO₂C EtO₂C</td>
<td>EtO₂C OMe EtO₂C</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>OH</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Boc N</td>
<td>Boc N O</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Ph +</td>
<td>Ph O</td>
<td>70</td>
</tr>
</tbody>
</table>

The authors have postulated that molecular sieves improve the conversion of the catalytic Pauson-Khand reaction, probably due to their ability to adsorb and keep carbon monoxide.

#### 1.4.2 Use of modified cobalt complexes

Various catalytic versions of the Pauson-Khand reaction where modified cobalt complexes have been employed have been reported in the literature and below is a summary of the most useful variations to date.
Jeong\textsuperscript{51} reported that one of the main obstacles to overcome in the development of the catalytic process were the formation of metal clusters or other inactive metal carbonyl species. They felt that use of other ligands might stabilise the active cobalt intermediates. Jeong has reported a catalytic conversion of enynes into cyclopentenones employing phosphites as coligands.\textsuperscript{51} Use of triphenyl phosphite (10 mol\%) as a coligand with dicobalt octacarbonyl (3 mol\%) gave 51-94\% yields in seven examples of intramolecular cycloaddition. An example is illustrated in Scheme 44.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{3 mol\% Co}_2(\text{CO})_8 \\
\text{EtO}_2\text{C} & \quad \text{10 mol\% P(OPh)}_3 \\
\text{CO (1 atm), DME} & \quad 120 \degree \text{C, 82\%} \\
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\hline
59 & \quad 61
\end{align*}
\]

Scheme 44

Jeong and Chung\textsuperscript{52} have also reported the use of a 1,5-cyclooctadiene (indenyl) cobalt (I) complex for the catalysis of both inter- and intramolecular cyloaditions. High yields (53-97\%) were reported for intermolecular cycloadditions of norbornene and norbornadiene with a variety of alkynes and 64-94\% yields were reported for two intramolecular versions. In these examples 1-2 mol\% of catalyst with high CO pressure (15 atm) at 100 \degree \text{C} were the standard conditions. Table 10 shows the reaction of norbornadiene 80 with various alkynes, using these reaction conditions. Terminal alkynes generally gave good yields of cyclopentenones (entries 1-4) whereas alkyne conjugated to a carbonyl (entry 5) did not give any corresponding product. A free hydroxyl group was shown to be compatible with the reaction conditions (entries 3 & 4). Disubstituted alkynes (entries 6 & 7) were not such good substrates for this reaction as terminal alkynes.
Table 10. Catalytic PKR using (indenyl)Co(Cod)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R1</th>
<th>R2</th>
<th>Product Yield (%)</th>
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</thead>
<tbody>
<tr>
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<td>Ph</td>
<td>H</td>
<td>137, 93</td>
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<tr>
<td>2</td>
<td>162</td>
<td>(CH2)3CH3</td>
<td>H</td>
<td>163, 95</td>
</tr>
<tr>
<td>3</td>
<td>164</td>
<td>C(CH3)2OH</td>
<td>H</td>
<td>165, 95</td>
</tr>
<tr>
<td>4</td>
<td>166</td>
<td>CH2CH2OH</td>
<td>H</td>
<td>167, 96</td>
</tr>
<tr>
<td>5</td>
<td>168</td>
<td>CO2Et</td>
<td>H</td>
<td>169, 0</td>
</tr>
<tr>
<td>6</td>
<td>170</td>
<td>Ph</td>
<td>Ph</td>
<td>171, 59</td>
</tr>
<tr>
<td>7</td>
<td>172</td>
<td>Ph</td>
<td>Me</td>
<td>173, 53</td>
</tr>
</tbody>
</table>

An intramolecular reaction was also tested with 2 mol% of the catalyst and reaction of compound 73 as shown in Scheme 45 yielded 94% of the product 74.

Scheme 45

Sugihara\textsuperscript{53} has reported the use of methylidynetricobalt nonacarbonyl as a catalyst. Alkylidynetricobalt nonacarbonyl clusters (174 in Figure 3) are easily prepared by the reaction of dicobalt octacarbonyl with trihaloalkanes. They are more stable against autooxidation than the parent dicobalt octacarbonyl and have a similar structure to dicobalt hexacarbonyl complex of alkynes (175 in Figure 3) in which one carbon vertex of the tetrahedron is replaced with a Co(CO)\textsubscript{3} unit.
Figure 3

Initial studies were carried out on the reaction in Scheme 46 below.

These studies showed that when dicobalt octacarbonyl was used in the absence of an activator, only low conversions were achieved. In contrast methylidyneetricobalt nonacarbonyl (R=H in 174, Figure 3), itself efficiently catalysed the reaction and did not need an activator. Clusters with relatively small substituents on the carbon unit (R = Cl, CH₃, COOC₂H₅) catalysed the desired cyclisation, while ones with aromatic substituents (R=C₆H₅) were detrimental to the catalysis. The best results were obtained by using the parent cluster methylidyneetricobalt nonacarbonyl (R=H in 174, Figure 3). Toluene was the solvent of choice and also 7 atm of CO was the optimum pressure required under these conditions. Examples of inter and intramolecular Pauson-Khand reaction catalysed by methylidyneetricobalt nonacarbonyl (R=H in 174, Figure 3) are shown in Scheme 47.
Studies on a series of substrates have shown that intramolecular reaction takes place independent of the substituents on the alkyne moiety. On the other hand, the number of substituents on the alkene is important as trisubstituted alkenes did not undergo the cyclisation reaction and led to recovery of starting material. Additionally an increase in tether length, from 3 to 4 carbon atoms, was detrimental to the cyclisation and led to low conversions. Heteroatom containing compounds such as tosylamides or ethers also cyclised effectively. Intermolecular Pauson-Khand reaction was also possible in the presence of norbornene and norbornadiene in combination with a terminal alkyne. The air stability and ease of preparation of the cluster are noted as the highlight of this procedure.

Periasamy has reported that Pauson-Khand reaction can be readily carried out with an alkyne complex generated in situ using a sub-stoichiometric amount of CoBr₂ (40 mol%) and Zn (43 mol%), in toluene / t-BuOH at 1 atmosphere pressure of CO. Their results are summarised in Scheme 48.
**Scheme 48**

As shown in Scheme 48, reactions with less strained alkenes such as cyclopentene (64) proved less efficient.

Chung\(^{55}\) reported that a combination of Co(acac)\(_2\) and NaBH\(_4\) in catalytic amount effectively promoted both inter- and intramolecular cycloaddition. It is postulated that a system of this reagent under pressure of CO produces Co\(_2\)(CO)\(_8\). A typical procedure involves 5-10 mol\% of Co(acac)\(_2\) and 10-20 mol\% of NaBH\(_4\) under 30-40 atm of CO at 80-100 °C. The yields of the reactions ranged from 30-95%. An inter- and intramolecular example are shown in Scheme 49.

\[
\begin{array}{c|c|c|c|c}
\text{R} & \text{Yield (\%)} & \text{R} & \text{Yield (\%)} \\
\hline
\text{Ph, 84} & 83 & \text{Ph, 65} & 32 \\
\text{\(n\)}\text{C}_5\text{H}_{11}, 181 & 88 & \text{\(n\)}\text{C}_6\text{H}_{13}, 182 & 30 \\
\text{\(n\)}\text{C}_8\text{H}_{17}, 177 & 85 & \text{\(n\)}\text{C}_8\text{H}_{17}, 183 & 35 \\
\end{array}
\]
New Substrates for PKR

Livinghouse and Belanger have found that some alkyne dicobalt hexacarbonyl complexes can serve as a source of an active cobalt catalyst for carboxylative enyne cyclisations and act as convenient substitutes for the relatively labile $\text{Co}_2(\text{CO})_8$ in the catalytic thermal Pauson-Khand reaction\textsuperscript{56}. A subsequent \textit{in situ} reduction of the initial alkyne complex with Et$_3$SiH was used to generate active cobalt catalyst. A series of $\text{Co}_2(\text{CO})_6$-alkyne complexes (e.g., complexes of: $\text{HO(CH}_3)_2\text{CC=CH}$, $\text{PhC=CH}$, $\text{PhC=CPh}$, TMSC=CtMS, $\text{HOCH}_2\text{C=CH}$, $\text{HOCH}_2\text{C=CCH}_2\text{OH}$ and $\text{MeO}_2\text{CC=CCO}_2\text{Me}$) were screened in combination with Et$_3$SiH as $\text{Co}_2(\text{CO})_8$ surrogates in the catalytic Pauson-Khand reaction involving enyne \textbf{59} (Scheme \textbf{50}). Of the various alkyne derivatives examined, the $\text{Co}_2(\text{CO})_6$ complexes of 2-methyl-3-butyn-2-ol and phenylacetylene were virtually identical as sources of highly active catalyst. The $\text{Co}_2(\text{CO})_6$ complex of 2-methyl-3-butyn-2-ol (\textbf{185}) was chosen as catalyst source due to its crystalline nature, shelf stability, ease of preparation and high decomplexation rate in the presence of Et$_3$SiH. Addition of cyclohexylamine to the reaction mixture led to improved yields in many cases.
Several enynes, containing both terminal and internal alkynes as well as disubstituted alkenes, undergo the cyclisation in an efficient manner. Heteroatom containing enynes such as tosylamides also cyclised efficiently. Yields ranged from 77-95% and some examples are illustrated in Table 11.
Table 11. Thermally promoted PKRs catalysed by complex 185

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)a</th>
</tr>
</thead>
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<td>1</td>
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<td>86b</td>
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<td></td>
<td>MeO₂C</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MeO₂C</td>
<td>187</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeO₂C</td>
<td>MeO₂C</td>
<td>95c</td>
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<td></td>
<td>MeO₂C</td>
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<tr>
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<td>189</td>
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<td></td>
</tr>
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<td>MeO₂C</td>
<td>190</td>
<td>(dr &gt; 20:1)</td>
</tr>
<tr>
<td></td>
<td>191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TsN</td>
<td>TsN</td>
<td>92d</td>
</tr>
<tr>
<td></td>
<td>146</td>
<td>147</td>
<td></td>
</tr>
</tbody>
</table>

a All reactions were performed using substrate concentration of 0.1 M with 5 mol% Et₃SiH, 15 mol% CyNH₂. b 7.5 mol% alkyne-cobalt complex. c 5 mol% alkyne-cobalt complex at 65 °C. d 10 mol% alkyne-cobalt complex.

Krafft⁵⁷ has reported a modification of the above procedure in which the reduction step is not needed. They carried out the Pauson-Khand reaction of a dicobalt hexacarbonyl complex of an enyne under a carbon monoxide atmosphere which generated the appropriate catalyst thus making the reduction step unnecessary. Although it may not always be practical, one can envision using a catalytic amount of the dicobalthexacarbonyl complex of the actual substrate of interest. Scheme 51 illustrates this concept.
**New Substrates for PKR**

![Chemical structures and reactions](image)

**Scheme 51**

**Table 12. Comparative PKR of enyne 59 catalysed by DCHC 60 or 89**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (%)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Co(_2)(CO)_8</td>
<td>10</td>
<td>65</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>10</td>
<td>70</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
<td>10</td>
<td>70</td>
<td>2</td>
<td>78</td>
</tr>
</tbody>
</table>

The yield of bicycle when the dicobalt hexacarbonyl complex of the substrate enyne 60 is used as the catalyst is 79% (entry 2), whereas the yield is 78% when the dicobalt hexacarbonyl complex of the nitrogen containing enyne 89 is used (entry 3). Another point worth noting is that the yield of the reaction when Co\(_2\)(CO)_8 is used is 80% (entry 1), hence these conditions do not improve the use of commercial dicobalt octacarbonyl. Advantages of this method over using commercial dicobalt octacarbonyl are (i) these complexes are air stable whereas dicobalt octacarbonyl is air sensitive and, (ii) reaction with dicobalt hexacarbonyl complexes goes to completion much faster than with dicobalt octacarbonyl, in most cases.

The range of substrates that undergo cyclisation under these conditions is the same as that reported by Livinghouse\(^5^6\). Yields of the reactions are also comparable. Again in the
presence of cyclohexylamine, the reaction proceeded in higher yields in some cases, however the outcome of adding CyNH₂ is unpredictable.⁵⁷

1.4.3 Photochemical catalytic Pauson-Khand reaction

Pagenkopf and Livinghouse⁵⁸ published a practical procedure for intramolecular photochemical catalytic Pauson-Khand reaction. They reported that high intensity visible light effectively promoted catalytic Pauson-Khand reaction at 50-55 °C and at 1 atmosphere of CO pressure. It was postulated that high intensity visible light might cause CO dissociation from the dicobalt hexacarbonyl complex of the enyne and therefore create a vacancy for the incoming alkene complexation. They stressed the importance of using high purity Co₂(CO)₈, the choice of an appropriate light source as well as reaction temperature in the range of 50-55 °C for successful catalytic reaction. Of the various solvents that were examined, 1,2-DME gave the best conversions.

In general carbonylative cyclisation of enynes (0.1M in degassed 1,2-DME) could be effected by stirring in the presence of 5 mol% of Co₂(CO)₈ under 1 atm of CO pressure at 50-55 °C with “Q beam irradiation” for 12 hours. A 10⁶ candlepower spotlight was also shown to be effective. Studies showed that tosylamides (Table 13, entry 1), terminal alkynes (Table 13, entry 2), free hydroxyl moieties (Table 13, entry 3), and ethers (Table 13, entry 4) were compatible with these reaction conditions. Yields obtained were between 67-95%.
Table 13. Catalytic Pauson-Khand Photocyclisations under 1 atm of CO

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsN</td>
<td>TsN</td>
<td>90a</td>
</tr>
<tr>
<td>2</td>
<td>EtO₂C</td>
<td>EtO₂C</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>MeO, HO</td>
<td>MeO, HO</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>MeO, MeO</td>
<td>MeO, MeO</td>
<td>67b</td>
</tr>
</tbody>
</table>

*Ratio of diastereomers = 1.1:1.0. 12.5 mol% Co₂(CO)₈ was used.

In a direct comparison between the thermal and photochemically promoted reactions, Livinghouse found the photochemically promoted catalytic Pauson-Khand reaction to be slightly more efficient as shown in Scheme 52 for enyne 59.

\[
\text{EtO}_2\text{C} \quad \text{EtO}_2\text{C} \quad \text{EtO}_2\text{C} \\
\quad \quad \quad \quad \quad \quad \underset{5 \text{ mol\% Co}_2(\text{CO})_8}{\rightarrow} \quad \text{EtO}_2\text{C} \\
\text{CO (1 atm), 1,2-DME} \quad \text{EtO}_2\text{C} \\
\]

Scheme 52

Photochemical 95%
Thermal 83%
1.4.4 Use of complexes of other metals

The use of alternative metals has been most effective in the development of a catalytic version of Pauson-Khand reaction and a brief overview follows.

Buchwald\textsuperscript{59} has reported a catalytic transformation of enynes to iminocyclopentenes employing triisopropylsilyl cyanide and a Ni(0) complex generated \textit{in situ} from Ni(cod\textsubscript{2}) and a bulky bikenimine ligand. Acidic hydrolysis of iminocyclopentenes led to bicyclic enones. This method is tolerant of esters, ketones, nitriles, ethers and amines and an example is shown in Scheme 53.

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {O};
\node (2) at (2,0) {Ph};
\node (3) at (4,0) {O};
\node (4) at (6,0) {Ph};
\node (5) at (2,-2) {200};
\node (6) at (4,-2) {60\%};
\node (7) at (2,-4) {Ph};
\node (8) at (3,-4) {N};
\node (9) at (4,-4) {N};
\node (10) at (5,-4) {Ph};
\node (11) at (2,-6) {L\textsubscript{2} = \text{---N---N---} Ph Ph};
\node (12) at (4,-6) {Ph};
\node (13) at (6,-6) {Ph};
\node (14) at (0,-0.5) {i) TIPSCN, 5 mol\% Ni(cod\textsubscript{2}/L\textsubscript{2} \rightarrow O};
\node (15) at (2,-0.5) {Ph DMF, 110 \degree C, 24 h};
\node (16) at (4,-0.5) {O};
\node (17) at (6,-0.5) {Ph};
\node (18) at (2,-2) {ii) H\textsubscript{3}O\textsuperscript{+}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 53}

Buchwald\textsuperscript{60} has also reported a catalytic Pauson-Khand reaction equivalent that utilises a titanocene as the catalytic species to promote cycloaddition between an enyne and an isocyanide. The resulting bicyclic iminocyclopentene is hydrolysed directly to the cyclopentenone. Cp\textsubscript{2}Ti(PMe\textsubscript{3})\textsubscript{2} was used as an air and moisture stable inexpensive titanocene source. The combination of Cp\textsubscript{2}TiCl\textsubscript{2} and 2 equivalents of EtMgBr (or n-BuLi) also functioned as \textit{in situ}-generated titanocene equivalent. It was found that 10 mol\% of Cp\textsubscript{2}Ti(PMe\textsubscript{3})\textsubscript{2}, under the conditions shown in Scheme 54, would convert enynes of type 202 and a slight excess of trialkylsilyl cyanide to the corresponding iminocyclopentene of type 203. Mild hydrolysis then afforded bicyclic cyclopentenone of type 204. Trialkylsilyl cyanides Me\textsubscript{3}SiCN, \textsuperscript{1}BuMe\textsubscript{2}SiCN and Et\textsubscript{3}SiCN all displayed similar activity.
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Scheme 54

For sterically hindered enynes, more than 10 mol% of catalyst was required for complete conversion. This effect was postulated by the authors to be steric in nature as binding to the titanocene species is more difficult. The cyclisation reaction successfully forms both 5,5- and 5,6-fused ring compounds and tolerates the presence of ethers, nitrogen containing compounds and esters. Yields range from 42-80%.

Jeong and co-workers developed the first rhodium(I) catalysed Pauson-Khand reaction. Of the various Rh catalysts tested, trans-[RhCl(CO)(dppp)]2 gave the best results. A typical reaction protocol involved treatment of enyne with 2.5 mol% of catalyst in toluene at reflux for 24 h under 1 atm of CO. A few examples are illustrated in Table 14. Internal alkynes (entries 1 & 2) performed better than the terminal alkyne (entry 3). While alkyl and aryl substituted alkynes 116 and 205 (entries 1 & 2 respectively) provided excellent chemical yields of products, trimethylsilyl-substituted alkyne 207 (entry 4) remained inert under the conditions described above. Oxygen and nitrogen containing enynes 200 and 209 (entries 5 & 6 respectively) also gave good yields in this reaction as shown in Table 14.
Table 14. trans-[RhCl(CO)(dppp)]$_2$ catalysed intramolecular PKRs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EtO$_2$C</td>
<td>117</td>
</tr>
<tr>
<td>2</td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>Ph</td>
<td>205</td>
</tr>
<tr>
<td></td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>206</td>
</tr>
<tr>
<td>3</td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>H</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EtO$_2$C</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>EtO$_2$C</td>
<td>TMS</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TMS</td>
<td>TMS</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>208</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td>201</td>
</tr>
<tr>
<td>6</td>
<td>TsN</td>
<td>TsN</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>Ph</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TsN</td>
<td>210</td>
</tr>
</tbody>
</table>

Narasaka$^{62}$ has reported that [RhCl(CO)$_2$]$_2$ serves as a catalyst of the intra- and intermolecular Pauson-Khand reaction. [RhCl(CO)$_2$]$_2$ served as a catalyst for the intramolecular cycloaddition reaction of 1,6- and 1,7-enynes which were converted to cyclopentenone under 1 atm of CO (Scheme 55).
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**Scheme 55**

Intermolecular reaction of ethylene 22 with 1-phenylprop-1-yn 172 was also reported (Scheme 56).

**Scheme 56**

Several advantages of using this catalyst were reported including the use of low CO pressure, using electron deficient alkenes as well as electron deficient alkynes in the enyne moiety.

Mitsudo\textsuperscript{63} reported the first example of employing ruthenium in catalytic Pauson-Khand reaction. A typical procedure involves heating 5 mol\% of Ru$_3$(CO)$_{12}$ and an enyne in $N,N$-dimethylacetamide at 140 °C under 15 atm of CO. Yields of reactions varied from 41%-89%. The reaction of enynes with an alkyl group either at the internal or external carbon of the olefinic moiety also proceeded to give the corresponding bicyclic cyclopentenones exclusively. Trimethylsilyl substituted enyne 207, which gave the
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desilylated product in the titanocene-catalysed reaction of enynes with silylcyanide, also gave the corresponding silylated product 208 in 85% yield as shown in Scheme 57.

![Scheme 57](image)

1.5 Natural product synthesis using the Pauson-Khand reaction

There has been a dramatic increase in the use of the Pauson-Khand reaction for the synthesis of numerous natural products. The cyclopentane ring is quite common in nature and the Pauson-Khand adducts are easily functionalised. Hence this reaction has been employed in various syntheses of natural products. These include the synthesis of prostaglandins, different triquinanes and polyquinanes like ceratopicanol\(^6\), kainic acid\(^6\), hirsutene\(^6\), epoxydictymine\(^6\), xestobergsterol\(^6\), spatan\(^6\), dendrobin\(^7\), hydroxymethylacylfulvene (HMAF)\(^7\), nortaylorione\(^7\) and \(\beta\)-cuparenone\(^7\).

Some recent examples are briefly discussed below.

Krafft\(^7\) has reported the total synthesis of a sesquiterpene, asteriscanolide 219. The synthesis is based on a regioselective Pauson-Khand reaction of 220 with propene 221 (Scheme 58). The formation of the cyclooctane ring is achieved in the final stages by means of a ring closing metathesis reaction.
The intramolecular variant of the Pauson-Khand cycloaddition has been particularly useful in the rapid synthesis of complex fused tricycles such as dendrobine. (-)-Dendrobine 223 is an alkaloid that exhibits antipyretic and hypotensive activity and has attracted much attention as a synthetic target. Cassayre and Zard\textsuperscript{70,71} completed an asymmetric synthesis of (-)-dendrobine, setting the stereochemical features of the tricycle with the Pauson-Khand cycloaddition of enyne 224. This step is shown in Scheme 59.

Scheme 58
Mukai has effected a total synthesis of 8α-hydroxystreptazolone in which the key step is an intramolecular Pauson-Khand reaction carried out on a 2-oxazolone derivative (Scheme 60). This implies the use of an enamine as the olefinic part of the reaction. The Pauson-Khand reaction is accomplished in a highly stereoselective manner in 51% yield as shown in Scheme 60. This compound is a natural product possessing antifungal and antibiotic properties.
Synthesis of monocyclic cyclopentenones can suffer from lack of regioselectivity. In their 1996 synthesis of monocyclic \( \beta \)-cuparenone 230, Moyano and Pericas\(^74\) avoided this problem by use of a removable sulfur tether to transform the reaction to the more predictable intramolecular variant. By utilisation of a chiral auxiliary, they were able to effect the transformation asymmetrically in 56% yield (Scheme 61). Removal of the chiral auxiliary and reductive cleavage of the sulfide afforded the desired monocyclic product.
1.6 Aims of the project

1.6.1 Silicon-tethered enynes

Numerous intramolecular Pauson-Khand reactions are known in which the chain linking the alkene and alkyne partners contains a heteroatom. In almost all of these examples, the heteroatom (O, N or S) is in the 4-position (233 in Figure 4). A novel and potentially interesting modification would thus be investigation of substrates with a heteroatom linked directly to the alkene (234 in Figure 4).

The ease of formation and cleavage of silicon-oxygen and silicon-carbon bonds suggested that vinyl silyl ethers (235 in Figure 4) would be readily synthesised and that their Pauson-Khand reaction would yield bicyclic products. It was hoped that further transformations of these Pauson-Khand adducts would lead to a wide range of structures.
The initial aim of the project was to fully explore the scope of silicon-tethered Pauson-Khand reactions and various transformations of the cyclopentenone products.

1.6.1.1 Advantages of using silicon-tethered reactions

An important goal in modern organic synthesis is the development of reliable stereoselective, preferably enantioselective chemical reactions. Intramolecular reactions possess a high degree of stereoselectivity which the corresponding intermolecular versions often do not possess. A temporary silicon connection, usually ether, can transform an intermolecular reaction into an intramolecular one, by transiently connecting both partners through a silicon linkage such as in 236 (Scheme 62). This temporary connection endows the reaction with entropic advantages, by bringing the reacting ends of the molecule closer, as well as regiospecificity and often stereoselectivity.77
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**Intermolecular reaction**

\[ A + B \rightarrow A\cdot B \]

**Silicon tethered reaction**

\[ \text{LAH} \]

\[ \text{MeLi} \]

\[ \text{TBAF} \]

\[ \text{H}_2\text{O}_2, \text{KF} \]

\[ \text{RX, Pd, F}^- \]

The choice of silicon group as a tether is mainly attributed to the ease of formation of silicon derivatives as well as their inert behaviour under most reaction conditions. The crucial silicon link of 236 is generally created by a simple silylation of a hydroxy group by a commercially available chlorosilane. Another incentive for using a silicon tether is the variety of products that can be obtained by further reaction of silacycle 237 as shown in Scheme 62. Silacycle 237 can be reduced using lithium aluminium hydride (LAH) to obtain a hydrosilane 238. Organometallic reagents like methyllithium will cleave the silacycle 237 to provide the trimethylsilyl alcohol 239. Tetra-n-butylammonium fluoride (TBAF) would reductively cleave the silacycle 237 and lead to the alcohol 240. Oxidative cleavage of silicon-carbon bond of silacycle 237, using Tamao oxidation conditions, would deliver diol 241 with retention of configuration. Palladium catalysed coupling of organosilanes with allyl, alkenyl and aryl halides and triflates has led to their use in carbon-carbon bond formation, as in the transformation of 237 to 242 (Scheme 62).
Use of a silicon tether has been applied to many different types of reaction including radical cyclisations, cycloadditions and nucleophilic additions. Use of a silicon tether in Diels-Alder reactions has been extensive. In contrast to the bimolecular case, intramolecular Diels-Alder reactions have the advantage of lower activation entropy because the two reacting components are already in proximity, resulting in favourable kinetics.

Stork and Sieburth have reported intramolecular Diels-Alder reactions of vinylsilanes by simply connecting dienols to vinylchlorosilanes. Thus the thermolysis (160-190 °C) of 245 results in the formation of silafuran 246, which can be transformed into alcohol 247, diol 248 or trimethylsilyl alcohol 249, in good overall yield as shown in Scheme 63. It is noteworthy that the overall formation of alcohol 247 from sorbyl alcohol 243 is equivalent to the use of ethylene as a dienophile, and that the steps in Scheme 63 can be consolidated into a single operation.
The disposable silyl substituent can influence the stereochemical outcome of this reaction. With the diene 243, a dimethylsilyl group yielded a 1:2 ratio of products in which the cis isomer was the major product (Scheme 64). Changing to a diphenylsilyl group gave a 1:1 ratio of products and the di-tert-butylsilyl group resulted in a trans/cis ratio of 4:1. Steric bulk around the silicon moiety thus tended to favour the trans product (Scheme 64).
These examples illustrate the various ways in which silicon tether can help control reactivity, regioselectivity and often stereoselectivity of various reactions.

1.6.1.2 Silicon tethered enynes as substrates for PKR

The initial goal of our research was to investigate the Pauson-Khand cyclisation of vinylsilyl enynes of the type 235 (Scheme 65). The cyclised silyl ether 252 may be converted to a diol 253 by Tamao oxidation, to an allylsilane 254 by ketone protection and addition of methyllithium, or to a desilylated alcohol 255, formally a product of a Pauson-Khand reaction with ethylene (Scheme 65).
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It was hoped that enynes 235a and 235b in Scheme 66 would be synthesised from silylation of propargyl alcohol 256 with commercially available silyl chlorides 244a and 244b. With these enynes in hand, formation of bicycles 252a and 252b would be optimised using various Pauson-Khand conditions. Further transformations of these bicycles would then be investigated as shown in Scheme 65 above.

\[
\begin{align*}
\text{Cl} & \quad \text{Si} \\
R & \quad R \\
\text{OH} & \quad \text{Et}_3\text{N} \\
\rightarrow & \quad \text{PKR} \\
\text{O} & \quad \text{Si} \\
R & \quad R \\
\text{R} & \quad \text{Si} \\
\end{align*}
\]

Scheme 66

Once optimum conditions for the Pauson-Khand cycloaddition have been found, variations in the substrates 235a and 235b would lead to conclusions about the scope and limitations of vinylsilyl enynes as substrates for Pauson-Khand reaction.

1.6.1.3 Precedent for using silicon tethered substrates in PKR

At the start of this project, there was only one report of using silicon tethered enynes as substrates in Pauson-Khand reaction, by Saigo and coworkers. They reported that attempted N-oxide promoted Pauson-Khand reaction of 3-sila-1,7-enynes led to a new cycloisomerisation reaction to give eight-membered cyclic dienylsilanes instead of bicyclic Pauson-Khand cycloadducts. During their initial studies on enyne 257, unexpected formation of dienylsilane 258 occurred instead of cyclopentenone derivative 259 (Scheme 67). Saigo has argued that this reaction, although unexpected at the time, is useful for the construction of eight-membered rings which are common in both natural and unnatural compounds.
Several examples demonstrate the generality and utility of the vinylsilane cycloisomerisation reaction, as illustrated in Table 15. Presence of a methyl substituent at the alkyne terminus is tolerated (entry 1) whereas a TMS substituent retarded the cycloisomerisation process. 1,7-Enynes that have a methyl substituent at the alkenyl moiety, (entry 2), also underwent cycloisomerisation. The enyne 264, where oxygen is replaced with a carbon (entry 3), also yielded cyclooctadiene 265.
Table 15. Cycloisomerisation reaction of 1,7-enynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O Ph Si Ph</td>
<td>O Ph Si Ph E/Z = 3:2</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>260</td>
</tr>
<tr>
<td>2</td>
<td>O Ph Si Ph</td>
<td>O Ph Si Ph</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>262</td>
</tr>
<tr>
<td>3</td>
<td>Ph Si Ph</td>
<td>Ph Si Ph</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>264</td>
</tr>
</tbody>
</table>

Neither the homologous 1,6-enyne (235b in Figure 5) nor 1,8-enyne (266 in Figure 5) underwent cycloisomerisation. In the reaction of allyl(propargyloxy)silane (267 in Figure 5), no cycloisomerised product was detected. In this case only decomposition of starting material occurred. This shows that this cycloisomerisation reaction is peculiar to 3-sila-1,7-enynes.

![Figure 5](image)

Both the mechanism of this transformation as well as the reasons for the mechanistic divergence are unclear. A possible explanation by Saigo involves the insertion of alkene into the distal C-Co bond, rather than proximal bond, leading to a key intermediate 269.
that can be converted to the observed product by successive β-hydride abstraction, reductive elimination and decomplexation (Scheme 68).

Substitution of carbons in the tether with heteroatoms such as nitrogen and oxygen leads to the expected Pauson-Khand cycloadducts.

During the course of our research, Pagenkopf reported the use of vinylsilane derived enynes and Brummond reported the use of silicon tethered allenes as substrates for Pauson-Khand reaction respectively. Their work will be discussed in chapter 2.

1.6.2 Silyl enol ethers as substrates in PKR

As the project developed, we decided to investigate silyl enol ethers of type (Scheme 69) as substrates for the Pauson-Khand reaction.

There are a few examples in the literature where alkyl enol ethers have been used in Pauson-Khand reaction, however silyl enol ethers of type have not been investigated as substrates for intramolecular Pauson-Khand reaction.
Pauson-Khand reaction of silyl enol ethers would lead to bicyclic cyclopentenones with β-OH functionality in the resulting cyclopentenone ring, after the removal of the silyl group. This would be useful for further manipulation of the bicycle and may prove useful in the synthesis of several natural products.

Initially, we decided to synthesise two substrates, 272a and 272b, to find the optimum reaction conditions for cyclisation.

We then hoped to synthesise substrates with varying substituents on both the alkene and the alkyne moiety to define the scope and limitations of using silyl enol ethers as substrates for Pauson-Khand reaction.
2. Results and Discussion

2.1 Vinylsilane-derived enynes as substrates for the Pauson-Khand reaction

2.1.1 Synthesis of Substrates

The initial goal of the research was to investigate the Pauson-Khand cyclisation of silicon tethered enynes 235a and 235b (Scheme 70).

Enynes 235a and 235b were synthesised from the commercially available starting materials propargyl alcohol 256 and chlorosilanes, chlorodimethylvinylsilane 244a and chlorodiphenylvinylsilane 244b using a literature procedure as shown in Scheme 71. The synthesis of dimethyl enyne 235a proceeded in low yield (8%), due to its volatility.

The synthesis of diphenyl enyne 235b proceeded with ease. The purification of this enyne by flash column chromatography using silica led to complete decomposition. Use of deactivated grade III alumina as solid support led to decomposition of the enyne 235b into diphenylvinylsilanol 273, which was characterised, and presumably propargyl
alcohol 256 (Scheme 72). Enyne 235b could however be purified by flash column chromatography on Florisil®, which is neutral, and led to 73% yield. We selected enyne 235b, for our preliminary cyclisation studies. It was used crude.

We decided to synthesise a literature substrate, diethyl allylpropargylmalonate 59, known to undergo Pauson-Khand cyclisation reaction along with our silicon tethered enyne 235b, so that the reactivities of both substrates could be compared under the same cyclisation conditions. Enyne 59 was synthesised using literature procedures and is illustrated in Scheme 73. Commercially available diethyl malonate 274 was deprotonated with sodium ethoxide and then propargylated using propargyl bromide 275 yielding diethyl propargylmalonate 276a in 45% yield. A side product of the reaction was diethyl dipropargylmalonate 277a which was isolated as a white crystalline solid in 12% yield. Allylation of diethyl propargylmalonate 276a using potassium carbonate as base and allylbromide 278 as the alkylation agent yielded the desired enyne 59 in 59% yield.
2.1.2 **Pauson-Khand reactions of silicon-tethered enyne 235b and malonate-derived enyne 59**

Initially we decided to synthesise and isolate dicobalt hexacarbonyl complexes 279 from 235b and 60 from 59 (Scheme 74). It was hoped that isolation of these complexes would lead to rapid studies on the PKR of these two substrates under various conditions, and hence lead to optimisation of reaction conditions. Once the optimum conditions were found, we hoped to synthesise a series of substrates to analyse the scope and limitations of the Pauson-Khand reaction of silicon-tethered enynes.

Dicobalt hexacarbonyl complexes 279 and 60 were synthesised by stirring the substrate with approximately 1.2 equivalents of dicobalt octacarbonyl in a hydrocarbon or ethereal solvent at room temperature for 1.5 hours under nitrogen atmosphere as shown in Scheme 74.
Purification of the dicobalt hexacarbonyl complex 279 of silicon-tethered enyne 235b by flash column chromatography proved to be very difficult as the signals in the $^1$H NMR spectrum were very broad, presumably due to the presence of paramagnetic cobalt species, and hence were very difficult to interpret. The dicobalt hexacarbonyl complex 279 was isolated only once by flash column chromatography using silica as solid support. Hexane was first used to remove inorganic cobalt impurities and then solvent of increasing polarity (1-50% ether in hexane) was used to obtain the desired complex 279 in 46% yield. Although the signals in the $^1$H NMR spectrum were still broad, it showed that the terminal alkyne H in the complex 279 shifted downfield to 5.89 ppm from 2.39 ppm in the starting enyne 235b. However this desired complex 279 proved to be thermally unstable. The deep red oil decomposed to a black solid on rotary evaporator at ca. 40 °C.

Due to the above mentioned difficulties in the isolation of complex 279, we decided to synthesise it in situ, by stirring enyne 235b and dicobalt octacarbonyl in a suitable solvent at room temperature under nitrogen. The crude complex was then subjected to Pauson-Khand cycloaddition conditions.
The dicobalt hexacarbonyl complex 60 of literature substrate 59 was also synthesised in situ and subjected to Pauson-Khand reaction without further purification. The PKR of substrates 235b and 59 was expected to yield Pauson-Khand adducts 252b and 61 respectively (Scheme 75).

Scheme 75

The results of Pauson-Khand studies for both the substrates 235b and 59 are shown in Table 16.

Table 16. Pauson-Khand reactions of enynes 235b and 59

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%) 252b</th>
<th>Yield (%) 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, reflux, N₂</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Toluene, reflux, CO&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN, 75 °C, N₂</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN, 75 °C, CO&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Degassed Hexane, 70 °C, CO&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>1:3 (w/v) 1,4-dioxane, 2M NH₄OH, 100 °C</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>NMO, CH₂Cl₂, rt, N₂</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>nBuSMe, 1,2-DCE, 83 °C</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>9</td>
<td>SiO₂, 50 °C, Air</td>
<td>0</td>
<td>55</td>
</tr>
</tbody>
</table>

<sup>a</sup> Co<sub>2</sub>(CO)<sub>8</sub> weighed under N₂ in a glove bag. <sup>b</sup> Pressure tube.
The crude dicobalt hexacarbonyl complexes 235b and 60 were subjected, in parallel, to various different literature conditions for Pauson-Khand reactions. This included both thermal promotion of the reaction as well as use of various promoters.

Reasonable yields of the bicycle 61 were obtained from literature substrate 59, however the silicon-tethered substrate 235b did not yield any of the desired cyclopentenone 252b under all the conditions tested (Table 16). Due to the presence of paramagnetic cobalt impurities in the crude reaction mixtures, peaks in the $^1$H NMR spectra were very broad and could not be interpreted. Hence it was necessary to carry out flash column chromatography on crude reaction mixtures to remove these impurities before obtaining any spectroscopic data. The mass recovery was very poor and samples were not clean enough to draw concrete conclusions about the course of the reactions. However cleavage of Si-O bond appeared to be occurring with loss of the silicon tether. Due to the inability to obtain $^1$H NMR spectra of the crude reaction mixtures, it was impossible to say whether the Pauson-Khand reaction was not taking place in the first instance and/or the starting material was decomposing during the course of the reaction. Formation of the product and its decomposition upon purification by flash column chromatography was another possibility.

As can be seen from Table 16 several literature conditions including thermal promotion (entries 1 & 3$^{91}$) as well as use of promoters such as amines$^{28}$ (entry 6) N-methylmorpholine oxide$^{25}$ (entry 7) and n-butyl methyl sulfide$^{29}$ (entry 8) were investigated, however none of the conditions tested yielded any desired product. Flash chromatography of the crude reaction mixtures, using silica, alumina as well as Florisil®, did not lead to any conclusions about the course of these reactions as mixtures of unidentifiable products were obtained. However in some cases cleavage of silicon tether appeared to be occurring. Use of anhydrous conditions, (as dicobalt octacarbonyl is air and moisture sensitive) where dicobalt octacarbonyl was weighed under N$_2$ in a glove bag (entries 2, 3 & 4), use of CO pressure in a pressure tube (entries 2, 4 & 5) and use of degassed hexane (entry 5) also did not lead to isolation of the desired bicycle.
2.1.3 Pagenkopf's results

At this stage of our research, Pagenkopf\textsuperscript{85,86} published work on the Pauson-Khand reaction of vinylsilane derived enynes. Their results showed that carbons bound to the silicon tether were reduced during the course of this reaction.\textsuperscript{85}

In the initial experiments to identify the optimum conditions for their model substrate 280, several variants of Pauson-Khand reaction were tried. None led to the desired cyclopentenone 282, but instead metal decomplexation, hydrolysis of the silyl ether and/or decomposition occurred\textsuperscript{85}. However in refluxing acetonitrile containing 1\% H\textsubscript{2}O the dicobalt hexacarbonyl complex of 280 was converted to enone 281 in 62\% yield (Scheme 76). The use of anhydrous acetonitrile (conditions we had tried) had a deleterious effect on the efficiency of the reaction and led to lowering the yields reported in Table 17 by 30-65\%.

![Scheme 76](image)

A variety of substrates with varying substituents in alkynyl and propargylic positions were subjected to the above mentioned conditions to test the generality of this new reaction. Some of the results are shown in Table 17.
Table 17. Pagenkopf’s PKR of vinylsilane-derived enynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product &amp; additives</th>
<th>1% H$_2$O</th>
<th>1% D$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph — H</td>
<td>H</td>
<td>284, 45%</td>
<td>71% D</td>
</tr>
<tr>
<td></td>
<td>Me Si —</td>
<td>Me</td>
<td></td>
<td>D18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td>285, 8%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph — Ph</td>
<td>Ph</td>
<td>215, 74%</td>
<td>72% D</td>
</tr>
<tr>
<td></td>
<td>Me Si —</td>
<td>Me</td>
<td></td>
<td>D54% D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D</td>
<td>287, 56%</td>
<td>D28%</td>
</tr>
<tr>
<td>3</td>
<td>Ph — nPr</td>
<td>nPr</td>
<td>290, 65%</td>
<td>73% D</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td></td>
<td>nPr</td>
</tr>
<tr>
<td></td>
<td>R Si — R</td>
<td>R</td>
<td>290, 69%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td>291, 49%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>tBu — nPr</td>
<td>tBu</td>
<td>293, 65%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me Si —</td>
<td>Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td>294, 37%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>tBu — nPr</td>
<td>tBu</td>
<td>295, 37%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph Si — Ph</td>
<td>Ph</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Terminal alkynes participate in this reaction albeit with longer reaction times, 24 h in this case (entry 1). Enynes without substitution at the propargylic position (entry 2) also undergo this reaction and both the dimethyl and diphenyl silyl tethers behave in a similar fashion (entry 3). The reaction of pivaldehyde derived enynes 292 and 294 (entries 4 & 5) were anomalous in that no reduction at the propargylic position occurred in these substrates. Bicyclic enones were not observed in any of the above cases. Deuterium labelling was also carried out (Table 17, entries 1, 2 & 3) to study the mechanism of this reaction.

The enone products in Table 17 are formally the result of an intermolecular Pauson-Khand reaction of an alkyne with ethylene gas. Pagenkopf argues that this new method is superior to the reaction with ethylene for two main reasons; (i) the reaction does not require high pressures or special equipment and (ii) the use of traceless tether circumvents the regiochemical ambiguity observed in the carbonyl insertion when ethylene is used.

Pagenkopf has proposed a mechanistic hypothesis for this reductive Pauson-Khand reaction of the vinylsilane derived enynes based on deuterium labelling studies and products observed under dry conditions.

While Lewis acid mediated cleavage of the silicon-carbon bond may be expected with the enones of type 282 (Scheme 76), reduction of the carbon-oxygen bond indicates a more complicated mechanism. Simple deuterium labelling studies indicated that the two new enone hydrogens originated from water present in the nitrile solvent at the onset of the reaction and not from the aqueous work up or the nitrile. Given the high pressures required to effect the intermolecular Pauson-Khand reaction with ethylene, tether loss likely occurred after the first carbon-carbon bond forming step in a Magnus like mechanism. A mechanistic hypothesis proposed by Pagenkopf for this reductive Pauson-Khand reaction is depicted in Scheme 77.
NEW SUBSTRATES FOR PKR

RESULTS AND DISCUSSION

Scheme 77
Pagenkopf argued that although no bicyclic enones of type 296 were detected in the course of these investigations, invoking their formation and subsequent demise led to formulation of a reasonable reaction mechanism. According to Pagenkopf, facile desilylation of 296 led to the resonance stabilised enolate 297. Both ring strain and coordination by a cobalt carbonyl species were considered to facilitate loss of silicon. Carbon-oxygen bond cleavage and departure of the neutral tether remnants as polysiloxane can be envisaged to occur in a stepwise manner giving the trimethylene methane-like intermediate 298, followed by reduction to the cobalt(II)enolate 299a. Alternatively, donation of a second electron from cobalt into the enone π system of 297, likely generating an anion radical, subsequent loss of siloxane and transfer of a second electron leads to the same intermediate 299. Invocation of the dianionic intermediate 299 can be circumvented simply by enolate protonation prior to siloxane loss. In either case, the formation of a blue-green precipitate during the course of the reaction is consistent with cobalt serving as the reducing agent. Fissure of the carbon-oxygen bond did not occur with the pivaldehyde derived enynes 292 and 294 in Table 17, and the silanol 295 was characterised by x-ray crystallography. For the carbon-oxygen bond cleavage to occur in this case the already severe A(1,3) strain between the 'Bu group and the "Pr C(2) side chain would be exacerbated as the allylic carbon becomes trigonal planar.

At the temperature of refluxing acetonitrile, dienolate tautomerisation by [1,5]-H sigmatropic rearrangements is a viable alternative to intermolecular proton exchange, which did not seem to be occurring in light of the crossover experiments shown in Scheme 78. Spiking the reaction of enyne 288 with 1 equivalent of enone 215 showed that significant intermolecular exchange was not occurring (Scheme 78). The [1,5]-H sigmatropic rearrangement can account for deuterium incorporation at C(2) of enone 285 and C(5) of all the deuterium labelled enones in Table 17 (285, 287 & 291). The enol tautomers may also be subject to [1,5]-H sigmatropic rearrangement.
Obtention of new products along with the expected cyclopentenones under anhydrous conditions was also cited as support for the proposed mechanism. Under anhydrous conditions, interesting new products were obtained along with a decrease in the yield of expected cyclopentenone products. As shown in Scheme 79, in dry acetonitrile or propionitrile the benzaldehyde derived enynes 288 and 289 provided the solvent incorporated enones, 302a and 302b. Solvent inclusion occurred with either dimethyl or diphenyl substitution at silicon.
NEW SUBSTRATES FOR PKR

RESULTS AND DISCUSSION

Scheme 79

The reaction of enyne 286 provided the expected enone 215 (21%) and the new tricyclic enone 303 (27%) as shown in Scheme 80. Enone 303 appeared to have originated from an intermolecular Diels-Alder reaction of dienone 304.

Scheme 80

Further elaboration of the proposed mechanism described in Scheme 77 was used to rationalise the products generated under anhydrous conditions. Nitriles are excellent ligands for various transition metals, and cobalt complexes are particularly effective at activating nitriles to nucleophilic attack. This enhanced nitrile electrophilicity resulting from cobalt coordination may lead to an intramolecular alkylation proceeding through a six-membered transition state (306) as shown in Scheme 81. The enyne 288 which provided appreciable amounts of the nitrile alkylation products showed the highest amount of deuterium incorporation at C(5) in labelling experiments (Table 17, entry 3).
Formation of the Diels-Alder adduct 303 required cyclopentenone oxidation to the dienone 304. A [1,3]-hydride shift to the exocyclic cation in the zwiterionic intermediate 298b would lead to 304. Interestingly only enyne 286 generated appreciable amounts of Diels-Alder product and this was attributed to the formation of a
comparatively unstable carbocation (298, R = H). Alternatively it was proposed that a proton transfer from 299b to form an η⁵-CpCo complex such as 305 would also lead to requisite dienone oxidation state.

In conclusion, it was reported that the reductive PKR of tethered vinyl silanes proceeds as usual to the bicyclopentenones, however rapid loss of allylic silane initiates a fragmentation process culminating in reduction of the propargylic carbon. In the absence of protic solvent, the reactive intermediates can attack the nitrile solvent or undergo Diels-Alder dimerisation.
2.1.4 Pauson-Khand reaction of enyne 235b

After Pagenkopf's results were published we decided to subject our silicon tethered substrate 235b to Pagenkopf's cyclisation conditions. As can be seen from Scheme 82, 3-methylcyclopent-1-enone 307 was obtained in 8% yield. Low yield of this product is attributed in part to its volatile nature. With hindsight, this product could be observed in some unclean fractions obtained after flash column chromatography of reactions we investigated and which are listed in Table 16. However it was never isolated or characterised due to contamination from other decomposition products.

\[
\text{O} \quad \text{Si} \quad \text{Ph} \\
\text{Ph} \quad \text{CH}_3\text{CN, 1% H}_2\text{O} \quad \text{reflux} \quad 8\% \\
235b \\
307
\]

Scheme 82

In order to test the reproducibility of Pagenkopf's work we synthesised enyne 286 (60% yield) and subjected it to Pagenkopf's reaction conditions (Scheme 83). Cyclopentenone 215 was obtained in 63% yield which was comparable to yield reported by Pagenkopf (74%).

\[
\text{O} \quad \text{Si} \quad \text{Ph} \\
\text{CH}_3\text{CN, 1% H}_2\text{O} \quad \text{reflux} \quad 63\% \\
286 \\
215
\]

Scheme 83
2.1.5 Brummond’s silicon-tethered allenic Pauson-Khand reaction

At the same time as Pagenkopf’s above mentioned results, Brummond\textsuperscript{87} reported the results of a silicon-tethered allenic Pauson-Khand type reaction where normal bicyclic cyclopentenones were obtained. Their attempts to effect the Pauson-Khand cyclisation of cobalt complexes of silyl ethers of type 308 did not yield any cycloadducts (Scheme 84). PKR’s of these silyl ethers either led to decomplexation or decomposition.\textsuperscript{87}

\begin{equation}
\begin{array}{c}
\text{PKR} \\
\text{X >}
\end{array}
\end{equation}

\begin{align*}
\text{R} & = \text{Me} \\
\text{R} & = \text{Ph} \\
\text{R} & = \text{iBu}
\end{align*}

Scheme 84

Replacement of the alkene moiety with an allene did give a Pauson-Khand cycloadduct (presumably due to the increased reactivity of the allene) but in consistently low yields (Scheme 85). This was partly attributed to the instability of the substrate 310 due to Si-O bond.\textsuperscript{87}

\begin{equation}
\begin{array}{c}
\text{Ph} \\
\text{Si} \\
\text{O}
\end{array}
\text{Mo(CO)}_6, \text{DMSO}
\begin{array}{c}
\text{H} \\
\text{Ph} \\
\text{Si} \\
\text{O}
\end{array}
\end{equation}

\begin{align*}
\text{Ph} & = \text{Me} \\
\text{Ph} & = \text{Ph} \\
\text{Ph} & = \text{iBu}
\end{align*}

Scheme 85

Replacement of the silyl ether tether with a silyl carbon tether resolved the instability problem. Allene-containing substrates such as 310 underwent Pauson-Khand type
cyclisations to give bicycles 311 and 312, with the selectivity between the two products dependent on the conditions used (Scheme 86).  

\[ \text{Si Ph} \mid \text{Ph Ph} \mid \text{Si Ph} \]

Condition A: 1.2 equiv. Mo(CO)$_6$, DMSO, toluene, 90 °C; Condition B: 5 mol% [Rh(CO)$_2$Cl]$_2$, CO (1 atm), toluene, 90 °C.

Scheme 86

Cyclisation using stoichiometric molybdenum hexacarbonyl gave the 5,5-fused product 311, whereas use of 5 mol% of a rhodium(I) complex under an atmosphere of carbon monoxide gave exclusively the 6,5-fused ring system 312. Mo(CO)$_6$ appears to be intolerant of substitution on the alkyne terminus unlike [Rh(CO)$_2$Cl]$_2$. As can be seen from Table 18, replacement of hydrogen on the alkyne terminus with a butyl (entry 2), trimethylsilyl (entry 3) or phenyl (entry 4) substituent led to no reaction using Mo(CO)$_6$. Substituting a longer alkyl chain on the allene (entry 5) gave only a 36% yield of cycloadduct 323. Alkynyl allene (entry 6) gave α-methylene cyclopentenone 326 in 48% yield. Use of 5 mol% [Rh(CO)$_2$Cl]$_2$ on all of the above mentioned substrates (except 325) gave moderate to good yields of 6,5 fused bicycles.
Table 18. Brummond’s silicon-tethered allenic PKR

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>R^1</th>
<th>5,5-product a Yield (%)</th>
<th>6,5-product b Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>310</td>
<td>H</td>
<td>CH₃</td>
<td>311, 64</td>
<td>312, 64</td>
</tr>
<tr>
<td>2</td>
<td>313</td>
<td>Bu</td>
<td>CH₃</td>
<td>314, 0</td>
<td>315, 75</td>
</tr>
<tr>
<td>3</td>
<td>316</td>
<td>TMS</td>
<td>CH₃</td>
<td>317, 0</td>
<td>318, 74</td>
</tr>
<tr>
<td>4</td>
<td>319</td>
<td>Ph</td>
<td>CH₃</td>
<td>320, 0</td>
<td>321, 51</td>
</tr>
<tr>
<td>5</td>
<td>322</td>
<td>H</td>
<td>C₅H₁₁</td>
<td>323, 36</td>
<td>324, 55</td>
</tr>
<tr>
<td>6</td>
<td>325</td>
<td>H</td>
<td>H</td>
<td>326, 48</td>
<td>-</td>
</tr>
</tbody>
</table>

a Conditions: 1.2 equiv. Mo(CO)₆, DMSO, toluene, 90 °C. b Conditions: 5 mol% [Rh(CO)₂Cl]₂, CO(l atm), toluene, 90 °C.
2.2 Allylsilane-derived enynes

In the light of the failure of vinylsilane derived enynes to undergo Pauson-Khand reaction and of Pagenkopf’s proposed mechanism\textsuperscript{85,86} for the reductive PKR of vinylsilane derived enynes, we decided to synthesise allylsilane-derived enynes as substrates for the Pauson-Khand reaction. It was expected that the extra carbon in the alkene chain would prevent the loss of the silicon tether, (section 2.1.3, Scheme 77, p. 95), and hence lead to bicyclic cyclopentenones of type 328 in Scheme 87.

\[
\begin{align*}
327a, \ X = \text{CH}_3 & \quad 328a, \ X = \text{CH}_3 \\
327b, \ X = \text{Ph} & \quad 328b, \ X = \text{Ph}
\end{align*}
\]

Scheme 87

2.2.1 Synthesis of substrate 327a

Due to the commercial availability of allylchlorodimethylsilane 330a, we decided to synthesise the allyldimethylsilane-derived enyne 327a and to carry out optimisation of PKR conditions on its dicobalt hexacarbonyl complex 331a rather than its diphenyl equivalent (Scheme 88). This was despite the potential instability of dimethylsiloxy derivatives and the associated problems of purification by flash column chromatography on silica. We hoped to establish the optimum set of conditions for cyclisation of enyne 327a to bicyclic cyclopentenone 328a and then subject a range of substrates, containing substituents offering different electronic and steric properties at the alkyne and alkene positions, to the optimised Pauson-Khand cyclisation conditions for these substrates.
Silylation of 3-phenyl-2-propyn-1-ol 329 using allylchlorodimethylsilane 330a in the presence of triethylamine in dichloromethane led to enyne 327a in 78% yield after purification by flash column chromatography using silica as solid support (Scheme 88). This was in stark contrast to vinylsilane-derived enyne 235b, which decomposed completely on silica (section 2.1.1, p. 86).

2.2.2 Pauson-Khand reaction of dimethylsilyl ether 327a

The dicobalt hexacarbonyl complex 331a of enyne 327a was synthesised by stirring the enyne 327a and dicobalt octacarbonyl in dichloromethane at room temperature (Scheme 88). The yield of the dicobalt hexacarbonyl complex 331a was dependent on the solid support used for purification. Purification using silica as solid support led to decomposition of the complex whereas purification using Florisil®, which is neutral, led to the desired complex in 89% yield. Complex 331a also decomposed on gentle warming therefore solvent was removed in vacuo at room temperature. The $^1$H NMR spectrum of dicobalt hexacarbonyl complex 331a, although broad, showed that the OCH$_2$ protons had shifted downfield from 4.55 ppm in the starting enyne 327a to 5.01 ppm in the dicobalt hexacarbonyl complex 331a.

The dicobalt hexacarbonyl complex 331a was subjected to a wide range of Pauson-Khand cyclisation conditions from literature and the results are shown in Table 19.
New Substrates for PKR

(OC)$_3$Co$\rightleftharpoons$Co(OC)$_3$

PKR

$\text{O}\quad\text{Ph}$

$\text{O}\quad\text{Si}$

$\text{Si}\quad\text{O}$

$\text{331a}$

$\text{328a}$

Scheme 89

Table 19. Pauson-Khand reactions of DCHC 331a

<table>
<thead>
<tr>
<th>Entry</th>
<th>PKR Conditions</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, reflux</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$CN, reflux</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$CN, 1% H$_2$O, reflux</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$O, CTAB, Celite, 70 °C</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3.5 eq CyNH$_2$, 1,2-DCE, reflux</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3.5 eq $n$BuSMe, 1,2-DCE, reflux</td>
<td>72</td>
</tr>
</tbody>
</table>

$^a$ Florisil$^b$ was used for purification by flash column chromatography.

As discussed in introduction, (section 1.3.1, p. 24), yields of Pauson-Khand reactions generally increase in polar solvents such as acetonitrile compared to toluene. However, heating the dicobalt hexacarbonyl complex 331a, to reflux in toluene and acetonitrile$^{91}$ gave comparable yields of the bicycle 328a, 40% and 39% respectively (entries 1 & 2). Pagenkopf’s cyclisation conditions$^{86}$ were also attempted in order to see if the yields of the PKR of allylsilane derived enynes, like vinylsilane derived enynes, improved under these conditions. Addition of 1% H$_2$O to the reaction mixture led to lowering of the yield from 39% to 33% (entry 3), however this may be due to the decomposition of the dicobalt hexacarbonyl complex 331a or the bicycle 328a in H$_2$O. Thermal Pauson-Khand reaction in H$_2$O$^{25}$ (entry 4) and amine promoted Pauson-Khand reaction$^{28}$ (entry 5) did not lead to the desired bicycle 328a. $^1$H NMR spectra of the fractions obtained after flash column chromatography showed that the decomplexation of cobalt was occurring and impure enyne 327a was recovered along with unidentifiable products. The sulfide promoted Pauson-Khand reaction$^{29}$ gave the best yield of 72% for the cyclisation of the dicobalt hexacarbonyl complex 331a to the bicyclic cyclopentenone.
328a (entry 6). As can be seen from Scheme 23 (section 1.3.4, p. 36), sulfide promoted PKR seems to be a milder method than the amine promoted PKR.

Although the dicobalt hexacarbonyl complex 331a undergoes Pauson-Khand reaction in moderate to good yields, several problems were encountered with the purification of the Pauson-Khand reactions described above. As discussed in the previous section, presence of paramagnetic cobalt impurities made the analysis of the crude reaction mixtures by $^1$H NMR impossible. The complete decomposition of the bicycle 328a on silica led to Florisil® being used as the solid support for flash column chromatography but the fractions from the column were spotted on silica plates which showed the decomposition products as well as the desired bicycle 328a. Also the degree of separation of impurities from the desired compound 328a on Florisil® was very poor and gradient elution was used to separate the product from other impurities.

We therefore decided to attempt to remove the silicon tether of the bicycle 328a by Tamao oxidation$^{81}$ to form the diol 332. It was hoped that once conditions for the cleavage of the silicon tether were established, the crude Pauson-Khand reaction mixtures would be subjected directly to these conditions, which would solve any purification problems posed by the presence of a silyl ether in the bicycle.

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{Si}
\end{array} & \begin{array}{c}
\text{Ph}
\end{array} & \begin{array}{c}
\text{O}
\end{array} & \begin{array}{c}
\text{O}
\end{array} & \begin{array}{c}
\text{Ph}
\end{array} & \begin{array}{c}
\text{O}
\end{array} & \begin{array}{c}
\text{Ph}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{328a} & \xrightleftharpoons[\text{50°C}]{} ^{30\%}\text{H}_2\text{O}_2, \text{KHCO}_3 \quad \xrightarrow{\text{KF,MeOH/THF}} \quad \text{332} \\
& \quad \text{15%} \\
& \text{crude 28%}
\end{align*}
\]

**Scheme 90**

Tamao oxidation$^{92}$ of bicycle 328a led to not only the expected diol 332 (15%) but also epoxydiol 333 in 28% crude yield. This was due to the presence of basic H$_2$O$_2$, which led to the epoxidation of the double bond present in the bicycle 328a along with the
cleavage of the silicon tether. All attempts to purify the epoxydiol 333 by flash column chromatography or by preparative tlc were unsuccessful.

Attempts at removal of the tether by tetra-n-butylammonium fluoride (TBAF) led to unidentifiable and inseparable mixtures of compounds.

Due to the instability of the model enyne 327a, dicobalt hexacarbonyl complex 331a as well as the bicycle 328a on silica and perhaps even to some of the Pauson-Khand reaction conditions, we decided to synthesise enyne 327b and to study its Pauson-Khand reaction. Diphenylsilyl derivatives are known to be more robust than their dimethyl equivalents and can be purified using silica.

2.2.3 Synthesis of diphenylsilyl ether 327b

The synthesis of allyldiphenyl(3-phenylprop-2-ynyloxy)silane 327b was not straightforward due to the lack of commercial availability of allylchlorodiphenylsilane 330b. We initially decided to synthesise allylchlorodiphenylsilane 330b by Grignard addition of allylmagnesium bromide 334 to dichlorodiphenylsilane 335 using a published procedure. The 'H NMR spectrum of the crude reaction mixture showed too many aromatic protons compared to protons of the alkene. Chlorosilane 330b could not be isolated or purified either by reduced pressure distillation or by flash column chromatography. We attributed this finding to the moisture and acid sensitive nature of allyldiphenylchlorosilane 330b. Addition of freshly prepared allylmagnesium bromide 334 to dichlorodiphenylsilane 335 did not lead to allyldiphenylchlorosilane 330b. The 'H NMR spectra in some cases contained small amounts of desired chlorosilane 330b, however it could not be isolated by reduced pressure distillation or by flash column chromatography.

We therefore decided to synthesise the desired enyne 327b in one-pot without any purification of allylchlorodiphenylsilane 330b. We first attempted to synthesise the enyne 327b using the sequence of reactions shown in Scheme 91.
Table 20. Conditions used for attempted synthesis of 327b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent for Grignard addition</th>
<th>Conditions for silylation of alcohol 329</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₃, rt₉³</td>
<td>Et₃N, CH₂Cl₂, 0 °C to rt₉⁴</td>
</tr>
<tr>
<td>2</td>
<td>THF, rt</td>
<td>Et₃N, THF, 0 °C to rt₉⁵</td>
</tr>
<tr>
<td>3</td>
<td>THF, -78 °C to rt</td>
<td>Imidazole, THF, reflux</td>
</tr>
<tr>
<td>4</td>
<td>THF, rt</td>
<td>NaH, THF, rt</td>
</tr>
<tr>
<td>5</td>
<td>THF, -78 °C to rt</td>
<td>Imidazole, DMF, rt</td>
</tr>
<tr>
<td>6</td>
<td>PhCH₃, rt</td>
<td>Et₃N, 10 % DMAP, CH₂Cl₂, 0 °C to rt</td>
</tr>
</tbody>
</table>

The desired enyne 327b could not be synthesised by any of the procedures listed in Table 20. Toluene and THF were tried as solvents to carry out the Grignard addition and several bases were tried for the silylation of the alcohol 329, however none gave the desired enyne 327b. (Conditions described in entry 1 gave the desired product in 6% irreproducible yield).

Carrying out the reaction with the silylation of alcohol 329 first followed by Grignard addition as described in Table 21 for Scheme 92 again did not yield any desired product 327b.
New Substrates for PKR

RESULTS AND DISCUSSION

Scheme 92

Table 21. Conditions used for attempted synthesis of 327b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions for silylation of alcohol 329</th>
<th>Conditions for Grignard addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N, THF, 0 °C to rt</td>
<td>THF, rt</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N, THF, reflux&lt;sup&gt;95&lt;/sup&gt;</td>
<td>THF, rt</td>
</tr>
</tbody>
</table>

Both of the conditions described in Table 21 did not lead to the desired enyne 327b.

Successful disilylation of alcohol 329 with dichlorodiphenylsilane 335 to synthesise compound 337 (Scheme 93)<sup>95</sup> showed that the Grignard addition in the above sequence of steps was not taking place effectively.

Scheme 93

We then decided to synthesise the chlorosilane<sup>96</sup> 330b from commercially available allyltrichlorosilane 338 and to use it crude without further purification in one pot using the sequence of steps indicated in Scheme 94.<sup>94,96</sup>
Two equivalents of phenylmagnesium bromide were added to a solution of allyltrichlorosilane 338 in ether at -78 °C. The resulting reaction mixture was stirred at -78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 hours. The resulting solution of allyldiphenylchlorosilane 330b was added dropwise to a solution of phenylpropargyl alcohol 329 and triethylamine in dichloromethane at 0 °C, then stirred at room temperature overnight. The desired enyne 327b was obtained in 50% yield over two steps. The 1H NMR spectrum of the crude enyne 327b showed mostly desired product, however the yield after purification was lower due to decomposition of the enyne 327b on silica. Nevertheless, silica was preferred for flash column chromatography to Florisil® due to better separation of the product from other impurities.

### 2.2.4 Pauson-Khand reaction of diphenylsilyl ether 327b

The dicobalt hexacarbonyl complex 331b of enyne 327b was synthesised by stirring the enyne 327b and dicobalt octacarbonyl in dichloromethane at room temperature (Scheme 95). The deep red dicobalt hexacarbonyl complex 331b could be purified by flash column chromatography using Florisil® in 93% overall yield. The 1H NMR spectrum of the dicobalt hexacarbonyl complex 331b again showed a downfield shift of the OCH2 protons to 5.12 ppm from 4.63 ppm in the starting enyne 327b.
The dicobalt hexacarbonyl complex 331b was then subjected to a wide range of Pauson-Khand cyclisation conditions. The Pauson-Khand reaction of dicobalt hexacarbonyl complex 331b yielded the bicycle 328b (Scheme 96) and results are summarised in Table 22.

Table 22. Pauson-Khand reactions of 331b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, reflux</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN, reflux</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN, 1% H₂O, reflux</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>NMO, CH₂Cl₂, rt</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>Toluene, 4Å Molecular Sieve powder, reflux</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Toluene, 4Å Molecular Sieve powder, NMO, rt</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>3.5 eq CyNH₂, 1,2-DCE, reflux</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Florisil®, 50 °C, Air</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Silica, 50 °C, Air</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>3.5 eq n-BuSMe, 1,2-DCE, reflux</td>
<td>70</td>
</tr>
</tbody>
</table>
Heating the dicobalt hexacarbonyl complex \textbf{331b} to reflux in toluene led to the bicycle \textbf{328b} in 28\% yield (Table 22, entry 1). The use of polar solvent acetonitrile\textsuperscript{91} led to an improvement in the yield to 35\% (Table 22, entry 2). A higher yield of 48\% for bicycle \textbf{328b} (Table 22, entry 3) was obtained when Pagenkopf’s conditions\textsuperscript{86} were used for PKR of dicobalt hexacarbonyl complex \textbf{331b}. Use of NMO\textsuperscript{25} for the promotion of PKR of dicobalt hexacarbonyl complex \textbf{331b} yielded bicycle \textbf{328b} in 45\% yield (Table 22, entry 4). Some cleavage of the Si-O bond was also observed when NMO was used as a promoter of the reaction. Zeolites such as molecular sieves are also known to promote Pauson-Khand reactions (section 1.3.6, p. 39). Perez-Castells\textsuperscript{34} reported two different reaction conditions for promotion of the reaction by molecular sieves, one in the absence of amine-N-oxide and one in its presence. The reaction yields tended to be higher in the presence of both molecular sieves and TMANO together in the reaction mixture. However in the case of dicobalt hexacarbonyl complex \textbf{331b}, (i) in the presence of molecular sieves 16\% of the desired bicycle \textbf{328b} was obtained (entry 5) and (ii) use of both molecular sieves and NMO did not yield any desired bicycle \textbf{328b} (entry 6). In the case where only molecular sieves were used to promote the reaction, the bicycle \textbf{328b} could not be completely separated from unknown impurities and hence the yield is low. In the case where both molecular sieves and NMO were used as promoters of the reaction (entry 6), cleavage of the Si-O bond was observed. Some cleavage of the Si-O bond was also observed when only NMO was used as a promoter of the reaction (entry 4). Hence this cleavage may possibly be due the presence of NMO in the reaction mixture. The cleaved product \textbf{339} in Figure 7 could not be fully characterised as the identity of X could not be established. Use of cyclohexylamine as a promoter\textsuperscript{28} (entry 7) led to no reaction. Si-O bond cleavage was again observed in this case, however the decomposition product could not be fully characterised. Use of dry state adsorption conditions (DSAC)\textsuperscript{31} using either Florisil\textsuperscript{®} (entry 8) or silica (entry 9) as solid supports again did not yield any of the desired cycloadduct \textbf{328b}. Mixtures of unidentifiable and inseparable products were obtained. The best yield of 70\% was obtained in the case of sulfide promoted Pauson-Khand reaction\textsuperscript{29} (Table 22, entry 10). This was comparable to the reaction of dimethylsilyl dicobalt hexacarbonyl complex \textbf{331a}, which led to 72\% of the bicycle \textbf{328a} under the same conditions (Table 19, entry 6).
In the light of the results in Table 22 and described above, the more robust diphenylsilylethers were selected for the study of scope of this silicon tethered Pauson-Khand reaction. We decided to synthesise a range of allyldiphenylsilyl propargyl ethers, with substituents offering different properties at both the alkyne and alkene moiety. The sulfide promoted PKR was chosen as the method of choice for the Pauson-Khand reaction of these substrates as the highest yields of bicycles 328a and 328b were obtained under these conditions. It was hoped that PKR of these substrates would lead to bicyclic enones 328c-328j as shown in Scheme 97.

2.2.5 Synthesis of Substrates 327c-327j

All substrates shown in Table 23 were prepared using a similar procedure as for the synthesis of diphenylsilyl ether 327b, as illustrated in Scheme 94. It was hoped that Pauson-Khand reaction of these substrates would lead to cycloadducts 328c-328j (Scheme 97).
Table 23. Substrates synthesised for PKR

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>R&lt;sup&gt;4&lt;/sup&gt;</th>
<th>R&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>327c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>18&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>327d</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>32&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>327e</td>
<td>TMS</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>29&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>327f</td>
<td>Ph</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>47&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>327g</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>63&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>327h</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>39&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>327i</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>12&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>327j</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>29&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Purification using silica  
<sup>b</sup> Purification using Florisil  
<sup>c</sup> Purification using deactivated grade (III) alumina.

3-Trimethylsilylprop-2-ynyl-1-ol 340, required for the synthesis of 327e was prepared by deprotonation of propargyl alcohol 256 using n-BuLi followed by quenching with chlorotrimethylsilane (80% yield) and is illustrated in Scheme 98.<sup>97</sup>

```
i) n-BuLi, THF, -78 °C  
HO  
ii) TMSCI  
_80%_  

256  
340
```

Scheme 98

The synthesis of 327e was achieved after a small variation to the general procedure illustrated in Scheme 94. For the other substrates described in Table 23, allylchlorodiphenylsilane 330b was added to a solution of alcohol and triethylamine in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C and the resulting reaction mixture was then warmed to room temperature overnight. However this procedure did not yield the desired substrate 327e, instead a complex mixture of unidentifiable products was obtained. Repeating the above procedure several times did not lead to any isolable products. We then decided to synthesise 327e via the deprotonation of the crude substrate 327c using LHMDS followed by addition of chlorotrimethylsilane. However this procedure led to the isolation of compound 341 in 25% yield over 3 steps as illustrated in Scheme 99.
New Substrates for PKR

Results and Discussion

Scheme 99

However 327e was obtained in 29% yield when the allylchlorodiphenylsilane 330b was added to a solution of 3-trimethylsilanylprop-2-yn-1-ol 340, 4-dimethylaminopyridine and triethylamine in CH₂Cl₂ at -78 °C, stirred for 1 h at -78 °C and then allowed to warm to room temperature over 2 days. Considerable decomposition of 327e seemed to be occurring upon purification.

Secondary propargylic alcohols required for the synthesis of 327f and 327g were prepared using published literature procedure. Deprotonation of phenylacetylene 16 using n-BuLi followed by the addition of benzaldehyde 342 yielded 1,3-diphenylprop-2-yn-1-ol 343 (for the synthesis of 327f) in 90% yield. Addition of acetaldehyde 344 to deprotonated phenylacetylene led to 4-phenylbut-3-yn-2-ol 345 (for the synthesis of 327g) in 64% yield (Scheme 100). 327f and 327g were obtained in 47% and 63% yield (Table 23, entries 4 & 5 respectively).
NEW SUBSTRATES FOR PKR

RESULTS AND DISCUSSION

i) $n$-BuLi, THF, -78 °C

\[
\begin{array}{c}
\text{Ph} \quad \text{O} \\
\text{R} \quad \text{Ph}
\end{array}
\]

ii) $\text{HO}$

\[
\begin{array}{c}
\text{R} \quad \text{H}
\end{array}
\]

16 $\text{342, R=Ph}$ $\text{343, R=Ph, 90\%}$

$\text{344, R=CH}_3$ $\text{345, R=CH}_3$, 64%

Scheme 100

Trichlorosilanes required for the syntheses of $\text{327h}$, $\text{327i}$ and $\text{327j}$ in which the alkene moiety is substituted, were not commercially available and were synthesised using literature procedures. Trichloro(2-methylallyl)silane$^{99}$ $\text{348}$ was prepared by the addition of a mixture of trichlorosilane $\text{347}$ and 2-methallyl chloride $\text{346}$ to a mixture of triethylamine and cuprous chloride (Scheme 101). The required compound $\text{348}$ was purified by reduced pressure distillation in 68% yield and subsequently converted to $\text{327h}$ in 39% yield (Table 23, entry 6).

\[
\begin{array}{c}
\text{Cl} \\
\text{Et}_3\text{N}, \text{CuCl} \\
\text{Cl}_3\text{SiH}
\end{array}
\]

\[
\begin{array}{c}
\text{Et}_2\text{O} \\
68\%
\end{array}
\]

$\text{346}$ $\text{347}$ $\text{348}$

Scheme 101

(Z)-Trichloro(2-methylbut-2-enyl)silane$^{100}$ $\text{350}$ was prepared by heating trichlorosilane $\text{347}$, isoprene $\text{349}$, triphenylphosphine and bis(benzonitrile)palladium(II)chloride (Pd(PhCN)$_2$Cl$_2$) in a sealed tube at 70 °C (Scheme 102). The $^1$H NMR spectrum showed the crude product $\text{350}$ to be clean and it was used without further purification, hence the yield (12%) quoted for the synthesis of $\text{327i}$ (Table 23, entry 7) is over three steps.
(E)-Crotyltrichlorosilane\(^9\) \(\text{352}\) was prepared, using the same procedure as for the synthesis of trichloro(2-methylallyl)silane \(\text{348}\), from crotyl chloride \(\text{351}\), trichlorosilane \(\text{347}\) triethylamine and cuprous chloride (Scheme 103). Crotyl chloride \(\text{351}\) was only available as mixture of 1 : 6 \(cis\) : \(trans\) isomers. Silane \(\text{352}\) was purified by reduced pressure distillation and was obtained in 43% yield and as a 1 : 6 mixture of \(cis\) : \(trans\) diastereoisomers which were used for the synthesis of \(\text{327j}\) without separation. Surprisingly only \(trans\)-but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane \(\text{327j}\) was isolated from the reaction for the synthesis of \(\text{327j}\). The \(\text{H}^1\) NMR spectrum did not show any evidence of \(cis\)- but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane.

As can be seen from the Table 23, only \(\text{327d}\) could be purified using silica. Other substrates were purified using either deactivated grade (III) alumina or Florisil\(^\circledR\) as solid supports for flash column chromatography. These solid supports were not interchangeable for these substrates, \(e.g.\) \(\text{327c}\) decomposed on both alumina and silica and could only be purified using Florisil\(^\circledR\). Considerable decomposition seemed to be occurring on all three solid supports as \(\text{H}^1\) NMR spectra of crude products suggested that higher yields of desired products were present compared to the yields actually obtained.
New Substrates for PKR

Results and Discussion

We decided to synthesise di-tert-butyldipropargyl ethers to see if they would be more stable to purification by flash chromatography. Unfortunately we could not synthesise these ethers. Allyldi-tert-butyldichlorosilane could not be prepared by addition of t-BuLi or t-BuMgCl to allyltrimethylchlorosilane. One pot synthesis of di-tert-butyldipropargyl ethers using a similar procedure as for the synthesis of diphenylpropargyl ethers also failed to yield the desired enynes.

2.2.6 Results of Pauson-Khand studies for substrates 327c-327j

The results for the Pauson-Khand reaction of substrates synthesised during the course of our studies are listed in Table 24 for Scheme 104.

![Scheme 104](image)

**Table 24. Results of PKR of substrates 327c-327j**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( R^4 )</th>
<th>( R^5 )</th>
<th>Yield (%) of cycloadduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>327c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>328c, 0&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>327d</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>328d, 38&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>327e</td>
<td>TMS</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>328e, 14&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>327f</td>
<td>Ph</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>328f, 0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>327g</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>328g, 9&lt;sup&gt;a,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>327h</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>328h, 0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>327i</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>328i, 0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>327j</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>328j, 33&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Purification using Florisil<sup>b</sup> Purification using deactivated grade(III)alumina  
<sup>c</sup> The product was obtained as 1.5 : 1 mixture of diastereomers.
Unfortunately, few of the compounds synthesised proved to be good substrates for the Pauson-Khand reaction. A silyl ether derived from propargyl alcohol (327c, entry 1) did not undergo Pauson-Khand cycloaddition at all. Inseparable and unidentifiable product mixtures were obtained after flash column chromatography using either alumina or Florisil®. The \(^1\text{H}\) NMR spectrum of one of the fractions from a column on alumina showed the presence of protons associated with the alkene, but there was no evidence of protons associated with the alkyne moiety. This suggested that the decomposition of starting material via the cleavage of Si-O bond was occurring, either during the reaction or upon chromatography. An alkyne bearing a terminal methyl (327d, entry 2) or trimethylsilyl substituent (327e, entry 3) afforded the bicycles 328d and 328e in relatively poor yields of 38 % and 14 % respectively. For the PKR of 327e, some unclean starting enyne 327e was recovered from the column (23%). As described in section 2.2.5 (p. 115), the starting enyne 327e decomposes easily and hence may account for the poor yield of the bicycle 328e. The bicycle 328e may also be decomposing on the column due to the presence of a trimethylsilyl substituent, although no decomposition products were isolated.

We then investigated the effect of substitution at the propargylic position of these substrates. Two substrates 327f (with a Ph substituent at the propargylic position) and 327g (with a Me substituent at the propargylic position) were subjected to the sulfide promoted Pauson-Khand reaction. 327f (entry 4) did not give any of the desired product. Starting enyne 327f was recovered from the reaction mixture (23%) along with various unidentifiable products. The substrate with the propargylic methyl group (327g, entry 5) underwent cyclisation in very poor yield (9%) and with very low diastereoselectivity (1.5 : 1 in favour of the \(\text{exo}\) diastereomer). The two diastereomers (328g and 328g' in Figure 8) could not be separated by flash column chromatography. The relative stereochemistry of the two diastereomers was established using one-dimensional NMR experiments (\(^1\text{H}\) spectra and NOE) on the isolated mixture.
New Substrates for PKR

Results and Discussion

Figure 8

In the NOE experiment of the major isomer (328g) irradiation of H-9 generated an enhancement of some aromatic protons and of the methyl group. No enhancement of H-4 was observed. Irradiation of the methyl signal led to an enhancement in the signal of H-4 indicating a *trans* relative stereochemistry between H-9 and H-4. In the NOE experiment of minor isomer (328g'), irradiation of H-9 led to enhancement of some aromatic protons as well as of H-4. Irradiation of the methyl signal led only to enhancement of H-9 and crucially no positive enhancement of H-4 was observed indicating a *cis* relative stereochemistry between H-4 and H-9.

The tolerance of this silicon-tethered Pauson-Khand reaction to substitution on the alkene double bond was also studied. Of the three substrates prepared (327h, 327i and 327j) only 327j (entry 8) underwent Pauson-Khand cyclisation to yield cycloadduct 328j in 33% yield. Starting material 327j was also recovered in 13% yield from the reaction mixture. Only the isomer shown in Figure 9 below was isolated from the reaction mixture showing, as expected, the preservation of *trans* relative stereochemistry of H-4 and H-5 under the reaction conditions tested. In the NOE experiments, positive enhancement between H-4 and the methyl group was observed indicating the *trans* relative stereochemistry between H-4 and H-5.
In the case of disubstituted terminal alkene (327h, entry 6), impure starting material 327h was recovered (33%) from the reaction mixture. Trisubstituted alkene (327i, entry 7) also did not lead to the desired bicycle. Impure starting material 327i was recovered (28%) from the reaction mixture.

2.2.7 Conclusion

In conclusion we have shown that silyl ethers derived from allylsilyl chlorides and propargylic alcohols undergo Pauson-Khand reaction, although the substrate scope is currently limited. Yields are low due to purification problems associated with these cycloadducts and it is hoped that removal of silicon tether before any flash column chromatography may lead to easier isolation and enhanced yields of the desired compounds.

2.3 Silyl enol ethers as substrates for the Pauson-Khand reaction

As discussed in the introduction, (section 1.6.2, p. 84), at the start of this project there were no examples in the literature where silyl enol ethers had been used as substrates in an intramolecular Pauson-Khand reaction. We therefore decided to investigate the scope and limitations of using silyl enol ethers of type 270 in the Pauson-Khand reaction (Scheme 105). It was hoped that bicycle 271 obtained after the Pauson-Khand reaction could be further transformed and hence may prove useful in the synthesis of various natural products, a model substrate for ingenol 369 in our case.
2.3.1 Synthesis of substrates

We initially decided to synthesise two substrates, 272a (terminal alkyne) and 272b (internal alkyne), to find the optimum reaction conditions for the Pauson-Khand cyclisation of these substrates (Figure 10).

We then hoped to define the scope and limitations of this reaction by synthesising various substrates with different substituents on the alkene and alkyne moieties and subjecting them to the optimised reaction conditions.

Ketones 357a and 357b were synthesised, in 29% and 48% yield respectively, by Eschenmoser fragmentation of epoxy ketones 356a and 356b using a literature procedure\textsuperscript{101} (Scheme 106). Epoxy ketones 356a and 356b in turn were synthesised from basic epoxidation\textsuperscript{102} of isophorone 355a in the case of 356a and 2,3,5,5-tetramethylcyclohex-2-en-1-one\textsuperscript{103} 355b in the case of 356b. Isophorone is commercially available whereas 2,3,5,5-tetramethylcyclohex-2-en-1-one 355b was synthesised in 34% yield by Robinson annulation of mesityl oxide 353 and methyl-3-oxopentanoate 354 (Scheme 106).
We were unable to synthesise either the TMS or TBS enol ether of ketone 357a using either LDA or KHMDs for the deprotonation of 357a. Reactions for the synthesis of the TBS enol ether of 357a showed the presence of both starting ketone and small amounts of the desired silyl enol ether, but we were unable to isolate the desired silyl enol ether from impurities.

The silyl enol ether 272b derived from ketone 357b was synthesised in 10% yield. The low yield was attributed to the volatile nature of this silyl enol ether as well as its hydrolysis to starting ketone 357b (21% recovery) on silica (Scheme 106).
2.3.2 Pauson-Khand reaction of 272b

The Pauson-Khand reaction of the silyl enol ether 272b in acetonitrile at 75 °C led to the desired bicyclic cyclopentanone 358 in ~19% yield (Scheme 107), however it could not be fully characterised due to the presence of inseparable impurities. \(^1\)H NMR and mass spectra showed the isolated compound to be the desired bicycle 358. This result showed that silyl enol ethers of type 272 would undergo Pauson-Khand cyclisation.

```
\[
\begin{array}{c}
\text{CH}_3 \quad \text{i) Co}_2(\text{CO})_8, \text{CH}_3\text{CN, rt} \\
\text{OTMS} \\
\text{272b} \\
\text{CH}_3 \\
\text{ii) 75 °C} \\
\text{~19 %} \\
\text{OTMS} \\
\text{358}
\end{array}
\]
```

Scheme 107

2.3.2 Synthesis of diethyl malonate derivatives

Due to the volatile nature of both 272b and bicycle 358 and purification difficulties due to the presence of a trimethylsilyl moiety in both 272b and bicycle 358, we decided to synthesise diethyl malonate derivatives 361a and 361b and to investigate the Pauson-Khand reaction of their silyl enol ethers (Scheme 108). We hoped that this series of compounds would prove to be less volatile. The synthesis of two diethyl malonate derivatives 361a (terminal alkyne) and 361b (internal alkyne) is illustrated in Scheme 108.
Alkylation of diethyl malonate 274 with the appropriate propargyl bromides 275 and 359 using sodium ethoxide as a base yielded the desired monoalkylated products 276a and 276b as well as dialkylated side products 277a and 277b (Scheme 108). Propargyl bromide 275 is commercially available whereas 1-bromo-3-phenylprop-2-yne was prepared by bromination of 3-phenylprop-2-yn-1-ol as shown in Scheme 109. Second alkylation of 276a and 276b with chloroacetone 360 using potassium carbonate as a base yielded the two diethyl malonate derivatives 361a and 361b required for our studies. Yield of the reaction for the preparation of 361b was lower than for 361a due to presence of some unidentifiable and inseparable impurities in 361b. The purification of 361b was carried out using a chromatotron ("radial chromatography"), in small batches of 0.20g on silica plates of 4mm thickness.
We initially decided to synthesise the trimethylsilyl enol ethers 362a and 362c of the two substrates 361a and 361b using LDA as a base (Scheme 110 and Scheme 111).

Several attempts to synthesise the trimethylsilyl enol ether 362a as well as tert-butyldimethylsilyl enol (TBS) ether 362b of the terminal alkyne substrate 361a using 1.1 equivalents of LDA, KHMDS or LHMDS as bases proved unsuccessful. The reactions either led to recovery of the starting material 361a along with silyl impurities or unidentifiable product mixtures (Scheme 110). We suspected this to be due to the acidity of the terminal alkyne hydrogen (pKa 25) although the ketone hydrogen should be the more acidic (pKa 17-20). The use of 2 equivalents of LDA (to deprotonate both acidic protons) followed by trapping with TBS-Cl again did not lead to isolation of any products.

We did however successfully synthesise the trimethylsilyl enol ether 362c as illustrated in Scheme 111. The silyl enol ether 362c was used crude for Pauson-Khand studies as its purification, by flash column chromatography using Florisil® as solid support, led to considerable decomposition to the starting ketone 361b (46%) and only 26% of the silyl enol ether 362c was isolated.
2.3.4 Pauson-Khand reaction of Trimethylsilyl ether 362c

We decided to remove the trimethylsilyl group using para-toluenesulfonic acid in methanol after the Pauson-Khand cyclisation due to decomposition of the initial Pauson-Khand product. However $^1$H NMR spectrum of the isolated compound 363 after the PKR of 362c promisingly showed some of the AB systems associated with the protons of the two five membered rings (Figure 11).

The Pauson-Khand reactions were therefore carried out on crude trimethylsilyl enol ether 362c and the crude Pauson-Khand reaction mixtures were treated with para-toluenesulfonic acid to remove the TMS group. The results for the Pauson-Khand cyclisation of the trimethylsilyl enol ether 362c to yield 4-hydroxy cyclopentenone 364 under various Pauson-Khand reaction conditions are summarised in Table 25 for Scheme 112.
New Substrates for PKR

Results and Discussion

Table 25. Pauson-Khand reactions of 361b

<table>
<thead>
<tr>
<th>Entry</th>
<th>PKR conditions</th>
<th>Yield (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, reflux</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN, 75 °C⁹¹</td>
<td>23</td>
<td>361b (24%) contaminated with cobalt impurities</td>
</tr>
<tr>
<td>3</td>
<td>n-BuSMe, 1,2-DCE, 83 °C²⁹</td>
<td>24</td>
<td>361b (41%)</td>
</tr>
<tr>
<td>4</td>
<td>Toluene, 4Å MS, reflux²⁴</td>
<td>0</td>
<td>Inseparable product mixtures</td>
</tr>
<tr>
<td>5</td>
<td>NMO, CH₂Cl₂, rt²⁵</td>
<td>0</td>
<td>361b (23%) contaminated with cobalt impurities</td>
</tr>
<tr>
<td>6</td>
<td>CyNH₂, 1,2-DCE, 83 °C²⁸</td>
<td>0</td>
<td>361b (59%)</td>
</tr>
<tr>
<td>7</td>
<td>H₂O, CTAB, Celite, 70 °C³⁵</td>
<td>0</td>
<td>Monoester 365 (7%) along with unclean 361b</td>
</tr>
</tbody>
</table>

As can be seen from Table 25, 4-hydroxy cyclopentenone 364 was obtained under only three of the reaction conditions tested (entries 1, 2 & 3). The highest yield of bicycle 364 (29% over 3 steps) was obtained when the reaction was carried out in toluene (entry 1). The starting ketone 361b was recovered in most cases. An interesting reaction occurred when the Pauson-Khand reaction was carried out in aqueous medium³⁵ (entry 7). Along with some unclean starting ketone 361b, monoester 365 was also isolated in 7% yield (Figure 12).

Scheme 112

As can be seen from Table 25, 4-hydroxy cyclopentenone 364 was obtained under only three of the reaction conditions tested (entries 1, 2 & 3). The highest yield of bicycle 364 (29% over 3 steps) was obtained when the reaction was carried out in toluene (entry 1). The starting ketone 361b was recovered in most cases. An interesting reaction occurred when the Pauson-Khand reaction was carried out in aqueous medium³⁵ (entry 7). Along with some unclean starting ketone 361b, monoester 365 was also isolated in 7% yield (Figure 12).

Scheme 112

Table 25. Pauson-Khand reactions of 361b

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<td>0</td>
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As can be seen from Table 25, 4-hydroxy cyclopentenone 364 was obtained under only three of the reaction conditions tested (entries 1, 2 & 3). The highest yield of bicycle 364 (29% over 3 steps) was obtained when the reaction was carried out in toluene (entry 1). The starting ketone 361b was recovered in most cases. An interesting reaction occurred when the Pauson-Khand reaction was carried out in aqueous medium³⁵ (entry 7). Along with some unclean starting ketone 361b, monoester 365 was also isolated in 7% yield (Figure 12).

Figure 12
This was peculiar as generally decarboethoxylation of β-ketoesters requires forcing reaction conditions such as LiCl in refluxing DMSO (Krapcho decarboxylation\textsuperscript{105}). In order to see whether the presence of cobalt was necessary for this decarboethoxylation to occur we carried out two test reactions in the absence of Co\textsubscript{2}(CO)\textsubscript{8} as illustrated in Scheme 113 below.

![Scheme 113](image)

In both cases 100% recovery of starting materials was observed leading to the conclusion that presence of Co\textsubscript{2}(CO)\textsubscript{8} was necessary for this unusual reaction to occur.

### 2.3.5 Synthesis and Pauson-Khand reaction of Triisopropylsilyl ethers

In order to establish whether the sterically bulky silyl enol ethers such as TIPS enol ethers would also undergo Pauson-Khand reaction we decided to synthesise TIPS enol ethers of \textit{361a} and \textit{361b} as illustrated in Scheme 114.
During the synthesis of $367a$, $367b$ was also isolated in 18% yield along with the starting material $361a$ (26%). This showed that the terminal alkyne hydrogen was also being deprotonated along with the ketone hydrogen. TIPS enol ether $367c$ could be purified on silica, however a higher yield of 87% was obtained when Florisil® was used as solid support. This is most likely due to the hydrolysis of the enol ether $367c$ occurring on silica.

The results of the Pauson-Khand reaction of TIPS enol ethers in acetonitrile$^{91}$ ($367a$, $367b$ and $367c$) are illustrated in the Scheme 115, and Table 26.
In the case of terminal alkyne (367a, entry 1) unidentifiable product mixtures were obtained whereas PKR of 367b (entry 2) led to 84% recovery of the starting TIPS enol ether 367b. Only 367c led to the desired bicycle 368c, in 13% yield along with 65% recovery of the starting TIPS enol ether 367c. Incomplete complexation of all three substrates (367a-367c) with dicobalt octacarbonyl was observed.

2.3.7 Conclusion

The TMS enol ether of the internal alkyne substrate 362c undergoes Pauson-Khand reaction in moderate yields, however the TIPS enol ether 367c of the same substrate undergoes the cyclisation reaction in poor yield (13%). 367c was also recovered in 65% yield. The TIPS enol ethers of the terminal alkyne substrate 367a and 367b do not undergo Pauson-Khand reaction.

2.4 Model substrate for the synthesis of ingenol

We decided to apply the silyl enol ether methodology to a model substrate 369 for synthesis of compound 371 containing A, B and C rings of ingenol 372 (Scheme 116). Pauson-Khand reaction of the model substrate 369 would lead to the installation of B and C rings of ingenol in one step.
2.4.1 Origin, Biological activity and mode of action of ingenol

Ingenol\textsuperscript{106} \textsuperscript{372} is a highly oxygenated tetracyclic diterpene, isolated initially from the \textit{Euphorbia ingens} species of the \textit{Euphorbiaceae} plant family, by the Hecker group in 1968. Diverse ingenane types with different oxidation states at C-3, C-4, C-5, C-12, C-13, C-16 or C-20 have also been isolated.\textsuperscript{107} It has attracted considerable interest from both the chemical and biological communities because of its unique structure and an array of biological properties.

The identification of cellular signalling systems and the design and synthesis of small molecules that regulate these systems is at the forefront of modern drug design\textsuperscript{108}. Protein Kinase C is a central mediator of cellular signal transduction for a large class of hormones and cellular effectors that generate the lipophilic secondary messenger 1,2-diacylglycerol \textsuperscript{373}, \textit{e.g.}, through activation of phosphatidylinositol 4,5-bis(phosphate) turnover. Various esters of ingenol are able to substitute for 1,2-diacylglycerol \textsuperscript{373}, the endogenous activator of PKC. In addition to \textit{ingenol} \textsuperscript{372}, several other natural products...
including teleocidin 374, esters of phorbol 375 and asplysiatoxin 376 mimic the function of diacylglycerol 373 (Figure 13). Although several proposals for a pharmacophore common to these structurally dissimilar activators of PKC have been described, a conclusive structure-activity relationship has not been established. The synthesis and study of specifically modified analogues of these natural product leads should establish the structural requirements for the activation of PKC that are common to these dissimilar substances and ultimately lead to the development of new therapeutic drugs for the treatment of inflammatory and proliferative diseases.107

Ingenol esters were initially reported to be potent tumour promoters.106 Since then, numerous ingenol derivatives have been identified as tumour-promoting activators of
Paradoxically, as long ago as 1976, there have been reports of ingenol derivatives having antitumour such as antileukemic properties as well.\textsuperscript{111,112}

In several studies on the biological properties of ingenoids there have been clear separations between tumour-promotion and potentially therapeutic activities, suggesting that there may be a mechanistic pathway independent of PKC activation responsible for biological activity.\textsuperscript{113,114} The evaluation of antitumour activity and PKC activation of C-20 modified analogues of ingenol has shown that chemical manipulation can effectively dissect cytotoxicity and tumour-promoting activity of ingenoids.\textsuperscript{115}

Recently ingenol derivatives have been shown to affect HIV-1 replication. In acutely infected cells, ingenol derivatives were shown to be powerful inhibitors of viral adsorption to the host cell, greatly inhibiting viral replication.\textsuperscript{116}

An efficient synthetic route to ingenol will allow access to novel ingenoid analogues and their SAR studies will give insight into the detailed mechanism of activity of the ingenol esters, and possibly lead to new therapeutic treatments.

### 2.4.2 Inside-outside stereochemistry of ingenol

Ingenol 372 is a highly oxygenated tetracyclic diterpene possessing a bicyclo[4.4.1]undecane skeleton in BC rings. While the high degree of oxygenation, notably the cis-triol (from C-3 to C-5 on the β face of A and B rings), represents an important challenge to the synthesis, the most imposing obstacle to the synthesis of ingenol is the establishment of highly strained ‘inside-outside’ or \textit{trans} intrabridgehead stereochemistry of the B, C ring system. This unique stereochemical feature appears to play a very important role in the biological properties of the ingenanes, as Paquette\textsuperscript{117} has reported that a highly functionalised ingenane analogue 377, (\textbf{Figure 14}), which has a \textit{cis} rather than \textit{trans} intrabridgehead stereochemistry (the C-8 epimer of ingenol), possessing the fully functionalised A and B rings of ingenol, is completely devoid of biological activity.
Bridged bicyclic systems can exist as three different stereoisomers\textsuperscript{118}: an out-out isomer 378, an in-in isomer 379 and an in-out isomer 380 (Figure 15). Usually the in-in isomer 379 is most unstable because of the severe repulsive interaction between the inside atoms. However, the energy difference between in-out and out-out isomers varies depending on the system. In the ingenane ring system, the in-out isomer is generally more strained than the out-out isomer.\textsuperscript{119} According to MM2 calculations, in-out bicyclo[4.4.1]undecane 382 is more strained than its out-out isomer 381 by 6.3 kcal mol\textsuperscript{-1}, whereas the analogous out-out and in-out bicyclo[4.4.1]undecan-7-one configurations (substructure present in ingenol) differ in strain energy by 3.3 kcal mol\textsuperscript{-1}. Ingenol itself is more strained than its out-out isomer (isoingenol) by 5.9 kcal mol\textsuperscript{-1}.\textsuperscript{119}
Total synthesis of ingenol has proved very challenging because of this highly strained C-8/C-10 trans intrabridgehead system and has stimulated the interest of many synthetic organic chemists.

2.4.3 Previous syntheses of ingenol

Although several groups have been working towards the total synthesis of ingenol since the early 1980s, the first total synthesis of ingenol was reported by Winkler in 2002\textsuperscript{120}. Since then two other total syntheses, first by Kuwajima in 2003\textsuperscript{121} and second by Wood in 2004\textsuperscript{122} have been reported. One formal synthesis of ingenol was also reported by Kigoshi in 2004\textsuperscript{123}.

2.4.3.1 Winkler’s first total synthesis of Ingenol\textsuperscript{120}

The total synthesis of (±)ingenol proceeded in 43 steps with an 80% average yield per step. Winkler and coworkers\textsuperscript{120} employed an intramolecular dioxenone photoaddition-fragmentation approach to set up the trans intrabridgehead stereochemistry of C-8/C-10 of ingenol.
 Irradiation of dioxeneone substrate 383 led to the desired photoadduct 384 in low (16%) yield, however photocycloaddition of the allylic chloride 385 derived from 383 proceeded in 60% yield to give desired photoadduct 386 (Scheme 117). Fragmentation of 386 with methanolic potassium carbonate, followed by LAH reduction of the derived ester, elimination of the chloride and silylation of the primary alcohol gave 387 as a 7:1 ratio of C-6 α:β epimers in 35 % yield over four steps. This compound 387, with desired C-8/C-10 in-out stereochemistry, was further transformed into (±)-ingenol over several steps.

\[
\text{Scheme 117}
\]

Kuwajima and coworkers carried out the total synthesis of (±)-ingenol in 45 steps in approximately 0.1 % overall yield. They employed a novel intramolecular cyclisation reaction of acetylene dicobalt complex 388 and a rearrangement reaction of epoxy alcohol 391 for constructing the ingenane skeleton.

Cobalt complex 388, under the influence of methylaluminium bis(2,6-dimethyl-4-nitrophenoxide), underwent a cyclisation reaction to afford allyl alcohol 389 containing the C(11) α-methyl group. The dicobalt acetylene complex moiety of 389 was used for stereoselective construction of the D ring through Birch reduction,
dibromocyclopropanation, and methylation. Transformation of the tetracyclic carbon framework into an ingenane skeleton was achieved via stereoselective epoxidation of allyl alcohol 390 followed by treatment with trimethylaluminium to set up the trans intrabridgehead C-8/C-10 stereochemistry of ingenol, as illustrated in Scheme 118. 392 was converted to (±)-ingenol over several steps.

\[
\begin{align*}
\text{OAc} & \quad \text{Co(CO)₃} \\
\text{OH} & \quad \text{Co(CO)₃} \\
\text{OMe} & \quad \text{bis(2,6-dimethyl-4-nitrophenoxide)} \\
\text{OTIPS} \quad \rightarrow \quad \text{CH₂Cl₂} \\
\text{388} & \quad \text{389}
\end{align*}
\]

i) Li, liq NH₃, 67% over 2 steps

\[
\begin{align*}
\text{ii) CHBr₃, NaOH} & \quad \text{BnEt₃NCl, CH₂Cl₂, H₂O, 71%} \\
\rightarrow & \quad \text{OH} \\
\text{TBHP, Ti(OiPr)₄ O} & \quad \text{4Å MS, CH₂Cl₂} \\
\rightarrow & \quad \text{OH} \\
\text{390} & \quad \text{391}
\end{align*}
\]

\[
\begin{align*}
\text{iii) Me₃CuLi₂, Et₂O} & \quad \text{then Mel, 95%} \\
\rightarrow & \quad \text{OMe} \\
\text{390} & \quad \text{391}
\end{align*}
\]

\[
\begin{align*}
\text{Me₂Al, CH₂Cl₂} & \quad 76\% \text{ in 2 steps} \\
\rightarrow & \quad \text{HO} \\
\text{MeO} & \quad \text{OTIPS} \\
\text{392}
\end{align*}
\]

Scheme 118

2.4.3.3 Kigoshi’s formal total synthesis of Ingenol

Kigoshi and coworkers have developed a direct cyclisation method for the construction of highly strained skeleton of ingenol via ring closing olefin metathesis.
The compound 394, obtained after the ring closing metathesis reaction of 393, was further elaborated to Winkler’s aldehyde\cite{120} 395, a key intermediate in Winkler’s total synthesis of ingenol.

\begin{center}
\includegraphics[width=\textwidth]{scheme119.png}
\end{center}

\textbf{Scheme 119}

\textbf{2.4.4 Retrosynthetic analysis of our model substrate}

We decided to investigate the synthetic utility of the Pauson-Khand reaction of a silyl enol ether 369, for synthesis of the ingenane skeleton. We hoped that the Pauson-Khand reaction of key intermediate 369 would form the tetracyclic compound 370, which would undergo retro aldol reaction to relieve ring strain and therefore lead to compound 371 containing the ingenane ring skeleton (Scheme 120).

\begin{center}
\includegraphics[width=\textwidth]{scheme120.png}
\end{center}

\textbf{Scheme 120}

Silyl enol ether 369 will be synthesised from cyclobutanone 396. Scheme 121 below shows retrosynthetic analysis of the key intermediate 396.
Cyclobutanone 396 will be synthesised from [2+2] cycloaddition of ketene 397 generated \textit{in situ} from acid chloride 398. Monocarboxylic acid 399 will be synthesised by decarboxylation of dicarboxylic acid 400 which in turn will be generated from ester hydrolysis of diethyl malonate derivative 401. Dialkylation of diethyl malonate, first with 5-bromopent-1-ene and then alkylation of derivative 402 with 6-chlorohex-1-yne will lead to diethyl dialkylmalonate derivative 401. Synthesis of silyl enol ether from cyclobutanone 396 will yield model substrate for the synthesis of ingenol skeleton.
2.4.5 Synthesis of Cyclobutanone 396

As shown in the retrosynthetic analysis, we initially decided to carry out the synthesis of carboxylic acid 399 from diethyl malonate 274 (Scheme 122). The alkylation of diethyl malonate 274 with commercially available 5-bromopent-1-ene 403 using sodium ethoxide led to the monoalkylated malonate derivative 402 in 83% yield. The dialkylated derivative 404 was also obtained in 5% yield. Carrying out this initial alkylation of diethyl malonate 274 using NaH, as a base, in THF, 124 led to the desired compound 402 in only 43% yield. We initially decided to carry out the second alkylation of intermediate 402 with 6-chlorohex-1-yne 405 using potassium carbonate as a base, in the presence of 10 mol% NaI, in acetone. 90 However this reaction led to the recovery of intermediate 402. Use of NaH as a base in THF also led to the recovery of intermediate 402.123 We therefore decided to synthesise 6-iodohex-1-yne125 406 from 6-chlorohex-1-yne 405 using the Finkelstein reaction conditions (NaI in acetone, reflux). This reaction is widely used for Sn2 displacement of one alkyl halide with another halide. With the 6-iodohex-1-yne 406 in hand, we carried out the second alkylation of intermediate 402 using two different bases. Use of sodium ethoxide as a base yielded the desired compound 401 in 58% yield whereas use of NaH in DMF led to the desired dialkylated diethyl malonate derivative 401 in 86% yield along with the minor transesterification product 407 in 4% yield. The transesterification product 407, most likely originated by the presence of small amounts of moisture in the reaction mixture which led to the hydrolysis of the iodide 406 to the corresponding alcohol. This in turn reacted with one of the diethyl malonate esters of 401. The hydrolysis of 401 using 50% aqueous NaOH solution126 led to the diacid 400 in a disappointingly low yield of 34%, most likely due to its solubility in aqueous phase and hence reduced extraction into the organic phase. We then attempted the decarboxylation of the diacid 400 using 3 different reaction conditions including (i) heating a solution of the diacid 400 in 6 M H2SO4, 127 (ii) heating the diacid 400 neat without any solvent128 and (iii) heating a solution of the diacid 400 in toluene. None of these conditions led to the desired monoacid 399 and unidentifiable reaction mixtures were obtained.
Due to the low yield of diacid 400 and failure to cause its decarboxylation led to a revised synthesis of monoacid 399, as illustrated in Scheme 123. We decided to use Krapcho reaction conditions (LiCl, DMSO, reflux) for decarboethoxylation of diester.
to synthesise the monoester 408 in 79% yield. The basic hydrolysis\(^{129}\) of this monoester 408 led to the desired monoacid 399 in 96% yield (Scheme 123).

\[
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{LiCl, DMSO/H}_2\text{O} \quad \text{H} \quad \text{CO}_2\text{Et}
\]

\text{reflux} \quad \text{79%}

\[
\begin{align*}
\text{401} & \quad \text{2M KOH in EtOH} \quad \text{reflux} \quad \text{96%} & \quad \text{408} \\
\end{align*}
\]

\[
\begin{align*}
\text{399} & \quad \text{H} \quad \text{CO}_2\text{H} \\
\end{align*}
\]

Scheme 123

Initially we carried out the Krapcho reaction, to synthesise monoester 408, at 300–500 mg scale and the yields were low (ranging from 47%-53%). However the yield of the reaction improved when carried out on larger scale of 2.3 g leading to 79% yield of the desired monoester 408. Since Krapcho reaction takes place by the nucleophilic attack of the chloride ion on the carbon of the ester (as illustrated in Scheme 124), we hoped that the yield of this reaction would improve further when carried out on analogous dimethyl malonate derivative compared to the diethyl malonate derivative 401 since OCH\(_3\) is less sterically hindered than OCH\(_2\)CH\(_3\) and therefore nucleophilic attack of Cl\(^{-}\) ion would be facilitated.
The dimethyl malonate derivative 414 was synthesised using the same sequence of steps and procedures as for diethyl malonate derivative 401 and is illustrated in Scheme 125. As can be seen from Scheme 125, (i) yield of monoalkylated dimethyl malonate derivative 412 decreased considerably (57%) compared to its diethyl malonate analogue (83%), (ii) transesterification product was not obtained after the second alkylation and (iii) most importantly the yield of the Krapcho reaction did not increase as expected, instead mono ester 415 was obtained in only 48% yield compared to its ethyl analogue 408 which was obtained in 79% yield. We therefore decided to use the diethyl malonate derivatives for our studies. The basic hydrolysis of the monoester 415 led to the monoacid 399 in 75% yield.
Cyclobutanone 396 was obtained, in 65% yield, by the synthesis of acid chloride from monoacid 399 and then by \textit{in situ} generation of ketene, using triethylamine as a base, which underwent [2+2] cycloaddition (Scheme 126).\textsuperscript{130}
Scheme 126

The synthesis of cyclobutanone 396 was also attempted using the route shown in Scheme 127 via the tosylate 416. The tosylate 416 could be purified by flash column chromatography, however it did not lead to the generation of cyclobutanone 396. \(^1\)H NMR spectra of the fractions obtained after flash column chromatography showed alkene protons as well as protons of the tosylate, indicating that the ketene was not formed during the reaction.

Scheme 127


2.4.6 Synthesis and Pauson-Khand reaction of trimethylsilyl enol ether 417

We decided to study the Pauson-Khand reaction of trimethylsilyl enol ether 417, generated from cyclobutanone 396. Trimethylsilyl enol ether was chosen as in our previous methodology studies, (section 2.3.4, p. 128), TMS enol ethers led to the best results for Pauson-Khand cyclisations. The silyl enol ether 417 was generated from cyclobutanone 396 using LHMDS as a base (Scheme 128). \(^1\)H NMR spectrum of the crude 417 showed it to be clean containing only minor trimethylsilyl impurities.

\[
\begin{align*}
\text{O} & \\
\text{H} & \\
\text{H} & \\
\text{396} & \quad \text{i) 1.05 eq LHMDS, THF, -78°C} \\
\text{H} & \quad \text{ii) TMSCl, -78 °C then warmed to rt} & \quad \text{OTMS} \\
\text{417} & \quad 93\% \text{ crude}
\end{align*}
\]

Scheme 128

Again as in the case of substrate 361b, (section 2.3.4, p. 128), we decided to use the TMS enol ether 417 crude for our Pauson-Khand studies due to the purification problems associated with the TMS moiety. This group was also removed using para-toluenesulfonic acid before any flash column chromatography was carried out on Pauson-Khand reaction mixtures. It was hoped that after the removal of the TMS group, the Pauson-Khand adduct 418 would spontaneously undergo retro-aldol reaction in order to relieve ring strain and hence lead to the formation of the desired compound 371, containing the A, B and C rings of ingenol (Scheme 129).
New Substrates for PKR

Results and Discussion

Scheme 129

The Pauson-Khand reaction of 417 mediated by n-butyl methyl sulfide\(^{29}\) generated a complex reaction mixture containing various unidentifiable compounds. 419 was the only compound identified and characterised after flash column chromatography and was obtained in 5% yield (from cyclobutanone 396). Surprisingly, transfer of the TMS moiety onto the terminal alkyne was observed (Figure 16).

TMS

Figure 16
The Pauson-Khand reaction of 417 in acetonitrile\(^\text{91}\) at reflux also led to complex and unidentifiable reaction mixtures. During the synthesis of the dicobalt hexacarbonyl complex of 417, acetonitrile appeared to be forming a complex with dicobalt octacarbonyl (Co\(_2\)(CO)\(_8\)), as addition of dry acetonitrile to Co\(_2\)(CO)\(_8\) led to release of gas bubbles, presumably carbon monoxide and change of the colour of the solution from orange brown to deep red was also observed. Therefore the dicobalt hexacarbonyl complex of silyl enol ether 417 was not being formed and hence Pauson-Khand reaction was not taking place. In that case we would expect to isolate cyclobutanone 396 after the acidic workup, however none was isolated. The Pauson-Khand reaction of 417 in toluene at reflux also generated complex and unidentifiable reaction mixtures. Some cyclobutanone 396, contaminated with unidentifiable impurities, was recovered in 31\% crude yield.

2.4.7 Synthesis and Pauson-Khand reaction of trimethylsilyl enol ether 420

Along with the terminal alkyne trimethylsilyl enol ether 417 we decided to synthesise the TMS enol ether 420 to study the effect of substitution at the alkyne position. 420 was easily synthesised in 2 steps from cyclobutanone 396 as illustrated in Scheme 130 using LHMDS as a base.\(^\text{132}\)
First deprotonation with LHMDS followed by capturing of the enolate with trimethylchlorosilane led to 417. Use of 1.1 equivalent of LHMDS deprotonated the terminal alkyne which was then silylated using trimethylchlorosilane. This sequence of steps led to trimethylsilyl enol ether 420. $^1$H NMR spectrum of the crude 420 showed it to be clean containing only minor trimethylsilyl impurities. Again, 420 was used crude for Pauson-Khand studies and the TMS ether was removed before any purification of Pauson-Khand reactions was carried out. In case of this substrate we hoped to isolate 422, after retro-aldol reaction of Pauson-Khand adduct 421 (Scheme 131).
The Pauson-Khand reaction of 420 promoted by \( n \)-butyl methyl sulfide\(^{29} \) led to the isolation of the compound 419 (Figure 16) in 34% yield as in the case of terminal alkyne silyl enol ether 417. This indicated that some of the substrate 420 did not react and only acid work up after the Pauson-Khand reaction accounted for the loss of the TMS moiety of the cyclobutanone in substrate 420. Various other unidentifiable products were also isolated from the reaction mixture. The Pauson-Khand reaction of 420 in toluene at reflux also generated complex reaction mixture. Compound 419 was isolated in 3% yield.

2.4.8 Conclusion

The synthesis of important intermediate cyclobutanone 396 was achieved via a high yielding route. Two trimethylsilyl enol ethers 417 (terminal alkyne) and 420 (TMS substituted alkyne) were synthesized using LHMDS as a base and subjected to Pauson-Khand reaction, however desired compounds were not isolated in either case.
3. Conclusion and Future Work

Silicon tethered enynes as substrates for Pauson-Khand reaction

Vinylsilane derived enynes such as \(235b\) undergo a new type of reductive Pauson-Khand reaction\(^{85,86}\) and leads to the synthesis of \(307\) rather than expected \(252b\), as reported by Pagenkopf (Scheme 132). In these vinylsilane derived enynes, carbons bound to the silicon tether are reduced during the course of the reaction and monocyclic cyclopentenones are formed instead of the expected bicyclic cyclopentenones. Pauson-Khand reaction of substrate \(235b\) using Pagenkopf's reaction conditions yielded cyclopentenone \(307\) in 8\% yield. Usually in order to synthesise monocyclic cyclopentenones, high pressures of ethylene gas as well as high temperature are required. This new method is superior to the reaction with ethylene for two main reasons; (i) the reaction does not require high pressures or special equipment and (ii) the use of traceless tether circumvents the regiochemical ambiguity observed in the carbonyl insertion when ethylene is used.

![Reaction Scheme](image)

Scheme 132

The failure of vinylsilane derived enynes to undergo Pauson-Khand reaction to form bicyclic cyclopentenones led to the synthesis of allylsilane derived enynes as substrates for Pauson-Khand reaction. These silicon tethered substrates do undergo Pauson-Khand reaction and the best yields of bicyclic cyclopentenones were obtained when \(n\)-butyl methyl sulfide was used as a promoter of the reaction. However, the desired bicyclic cyclopentenones were obtained in only moderate to poor yields. Several different enynes were prepared with varying substituents at various positions and subjected to the
sulfide promoted Pauson-Khand reaction (Scheme 133). The results of these studies show that substrate scope for silicon tethered Pauson-Khand reaction is currently limited. Yields of this reaction are low and this is attributed in part to the purification problems associated with these cycloadducts and it is hoped that removal of the silicon tether before any flash column chromatography may lead to easier isolation and enhanced yields of the desired compounds.

![Scheme 133](image)

Future work on this methodology would thus involve the removal of the silicon tether by various different methods available, (e.g. Tamao oxidation, use of TBAF) before any purification of the reaction mixture. Future work on this methodology would also involve investigation and optimisation of catalytic Pauson-Khand reaction conditions to effect the cyclisation of allylsilane derived enynes.

**Silyl enol ethers as substrates for the Pauson-Khand reaction**

The trimethylsilyl enol ether derived from diethyl malonate derivative 361b undergoes Pauson-Khand reaction to yield β-hydroxycyclopentenone 364 in 29% yield over 3 steps (Scheme 134).
NEW SUBSTRATES FOR PKR

CONCLUSION AND FUTURE WORK

TMS or TBS enol ethers of the terminal alkyne substrate 361a could not be synthesised (Scheme 135).

The TIPS enol ether of the substrate 361b yielded the desired bicyclic cyclopentenone in only 13% yield whereas the TIPS enol ethers of the terminal alkyne substrate 361a did not undergo Pauson-Khand reaction at all. These results indicate that TIPS may be too sterically demanding a group for the Pauson-Khand reaction to take place.

This methodology was applied to the synthesis of a model substrate for ingenol. Ingenol 372 (Figure 17), is a highly oxygenated tetracyclic diterpene which possesses a unique structure and an array of biological properties. The most imposing obstacle to the synthesis of ingenol is the establishment of highly strained 'inside-outside' or trans intrabridgehead stereochemistry of the B, C ring system.
We hoped that the Pauson-Khand reaction of a silyl enol ether of type 369 would lead to intermediate 370. The retro aldol reaction of this highly strained intermediate 370 would hence lead to the synthesis of A, B and C rings of Ingenol (Scheme 136).

The important intermediate cyclobutanone 396 and its trimethylsilyl enol ethers 417 and 420 were successfully synthesised and subjected to various Pauson-Khand cyclisation conditions, both thermal (toluene, reflux and acetonitrile, reflux) and sulfide promoted (Scheme 137). Unfortunately neither yielded the desired compounds containing the ingenane ring skeleton.
Future work would involve a comprehensive study of Pauson-Khand reaction of the two silyl enol ethers 417 and 420 under a more extensive range of literature conditions for promoting Pauson-Khand reactions.
4. EXPERIMENTAL

4.1 General Experimental Procedures

Melting points were obtained using a Reichert-Jung thermovar hot stage apparatus and are uncorrected.

Proton NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants are recorded in Hertz to the nearest 0.1 Hz.

Carbon-13 NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on Bruker AMX400 spectrometer or 125 MHz on Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Where indicated, carbon-13 NMR were recorded in the presence of a small amount of Cr(acac)$_3$. Where necessary, carbon atoms were assigned using DEPT, HMQC and HMBC experiments. NOE experiments were carried out on a Bruker AVANCE500 spectrometer.

Infrared spectra were recorded as thin films, KBr discs or CHCl$_3$ casts on a SHIMADZU FT-IR 8700 Fourier transform spectrometer. Major features of each spectrum are reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

Low-resolution and high-resolution mass spectra were recorded by the University of London Intercollegiate Research Service and by John Hill (UCL chemistry department service). Low-resolution mass spectra were recorded on a Micromass 70-SE spectrometer and a Micromass ZAB-SE spectrometer using chemical ionisation (CI), electron impact (EI), fast atom bombardment (FAB) or electrospray (esp). Mass spectra marked * were obtained using a Micromass ZAB-SE spectrometer at The University of
London School of Pharmacy. Only molecular ions, fragments from molecular ions and major peaks are reported. High-resolution mass spectra were recorded on a Micromass 70-SE spectrometer.

Microanalyses were performed by Mrs. J. Maxwell, Christopher Ingold Laboratories on a Perkin Elmer 2400 CHN elemental analyser.

Flash chromatography was carried out on BDH silica gel (40-63 μm), Aldrich neutral aluminium oxide (deactivated with 6 wt% water (Grade III), ca. 150 mesh) or Acros Florisil® (100-200 mesh). Thin layer chromatography was performed on pre-coated, aluminium-backed normal phase Merck gel 60 F\textsubscript{254} silica plates. Components were visualised by the quenching of u.v. fluorescence ($\lambda_{\text{max}}$ 254 nm) as well as staining with iodine, vanillin, potassium permanganate or phosphomolybdic acid, all followed by heat.

All reactions in non-aqueous solution were performed under an inert atmosphere of nitrogen or argon, using anhydrous solvents. All glassware was oven-dried (120 °C) and the glassware used for moisture sensitive reactions was flame dried and cooled under a nitrogen or argon atmosphere prior to use.

All solvents were distilled before use. Anhydrous dichloromethane, benzene, toluene, 1,2-dichloroethane and diisopropylamine were obtained by distillation from calcium hydride under a nitrogen atmosphere. Anhydrous diethyl ether and anhydrous THF were obtained by distillation from sodium/benzophenone ketyl under a nitrogen atmosphere. Anhydrous dimethyl sulfoxide, and N,N-dimethylformamide were obtained by stirring over calcium hydride followed by distillation under reduced pressure. Anhydrous acetonitrile was obtained by stirring over phosphorus pentoxide followed by distillation. Petroleum ether 30-40 refers to the fraction of light petroleum ether boiling between 30-40 °C, petroleum ether 40-60 refers to the fraction of light petroleum ether boiling between 40-60 °C and petroleum ether 60-80 refers to the fraction of light petroleum ether boiling between 60-80 °C. Ether refers to diethyl ether.
All other reagents were purified in accordance with the methods described in D. D. Perrin and W. L. F. Armarego, "Purification of laboratory chemicals", Pergamon Press, Third edition, 1988 or used as obtained from commercial sources.

Chemicals were purchased from Sigma-Aldrich Co. Ltd., Lancaster, Fluka, Acros and Avocado.

4.2 Experimental procedures

4.2.1 Synthesis of vinylsilane-derived enynes

**Synthesis of 3-(Dimethylvinylsilyloxy)prop-1-yne 235a**

Using the procedure of Sieburth et al., propargyl alcohol (256, 0.20 g, 3.6 mmol), chlorodimethylvinylsilane (244a, 0.51 mL, 3.8 mmol) and diisopropylethylamine (0.68 mL, 3.9 mmol) were stirred in benzene (3 mL) at rt under nitrogen overnight.

Diethyl ether (5 mL) was added and the reaction mixture was washed with H₂O (2 x 10 mL). The ethereal extract was dried (Na₂SO₄) and concentrated in vacuo to obtain an oil which was purified by flash chromatography (SiO₂, Petrol 60-80 / Ether 99 : 1) to obtain 3-(dimethylvinylsilyloxy)prop-1-yne (235a, 39 mg, 8%) as a pale yellow oil.

δ_H (300 MHz; CDCl₃) 6.15 (1H, dd, J 20.1, 14.9, CH₂=CH), 5.95 (1H, dd, J 14.8, 4.1, 1 of CH₂=CH (cis)), 5.76 (1H, dd, J 20.1, 4.1, 1 of CH₂=CH (trans)), 4.22 (2H, d, J 2.4, HC=CCH₂), 2.40 (1H, t, J 2.4, HC=CCH₂), 0.10 (6H, s, 2 x CH₃).

**Synthesis of 3-(Diphenylvinylsilyloxy)prop-1-yne 235b**

Using the procedure of Sieburth et al., propargyl alcohol (235b, 0.40 g, 7.1 mmol), chlorodiphenylvinylsilane (244b, 1.66 mL, 7.5 mmol) and triethylamine (1.1 mL, 7.9 mmol) were stirred at rt in dry dichloromethane (6 mL) overnight under nitrogen.

Diethyl ether (10 mL) was added to the reaction mixture, which was washed with H₂O (2 x 20 mL). The combined aqueous layers were extracted with diethyl ether (2 x 10
mL). The combined ethereal extracts were dried (MgSO₄) and concentrated in vacuo to obtain 3-(diphenylvinylsilyloxy)prop-1-yne (235b, 1.88 g, 100%) as a clear yellow oil.

120 mg of the product was subjected to flash chromatography (Al₂O₃, Petrol 30-40 / Ether 99 : 1) which led to the decomposition product diphenylvinylsilanol (273, 61.3 mg, 52%)

ν_max (neat)/cm⁻¹ 3267s (O-H), 3049m (=C-H₂), 3000w (C-H), 1591m (C=C), 1428s, 1405m; δ_H (300 MHz; CDCl₃) 7.66-7.62 (4H, m, arom.H), 7.42-7.36 (6H, m, arom.H), 6.51 (1H, dd, J 20.2, 14.9, HC=CH₂), 6.27 (1H, dd, J 14.9, 3.8, 1 of HC=CH₂ (cis)), 5.95 (1H, dd, J 20.2, 3.8, 1 of HC=CH₂ (trans)), 2.30 (1H, s, OMe); δ_C (75 MHz, CDCl₃) 136.5 (HC=CH₂), 135.2 (arom.C₆), 134.61 (HC=CH₂), 134.60 (arom.CH), 130.1 (arom.C₆), 127.9 (arom.CH); m/z (FAB pos)* 227 (MH⁺, 12%), 209 (68), 199 (63), 149 (100), 123 (76), 105 (51).

140 mg of the crude silyl ether was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 99 : 1) to obtain 3-(diphenylvinylsilyloxy)prop-1-yne (235b, 0.10 g, 73%) as an oil.

Found C 77.2, H 6.2; C₁₇H₁₆O₃Si requires C 77.2, H 6.1%; ν_max (neat)/cm⁻¹ 3296m (C=C-H), 3069m (=C-H₂), 3051m (C-H), 1591m (C=C), 1429s, 1404m, 1371m; δ_H (300 MHz; CDCl₃) 7.66-7.63 (4H, m, arom.H), 7.45-7.37 (6H, m, arom.H), 6.53 (1H, dd, J 20.2, 14.9, HC=CH₂), 6.31 (1H, dd, J 15.0, 3.9, 1 of HC=CH₂ (cis)), 5.96 (1H, dd, J 20.1, 3.8 Hz, 1 of HC=CH₂ (trans)), 4.42 (2H, d, J 2.4, H₂CC=CH-H), 2.39 (1H, t, J 2.4, H₂CC=CH-H); δ_C (75 MHz, CDCl₃) 137.6 (HC=CH₂), 135.1 (arom.CH), 133.4 (arom.C₆), 132.9 (HC=CH₂), 130.2 (arom.CH), 127.9 (arom.CH), 81.7 (HC≡C), 73.5 (HC≡C), 52.0 (OCH₂); m/z (FAB pos) 265 (MH⁺, 20%), 209 (MH⁺-CH≡CCH₂OH, 100), 183 (54), 157 (96), 133 (65), 105 (42).
Synthesis of Dicobalt hexacarbonyl complex of 3-(diphenylvinylsilyloxy)prop-1-yne

Using the procedure of Mukai et al., a solution of 3-(diphenylvinylsilyloxy)prop-1-yne (235b, 0.10 g, 0.4 mmol) in hexane (3 mL) was added to dicobalt octacarbonyl (0.16 g, 0.45 mmol), weighed under nitrogen in a glove bag and stirred at rt for 40 minutes.

The reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO₂, hexane / Ether 99 : 1 to 50 : 50) to obtain the dicobalt hexacarbonyl complex of 3-(diphenylvinylsilyloxy)prop-1-yne (279, 0.10 g, 46%) as a dark red oil.

δH (300 MHz; CDCl₃) 7.64 (4H, br s, arom.H), 7.41 (6H, br s, arom.H), 6.48 (1H, br d, J 18.2, HC=CH₂), 6.31 (1H, br d, J 11.5, HC=CH₂ cis), 5.99-5.90 (1H, m, HC=CH₂ trans), 5.89 (1H, br s, OCH₂CCH), 4.93 (2H, br s, OCH₂).

Synthesis of Diethyl propargylmalonate 276a

Using the procedure of Marvel and Hager, diethyl malonate (274, 15.5 g, 97 mmol) was added to a solution of sodium ethoxide prepared by the addition of sodium (1.93 g, 84 mmol), in small pieces, to ethanol (37 mL) under nitrogen. The reaction mixture was warmed to 50 °C and propargyl bromide (275, 12.5 mL, 84 mmol) was added dropwise. The reaction mixture was heated to reflux for 4 h.

Ethanol was removed in vacuo and H₂O (30 mL) was added. The organic layer was removed and the aqueous layer was extracted with diethyl ether (5 x 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Toluene / EtOAc 99 : 1) afforded diethyl propargylmalonate (276a, 7.5 g, 45%) as a colourless oil.
New Substrates for PKR

(O$_2$CCHCO$_2$), 18.4 (H$_2$CC=CH), 14.0 (OCH$_2$CH$_3$); m/z (FAB pos) 221 (MNa$^+$, 28%), 217 (50), 176 (100); HRMS calculated for C$_{18}$H$_{14}$O$_4$ (MNa$^+$) 221.0790 Found 221.0793.

A side product of the reaction diethyl dipropargylmalonate (277a, 2.4 g, 12%) was isolated as a white crystalline solid.

SYNTHESIS OF DIETHYL ALLYLPROPARGYLMALONATE 59

Using the procedure of Trost et al.$^{90}$, a mixture of diethyl propargylmalonate (274, 0.85 g, 4.3 mmol), allyl bromide (278, 1.56 g, 12.9 mmol) and K$_2$CO$_3$ (1.78 g, 12.9 mol) in acetone (15 mL) under nitrogen was heated to reflux overnight.

The reaction mixture was filtered and concentrated to obtain a yellow oil, which was purified by flash chromatography (SiO$_2$, hexane / Ether 4 : 1) to obtain diethyl allylpropargylmalonate (59, 0.55 g, 54%) as a clear colourless oil.

Found C 65.4 H 7.8; C$_{13}$H$_{18}$O$_4$ requires C 65.5 H 7.6%; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3287m (C≡C-H), 2982m & 2937w (C-H), 1738s (C=O), 1650w (C=C), 1444m, 1367m; $\delta_{\text{H}}$ (500 MHz; CDCl$_3$) 5.62 (1H, ddt, J 17.5, 10.1, 7.5, HC=CH$_2$), 5.18 (1H, ddt, J 17.0, 1.9, 1.3, 1 of HC=CH$_2$ (trans)), 5.12 (1H, ddt, J 10.1, 2.0, 1.0, 1 of HC=CH$_2$ (cis)), 4.21 (4H, q, J 7.2, OCH$_2$), 2.80 (2H, dt, J 7.5, 1.0, H$_2$CH=CH$_2$), 2.79 (2H, d, J 2.7, HC=CCH$_2$), 2.01 (1H, t, J 2.7, HC=C), 1.25 (6H, t, J 7.2, CH$_3$); $\delta_{\text{C}}$ (125 MHz, CDCl$_3$) 169.7 (C=O), 131.7 (H$_2$C=CH), 119.8 (H$_2$C=CH), 78.9 (HC=C), 71.4 (HC=C), 61.7 (OCH$_2$), 56.6 (CO$_2$CCO$_2$), 36.3 (H$_2$C=CHCH$_2$), 22.5 (HC=CHCH$_2$), 14.0 (CH$_3$); m/z (FAB pos$^*$) 239 (MH$^+$, 100%), 137 (49), 105 (10).
Synthesis of Diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate 61

Method 1
A solution of dicobalt octacarbonyl (0.17 g, 0.5 mmol) in dichloromethane (3 mL) was added to diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) and stirred at rt under nitrogen for 1 h. The reaction mixture was concentrated to obtain a reddish brown residue which was purified by flash chromatography (Petrol 30-40 / Et₂O 99 : 1) to obtain a brown oil. The ¹H NMR spectrum was broad and inconclusive, however IR showed a Co-C=O stretch at 2100 cm⁻¹. The complex (60) was heated to reflux in toluene (2 mL) for 1 h. The reaction mixture was filtered through Celite® and concentrated in vacuo to obtain a brown solid which was purified by flash chromatography (SiO₂, hexane / EtOAc 7 : 3) to obtain diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 18 mg, 30%) as a light yellow oil.

Method 2
Using the procedure of Mukai et al., a solution of dicobalt octacarbonyl (0.17 g, 0.5 mmol) in dichloromethane (4 mL) was added to diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) and stirred at rt under nitrogen for 1 h. The reaction mixture was concentrated to obtain the crude complex (60), which was dissolved in acetonitrile (5 mL) and heated at 75 °C under nitrogen for 1 h. The mixture was concentrated in vacuo and the residue purified by flash chromatography (SiO₂, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 49.8 mg, 44%) as a yellow oil.

Method 3
Using the procedure of Schreiber et al., a solution of dicobalt octacarbonyl (0.17 g, 0.5 mmol) in dichloromethane (3 mL) was added to diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) and stirred at rt under nitrogen for 1 h. The reaction mixture was concentrated in vacuo to obtain the complex (60), which was dissolved in THF (15 mL) and added to N-methylmorpholine-N-oxide monohydrate (0.40 g, 3 mmol), at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 4 h, then filtered through Celite®.
concentrated \textit{in vacuo} and purified by flash chromatography (SiO$_2$, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 29.0 mg, 23%) as a yellow oil.

\textbf{Method 4}

Using the procedure of Sugihara \textit{et al.}\textsuperscript{28}, a solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in ether (3 mL) was added to dicobalt octacarbonyl (0.17 g, 0.50 mmol), weighed under nitrogen in a glove bag. The resulting mixture was stirred at rt under nitrogen for 30 minutes, then concentrated \textit{in vacuo} and the resulting complex dissolved in 1:3 dioxane/2 M NH$_4$OH (4.20 mL) and heated at 100 °C for 1 h. Diethyl ether (10 mL) was added to the reaction mixture and the resulting suspension filtered through cotton wool. The filtrate was washed with H$_2$O (2 x 50 mL) and the combined aqueous layers were extracted with diethyl ether (4 x 20 mL). The ethereal extracts were combined and successively washed with 5% HCl (2 x 50mL), saturated NaHCO$_3$ (2 x 50mL), dried (MgSO$_4$), and concentrated \textit{in vacuo} to obtain the crude product which was purified by flash chromatography (SiO$_2$, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 35 mg, 31%) as a yellow oil.

\textbf{Method 5}

Using the procedure of Sugihara \textit{et al.}\textsuperscript{29}, a solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in 1,2-dichloroethane (4.2 mL) was added to dicobalt octacarbonyl (0.17 g, 0.5 mmol), which was weighed in a glove bag under nitrogen and stirred at rt for 20 minutes. \textit{n}-Butyl methyl sulfide (0.15 g, 1.5 mmol) was added to the reaction mixture and heated to reflux for 50 minutes. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO$_2$, hexane / EtOAc 7 : 3) to obtain diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 38 mg, 34%) as a yellow oil.

\textbf{Method 6}

Using the procedure of Smit \textit{et al.}\textsuperscript{31}, a solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in ether (3 mL) was added to dicobalt octacarbonyl (0.17 g, 0.5 mmol), which was weighed under nitrogen in a glove bag, and stirred at rt for 15 minutes. The reaction mixture was concentrated \textit{in vacuo} and the resulting dark
orange/brown complex was dissolved in pentane (15 mL). Silica gel (3.8 g) was added and the reaction mixture was agitated on a rotary evaporator at atmospheric pressure for 40 minutes. The solvent was removed \textit{in vacuo} and the residue was heated to 50 °C on a rotary evaporator for 3.5 h in a stream of air. The residue was loaded directly onto a flash chromatography column. Flash chromatography (SiO\textsubscript{2}, hexane / EtOAc 7 : 3) afforded diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 62 mg, 55%) as a slightly yellow oil.

**Method 7**

Dicobalt octacarbonyl (0.17 g, 0.50 mmol) was weighed into a pressure tube under nitrogen in a glove bag. A solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in acetonitrile (5 mL) was added and the mixture was stirred at rt for 1 h. Carbon monoxide was bubbled through the solution for 1 minute and the sealed tube was then heated at 75 °C for 2.5 h. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 28 mg, 25%) as a yellow oil.

**Method 8**

Dicobalt octacarbonyl (0.20 g, 0.6 mmol) was weighed into a pressure tube under nitrogen in a glove bag. A solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in toluene (5 mL) was added and the reaction mixture was stirred at rt for 30 minutes. Carbon monoxide was bubbled through the solution for about 1 minute and the sealed tube was then heated at 80 °C overnight. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 17 mg, 15%) as a yellow oil.

**Method 9**

Dicobalt octacarbonyl (0.19 g, 0.55 mmol) was weighed into a pressure tube under nitrogen in a glove bag. A solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in toluene (5 mL) was added and the reaction mixture was stirred at rt for 20 minutes. Carbon monoxide was bubbled through the solution for 1 minute and the
sealed tube was heated at 110 °C for 6 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO₂, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 23 mg, 20%) as a pale yellow oil.

**Method 10**
A solution of diethyl allylpropargylmalonate (59, 0.10 g, 0.4 mmol) in degassed hexane (3 mL) was added to dicobalt octacarbonyl (0.17 g, 0.5 mmol), weighed into a pressure tube in a glove bag under nitrogen, and stirred at rt for 20 minutes. Carbon monoxide was bubbled through the reaction mixture for 1 minute and the sealed pressure tube was heated to 69 °C for 1.5 h.

The reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography (SiO₂, hexane / EtOAc 7 : 3) to obtain diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (61, 65 mg, 58%) as a yellow oil.

\[ \text{v}_{\text{max}} (\text{neat})/\text{cm}^{-1}: 2983 \text{m}, 2937 \text{s} (\text{C-H}), 1732 \text{s} (\text{C=O ester}), 1713 \text{s} (\text{C=O ketone}), 1635 \text{s} (\text{C=C}), 1447 \text{s}, 1367 \text{s}; \delta_{\text{H}} (400 \text{ MHz}; \text{CDCl}_3) 5.93 (1H, br s, \text{H}C=\text{C}), 4.24 (2H, q, J 7.1, \text{OCH}_2), 4.20 (2H, q, J 7.1, \text{OCH}_2), 3.35 (1H, d, J 19.0, 1 of H_2\text{CC=CH}), 3.25 (1H, d, J 18.8, 1 of H_2\text{CC=CH}), 3.10-3.05 (1H, m, H_2\text{CCHCH}_2), 2.79 (1H, dd, J 12.8, 7.7, 1 of OCCHCH_2), 2.63 (1H, dd, J 17.9, 6.4, 1 of CH_2CHCHCH_2), 2.13 (1H, dd, J 17.9, 3.3, 1 of CH_2CHCHCH_2), 1.73 (1H, t, J 12.7, 1 of OCCHH_2), 1.28 (3H, t, J 7.1, CH_3), 1.25 (3H, t, J 7.1, CH_3); \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 209.5 (\text{C=O ketone}), 185.5 (\text{C=O ester}), 171.5 (\text{C=O ester}), 170.4 (\text{C=CH}), 125.6 (\text{C=CH}), 62.1 (\text{OCH}_2), 62.0 (\text{OCH}_2), 60.8 (\text{CO}_2\text{CCO}_2), 45.0 (\text{CH}), 42.1 (\text{HC=CCCH}_2), 38.9 (\text{OCCH}_2), 35.1 (\text{CH}_2\text{CHCHCH}_2), 14.0 (\text{CH}_3); m/z (\text{EI}^*) 267 (\text{MH}^+, 40\%), 266 (\text{M}^+, 99), 221 (50), 192 (100), 173 (55), 165 (68); \text{HRMS calculated for C}_{14}\text{H}_{19}\text{O}_5 (\text{MH}^+) 267.1240 \text{ Found 267.1232.}

**Synthesis of Dimethyl(3-phenylprop-2-ynyloxy)vinylsilane 286**

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{Si} \\
\end{array}
\]

Chlorodimethylvinylsilane (244a, 0.22 mL, 1.6 mmol) was added dropwise to a solution of 3-phenyl-2-propyn-1-ol (329, 0.20 g, 1.5 mmol) and triethylamine (0.23 mL, 1.7 mmol) in dichloromethane (10 mL) under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes and then at rt overnight.
The reaction mixture was quenched with sat. aqueous NH₄Cl (10 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried (MgSO₄) then concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, hexane / EtOAc 97 : 3) afforded dimethyl(3-phenylprop-2-ynyloxy)vinylsilane (286, 0.20 g, 60%) as a clear yellow oil.

\[ v_{\text{max}} \text{ (neat)/cm}^{-1} \] 3013m (=C-H₂), 2959m & 2856m (C-H), 2280w (C=C), 1595w (C=C aromatic), 1489s (C=C aromatic), 1367s, 1256s; \( \delta_1 \) (300 MHz; CDCl₃) 7.45-7.41 (2H, m, arom.H), 7.31-7.28 (3H, m, arom.H), 6.21 (1H, dd, \( J = 20.0 \), 15.0, \( H_2 \text{C}=CH \)), 6.07 (1H, dd, \( J = 15.0 \), 4.4, 1 of \( H_2 \text{C}=CH \) (cis)), 5.85 (1H, dd, \( J = 20.0 \), 4.4, 1 of \( H_2 \text{C}=CH \) (trans)), 4.52 (2H, s, OCH₂), 0.29 (6H, s, 2 x CH₃); 8C (75 MHz; CDCl₃) 136.9 (HC=CH₂), 133.7 (SiCH), 131.6 (arom.CH), 128.3 (arom.CH), 128.2 (arom.CH), 122.9 (arom.C₆), 87.5 (PhC=O), 85.1 (OCH₂C=C), 51.8 (OCH₂), -1.9 (2 x CH₃); \( m/z \) (El) 216 (M⁺, 18%), 201 (65), 171 (100), 115 (89), 75 (60).

**Synthesis of 3-Methyl-2-phenylcyclopent-2-enone 215**

A solution of dimethyl(3-phenylprop-2-ynyloxy)vinylsilane (286, 0.14 g, 0.63 mmol) in acetonitrile (0.5 mL) was added to a stirred solution of dicobalt octacarbonyl (0.22 g, 0.63 mmol) and H₂O (23 µL, 1.3 mmol) in acetonitrile (2.5 mL), under nitrogen. After stirring for 1h at rt, the reaction flask was placed into a preheated oil bath (135 °C) to bring the reaction mixture quickly to reflux. After 30 minutes the reaction flask was removed from the oil bath and allowed to cool to rt. The volatile components were removed in vacuo and the residue was purified by flash chromatography (SiO₂, hexane / EtOAc 3 : 2) to afford 3-methyl-2-phenylcyclopent-2-enone (215, 69 mg, 63%) as a pale yellow oil.

\[ v_{\text{max}} \text{ (CHCl₃ cast)/cm}^{-1} \] 2922s & 2852s (C-H), 1682s (C=O), 1634s (C=C aromatic), 1495s (C=C aromatic), 1464s, 1379s; \( \delta_1 \) (300 MHz; CDCl₃) 7.41-7.36 (2H, m, arom.H), 7.31-7.27 (3H, m, arom.H), 2.66-2.63 (2H, m, OCCCH₂), 2.55-2.52 (2H, m, OCCH₂CH₂), 2.16 (3H, s, CH₃); 8C (75 MHz; CDCl₃) 207.4 (C=O), 171.5 & 140.4 (C=C), 131.8 (arom.C₆), 129.1 (arom.CH), 128.2 (arom.CH), 127.5 (arom.CH), 34.8 (OCCH₂), 31.8 (OCCH₂CH₂), 18.3 (CH₃); \( m/z \) (El) 172 (M⁺, 11%), 129 (86), 115 (100).
NEW SUBSTRATES FOR PKR

EXPERIMENTAL

Synthesis of 3-Methylcyclopent-2-enone

Using the procedure of Pagenkopf et al.⁸⁶, a solution of 3-O (diphenylvinylsilyloxy)prop-1-yn (235b, 0.19 g, 0.72 mmol) in acetonitrile (0.66 mL) was added to a stirred solution of dicobalt octacarbonyl (0.22 g, 0.7 mmol) and H₂O (26 µL, 1.4 mmol) in acetonitrile (2.9 mL) under nitrogen. After stirring for 1 h at rt, the reaction flask was placed into a preheated oil bath (135 °C) to bring the reaction mixture quickly to reflux. After 30 minutes the reaction flask was removed from the oil bath and allowed to cool to rt. The volatile components were removed in vacuo and the residue was purified by flash chromatography (SiO₂, hexane / EtOAc 3 : 2) to afford 3-methylcyclopent-2-enone (307, 5 mg, 8%) as a pale yellow oil.

υ max (CHCl₃ cast)/cm⁻¹: 2924m & 2361s (C-H), 1618 br, m (C=O + C=C); δH (300 MHz; CDCl₃) 5.95 (1H, s, C=CH), 2.59-2.57 (2H, m, OCCH₂), 2.43-2.40 (2H, m, OCCH₂CH₂), 2.14 (3H, s, CH₃); δC (75 MHz; CDCl₃) 209.5 (C=0), 178.7 (H₃CC=CH), 130.3 (H₃CC=CH), 35.4 (OCCH₂), 32.7 (OCCH₂CH₂), 19.1 (CH₃); m/z (EI) 96 (M⁺, 100%); HRMS calculated for C₆H₉O (M⁺) 96.0575, Found 96.0571.

4.2.2 Synthesis of allylsilane-derived enynes

Synthesis of Allyldimethyl(3-phenylprop-2-ynyloxy)silane 327a

Using the procedure of Pagenkopf et al.⁸⁶, allylchlorodimethylvinylsilane (330a, 0.34 mL, 2.2 mmol) was added dropwise to a solution of 3-phenyl-2-propyn-1-ol (329, 0.31 g, 2.4 mmol) and triethylamine (0.62 mL, 4.5 mmol) in dichloromethane (8 mL) under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes and then at rt overnight. The reaction mixture was quenched with sat. aqueous NH₄Cl (8 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed successively with H₂O (20 mL) and brine (20 mL). The organic layer was dried (Na₂SO₄) and then concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Petrol 40-60 / Ether 98 : 2) afforded allyldimethyl(3-phenylprop-2-ynyloxy)silane (327a, 0.14 g, 78%) as a yellow oil.
New Substrates for PKR

Experimental

\[ \text{v}_{\text{max}} \text{(neat/cm}^{-1} 3077\text{m (=C-H}), 2959\text{m} \& 2859\text{m (C-H)}, 1630\text{s} \text{(C=C)}, 1599\text{m (C=C aromatic)}, 1490\text{s (C=C aromatic)}, 1443\text{m}, 1419\text{m}, 1368\text{s}; \delta_H (400 \text{MHz}; \text{CDCl}_3) 7.46-7.43 \text{(2H, m, arom.H)}, 7.33-7.30 \text{(3H, m, arom.H)}, 5.85 \text{(1H, ddt, J 16.8, 10.0, 8.1, SiCH}_2\text{CH}_2) 4.97-4.89 \text{(2H, m, C=CH}_2) 4.55 \text{(2H, s, OCH}_2) 1.74 \text{(2H, d, J 8.1, SiCH}_2) 0.23 \text{(6H, s, 2 x CH}_3); \delta_C (75 \text{MHz; CDCl}_3) 133.7 \text{(HC=CH}_2) 131.6 \text{(arom.CH)} 128.32 \text{(arom.CH)} 128.26 \text{(arom.CH)} 122.8 \text{(arom.C}_q) 114.0 (=\text{CH}_2) 87.4 \& 85.1 \text{(C=C)} 51.9 \text{(OCH}_2) 24.5 \text{(SiCH}_2) -2.3 (2 x \text{CH}_3); \text{m/z (Cl pos) 230 (M}^+, 41%), 229 (62), 189 (100), 115 (79).

Synthesis of Dicobalt hexacarbonyl complex of Allyldimethyl(3-phenylprop-2-ynyloxy)silane 331a

\[
\text{(OC)}_3\text{Co} - \text{Co(CO)}_3
\]

Using the procedure of Mukai et al.\textsuperscript{91}, a solution of allyldimethyl(3-phenylprop-2-ynyloxy)silane (327a, 0.10 g, 0.4 mmol) in dichloromethane (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.39 g, 1.1 mmol) in dichloromethane (2 mL), under nitrogen at rt. The resulting reaction mixture was stirred at rt for 1 h and then concentrated \textit{in vacuo} at rt. The residue was purified by flash chromatography (Florisil\textsuperscript{®}, Petrol 40-60) to afford dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (331a, 0.20 g, 89%) as a deep red oil.

\[ \text{v}_{\text{max}} \text{(CHCl}_3 \text{ cast/cm}^{-1} 2960\text{w (=C-H)}, 2918\text{m (C-H)}, 2091\text{s} \& 2051\text{s (Co-C=O)}, 1650\text{m (C=C)}, 1475\text{m (C=C aromatic)}, 1425\text{m}, 1258\text{s}; \delta_H (300 \text{MHz; CDCl}_3) 7.54-7.52 \text{(2H, br m, arom.H)}, 7.34-7.32 (3H, br m, arom.H), 5.92-5.78 \text{(1H, br m, HC=CH}_2) 5.01 \text{(2H, br s, OCH}_2) 4.97-4.88 \text{(2H, br m, C=CH}_2) 1.72 \text{(2H, br d, J 7.9, SiCH}_2) 0.21 \text{(6H, s, 2 x CH}_3); \delta_C (75 \text{MHz; CDCl}_3 + \text{Cr(acac)}_3) 199.5 \text{(C=O)} 137.8 \text{(arom.C}_q) 133.7 \text{(HC=CH}_2) 129.7 \text{(arom.CH)} 128.8 \text{(arom.CH)} 127.8 \text{(arom.CH)} 114.0 \text{(HC=CH}_2) 97.1 \& 89.7 ((\text{OC})_3\text{CoC=CCo(CO)}_3) 63.5 \text{(OCH}_2) 24.3 \text{(SiCH}_2) -2.8 (2 x \text{CH}_3); \text{m/z (ES pos) 413 (37), 349 (29), 305 (45), 301 (39), 261 (100).} \]
Synthesis of 3,3-Dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328a

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{Si} \\
\text{O}
\end{array}
\]

**Method 1**

A solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (331a, 0.10 g, 0.2 mmol) in toluene (1 mL) was heated to reflux under nitrogen for 2 h. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328a, 20 mg, 40%) as a yellow oil.

**Method 2**

Using the procedure of Mukai et al.\(^{91}\), a solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (331a, 0.10 g, 0.2 mmol) in acetonitrile (1 mL) was heated to reflux under nitrogen overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328a, 20 mg, 39%) as a yellow oil.

**Method 3**

Using the procedure of Pagenkopf et al.\(^{86}\), a solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (331a, 0.10 g, 0.2 mmol) and H\(_2\)O (7.7 \(\mu\)L, 0.39 mmol) in acetonitrile (0.77 mL) under nitrogen was heated to reflux overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328a, 16 mg, 33%) as a yellow oil.

**Method 4**

Using the procedure of Sugihara et al.\(^{29}\), a solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (331a, 0.20 g, 0.4 mmol) and n-butyl
methyl sulfide (0.17 mL, 1.4 mmol) in 1,2-dichloroethane (3.9 mL) under nitrogen was heated to reflux overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328a, 72 mg, 72%) as a yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2955m & 2922m (C-H), 1699s (C=O), 1630w (C=C aromatic), 1495m (C=C aromatic), 1445m, 1406m, 1254s; $\delta_h$ (400 MHz; CDCl$_3$) 7.42-7.25, (5H, m, arom.$H$), 4.95 (1H, d, $J$ 16.3, 1 of OCH$_2$), 4.80 (1H, d, $J$ 16.3, 1 of OCH$_2$), 3.25-3.19 (1H, m, SiCH$_2$CH), 2.93 (1H, dd, $J$ 18.9, 6.4, 1 of OCCH$_2$), 2.25 (1H, dd, $J$ 18.2, 1.6, 1 of OCCH$_2$), 1.35 (1H, dd, $J$ 14.3, 5.1, 1 of SiCH$_2$), 0.76 (1H, t, $J$ 13.9, 1 of SiCH$_2$), 0.31 (3H, s, CH$_3$), 0.21 (3H, s, CH$_3$); $\delta_C$ (75 MHz; CDCl$_3$) 128.3 (O=CPh), 130.7 (arom.$C_\alpha$), 128.9 (arom.CH), 128.3 (arom.CH), 130.0 (OCH$_2$C=C), 138.0 (C=CPh), 62.3 (OCH$_2$), 45.8 (OCCH$_2$), 35.4 (SiCH$_2$CH), 21.6 (SiCH$_2$), -0.85 (CH$_3$), -2.0 (CH$_3$); m/z (CI pos) 259 (MH$^+$, 98%), 185 (25), 40 (100); HRMS calculated for C$_{15}$H$_{19}$O$_2$Si (MH$^+$) 259.11543 Found 259.11504.

Synthesis of 3,4-Di(hydroxymethyl)-2-phenylcyclopent-2-enone 332

Using the procedure of Tamao et al.\textsuperscript{92}, a solution 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328a, 72 mg, 0.28 mmol) in 1:1 THF/MeOH (0.76 mL) was added to a flask containing potassium hydrogen carbonate (28.0 mg, 0.28 mmol) and potassium fluoride (32.0 mg, 0.56 mmol) under nitrogen at rt. The flask was opened to air and 30% hydrogen peroxide in water (0.11 mL, 0.92 mol) was added in one portion. The resulting reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt. The reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt.
dd, *J* 10.2, 8.8, 1 of HOC=CH), 3.39-3.35 (1H, m, HOCH=CH), 2.75 (1H, dd, *J* 18.8, 7.1, 1 of OCCH), 2.21 (1H, dd, *J* 18.8, 2.5, 1 of OCCH); δC (100 MHz; CDCl₃) 206.0 (C=O), 172.2 (HOCH=C=O), 141.5 (C=CPh), 130.6 (arom.C₆), 129.2 (arom.CH), 128.38 (arom.CH), 128.37 (arom.CH), 65.3 (HOCH₂C=O), 60.0 (HOCH₂CH), 41.8 (OCCH₂) 38.1 (HOCH₂CH); *m/z* (ES pos) 241 (MNa⁺, 100%), 200 (18), 102 (29); HRMS calculated for C₁₃H₁₄O₃Na (MNa⁺) 241.0835 Found 241.0842.

18 mg of another impure compound was also isolated and could be tentatively identified as 2,3-epoxy-3,4-di(hydroxymethyl)-2-phenylcyclopentanone 333, by the following signals in its ¹H NMR spectrum.

![2,3-epoxy-3,4-di(hydroxymethyl)-2-phenylcyclopentanone](image)

δH (300 MHz; CDCl₃) 3.70 (1H, d, *J* 12.7, 1 of OCCHOH), 3.50 (1H, d, *J* 12.7, 1 of OCCH₂OH), 2.98-2.93 (1H, m, HOCH₂CH), 2.79 (1H, dd, *J* 17.9, 8.8, 1 of HOCH₂CH), 2.43 (1H, dd, *J* 18.1, 8.7, 1 of OCCH₂), 2.15 (1H, dd, *J* 17.9, 1.1, 1 of HOCH₂CH), 2.14 (1H, dd, *J* 18.1, 8.4, 1 of OCCH₂).

**Synthesis of Diphenyldi(3-phenylprop-2-ynyloxy)silane 337**

Using the procedure of Wei et al.⁹⁵, a solution of triethylamine (0.33 mL, 2.4 mmol) and 3-phenyl-2-propyn-1-ol (329, 0.21 g, 1.60 mmol) in THF (1.3 mL) was added dropwise to a stirred solution of dichlorodiphenylsilane (335, 0.17 mL, 0.79 mmol) in THF (0.4 mL) at rt under argon was added. The reaction mixture was heated to reflux for 2.5 h.

The reaction mixture was quenched with sat. aqueous NH₄Cl (5 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (5 x 15 mL). The combined organic extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 97 : 3) afforded diphenyldi(3-phenylprop-2-ynyloxy)silane (337, 0.20 g, 57%) as a colourless oil.
**NEW SUBSTRATES FOR PKR**

\[ v_{\text{max}} \text{ (neat)/cm}^{-1} \]

- 3071 s (C-H), 2972 m & 2922 m (C-H), 2359 w (C=C), 1591 s (C=C aromatic), 1570 m (C=C aromatic), 1489 s (C=C aromatic), 1443 s, 1429 s, 1375 s; \( \delta_H \) (300 MHz; CDCl\(_3\)) 7.82-7.79 (4H, m, arom.\( H \)), 7.47-7.36 (10H, m, arom.\( H \)), 7.31-7.27 (6H, m, arom.\( H \)), 4.78 (4H, s, OCH\(_2\)); \( \delta_C \) (75 MHz; CDCl\(_3\)) 135.1 (arom.\( CH \)), 131.70 (arom.\( CH \)), 130.6 (arom.\( CH \)), 128.3 (arom.\( CH \)), 128.2 (arom.\( CH \)), 127.9 (arom.\( CH \)), 122.8 (arom.\( C_q \)), 87.0 & 85.4 (C=C), 52.4 (OCH\(_2\)); \( m/z \) (FAB pos) 467 (MNa\(^+\), 17%), 444 (M\(^+\), 20), 307 (52), 283 (100), 223 (35), 199 (45); HRMS calculated for C\(_{30}\)H\(_{24}\)O\(_2\)Si (M\(^+\)) 444.1546 Found 444.1540.

**Experimental**

**Synthesis of Allyldiphenyl(3-phenylprop-2-ynyloxy)silane 327b**

Using the procedure of Garner et al.\(^{94,96}\), a solution of phenylmagnesium bromide (1.0M in THF, 2.3 mL, 2.3 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (338, 0.17 mL, 1.1 mmol) in diethyl ether (1 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (330b) in solution. This solution was cooled to rt and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (329, 0.15 g, 1.1 mmol) and triethylamine (0.16 mL, 1.1 mmol) in dichloromethane (8 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 3.4 mL) were also transferred to the flask containing 3-phenyl-2-propyn-1-ol and triethylamine. The reaction mixture was stirred at 0 °C for 40 minutes followed by stirring at rt overnight under argon.

The reaction mixture was quenched with sat. aqueous NH\(_4\)Cl (15 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO\(_2\), hexane / Et\(_3\)N 99 : 1) afforded allyldiphenyl(3-phenylprop-2-ynyloxy)silane (327b, 0.20 g, 50%) as a colourless oil.

\[ v_{\text{max}} \text{ (CHCl}_3\text{ cast)/cm}^{-1} \]

- 3071 s (=C-H\(_2\)), 2972 m & 2862 m (C-H), 2150 w (C=C), 1630 s (C=C), 1589 m (C=C aromatic), 1489 s (C=C aromatic), 1443 m, 1429 m, 1371 s; \( \delta_H \) (500 MHz; CDCl\(_3\)) 7.68-7.66 (4H, m, arom.\( H \)), 7.44-7.29 (11H, m, arom.\( H \)), 5.90 (1H, ddt, \( J \) 18.0, 10.1, 7.9, \( HC=CH\(_2\) \)), 4.99 (1H, ddt, \( J \) 17.0, 1.9, 1.5, 1 of \( HC=CH\(_2\) \) (trans)), 4.92
NEW SUBSTRATES FOR PKR

(1H, ddt, J 10.1, 1.9, 1.0, 1 of HC=CH2 (cis)), 4.63 (2H, s, OCH2), 2.30 (2H, dt, J 7.9, 1.2, SiCH2); δC (75 MHz; CDCl3) 134.9 (arom.CH), 133.9 (arom.Cq), 132.7 (HC=CH2), 131.6 (arom.CH), 130.1 (arom.CH), 128.3 (arom.CH), 128.2 (arom.CH), 127.9 (arom.CH), 122.8 (arom.Cq), 115.4 (C=CH2), 87.3 & 85.6 (C=C), 52.8 (OCH2), 22.0 (SiCH2); m/z (FAB pos) 377 (MNa+, 2%), 338 (9), 313 (35), 283 (100) 199 (41); HRMS calculated for C24H22OSiNa (MNa+) 377.1338 Found 377.1334.

**Synthesis of Dicobalt hexacarbonyl complex of Allyldiphenyl(3-phenylprop-2-ynylxylosilane 331b**

Using the procedure of Mukai et al.91, a solution of allyldiphenyl(3-phenylprop-2-ynylxylosilane (327b, 0.58 g, 1.6 mmol) in dichloromethane (6 mL) was added to a solution of dicobalt octacarbonyl (0.76 g, 2.2 mmol) in dichloromethane (7 mL) under argon at rt. The resulting reaction mixture was stirred at rt for 6 h. The reaction mixture was concentrated in vacuo at rt and the residue was purified by flash chromatography (Florisil®, hexane / Ether 100 : 0 to 99 : 1) to afford dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynylxylosilane (331b, 0.97 g, 93%) as a deep red oil.

νmax (neat)/cm⁻¹ 3072s (=C=H2), 3055s (C-H), 2091s & 2016s (Co-C=O), 1632s (C=C), 1575m (C=C aromatic), 1483m (C=C aromatic), 1443m, 1429s, 1356m; δH (400 MHz; CDCl3) 7.67(4H, br m, arom./), 7.50-7.30 (11H, br m, arom./), 5.88 (1H, br m, HC=CH2), 5.12 (2H, s, OCH2), 4.99 (1H, br d, J 16.9, HC=CH2 (trans)), 4.93 (1H br d, J 9.9 HC=CH2 (cis)), 2.28 (2H, br d, J 7.7, SiCH2); δC (100 MHz; CDCl3 + Cr(acac)3) 199.3 (C=O), 137.7 (arom.Cq), 134.8 (arom.CH), 133.6 (arom.Cq), 132.6 (HC=CH2), 130.2 (arom.CH), 129.7 (arom.CH), 128.8 (arom.CH), 127.9 (arom.CH), 127.8 (arom.CH), 115.4 (HC=CH2), 96.0 & 90.1 ((OC)3CoC–CCo(CO)3), 64.4 (OCH2), 21.6 (SiCH2); m/z (Cl Pos) 641 (MH+, 3%), 556, (63), 472 (45), 401 (100); HRMS calculated for C30H32O7SiCo2 (MH+) 640.9877 Found 640.9896.
NEW SUBSTRATES FOR PKR

SYNTHESIS OF 3,3,7-TRIPHENYL-4-OXA-3-SILABICYCLO[4.3.0]NON-6-EN-8-ONE 328b

Method 1
A solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (331b, 0.16 g, 0.25 mmol) in toluene (2.5 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO₂, hexane / Ether 7 : 3) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328b, 27 mg, 28%) as a white foam.

Method 2
Using the procedure of Mukai *et al*., a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (331b, 0.13 g, 0.2 mmol) in acetonitrile (0.8 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO₂, Petrol 40-60 / Ether 3 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328b, 27 mg, 35%) as a white foam.

Method 3
Using the procedure of Pagenkopf *et al*., a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (331b, 0.13 g, 0.20 mmol) and H₂O (8.1 µL, 0.44 mmol) in acetonitrile (0.8 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO₂, Petrol 40-60 / Ether 3 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328b, 37 mg, 48%) as a white foam.

Method 4
Using the procedure of Perez-Castells *et al*., a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (331b, 0.14 g, 0.22 mmol) in
toluene (8.7 mL) containing activated 4Å molecular sieve powder (1.12 g), was stirred at rt under argon for 1 h. The reaction mixture was heated to reflux under argon for 4.5 h, then cooled, concentrated in vacuo and the residue was purified by flash chromatography (SiO₂, Petrol 40-60 / Ether 7 : 3) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328b, 13 mg, 15%) as a white foam.

**Method 5**

Using the procedure of Schreiber et al.²⁵, a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynloxy)silane (331b, 0.14 g, 0.22 mmol) in dichloromethane (40 mL) under argon was treated with a single portion of 4-methylmorpholine-N-oxide monohydrate (0.18 g, 1.3 mmol). The resulting reaction mixture was stirred at rt overnight, then concentrated in vacuo and purified by flash chromatography (SiO₂, Petrol 40-60 / Ether 4 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328b, 37 mg, 45%) as a white foam.

**Method 6**

Using the procedure of Sugihara et al.²⁹, a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynloxy)silane (331b, 0.16 g, 0.24 mmol) and n-butyl methyl sulfide (0.11 mL, 0.85 mmol) in 1,2-dichloroethane (2.44 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated in vacuo and the residue was purified by flash chromatography (SiO₂, Petrol 40-60 / Ether 3 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328b, 65 mg, 70%) as a white foam.

m.p.: 59 °C; ν max (KBr)/cm⁻¹ 2924s & 2853m (C-H), 1701s (C=O), 1429m (C=C aromatic), 1105s; δ H (500 MHz; CDCl₃) 7.73-7.71 (2H, m, arom.H), 7.54-7.52 (2H, m, arom.H), 7.47-7.46 (3H, m, arom.H), 7.41-7.35 (6H, m, arom.H), 7.25-7.23 (2H, m, arom.H), 5.15 (1H, d, J 16.2, 1 of OCH₂), 4.98 (1H, d, J 16.2, 1 of OCH₂), 3.34-3.31 (1H, m, SiCH₂CH₂), 2.94 (1H, dd, J 18.9, 6.5, 1 of OCCH₂), 2.34 (1H, dd, J 18.9, 2.1, 1 of OCCH₂), 1.90 (1H, dd, J 14.6, 4.9, 1 of SiCH₂), 1.24 (1H, dd, J 14.5, 13.7, 1 of SiCH₂); δC (125 MHz; CDCl₃) 205.7 (C=O), 172.1 (OCH₂C=C), 138.5(C=CPh), 134.3 (arom.CH), 134.2 (arom.CH), 133.8 (arom.C₆), 133.5 (arom.C₆), 130.6 (arom.CH), 130.54 (arom.CH), 130.49 (arom.C₆), 129.0 (arom.CH), 128.4 (arom.CH), 128.3
New Substrates for PKR

Experimental

Synthesis of Allyldiphenylprop-2-ynyloxysilane 327c

Using the procedure of Garner et al.94,96, a solution of phenylmagnesium bromide (1.0M in THF, 4.6 mL, 4.6 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (338, 0.33 mL, 2.3 mmol) in diethyl ether (2 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodi phenylsilane (330b) in solution. This solution was cooled to rt, diluted with dichloromethane (3.8 mL) and added dropwise to a solution of propargyl alcohol (256, 0.13 g, 2.3 mmol) and triethylamine (0.32 mL, 2.3 mmol) in dichloromethane (19 mL) under argon at 0 °C. The washings from the flask containing allylchlorodi phenylsilane (dichloromethane, 2 mL) were transferred to the flask containing propargyl alcohol and triethylamine. The reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon overnight. The reaction mixture was quenched with sat. aqueous NH₄Cl (15 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (120 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60) afforded allyldiphenylprop-2-ynyloxysilane (327c, 0.11 g, 18%) as a colourless oil.

ν max (neat)/cm⁻¹ 3292s (C≡C-H), 3025s (=C-H₂), 2999m & 2866m (C-H), 2100w (C≡C), 1630s (C=C), 1589m (C=C aromatic), 1487w (C=C aromatic), 1429s, 1371m, 1263m; δH (500 MHz; CDCl₃) 7.65-7.63 (4H, m, arom. 7/), 7.47-7.38 (6H, m, arom./), 5.87 (1H, ddt, J 17.0, 10.1, 7.9, HC=CH₂), 4.99 (1H, ddt, J 17.0, 1.9, 1.5, 1 of HC=CH₂ (trans)), 4.93 (1H, ddt, J 10.1, 1.9, 1.1, 1 of HC=CH₂ (cis)), 4.39 (2H, d, J 2.4, OCH₂), 2.41 (1H, t, J 2.4, C≡C-H), 2.26 (2H, dt, J 7.9, 1.3, SiCH₂); δC (100 MHz; CDCl₃) 134.8 (arom.CH), 133.5 (arom.Cq), 132.6 (HC=CH₂), 130.2 (arom.CH), 127.9 (arom.CH), 115.4 (HC=CH₂), 81.7 (C≡C-H), 73.5 (C≡C-H), 52.0 (OCH₂), 21.8
**New Substrates for PKR**

(SiCH₂); m/z (FAB pos) 360 (100%), 301 (MNa⁺, 10), 237 (28), 207 (75); HRMS calculated for C₁₉H₁₈OSiNa (MNa⁺) 301.1025 Found 301.1020.

**Synthesis of Allylbut-2-ynyloxydiphenylsilane 327d**

Using the procedure of Garner et al.⁹⁴,⁹⁶, a solution of phenylmagnesium bromide (1.0M in THF, 4.6 mL, 4.6 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (338, 0.33 mL, 2.3 mmol) in diethyl ether (2 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 30 minutes, warmed to rt and then heated to reflux for 2h to obtain allylchlorodiphenylsilane (330b) in solution. This solution was cooled to rt and added dropwise to a solution of but-2-yn-1-ol (0.16 g, 2.3 mmol) and triethylamine (0.32 mL, 2.3 mmol) in dichloromethane (19 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 3.8 mL) were transferred to the flask containing but-2-yn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon overnight.

The reaction mixture was quenched with sat. aqueous NH₄Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (120 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, hexane / Et₃N 99 : 1) afforded allylbut-2-ynyloxydiphenylsilane (327d, 0.22 g, 32%) as a colourless oil.

v_{max} \text{ (neat)/cm}^{-1}: 3071 s (=C-H₂), 2999 m & 2866 m (C-H), 2235 w (C=C), 1630 s (C=C), 1589 m (C=C aromatic), 1487 w (C=C aromatic), 1429 s, 1371 m; δ₁H (500 MHz; CDCl₃) 7.65-7.63 (4H, m, arom.H), 7.45-7.38 (6H, m, arom.H), 5.88 (1H, ddt, J 17.0, 10.1, 7.9, HC=CH₂), 4.98 (1H, ddt, J 17.0, 1.9, 1.5, 1 of HC=CH₂ (trans)), 4.92 (1H, ddt, J 10.1, 2.0, 1.1, 1 of HC=CH₂ (cis)), 4.37 (2H, q, J 2.4, OCH₂), 2.26 (2H, dt, J 7.9, 1.3, SiCH₂), 1.80 (3H, t, J 2.4, CH₃); δ₁C (100 MHz; CDCl₃) 134.8 (arom.CH), 133.9 (arom.C₆), 132.8 (HC=CH₂), 130.0 (arom.CH), 127.8 (arom.CH), 115.2 (HC=CH₂), 81.8 (OCH₂C=CH), 77.2 (C=CC₃H₃), 52.5 (OCH₂), 21.9 (SiCH₂), 3.6 (CH₃); m/z (FAB pos) 315 (MNa⁺, 29%), 251 (35), 221 (100); HRMS calculated for C₁₉H₂₉OSiNa (MNa⁺) 315.1181 Found 315.1182.
Synthesis of 7-Methyl-3,3-diphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328d

Using the procedure of Sugihara et al.29, a solution of allylbut-2-ynyloxydiphenylsilane (327d, 0.16 g, 0.55 mmol) in 1,2-dichloroethane (3.5 mL) was added to a solution of dicobalt octacarbonyl (0.40 g, 1.2 mmol) in 1,2-dichloroethane (2 mL) under argon at rt. The reaction mixture was stirred at rt for 85 minutes. n-Butyl methyl sulfide (0.24 mL, 1.93 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled, concentrated in vacuo and the residue was purified by flash chromatography (Florisil®, Dichloromethane) to afford 7-methyl-3,3-diphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328d, 67 mg, 38%) as a yellow oil.

v \text{max} \ (\text{neat}/\text{cm}^{-1}) \quad 2922\text{m} & 2853\text{w} \ (\text{C-H}), \ 1701\text{s} \ (\text{C=O}), \ 1647\text{s} \ (\text{C=C}), \ 1589\text{m} \ (\text{aromatic}), \ 1429\text{s}, \ 1408\text{s}, \ 1380\text{w}; \ \delta_{\text{H}} \ (500 \text{ MHz}; \ \text{CDCl}_3) \quad 7.72-7.70 \ (2\text{H}, \text{m}, \text{arom.H}), \ 7.55-7.54 \ (2\text{H}, \text{m}, \text{arom.H}), \ 7.49-7.43 \ (4\text{H}, \text{m}, \text{arom.H}), \ 7.41-7.36 \ (2\text{H}, \text{m}, \text{arom.H}), \ 5.07 \ (1\text{H}, \text{d, } J 16.2, \text{1 of OCH}_2), \ 4.86 \ (1\text{H}, \text{d, } J 16.2, \text{1 of OCH}_2), \ 3.15-3.09 \ (1\text{H}, \text{m, SiCH}_2\text{CH}), \ 2.79 \ (1\text{H}, \text{dd, } J 18.8, 6.3, \text{1 of OCCH}_2), \ 2.16 \ (1\text{H}, \text{dd, } J 18.8, 1.5, \text{1 of OCCH}_2), \ 1.81 \ (1\text{H}, \text{dd, } J 14.5, 4.8, \text{1 of SiCH}_2), \ 1.70 \ (3\text{H}, \text{br s, CH}_3), \ 1.21 \ (1\text{H}, \text{t, } J 14.3, \text{1 of SiCH}_2); \ \delta_{\text{C}} \ (125 \text{ MHz}; \ \text{CDCl}_3) \quad 207.9 \ (\text{C}=\text{O}), \ 170.6 \ (\text{C}=\text{CCH}_3) \ & \text{134.5} \ (\text{C}=\text{CCH}_3), \ 134.2 \ (\text{arom.CH}), \ 134.1 \ (\text{arom.CH}), \ 134.0 \ (\text{arom.C}_9), \ 133.6 \ (\text{arom.C}_9), \ 130.5 \ (\text{arom.CH}), \ 130.4 \ (\text{arom.CH}), \ 128.2 \ (\text{arom.CH}), \ 128.1 \ (\text{arom.CH}), \ 62.8 \ (\text{OCH}_2), \ 45.1 \ (\text{OCCH}_2), \ 35.3 \ (\text{SiCH}_2\text{CH}), \ 18.8 \ (\text{SiCH}_2), \ 7.7 \ (\text{CH}_3); \ m/z \ (\text{FAB pos}) \quad 321 \ (\text{MH}^+, \text{25%}), \ 307 \ (40), \ 289 \ (18), \ 154 \ (100); \ \text{HRMS} \ \text{calculated for } \text{C}_{20}\text{H}_{21}\text{O}_2\text{Si} (\text{MH}^+) \quad 321.1311 \ \text{Found 321.1303.}

Synthesis of 3-Trimethylsilanylprop-2-yn-1-ol 340

n-Butyllithium (1.6 M in hexane, 44.6 mL, 71.4 mmol) was added dropwise to a stirred solution of propargyl alcohol (256, 2.11 mL, 35.7 mmol) in THF (150 mL) at -78 °C under argon and the reaction mixture was stirred at -78 °C for 1 h. Chlorotrimethylsilane (9.1 mL, 71 mmol) was added dropwise and the resulting reaction mixture was stirred at -78 °C for 30 minutes followed by stirring at rt overnight.
The reaction mixture was quenched with sat. aqueous NH₄Cl (25 mL) and THF removed in vacuo at rt. The residue was extracted with diethyl ether (3 x 75 mL). The combined ethereal extracts were washed with brine (150 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Et₃N / Ether / Petrol 40-60 0.5 : 0 : 99.5 to 0.5 : 15 : 84.5) afforded 3-trimethylsilanylprop-2-yn-1-ol (340, 3.66 g, 80%) as a yellow oil.

ν<sub>max</sub> (neat)/cm⁻¹: 3306 br s (O-H), 2959s (C-H), 2176s (C=C), 1410s, 1352s; δ<sub>H</sub> (500 MHz; CDCl₃) 4.23 (2H, s, OCH₂), 2.57 (1H, br s, OH), 0.14 (9H, s, Si(CH₃)₃); δ<sub>C</sub> (125 MHz; CDCl₃) 103.9 (C=CSi(CH₃)₃), 90.4 (C=CSi(CH₃)₃), 51.3 (OCH₂), -0.3 (Si(CH₃)₃); m/z (Cl pos) 129 (MH⁺, 26%), 113 (100), 100 (20); HRMS calculated for C₆H₁₃OSi (MH⁺) 129.0736 Found 129.0742.

Synthesis of 1- Allyl-3,3,3-trimethyl-1,1-diphenyldisiloxane 341

Using the procedure of Garner et al.⁹⁴,⁹⁶ a solution of phenylmagnesium bromide (1.0M in THF, 3.4 mL, 3.4 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (338, 0.25 mL, 1.7 mmol) in diethyl ether (1.5 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 1 h, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (330b) in solution. This solution was cooled to rt and added dropwise to a solution of propargyl alcohol (256, 0.10 g, 1.7 mmol) and triethylamine (0.24 mL, 1.7 mmol) in dichloromethane (17 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 2 mL) were transferred to the flask containing propargyl alcohol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt overnight under argon. The reaction mixture was quenched with sat. aqueous NH₄Cl (10 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude allyldiphenylprop-2-ynylsiloxane (327c, 0.45 g).

Lithium (bistrimethyl)silylamide (1.2 M in THF, 0.33 mL, 0.4 mmol) was added dropwise to a stirred solution of crude allyldiphenylprop-2-ynylsiloxane (327c, 0.10 g, 0.4 mmol) in THF (1 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 130 minutes. Chlorotrimethylsilane (43 mg, 50 µL, 0.4 mmol) was added.
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dropwise and the resulting reaction mixture was stirred at −78 °C for 30 minutes followed by stirring at rt overnight.

The reaction mixture was quenched with sat. aqueous NH₄Cl (1 mL) and extracted with diethyl ether (4 x 10 mL). The combined ethereal extracts were washed with brine (30 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (Al₂O₃, Petrol 40-60) afforded 1-allyl-3,3,3-trimethyl-1,1-diphenyldisiloxane (341, 28 mg, 25%) as a colourless oil.

\[
\text{v}_{\text{max}} \text{(neat)/cm}^{-1} \ 3071 \text{s (}=C-\text{H}_2), \ 2957 \text{s} \ & 2916 \text{m} (\text{C-H}), \ 1630 \text{s} (\text{C=C aromatic}), \ 1487 \text{w} (\text{C=C aromatic}), \ 1429 \text{s}, \ 1418 \text{m}, \ 1389 \text{m}; \ \delta_\text{H} (500 \text{ MHz; CDCl}_3) 7.58-7.56 (4\text{H, m, arom.}H), \ 7.41-7.36 (6\text{H, m, arom.}H), \ 5.82 (1\text{H, ddt, } J 17.0, 10.1, 7.9, \ \text{HC=CH}_2), \ 4.94 (1\text{H, ddt, } J 17.0, 2.1, 1.5, 1 \text{ of } \text{HC=CH}_2 (\text{trans}), \ 4.90 (1\text{H, ddt, } J 10.1, 2.1, 1.1, 1 \text{ of } \text{HC=CH}_2 (\text{cis}), \ 2.12 (2\text{H, dt, } J 7.9, 1.2, \text{SiCH}_2), \ 0.13 (9\text{H, s, Si(CH}_3)_3); \ \delta_\text{C} (125 \text{ MHz; CDCl}_3) 136.6 (\text{arom.}C_\text{q}), \ 134.2 (\text{arom.CH}), \ 133.3 (\text{HC=CH}_2), \ 129.6 (\text{arom.CH}), \ 127.7 (\text{arom.CH}), \ 114.7 (\text{HC=CH}_2), \ 23.8 (\text{SiCH}_2), \ 2.0 (\text{Si(CH}_3)_3); \ m/z (\text{FAB pos}) 313 (\text{MH}^+, 2\%), \ 297 (30), \ 271 (100), \ 235 (65), \ 178 (15), \ 79 (20).
\]

**Synthesis of Allyldiphenyl(3-trimethylsilanylprop-2-ynloxy)silane 327e**

Using the procedure of Garner et al., a solution of phenylmagnesium bromide (1.0M in THF, 5.7 mL, 5.7 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (338, 0.41 mL, 2.9 mmol) in diethyl ether (2.4 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (330b) in solution. This solution was cooled to rt and added dropwise to a solution of 3-trimethylsilanylprop-2-yn-1-ol (340, 0.37 g, 2.9 mmol), 4-dimethylaminopyridine (35 mg, 0.28 mmol) and triethylamine (0.40 mL, 2.9 mmol) in dichloromethane (28.5 mL) under argon at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, followed by stirring at rt for 2 days.

The reaction mixture was quenched with sat. aqueous NH₄Cl (20 mL) and extracted with dichloromethane (3 x 60 mL). The combined organic extracts were washed with brine (200 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (Florisil®), Petrol 40-60 / Ether 99.75 : 0.25) afforded
allyldiphenyl(3-trimethylsilylprop-2-ynloxy)silane (327e, 0.29 g, 29%) as a pale yellow oil.

\[ \text{n}_{\text{max}} (\text{neat})/\text{cm}^{-1} 3071 \text{s} (=\text{C-H}), 2961 \text{s} & 2860 \text{m} (\text{C-H}), 2179 \text{m} (\text{C=C}), 1630 \text{m} (\text{C=C}), 1589 \text{m} (\text{C=C aromatic}), 1489 \text{m} (\text{C=C aromatic}), 1452 \text{m}, 1429 \text{s}, 1389 \text{m}; \delta_{\text{H}} (500 \text{ MHz}; \text{CDCl}_3) 7.67-7.65 (4\text{H}, \text{m}, \text{arom. H}), 7.46-7.38 (6\text{H}, \text{m}, \text{arom. H}), 5.89 (1\text{H}, \text{dtt}, J 17.0, 10.1, 7.9, \text{H} \text{C=CH}_2), 4.99 (1\text{H}, \text{dtt}, J 17.0, 2.0, 1.5, 1 \text{ of } \text{H} \text{C=CH}_2 (\text{trans})), 4.93 (1\text{H}, \text{dtt}, J 10.1, 2.0, 1.1, 1 \text{ of } \text{H} \text{C=CH}_2 (\text{cis})), 4.41 (2\text{H}, \text{s}, \text{OCH}_2), 2.28 (2\text{H}, \text{dt}, J 7.8, 1.3, \text{SiCH}_2), 0.17 (9\text{H}, \text{s}, \text{Si(CH}_3)_3); \delta_{\text{C}} (125 \text{ MHz}; \text{CDCl}_3) 134.9 (\text{arom. CH}), 133.8 (\text{arom. Cq}), 132.8 (\text{H} \text{C=CH}_2), 130.1 (\text{arom. CH}), 127.8 (\text{arom. CH}), 115.3 (\text{H} \text{C=CH}_2), 103.7 (\text{C=CSi(CH}_3)_3), 90.5 (\text{C=CSi(CH}_3)_3), 52.8 (\text{OCH}_2), 22.0 (\text{SiCH}_2), -0.3 (\text{Si(CH}_3)_3); m/z (\text{FAB pos}) 373 (\text{MNa}^+, 30\%), 209 (15), 279 (100); \text{HRMS calculated for } \text{C}_{21}\text{H}_{26}\text{OSi}_2\text{Na (MNa}^+) 373.1420 \text{ Found 373.1424.}

**Synthesis of 3,3-Diphenyl-7-trimethylsilyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328e**

Using the procedure of Sugihara et al.\textsuperscript{29}, a solution of allyldiphenyl(3-trimethylsilylprop-2-ynloxy)silane (327e, 0.12 g, 0.34 mmol) in 1,2-dichloroethane (1.9 mL) was added to a solution of dicobalt octacarbonyl (0.18 g, 0.51 mmol) in 1,2-dichloroethane (1.5 mL) under argon at rt. The reaction mixture was stirred at rt for 1 h. \textit{n}-\textit{Butyl methyl sulfide} (0.15 mL, 1.2 mmol) was added and the resulting reaction mixture was heated to reflux for 3 days.

The reaction mixture was cooled, concentrated \textit{in vacuo} and the residue was purified by flash chromatography (Florisil\textsuperscript{®}, Petrol 40-60 / Ether 7 : 3) to afford 3,3-diphenyl-7-trimethylsilyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328e, 18 mg, 14%) as a yellow oil.

\[ \text{n}_{\text{max}} (\text{neat})/\text{cm}^{-1} 2955 \text{m} & 2899 \text{m} (\text{C-H}), 1690 \text{ br s} (\text{C=O}), 1589 \text{s} (\text{C=C aromatic}), 1429 \text{s}, 1406 \text{m}, 1250 \text{s}; \delta_{\text{H}} (500 \text{ MHz}; \text{CDCl}_3) 7.69-7.68 (2\text{H}, \text{m}, \text{arom. H}), 7.57-7.56 (2\text{H}, \text{m}, \text{arom. H}), 7.49-7.35 (6\text{H}, \text{m}, \text{arom. H}), 5.12 (1\text{H}, \text{d}, J 17.1, 1 \text{ of } \text{OCH}_2), 4.98 (1\text{H}, \text{d}, J 17.1, 1 \text{ of } \text{OCH}_2), 3.30-3.23 (1\text{H}, \text{m}, \text{SiCH}_2\text{CH}_2), 2.75 (1\text{H}, \text{dd}, J 18.5, 6.0, 1 \text{ of } \text{OCCCH}_2), 2.13 (1\text{H}, \text{dd}, J 18.6, 2.5, 1 \text{ of } \text{OCCH}_2), 1.80 (1\text{H}, \text{dd}, J 14.7, 4.9, 1 \text{ of } \text{SiCH}_2), 1.19 (1\text{H},
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$J_{14.4, 1}$ of SiCH$_2$), 0.21 (9H, s, Si(CH$_3$)$_3$); $\delta_C$ (125 MHz; CDCl$_3$) 211.7 (C=O), 187.1 (C=CSi(CH$_3$)$_3$), 138.1 (C=CSi(CH$_3$)$_3$), 134.22 (arom.CH), 134.21 (arom.CH), 134.0 (arom.C$_q$), 133.7 (arom.C$_q$), 130.6 (arom.CH), 130.5 (arom.CH), 128.2 (arom.CH), 128.1 (arom.CH), 64.6 (OCH$_2$), 46.2 (OCCH$_2$), 38.5 (SiCH$_2$CH), 18.4 (SiCH$_2$), -0.6 (Si(CH$_3$)$_3$); $m/z$ (CI pos) 379 (MH$^+$, 11%), 363 (15), 309 (70), 273 (85), 199 (100), 163 (80); HRMS calculated for C$_{22}$H$_{27}$O$_2$Si$_2$ (MH$^+$) 379.1550 Found 379.1560.

**Synthesis of 1,3-Diphenylprop-2yn-1-ol 343**

$n$-Butyllithium (1.6 M in hexane, 6.2 mL, 9.9 mmol) was added dropwise to a stirred solution of phenylacetylene (16, 1.1 mL, 9.8 mmol) in THF (6.5 mL) at -78 °C, under argon, and stirred for 10 minutes. Benzaldehyde (342, 1.0 mL, 9.8 mmol) was added dropwise and the resulting reaction mixture stirred at -78 °C for 10 minutes followed by stirring at rt overnight. The reaction mixture was quenched with sat. aqueous NH$_4$Cl (20 mL) and extracted with diethyl ether (2 x 100 mL). The combined ethereal extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO$_2$, Petrol 40-60 / EtOAc 85 : 15) afforded 1,3-diphenylprop-2yn-1-ol (343, 1.8 g, 90%) as a pale yellow oil.

$\nu_{max}$ (neat)/cm$^{-1}$

3346 br s (O-H), 3063m (C-H), 2199m (C=C aromatic), 1489m (C=C aromatic), 1443s, 1387m, 1286m; $\delta_H$ (300 MHz; CDCl$_3$) 7.66-7.64 (2H, m, arom.H), 7.53-7.50 (2H, m, arom.H), 7.45-7.33 (6H, m, arom.H), 5.71 (1H, s, HOCH$_2$), 2.94 (1H, br s, OH); $\delta_C$ (75 MHz; CDCl$_3$) 140.5 (arom.C$_q$), 131.7 (arom.CH), 128.54 (arom.CH), 128.48 (arom.CH), 128.3 (arom.CH), 128.2 (arom.CH), 126.7 (arom.CH), 122.3 (arom.C$_q$), 88.7 & 86.5 (C=C), 64.9 (HOCH); $m/z$ (FAB pos) 208 (M$^+$, 5%), 191 (25), 154 (100), 136 (70), 77 (40); HRMS calculated for C$_{15}$H$_{12}$O (M$^+$) 208.0888 Found 208.0882

**Synthesis of Allyl(1,3-diphenylprop-2-ynyloxy)diphenylsilane 327f**

Using the procedure of Garner et al.\textsuperscript{94,96}, a solution of phenylmagnesium bromide (1.0M in THF, 6.8 mL, 6.8 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (338, 0.50 mL, 3.4 mmol) in diethyl ether (3 mL) at -78 °C under argon.
The reaction mixture was stirred at \(-78^\circ\text{C}\) for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (330b) in solution. This solution was cooled to rt and added dropwise to a solution of 1,3-diphenylprop-2yn-1-ol (343, 0.71 g, 3.4 mmol), 4-dimethylaminopyridine (42 mg, 0.34 mmol) and triethylamine (0.48 mL, 3.4 mmol) in dichloromethane (30 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 4.2 mL) were transferred to the flask containing 1,3-diphenylprop-2yn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon overnight.

The reaction mixture was quenched with sat. aqueous NH\(_4\)Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (4 x 75 mL). The combined organic extracts were washed with brine (300 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to obtain the crude product. Flash chromatography (Al\(_2\)O\(_3\), Petrol 40-60) afforded allyl(1,3-diphenylprop-2-ynyloxy)diphenylsilane (327f, 0.69 g, 47%) as a thick yellow oil.

\[ \text{v}_{\text{max}} (\text{neat})/\text{cm}^{-1} \text{ 3070s (=C-H2), 3027s (C-H), 2200w (C=C), 1685m (C=C aromatic), 1630m (C=C), 1599m (C=C aromatic), 1490m (C=C aromatic), 1450m, 1443m, 1428s; } \]

\[ \delta_{\text{H}} (500 \text{ MHz; CDCl}_3) 7.74-7.70 (4H, m, arom.H), 7.59-7.57 (2H, m, arom.H), 7.48-7.44 (2H, m, arom.H), 7.42-7.38 (6H, m, arom.H), 7.36-7.28 (6H, m, arom.H), 5.92 (1H, ddt, J 17.0, 10.1, 8.0, HC=CH\(_2\)), 5.81 (1H, s, OCH), 4.99 (1H, ddt, J 17.0, 2.0, 1.4, 1 of HC=CH\(_2\) (trans)), 4.93 (1H, ddt, J 10.1, 2.1, 1.0, 1 of HC=CH\(_2\) (cis)), 2.39 (1H, ddt, J 14.1, 7.7, 1.3, 1 of SiCH\(_2\)), 2.35 (1H, ddt, J 14.1, 8.1, 1.3, 1 of SiCH\(_2\)); \delta_{\text{C}} (125 \text{ MHz; CDCl}_3) 141.1 (arom.C\(_q\)), 135.05 (arom.CH), 135.0 (arom.CH), 134.2 (arom.C\(_q\)), 134.1 (arom.C\(_q\)), 132.9 (HC=CH\(_2\)), 131.6 (arom.CH), 130.04 (arom.CH), 130.0 (arom.CH), 128.4 (arom.CH), 128.3 (arom.CH), 128.1 (arom.CH), 127.9 (arom.CH), 127.8 (arom.CH), 127.7 (arom.CH), 126.5 (arom.CH), 122.6 (arom.C\(_q\)), 115.3 (HC=CH\(_2\)), 89.5 & 86.5 (C=C), 65.9 (OCH), 22.3 (SiCH\(_2\)); m/z (FAB pos) 453 (MNa\(^+\), 1%), 389 (15), 283 (35), 191 (100); HRMS calculated for C\(_{30}\)H\(_{26}\)OSiNa (MNa\(^+\)) 453.1651 Found 453.1661.
Synthesis of 4-Phenylbut-3-yn-2-ol 345

\[ \text{Ph} \quad H_3C \quad OH \]

\( n \)-Butyllithium (1.6 M in hexane, 9.27 mL, 14.83 mmol) was added dropwise to a stirred solution of phenylacetylene (16, 1.61 mL, 14.7 mmol) in THF (10 mL) at -78 °C under argon and stirred for 15 minutes. Acetaldehyde (344, 0.82 mL, 14.7 mmol) was added dropwise and resulting reaction mixture stirred at -78 °C for 30 minutes followed by stirring at rt overnight. The reaction mixture was quenched with sat. aqueous NH\(_4\)Cl (20 mL) and extracted with diethyl ether (2 x 100 mL). The combined ethereal extracts were dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo} to obtain the crude product. Flash chromatography (SiO\(_2\), Petrol 40-60 / EtOAc 9 : 15) afforded 4-phenylbut-3-yn-2-ol (345, 1.4 g, 64%) as a yellow oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \] 3320 br s (O-H), 2981 s (C-H), 2150 w (C=C), 1598 s (C=C aromatic), 1490 w (C=C aromatic), 1443 s, 1370 s, 1330 s; \( \delta_H \) (400 MHz; CDCl\(_3\)) 7.44-7.41 (2H, m, arom.H), 7.31-7.29 (3H, m, arom.H), 4.76 (1H, q, \( J = 6.6 \), HOCH), 2.36 (1H, br s, OH), 1.55 (3H, d, \( J = 6.6 \), CH\(_3\)); \( \delta_C \) (100 MHz; CDCl\(_3\)) 131.6 (arom.CH), 128.3 (arom.CH), 128.2 (arom.CH), 122.5 (arom.C\(_q\)), 90.9 (C=CPh), 83.9 (C=CPh), 58.7 (HOCH), 24.3 (CH\(_3\)); \m/z (Cl pos) 147 (MH\(^+\), 22%), 129 (100), 103 (20); HRMS calculated for C\(_{10}\)H\(_{11}\)O (MH\(^+\)) 147.0810 Found 147.0804.

Synthesis of Allyldiphenyl(4-phenylbut-3-yn-2-yloxy)silane 327g

Using the procedure of Garner \textit{et al.}\(^{94,96} \), a solution of phenylmagnesium bromide (1.0M in THF, 6.8 mL, 6.8 mmol) was added to a stirred solution of allyltrichlorosilane (338, 0.50 mL, 3.4 mmol) in diethyl ether (3 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (330\(b\)) in solution. This solution was cooled to rt, diluted with dichloromethane (4.2 mL) and added dropwise to a solution of 4-phenylbut-3-yn-2-ol (345, 0.50 g, 3.4 mmol), 4-dimethylaminopyridine (42 mg, 0.34 mmol) and triethylamine (0.48 mL, 3.4 mmol) in dichloromethane (30 mL) under argon at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt, under argon for 3 days.
The reaction mixture was quenched with sat. aqueous NH₄Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 75 mL). The combined organic extracts were washed with brine (120 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (Al₂O₃, Petrol 40-60) afforded allyldiphenyl(4-phenylbut-3-yn-2-yloxy)silane (327g, 0.79g, 63%) as a light yellow oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \] 3070m (=C-H₂), 2999m (C-H), 2200w (C≡C), 1630m (C=C aromatic), 1490s (C=C aromatic), 1428s, 1325w; \( \delta_H \) (500 MHz; CDCl₃) 7.75-7.73 (4H, m, arom.H), 7.49-7.41 (6H, m, arom.H), 7.35-7.30 (5H, m, arom.H), 5.97 (1H, ddt, \( J = 17.0, 10.1, 7.9 \)), 5.04 (1H, ddt, \( J = 17.0, 2.0, 1.5 \)), 1 of HC=CH₂ (trans)), 4.97 (1H, ddt, \( J = 10.1, 2.0, 1.0 \)), 1 of HC=CH₂ (cis)), 4.89 (1H, q, \( J = 6.5 \)), 2.37-2.36 (2H, m, SiCH₂), 1.61 (3H, d, \( J = 6.5 \)), CH₃); \( \delta_C \) (125 MHz; CDCl₃) 134.93 (arom.CH), 134.91 (arom.CH), 134.40 (arom.Cq), 134.38 (arom.Cq), 133.0 (HC=CH₂), 131.5 (arom.CH), 129.94 (arom.CH), 129.91 (arom.CH), 128.1 (arom.CH), 127.8 (arom.CH), 127.7 (arom.CH), 122.8 (arom.Cq), 115.2 (HC=CH₂), 91.2 & 84.1 (C≡C), 60.2 (OCH), 25.2 (CH₂), 22.3 (SiCH₂); \( m/z \) (FAB pos) 369 (MH⁺, 4%), 327 (100), 291 (70), 267 (60), 129 (90); HRMS calculated for C₂₅H₂₅OSi (MH⁺) 369.1675 Found 369.1672.

**Synthesis of 5-Methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328g**

Using the procedure of Sugihara et al.,²⁹ a solution of allyldiphenyl(4-phenylbut-3-yn-2-yloxy)silane (327g, 0.15 g, 0.41 mmol) in 1,2-dichloroethane (2.5 mL) was added to a solution of dicobalt octacarbonyl (0.17 g, 0.49 mmol) in 1,2-dichloroethane (1.6 mL) under argon at rt. The reaction mixture was stirred at rt for 1 h. \( n \)-Butyl methyl sulfide (0.18 mL, 1.4 mmol) was added and the reaction mixture was heated to reflux under argon overnight.

The reaction mixture was cooled, concentrated in vacuo and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / EtOAc 85 : 15) to afford 5-methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328g, 15 mg, 9%) as an inseparable mixture of endo:exo diastereoisomers in the ratio of 1:1.5.
New Substrates for PKR

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2925s (C-H), 1710s (C=O), 1699s (C=C), 1682m (C=C aromatic), 1428s (C=C aromatic), 1278w, 1120s, 1071s; $\delta_H$ (500 MHz; CDCl$_3$, major isomer) 7.74-7.72 (2H, m, arom.H), 7.53-7.51 (2H, m, arom.H), 7.48-7.30 (9H, m, arom.H), 7.20-7.18 (2H, m, arom.H), 5.42 (1H, q, $J$ 6.6, OCH), 3.46-3.42 (1H, m, SiCH$_2$CH), 2.95 (1H, dd, $J$ 18.9, 6.5, 1 of OCCH$_2$), 2.35 (1H, dd, $J$ 18.9, 1.7, 1 of OCCH$_2$), 1.98 (1H, dd, $J$ 14.7, 5.2, 1 of SiCH$_2$), 1.40 (3H, d, $J$ 6.7, $CH_3$), 1.22 (1H, dd, $J$ 14.7, 13.3, 1 of SiCH$_2$); $\delta_H$ (500 MHz; CDCl$_3$, minor isomer) 7.68-7.66 (2H, m, arom.H), 7.62-7.60 (2H, m, arom.H), 7.48-7.30 (9H, m, arom.H), 7.22-7.21 (2H, m, arom.H), 5.63 (1H, qt, $J$ 6.9, 1.1, OCH), 3.46-3.42 (1H, m, SiCH$_2$CH), 2.96 (1H, ddd, $J$ 18.9, 6.5, 1.2, 1 of OCCH$_2$), 2.34 (1H, dd, $J$ 18.8, 2.8, 1 of OCCH$_2$), 1.77 (1H, dd, $J$ 14.7, 4.0, 1 of SiCH$_2$), 1.36 (1H, t, $J$ 14.5, 1 of SiCH$_2$), 1.13 (3H, d, $J$ 6.7, $CH_3$); $\delta_C$ (125 MHz; CDCl$_3$) 206.3 (C=O major), 205.7 (C=O minor), 179.0 (C=CPh minor), 176.8 (C=CPh major), 138.5 (C=CPh minor), 138.3 (C=CPh major), 135.7 (arom.C$_q$ minor), 135.0 (arom.C$_q$ major), 134.9 (arom.C$_q$ major), 134.6 (arom.C$_q$ minor), 134.3 (arom.CH minor), 134.21 (arom.CH minor), 131.9 (C=Carom.C$_q$ minor), 131.0 (C=Carom.C$_q$ major), 130.4 (arom.CH), 130.32 (arom.CH), 130.30 (arom.CH), 128.8 (C=Carom.CH major), 128.62 (C=Carom.CH minor), 128.6 (arom.CH), 128.5 (arom.CH), 128.11 (arom.CH), 128.08 (arom.CH), 128.05 (arom.CH), 128.03 (arom.CH), 127.99 (arom.CH), 70.9 (OCH minor), 69.1 (OCH major), 45.7 (OCCH$_2$ major), 45.3 (OCCH$_2$ minor), 35.7 (SiCH$_2$CH minor), 32.7 (SiCH$_2$CH major), 23.9 (CH$_3$ minor), 23.4 (CH$_3$ major), 20.3 (SiCH$_2$ major), 16.6 (SiCH$_2$ minor); $m/z$ (Cl pos) 397 (MH$^+$, 100%), 319 (38), 199 (35); HRMS calculated for C$_{26}$H$_{25}$O$_2$Si (MH$^+$) 397.1624 Found 397.1631.

Synthesis of Trichloro(2-methylallyl)silane 348

A mixture of trichlorosilane (347, 3.68 mL, 36.4 mmol) and 2-methylallyl chloride (346, 3.23 mL, 33.1 mmol) was added dropwise, under argon, into a mixture of triethylamine (4.62 mL, 33.1 mmol), cuprous chloride (0.16 g, 1.66 mmol) and diethyl ether (17 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then at rt for 4 h under argon. The reaction mixture was filtered through Celite® to remove precipitate and the filtrate was concentrated at rt to obtain crude product. Reduced pressure distillation yielded trichloro(2-methylallyl)silane (348, 4.24 g, 68%) as a clear colourless liquid.
New Substrates for PKR

Experimental

b.p.: 70 °C (70 mmHg) [lit°9 136 °C]; δH (500 MHz; CDCl3) 4.94 (1H, dq, J 3.0, 1.5, 1 of C=CH2), 4.85-4.84 (1H, m, 1 of C=CH2), 2.37 (2H, d, J 1.0, SiCH2), 1.88 (3H, dd, J 1.4, 0.9, CH3); δC (125 MHz; CDCl3) 136.3 (H2C=C(CH3)), 114.8 (C=CH2), 34.7 (SiCH2), 24.5 (CH3); m/z (EI) 333 (29 %), 284 (45), 219 (25), 146 (30), 69 (100).

Synthesis of (2-Methylallyl)diphenyl(3-phenylprop-2ynyloxy)silane 327h

Using the procedure of Garner et al.°4,°6, a solution of phenylmagnesium bromide (1.0M in THF, 4.2 mL, 4.2 mmol) was added dropwise to a stirred solution of trichloro(2-methylallyl)silane (348, 0.40 g, 2.1 mmol) in diethyl ether (1.8 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain (2-methylallyl)diphenylchlorosilane in solution. This solution was cooled to rt and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (329, 0.28 g, 2.1 mmol), 4-dimethylaminopyridine (26 mg, 0.21 mmol) and triethylamine (0.29 mL, 2.1 mmol) in dichloromethane (21 mL) under argon at 0 °C. The washings from the flask containing (2-methylallyl)diphenylchlorosilane (dichloromethane, 3 mL) were transferred to the flask containing 3-phenyl-2-propyn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon for 2 days.

The reaction mixture was quenched with sat. aqueous NH4Cl (15 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na2SO4) and concentrated in vacuo to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 99 : 1) afforded (2-methylallyl)diphenyl(3-phenylprop-2ynyloxy)silane (327h, 0.30 g, 39 %) as a colourless oil.

νmax (neat)/cm⁻¹ 3071s (=C-H2), 2914s & 2860m (C-H), 2260w (C=C), 1639s (C=C), 1589m (C=C aromatic), 1489s (C=C aromatic), 1443s, 1429s, 1375s, 1279s; δH (500 MHz; CDCl3) 7.70-7.68 (4H, m, arom.H), 7.46-7.29 (11H, m, arom.H), 4.67-4.66 (1H, m, 1 of C=CH2), 4.62-4.61 (1H, m, 1 of C=CH2), 4.61 (2H, s, OCH2), 2.29 (2H, d, J 1.0, SiCH2), 1.66 (3H, dd, J 1.3, 0.8, CH3); δC (125 MHz; CDCl3) 141.5 (C=CH2), 134.9 (arom.CH), 134.0 (arom.Cq), 131.6 (arom.CH), 130.0 (arom.CH), 128.3 (arom.CH), 128.2 (arom.CH), 127.8 (arom.CH), 122.8 (arom.Cq), 110.9 (C=CH2), 87.3 & 85.5
(C≡C), 52.8 (OCH2), 25.8 (SiCH2), 25.4 (CH3); m/z (FAB pos) 391 (MNa+, 41%), 283 (100), 199 (50), 176 (75); HRMS calculated for C25H24OSiNa (MNa+) 391.1494 Found 391.1498.

**Synthesis of (Z)-2-Methylbut-2-enyl-diphenyl-3-phenylprop-2-ynyloxysilane 327i**

Trichlorosilane (347, 0.45 mL, 4.4 mmol), isoprene (349, 0.49 mL, 4.9 mmol), bis(benzonitrile)palladium(II) chloride (3.7 mg, 9.8 μM) and triphenylphosphine (5.8 mg, 0.02 mmol) were heated in a sealed tube at 70 °C for 6 h. The reaction mixture was cooled down. 1H NMR spectrum showed it to contain almost exclusively (Z)-Trichloro(2-methylbut-2-enyl)silane100 (350).

δH (400 MHz; CDCl3) 5.43 (1H, br q, J 6.8, C=CH), 2.39 (2H, t, J 0.7, SiCH2), 1.83 (3H, dt, J 3.0, 1.5, (C//3)C=CH(CH3)), 1.60 (3H, dtq, J 6.7, 1.5, 0.7, C=CH(CH3)).

Using the procedure of Garner et al.94,96, a solution of phenylmagnesium bromide (1.0M in THF, 8.9 mL, 8.9 mmol) was added dropwise to a solution of (Z)-trichloro(2-methylbut-2-enyl)silane (350), in the sealed tube, in diethyl ether (3.8 mL) and cooled to -78 °C under argon. The resulting reaction mixture was stirred at -78 °C for 30 minutes followed by stirring at rt overnight. The reaction mixture was diluted with dichloromethane (4mL) and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (329, 0.59 g, 4.4 mmol), 4-dimethylaminopyridine (54 mg, 0.44 mmol) and triethylamine (0.62 mL, 4.4 mmol) in dichloromethane (44 mL) under argon at 0 °C.

The reaction mixture was stirred at 0 °C for 1 h followed by stirring at rt for 2 days. The reaction mixture was quenched with sat. aqueous NH4Cl (30 mL) and extracted with dichloromethane (3 x 80 mL). The combined organic extracts were washed with brine (200 mL), dried (Na2SO4) and concentrated in vacuo to obtain the crude product. Flash chromatography (Al2O3, Petrol 40-60) afforded (Z)-2-methylbut-2-enyl-diphenyl-3-phenylprop-2-ynyloxysilane (327i, 0.20 g, 12%) as a colourless oil.

vmax (neat)/cm⁻¹ 3069m (C=C-H), 2914m & 2858m (C-H), 2220w (C≡C), 1600m (C=C), 1490s (C=C aromatic), 1428s, 1375s; δH (500 MHz; CDCl3) 7.73-7.70 (4H, m, arom.H), 7.49-7.30 (11H, m, arom.H), 5.14 (1H, br q, J 6.7, C=CH(CH3)), 4.61 (2H, s,
OCH$_2$, 2.25 (2H, br s, SiCH$_2$), 1.70 (3H, dt, $J$ 2.9, 1.4, (CH$_3$)C=CH(CH$_3$)), 1.34 (3H, br d, $J$ 6.7, C=CH(CH$_3$)); \( \delta_c \) (125 MHz; CDCl$_3$) 134.9 (arom.CH), 134.2 (arom.C$_q$), 131.6 (arom.CH), 131.4 (arom.C$_q$), 130.0 (arom.CH), 128.21 (arom.CH), 128.16 (arom.CH), 127.8 (arom.CH), 122.8 ((CH$_3$)C=CH(CH$_3$)), 118.2 ((CH$_3$)C=CH(CH$_3$)), 87.3 & 85.4 (C=C), 52.7 (OCH$_2$), 26.3 ((CH$_3$)C=CH(CH$_3$)), 20.8 (SiCH$_2$), 13.8 ((CH$_3$)C=CH(CH$_3$)); \( m/z \) (CI pos) 383 (MH$^+$, 40%), 330 (100), 313 (54), 216 (75); HRMS calculated for C$_{26}$H$_{27}$O$_2$Si (MH$^+$) 383.1831 Found 383.1822.

**Synthesis of Crotyltrichlorosilane 352$^{99}$**

A mixture of Z and E crotyl chloride (1 : 6) (351, 4.3 mL, 44 mmol) and trichlorosilane (347, 6.2 mL, 62 mmol) in diethyl ether (7 mL) was added to a suspension of cuprous chloride (0.14 g, 1.5 mmol) and triethylamine (7.40 mL, 53 mmol) in diethyl ether (22 mL) under argon at 0 °C. Another 20 mL of dry diethyl ether was added to the reaction mixture due to evaporation of solvent, after an exothermic reaction. After stirring at rt for 2 h, the purple precipitate was removed by filtration through Celite® and the filtrate concentrated at rt to obtain the crude product. The crotyltrichlorosilane (352, 3.6 g, 43 %) was isolated by reduced pressure distillation as an inseparable mixture of Z : E diastereoisomers in the ratio of 1 : 6.

b.p.: 70 °C (66 mmHg) [lit$^{99}$ 142-144 °C].

**(E)-Crotyltrichlorosilane**

\( \delta_h \) (500 MHz; CDCl$_3$) 5.61 (1H, dqt, $J$ 15.2, 6.5, 1.3, CH$_3$HC=C), 5.38 (1H, dtq, $J$ 15.2, 7.6, 1.7, HC=CHCH$_2$Si), 2.26 (2H, br d, $J$ 7.6, SiCH$_2$), 1.72 (3H, ddt, $J$ 6.5, 1.7, 1.2, CH$_3$); \( \delta_c \) (125 MHz; CDCl$_3$) 130.4 (CH$_3$HC=C), 119.2 (HC=CHCH$_2$Si), 29.2 (SiCH$_2$), 18.1 (CH$_3$).

**(Z)-Crotyltrichlorosilane**

\( \delta_h \) (500 MHz; CDCl$_3$) 5.73 (1H, dqt, $J$ 13.8, 6.9, 1.4, (CH$_3$)HC=C), 5.42 (1H, dtq, $J$ 14.5, 6.4, 1.7, HC=CHCH$_2$Si), 2.35 (2H, br d, $J$ 8.2, SiCH$_2$), 1.67 (3H, ddt, $J$ 6.9, 1.8, 0.8, CH$_3$); \( \delta_c \) (125 MHz; CDCl$_3$) 128.3 (CH$_3$HC=C), 118.6 (HC=CHCH$_2$Si), 24.7 (SiCH$_2$), 13.0 (CH$_3$).

\( m/z \) (CI pos) 293 (100), 269 (43), 189 (MH$^+$, 45%), 153 (60); HRMS calculated for C$_4$H$_8$SiCl$_3$ (MH$^+$) 188.9461 Found 188.9462.
Synthesis of (E)-But-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane 327j

Using the procedure of Garner et al., a solution of phenylmagnesium bromide (1.0M in THF, 5.3 mL, 5.3 mmol) was added dropwise to a stirred solution of crottyltrichlorosilane (1 : 6 Z : E) (352, 0.50 g, 2.6 mmol) in diethyl ether (2.3 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain crottylchlorodiphenylsilane in solution. This solution was cooled to rt and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (329, 0.35 g, 2.6 mmol), 4-dimethylaminopyridine (32 mg, 0.26 mmol) and triethylamine (0.37 mL, 2.6 mmol) in dichloromethane (26 mL) under argon at 0 °C. The washings from the flask containing crottylchlorodiphenylsilane (dichloromethane, 4 mL) were transferred to the flask containing 3-phenyl-2-propyn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon for 2 days.

The reaction mixture was quenched with sat. aqueous NH₄Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 99.8 : 0.2) afforded (E)-but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane (327j, 0.28 g, 29 %) as a colourless oil.

νₓ(mx)(neat)/cm⁻¹ 3069s (=C-H), 2916s & 2855s (C-H), 2270w (C≡C), 1610m (C=C), 1589m (C=C aromatic), 1489s (C=C aromatic), 1443m, 1429s, 1371s; δₓH (500 MHz; CDCl₃) 7.69-7.67 (4H, m, arom.H), 7.46-7.29 (11H, m, arom.H), 5.52 (1H, dtq, J 15.1, 7.6, 1.5, HC=CH₂CH₂Si), 5.41 (1H, dqt, J 15.1, 6.3, 1.3, CH₂HC≡C), 4.63 (2H, s, OCH₂), 2.21 (2H, br d, J 7.6, SiCH₂), 1.61 (3H, ddt, J 6.3, 1.4, 1.3, CH₃); δₓC (125 MHz; CDCl₃) 134.9 (arom.CH), 134.2 (arom.Cₘ), 131.6 (arom.CH), 129.0 (arom.CH), 128.24 (arom.CH), 128.17 (arom.CH), 127.8 (arom.CH), 125.9 & 124.4 (C≡C), 122.8 (arom.Cₘ), 87.3 & 85.4 (C≡C), 52.8 (OCH₂), 20.0 (SiCH₂), 18.1 (CH₃); m/z (Cl pos) 369 (MH⁺, 9%), 313 (100), 283 (100), 199 (45); HRMS calculated for C₂₅H₂₅OSi (MH⁺) 369.1675 Found 369.1664.
Synthesis of exo-9-Methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328j

Using the procedure of Sugihara et al., a solution of (E)-but-2-etyl diphenyl(3-phenylprop-2-ynyloxy)silane (327j, 0.12 g, 0.33 mmol) in 1,2-dichloroethane (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.16 g, 0.47 mmol) in 1,2-dichloroethane (1.5 mL) under argon at rt. The reaction mixture was stirred at rt for 1 h. n-Butyl methyl sulfide (0.14 mL, 1.1 mmol) was added and the reaction mixture was heated to reflux under argon for 2 days.

The reaction mixture was cooled, concentrated in vacuo and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 7 : 3) to afford exo-9-methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328j, 43 mg, 33%) as a pale yellow oil.

ν<sub>max</sub> (neat)/cm<sup>-1</sup> 2926m & 2852m (C-H), 1705br s (C=O & C=C), 1589m (C=C aromatic), 1495m (C=C aromatic), 1445m, 1429s; δ<sub>H</sub> (500 MHz; CDCl<sub>3</sub>) 7.75-7.73 (2H, m, arom.H), 7.58-7.56 (2H, m, arom.H), 7.52-7.47 (2H, m, arom.H), 7.44-7.33 (7H, m, arom.H), 7.28-7.26 (2H, m, arom.H), 5.19 (1H, d, J 16.6, 1 of OCH<sub>2</sub>), 5.00 (1H, dd, J 16.5, 1.3, 1 of OCH<sub>2</sub>), 2.90-2.84 (1H, m, SiCH<sub>2</sub>CH<sub>3</sub>), 2.29 (1H, qd, J 7.3, 2.5, OCCH(CH<sub>3</sub>)), 1.97 (1H, dd, J 14.6, 5.0, 1 of SiCH<sub>2</sub>), 1.30 (3H, d, J 7.4, CH<sub>3</sub>), 1.26 (1H, dd, J 14.3, 13.5, 1 of SiCH<sub>2</sub>); δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 207.8 (C=O), 169.9 (C=CPh), 137.2 (OCH<sub>2</sub>C=CPh), 134.3 (arom.CH), 134.2 (arom.CH), 134.0 (arom.C<sub>q</sub>), 133.5 (arom.C<sub>q</sub>), 130.7 (arom.C<sub>q</sub>), 130.54 (arom.CH), 130.53 (arom.CH), 129.0 (arom.CH), 128.34 (arom.CH), 128.30 (arom.CH), 128.11 (arom.CH), 128.08 (arom.CH), 63.1 (OCH<sub>2</sub>), 51.7 (OCCH(CH<sub>3</sub>)), 44.3 (SiCH<sub>2</sub>CH<sub>3</sub>), 17.5 (SiCH<sub>2</sub>), 14.6 (CH<sub>3</sub>); m/z (CI pos) 397 (MH<sup>+</sup>, 100%), 319 (55), 199 (15); HRMS calculated for C<sub>26</sub>H<sub>25</sub>O<sub>2</sub>Si (MH<sup>+</sup>) 397.1624 Found 397.1631
4.2.3 Synthesis of silyl enol ethers

Synthesis of isophorone oxide 356a

In a 3-necked flask, equipped with a thermometer, was placed a solution of isophorone (355a, 1.0 g, 7.2 mmol) and 30% aqueous hydrogen peroxide (2.5 mL, 22 mmol), in methanol (8 mL). After the contents of the flask had been cooled to 15 °C, 6M sodium hydroxide (0.6 mL, 3.6 mmol) was added dropwise, with stirring. During the addition, the temperature of the reaction was maintained at 20-25 °C. The resulting reaction mixture was stirred at 20-25 °C for 105 minutes.

The reaction mixture was then poured into H$_2$O (30 mL). The resulting mixture was extracted with diethyl ether (4 x 25 mL) and the combined ethereal extracts were dried (MgSO$_4$) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO$_2$, Hexane / EtOAc 9 : 1) afforded isophorone oxide (356a, 0.77 g, 69%) as a colourless oil.

$\nu_{max}$ (neat)/cm$^{-1}$ 2872s (C-H), 1717s (C=O), 1448m, 1398s, 1309m; $\delta_H$ (500 MHz; CDCl$_3$) 2.99 (1H, br s, O=CCH$_2$), 2.56 (1H, dd, J 13.3, 0.7, 1 of O=CCH$_2$), 2.02 (1H, br d, J 15.0, 1 of CH$_2$), 1.75 (1H, ddd, J 13.4, 3.1, 1.0, 1 of O=CCH$_2$), 1.64 (1H, dd, J 14.9, 2.1, 1 of CH$_2$), 1.37 (3H, s, OCCH$_3$), 0.97 (3H, s, CH$_3$), 0.86 (3H, s, CH$_3$); $\delta_C$ (125 MHz; CDCl$_3$) 207.8 (C=O), 64.2 (OCCH$_3$), 61.3 (OCH), 47.9 (O=CCH$_2$), 42.7 (CH$_2$), 36.0 (C(CH$_3$)$_2$), 30.7 (CH$_3$), 27.8 (CH$_3$), 23.9 (OCCH$_3$); $m/z$ (Cl pos) 155 (MH$^+$, 71%), 141 (75), 109 (100); HRMS calculated for C$_9$H$_{15}$O$_2$(MH$^+$) 155.1072 Found 155.1072.

Synthesis of 4,4-dimethyl-6-heptyn-2-one 357a

A solution of isophorone oxide (356a, 5.0 g, 32 mmol) and (p-toluenesulfonyl)hydrazine (6.0 g, 32 mmol) in ethanol (260 mL) under nitrogen, were stirred at rt for 2 h. A light yellow precipitate was formed. The reaction mixture was heated to 55 °C under nitrogen overnight.

The clear orange solution was cooled to rt, diluted with H$_2$O (65 mL), and extracted with chloroform (4 x 150 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO$_2$, Hexane...
New Substrates for PKR

Experiment

/ EtOAc 9 : 1) afforded 4,4-dimethyl-6-heptyn-2-one (357a, 1.3 g, 29%) as a colourless oil.

v<sub>max</sub> (CHCl<sub>3</sub> cast)/cm<sup>-1</sup> 3296s (C=C-H), 2878s (C-H), 2116w (C=O), 1713s (C=O), 1366s, 1159m, 1049m; δ<sub>H</sub> (500 MHz; CDCl<sub>3</sub>) 2.46 (2H, s, OCH<sub>2</sub>); 2.24 (2H, d, J 2.7, HC=CCH<sub>2</sub>); 2.11 (3H, s, OCH<sub>3</sub>); 1.98 (1H, t, J 2.7, HCC=C), 1.06 (6H, s, 2 x CH<sub>3</sub>); δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 208.2 (C=O), 82.1 (C=C-H), 70.3 (C=C-H), 52.2 (OCCH<sub>2</sub>), 33.2 (C(CH<sub>3</sub>)<sub>2</sub>), 32.0 (OCCH<sub>3</sub>), 31.2 (H<sub>2</sub>CC=C-H), 27.0 (2 x CH<sub>3</sub>).

Synthesis of 2,3,5,5-tetramethylcyclohex-2-en-1-one 355b<sup>103</sup>

To a solution of sodium ethoxide, prepared by reacting sodium (0.46 g, 20 mmol) with ethanol (9.4 mL), was added over 20 minutes a solution of mesityl oxide (353, 2.0 g, 20 mmol) and methyl-3-oxopentanoate (354, 2.7 g, 21 mmol) in ethanol (11.7 mL). The reaction mixture was heated to 80 °C under nitrogen, overnight.

The reaction mixture was poured into cold 25% aqueous HCl, extracted with 50% diethyl ether in hexane (4 x 100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was distilled under reduced pressure to obtain 2,3,5,5-tetramethylcyclohex-2-en-1-one (355b, 1.1 g, 34%) as a clear oil.

b.p.: 62-66 °C (2 mmHg) [lit<sup>103</sup> 71-74 °C (1 mmHg)]; v<sub>max</sub> (neat)/cm<sup>-1</sup> 2957s & 2868s (C-H), 1667s & 1639s (C=O & C=C); δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 2.24 (2H, s, OCCH<sub>2</sub>); 2.21 (2H, s, CH<sub>2</sub>); 1.90 (3H, s, OCC(CH<sub>3</sub>)=C(CH<sub>3</sub>)); 1.77 (3H, s, OCC(CH<sub>3</sub>)=C(CH<sub>3</sub>)); 1.00 (6H, s, 2 x CH<sub>3</sub>); δ<sub>C</sub> (75 MHz; CDCl<sub>3</sub>) 199.3 (C=O), 152.3 & 130.1 (C=C), 51.1 (OCCH<sub>2</sub>), 47.0 (CH<sub>2</sub>), 32.7 (C(CH<sub>3</sub>)<sub>2</sub>), 28.3 (2 x CH<sub>3</sub>), 21.6 & 10.5 (CH<sub>3</sub>C=CCH<sub>3</sub>); m/z (EI pos) 152 (M<sup>+</sup>, 70%), 131 (39), 96 (100); HRMS calculated for C<sub>10</sub>H<sub>16</sub>O (M<sup>+</sup>) 152.1201 Found 152.1202.

Synthesis of 2,3-Epoxy-2,3,5,5-tetramethylcyclohexanone 356b

Using the procedure of House<sup>102</sup>, in a 2-necked flask, equipped with a thermometer, was placed a solution of 2,3,5,5-tetramethylcyclohex-2-en-1-one (355b, 2.25 g, 14.8 mmol) and 30% aqueous hydrogen peroxide (5.0 mL, 44 mmol), in methanol (17.3 mL). After the
contents of the flask had been cooled to 15 °C, 6M sodium hydroxide (1.2 mL, 7.4 mmol) was added dropwise, with stirring. During the addition, the temperature of the reaction was maintained at 20-25 °C. The resulting reaction mixture was stirred at rt, overnight.
The reaction mixture was then poured into H₂O (30 mL). The resulting mixture was extracted with diethyl ether (4 x 50 mL) and the combined ethereal extracts were dried (MgSO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Hexane / EtOAc 95 : 5) afforded 2,3-epoxy-2,3,5,5-tetramethylcyclohexanone (356b, 1.77 g, 71%) as a colourless oil.

ν_max (CHCl₃ cast)/cm⁻¹ 2932s (C-H), 1713s (C=O), 1369m, 1348m, 1105m; δ_H (500 MHz; CDCl₃) 2.74 (1H, d, J 13.2, 1 of O=CCCH₂), 2.10 (1H, d, J 14.9, 1 of CH₂), 1.84 (1H, dd, J 13.2, 2.3, 1 of O=CCH₂), 1.68 (1H, dd, J 15.0, 2.2, 1 of CH₂), 1.41 (3H, s, OCCH₃), 1.40 (3H, s, OCCH₃), 0.99 (3H, s, CH₃), 0.86 (3H, s, CH₃); δ_C (125 MHz; CDCl₃) 208.7 (C=O), 67.6 (O=CCCH₃), 64.0 (OCCH₃), 48.2 (O=CCH₂), 44.4 (CH₂), 35.0 (C(CH₃)₂), 30.9 (CH₃), 27.9 (CH₃), 21.6 (OCCH₃), 11.2 (OCCH₃); m/z (EI pos) 168 (M⁺, 26%), 153 (60), 111 (42), 97 (46), 85 (65), 71 (75), 57 (100); HRMS calculated for C₁₀H₁₆O₂ (M⁺) 168.1150 Found 168.1149.

Synthesis of 4,4-Dimethyloct-6-yn-2-one 357b
Using the procedure of Wei et al.¹⁰¹, a solution of 2,3-epoxy-2,3,5,5-tetramethylcyclohexanone (356b, 0.30 g, 1.8 mmol) and (p-toluenesulfonyl)hydrazine (0.33 g, 1.8 mmol) in ethanol (16 mL) under nitrogen, were stirred at rt for 2 h. The reaction mixture was heated to 55 °C under nitrogen, for 2 h.
The clear orange solution was cooled to rt, diluted with H₂O (50 mL), and extracted with chloroform (3 x 50 mL). The combined organic extracts were washed with H₂O (100 mL), dried (MgSO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Hexane / EtOAc 9 : 1) afforded 4,4-dimethyloct-6-yn-2-one (357b, 0.13 g, 48%) as a colourless oil.

ν_max (CHCl₃ cast)/cm⁻¹ 2874s (C-H), 1715s (C=O), 1364m, 1157m; δ_H (300 MHz; CDCl₃) 2.42 (2H, s, OCCH₂), 2.16 (2H, q, J 2.5, CH₂C=CCCH₃), 2.14 (3H, s, OCCH₃),
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1.79 (3H, t, J 2.5, H₃CC≡C), 1.05 (6H, s, 2 x CH₃); δC (75 MHz; CDCl₃) 208.6 (C=O), 77.6 & 76.7 (C≡C), 52.7 (OCCH₂), 33.7 (C(CH₃)₂), 32.2 (OCCH₃), 32.1 (H₂CC≡CCH₃), 27.0 (2 x CH₃), 3.4 (C≡CCH₃; m/z (EI pos) 175 (81%), 151 (M-H⁺, 26), 137 (20), 123 (55), 109 (95), 91 (100).

Synthesis of 4,4-Dimethyl-2-trimethylsilyloxyoct-1-en-6-yne 272b

n-Butyllithium (1.6 M in hexane, 0.34 mL, 0.54 mmol) was added dropwise to a solution of diisopropylamine (80 μL, 0.57 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to -78 °C and a solution of 4,4-dimethyloct-6-yn-2-one (357b, 80 mg, 0.52 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, followed by addition of chlorotrimethylsilane (72 μL, 0.57 mmol). The reaction mixture was warmed to rt over 1 h, quenched with sat aqueous sodium hydrogen carbonate (2 mL) and extracted with diethyl ether (3 x 20 mL). The combined ethereal extracts were dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Hexane / EtOAc 99 : 1) afforded 4,4-dimethyl-2-trimethylsilyloxyoct-1-en-6-yne (272b, 12 mg, 10%) as a pale yellow oil.

νmax (neat)/cm⁻¹: 2961 s (C=CH₂), 2924 s & 2856 m (C-H), 1634 m (C=C), 1469 m, 1261 s; δH (300 MHz; CDCl₃) 4.10 (1H, s, 1 of C=CH₂), 4.07 (1H, s, 1 of C=CH₂), 2.08 (2H, q, J 2.5, CH₂C≡CCH₃), 2.01 (2H, s, CH₂C≡CCH₂), 1.80 (3H, t, J 2.5, H₂CC≡C), 0.98 (6H, s, 2 x CH₃), 0.21 (9H, s, OSi(CH₃)₃); δC (75 MHz; CDCl₃) 157.8 (C=CH₂), 92.4 (C=CH₂), 77.6 & 77.8 (C≡C), 47.7 (CH₂C≡CCH₂), 33.7 (C(CH₃)₂), 32.3 (H₂CC≡CCH₃), 27.1 (2 x CH₃), 3.4 (C≡CCH₃), 0.04 (OSi(CH₃)₃).

Synthesis of 2,7,7-Trimethyl-5-trimethylsilanyloxybicyclo[3.3.0]oct-1-en-3-one 358

Using the procedure of Mukai et al., a solution of 4,4-dimethyl-2-trimethylsilyloxyoct-1-en-6-yne (272b, 12 mg, 75 μmol) in acetonitrile (0.5 mL) was added to a stirred solution of dicobalt octacarbonyl (0.03 g, 91 μmol) in acetonitrile (0.5 mL), at rt under nitrogen and the mixture was stirred for 1 h. The resulting reaction mixture was heated to 75 °C overnight.
The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (Florisil®, Petrol 30-40 / Ether 99: 1 to 80 : 20) to obtain 2,7,7-trimethyl-5-trimethylsilyloxybicyclo[3.3.0]oct-1-en-3-one (358, 3 mg, 19%) as a yellow oil.

δ\(\text{H}(500\,\text{MHz};\,\text{CDCl}_3\)) 2.59 (1H, d, \(J\ 18.1, 1\) of OC\(\text{CH}_2\)), 2.55 (1H, d, \(J\ 16.4, 1\) of \(\text{CH}_2\text{C}=\text{C}\)), 2.40 (1H, d, \(J\ 18.0, 1\) of OC\(\text{CH}_2\)), 2.35 (1H, d, \(J\ 16.4, 1\) of \(\text{CH}_2\text{C}=\text{C}\)), 2.09 (1H, d, \(J\ 13.7, 1\) of \(\text{CH}_2\text{COSi(CH}_3)_3\)), 1.70 (3H, d, \(J\ 1.6, \text{C}=\text{CCH}_3\)), 1.38 (1H, d, \(J\ 13.7, 1\) of \(\text{CH}_2\text{COSi(CH}_3)_3\)), 1.34 (3H, s, \(\text{CH}_3\)), 1.01 (3H, s, \(\text{CH}_3\)), 0.08 (9H, s, OSi(CH\(_3\)_3)).

**Synthesis of Diethyl hept-6-yn-2-one-4,4-dicarboxylate 361a**

Using the procedure of Trost et al.\(^{90}\), a solution of diethyl propargylmalonate (276a, 1.10 g, 5.55 mmol), chloroacetone (360, 1.33 mL, 16.6 mmol), potassium carbonate (2.3 g, 17 mmol) and sodium iodide (83 mg, 0.56 mmol), in acetone (22 mL) was heated to reflux, under nitrogen, overnight.

The reaction mixture was filtered, concentrated in vacuo and the residue was purified by flash chromatography (SiO\(_2\), Hexane / EtOAc 7 : 3) to obtain diethylhept-6-yn-2-one-4,4-dicarboxylate (361a, 0.95 g, 67%) as a colourless oil.

\(\nu_{\text{max}}\,\text{(neat)/cm}^{-1}\) 3281s (C\(=\text{C-H}\)), 2984s & 2939m (C-H), 2120w (C\(=\text{C}\)), 1722br (C\(=\text{O}\) ester and ketone), 1467m, 1367s, 1286s; \(\delta_{\text{H}}(300\,\text{MHz};\,\text{CDCl}_3\)) 4.22 (2H, dq, \(J\ 10.8, 7.1, 2\) of O\(\text{CH}_2\)), 4.13 (2H, dq, \(J\ 10.8, 7.1, 2\) of O\(\text{CH}_2\)), 3.33 (2H, s, O\(=\text{CCH}_2\)), 3.00 (2H, d, \(J\ 2.7, \text{H}_2\text{CC}=\text{CH}\)), 2.17 (3H, s, O\(=\text{CCH}_3\)), 2.00 (1H, t, \(J\ 2.7, \text{C}=\text{CH}\)), 1.23 (6H, t, \(J\ 7.2, \text{OCH}_2\text{CH}_3\)); \(\delta_{\text{C}}(75\,\text{MHz};\,\text{CDCl}_3\)) 205.3 (C\(=\text{O}\) ketone), 169.0 (C\(=\text{O}\) ester), 79.3 (C\(=\text{CH}\)), 71.5 (C\(=\text{CH}\)), 61.9 (O\(\text{CH}_2\)), 54.3 (O\(_2\text{CCCO}_2\)), 45.1 (O\(=\text{CCH}_2\)), 30.1 (O\(=\text{CCH}_3\)), 23.1 (H\(_2\text{CC}=\text{CH}\)), 13.9 (O\(\text{CH}_2\text{CH}_3\)); \(m/z\) (Cl pos) 255 (MH\(^+\), 84%), 181 (100); HRMS calculated for C\(_{13}\)H\(_{19}\)O\(_5\) (MH\(^+\)) 255.1232 Found 255.1234.

**Synthesis of 1-Bromo-3-phenylprop-2-yn-1-ol 359**\(^{104}\)

To a mixture of 3-phenylprop-2yn-1-ol (329, 0.50 g, 3.8 mmol) and pyridine (40 \(\mu\text{L}, 0.5\) mmol) in diethyl ether (0.6 mL), under nitrogen
at 0 °C, was added phosphorus tribromide (0.47 mL, 4.9 mmol) dropwise. The resulting reaction mixture was heated to 50 °C for 2.5 h.

The reaction mixture was cooled and poured into ice\(\cdot\)\(\text{H}_2\text{O}\) (30 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (4 x 50 mL). The combined organic extracts were successively washed with sat. aqueous NaHCO\(_3\) (2 x 100 mL), \(\text{H}_2\text{O}\) (2 x 100 mL) and brine (2 x 100 mL). The organic layer was dried (\(\text{MgSO}_4\)) and concentrated \textit{in vacuo} to obtain the crude product. Flash chromatography (SiO\(_2\), Hexane) afforded 1-bromo-3-phenylprop-2-yne (359, 0.6 g, 82%) as a yellow oil.

\[v_{\text{max}} \text{ (neat)/cm}^{-1} \] 3057\(m\) (C-H), 2219\(s\) (C=C), 1597\(m\) (C=C aromatic), 1490\(s\) (C=C aromatic), 1441\(s\), 1271\(sm\) 1204\(s\); \(\delta\)\(H\) (300 MHz; CDCl\(_3\)) 7.47-7.44 (2H, m, arom.H), 7.35-7.31 (3H, m, arom.H), 4.17 (2H, s, \(CH_2\))

\[\delta\)\(C\) (75 MHz; CDCl\(_3\)) 131.8 (arom.CH), 128.8 (arom.CH), 128.3 (arom.CH), 122.1 (arom.C\(_q\)), 86.7 & 84.2 (C=C), 15.2 (\(CH_2\)); m/z (Cl pos) 197 & 195 (MH\(^+\), 36% & 38%), 133 (19), 115 (60), 105 (100).

\textbf{Synthesis of Diethyl 2-(3-phenylprop-2-ynyl)malonate 276b}

Using the procedure of Marvel and Hager,\(^8^9\), diethyl malonate (274, 4.1 g, 26 mmol) was added through a dropping funnel to a solution of sodium ethoxide prepared by the addition of sodium (0.59 g, 26 mmol), in small pieces, to ethanol (15 mL) under nitrogen. To this reaction mixture at 50 °C was added 1-bromo-3-phenylprop-2-yne (359, 5.0 g, 26 mmol) dropwise. The reaction mixture was heated to reflux, overnight.

Ethanol was removed \textit{in vacuo} and the residue was dissolved in \(\text{H}_2\text{O}\) (20 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (5 x 50 mL). The combined organic extracts were dried (\(\text{MgSO}_4\)) and concentrated \textit{in vacuo} to obtain the crude product. Flash chromatography (SiO\(_2\), Toluene / EtOAc 99 : 1) afforded diethyl 2-(3-phenylprop-2-ynyl)malonate (276b, 3.0 g, 43%) as a colourless oil.

\[v_{\text{max}} \text{ (neat)/cm}^{-1} \] 2982\(s\), 2938\(m\) & 2907\(m\) (C-H), 1733\(s\) (C=O), 1598\(m\) (C=C aromatic), 1491\(s\) (C=C aromatic), 1465\(m\), 1443\(s\), 1369\(s\); \(\delta\)\(H\) (300 MHz; CDCl\(_3\)) 7.38-7.35 (2H, m, arom.H), 7.28-7.27 (3H, m, arom.H), 4.25 (4H, q, \(J 7.2\), OCH\(_2\)), 3.65 (1H, t, \(J 7.7\), O\(_2\)CC\(\equiv\)CO\(_2\)), 3.00 (2H, d, \(J 7.7\), \(H_2\)C\(\equiv\)CPh), 1.29 (6H, t, \(J 7.2\), OCH\(_3\)CH\(_3\)); \(\delta\)\(C\) (75
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MHz; CDCl₃) 168.1 (C=O), 131.6 (arom.CH), 128.2 (arom.CH), 127.9 (arom.CH), 123.2 (arom.C₂), 85.4 & 82.4 (C≡C), 61.7 (OCH₂), 51.5 (O₂CCHCO₂), 19.4 (H₂CC≡CPh), 14.1 (OCH₂CH₃); m/z (CI pos) 275 (MH⁺, 90%), 229 (45), 201 (95), 161 (100); HRMS calculated for C₁₆H₁₀O₄ (MH⁺) 275.1283 Found 275.1284.

A side product of the reaction, diethyl 2,2-di-(3-phenylprop-2-ynyl)malonate (277b, 2.2 g, 22%) was isolated as a white crystalline solid.

EtO₂C ———— Ph

EtO₂C ———— Ph

m.p.: 81-82 °C; Found C 76.9, H 6.2; C₂₅H₂₄O₄ requires C 77.3, H 6.2%; νmax (CHCl₃ cast)/cm⁻¹ 2981s & 2936m (C-H), 1732 (C=O), 1598m (C=C aromatic), 1491s (C=C aromatic), 1465m, 1443s, 1367m, 1325s, 1297s; δH (300 MHz; CDCl₃) 7.40-7.37 (4H, m, arom.H), 7.29-7.27 (6H, m, arom.H), 4.27 (4H, q, j 7.2, OCH₂), 3.26 (4H, s, H₂CC≡CPh), 1.29 (6H, t, j 7.2, OCH₂CH₃); δC (75 MHz; CDCl₃) 168.9 (C=O), 131.7 (arom.CH), 128.2 (arom.CH), 128.0 (arom.CH), 123.2 (arom.C₂), 84.1 & 83.7 (C=C), 62.0 (OCH₂), 57.1 (O₂CCO₂), 23.7 (H₂CC≡CPh), 14.1 (OCH₂CH₃); m/z (CI pos) 389 (MH⁺, 12%), 242 (60), 193 (65), 165 (100), 115 (45), 91 (54).

Synthesis of Diethyl 7-phenylhept-6-yn-2-one-4,4-dicarboxylate 361b

Using the procedure of Trost et al.⁹⁰, a solution of diethyl 2-(3-phenylprop-2-ynyl)malonate (276b, 1.8 g, 6.6 mmol), chloroacetone (360, 1.6 mL, 20 mmol), potassium carbonate (2.7 g, 20 mmol) and sodium iodide (0.10 g, 0.7 mmol), in acetone (36 mL) was heated to reflux, under nitrogen, overnight.

The reaction mixture was filtered, concentrated in vacuo and the residue was purified by flash chromatography (SiO₂, Toluene / EtOAc 24 : 1) followed by chromatotron (SiO₂, Toluene / EtOAc 99 : 1) to obtain diethyl 7-phenylhept-6-yn-2-one-4,4-dicarboxylate (361b, 0.9 g, 41%) as a colourless oil.

νmax (neat)/cm⁻¹ 2982s & 2936s (C-H), 1722br (C=O ester & ketone), 1590m (C=C aromatic), 1491s (C=C aromatic), 1443s, 1391m, 1367s, 1286s; δH (300 MHz; CDCl₃) 7.34-7.32 (2H, m, arom.H), 7.28-7.26 (3H, m, arom.H), 4.21 (2H, dq, j 10.8, 7.2, 2 of
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OCH₂), 4.20 (2H, dq, J 10.8, 7.1, 2 of OCH₂), 3.38 (2H, s, O=CCH₂), 3.20 (2H, s, H₂CC≡CPh), 2.18 (3H, s, O=CCH₂), 1.24 (6H, t, J 7.1, OCH₂CH₃); δc (75 MHz; CDCl₃) 205.4 (C=O ketone), 169.2 (C=O ester), 135.6 (arom.CH), 128.2 (arom.CH), 128.0 (arom.CH), 123.1 (arom.C₄), 84.7 & 83.7 (C=C), 62.0 (OCH₂), 54.8 (O₃CCCO₂), 45.5 (O=CCH₂), 30.3 (O=CCH₃), 24.2 (H₂CC≡CPh), 14.0 (OCH₂CH₃); m/z (Cl pos) 331 (MH⁺, 100%), 257 (96), 215 (50), 161 (75), 105 (90); HRMS calculated for C₉H₂₃O₅ (MH⁺) 331.1545 Found 331.1547.

Synthesis of Diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate 362c

EtO₂C — E E r— Ph n-Butyllithium (1.6 M in hexane, 0.23 mL, 0.36 mmol) was added dropwise to a solution of diisopropylamine (51 µL, 0.36 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to −78 °C, a solution of 4,4-diethyl-7-phenylhex-6-yne-2-onemalonate (361b, 0.10 g, 0.30 mmol) in THF (1 mL) was added dropwise and stirred for 40 minutes. Chlorotrimethylsilane (46 µL, 0.36 mmol) was added dropwise and the reaction mixture stirred for 10 minutes. The reaction mixture was warmed to rt over 1 h, quenched with sat. aqueous sodium hydrogen carbonate (3 mL) and extracted with diethyl ether (3 x 10 mL). The combined ethereal extracts were dried (Na₂SO₄) and concentrated in vacuo to obtain diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (362c, 0.15 g) as a yellow oil, slightly contaminated with silyl impurities.

δH (300 MHz; C₆D₆) 7.45-7.41 (2H, m, arom.H), 6.99-6.94 (3H, m, arom.H), 4.38 (1H, s, 1 of C=CH₂), 4.19 (1H, s, 1 of C=CH₂), 4.14 (2H, dq, J 10.8, 7.1, 2 of OCH₂), 3.96 (2H, dq, J 10.8, 7.1, 2 of OCH₂), 3.52 (2H, s, CH₂C=C), 3.37 (2H, s, H₂CC≡CPh), 0.96 (6H, t, J 7.2, OCH₂CH₃), 0.17 (9H, s, Si(CH₃)₃); δc (75 MHz; C₆D₆) 169.9 (C=O), 155.3 (C=CH₂), 132.0 (arom.CH), 128.5 (arom.CH), 128.3 (arom.CH), 124.1 (arom.C₄), 93.5 (C=CH₂), 85.9 & 84.1 (C=C), 61.4 (OCH₂), 56.5 (O₃CCCO₂), 39.8 (CH₂C=CH₂), 24.0 (H₂CC≡CPh), 14.1 (OCH₂CH₃), -0.2 Si(CH₃)₃).
Synthesis of Diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate 364

Method 1
Using the procedure of Mukai et al.\textsuperscript{91}, a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (362c, 0.11 g, 0.27 mmol) in acetonitrile (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.11 g, 0.35 mmol) in acetonitrile (1 mL), at rt under nitrogen, and stirred for 1 h. The resulting reaction mixture was heated to 75 °C overnight.

The reaction mixture was cooled and a solution of para-toluenesulfonic acid monohydrate (0.10 g, 0.6 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 40 min. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, Petrol 40-60 / EtOAc 4 : 1) to obtain diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (364, 25 mg, 23%) as a thick oil which could be recrystallised from ether / hexane mixture to obtain a white crystalline solid.

Method 2
To a solution of dicobalt octacarbonyl (0.11 g, 0.33 mmol) in toluene (1 mL), at rt under nitrogen, was added a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (362c, 0.10 g, 0.25 mmol) in toluene (1 mL) and stirred for 1 h. The resulting reaction mixture was heated to reflux for 4.5 h.

The reaction mixture was cooled and a solution of para-toluenesulfonic acid monohydrate (0.10 g, 0.5 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, Petrol 40-60 / EtOAc 7 : 3) to obtain diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (364, 31 mg, 29%) as a thick oil which could be recrystallised from ether / hexane mixture to obtain a white crystalline solid.
Method 3

Using the procedure of Sugihara et al., a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (362c, 0.13 g, 0.33 mmol) in 1,2-dichloroethane (1.9 mL) was added to a solution of dicobalt octacarbonyl (0.21 g, 0.62 mmol) in 1,2-dichloroethane (1.4 mL) under argon at rt. The reaction mixture was stirred at rt for 1.5 h. n-Butyl methyl sulphide (0.14 mL, 1.2 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled and a solution of para-toluenesulfonic acid monohydrate (0.13 g, 0.53 mmol) in methanol (3 mL) was added and the mixture was stirred at rt for 3 h.

The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (SiO₂, Hexane / EtOAc 7 : 3) to obtain diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (364, 25 mg, 24%) as a thick oil which could be recrystallised from ether / hexane mixture to obtain a white crystalline solid.

m.p.: 112-113 °C; \( \nu_{\text{max}} \) (CHCl₃ cast)/cm\(^{-1}\) 3419 br s (O-H), 2928s (C-H), 1717s & 1699s (C=O), 1500m (C=C aromatic), 1447m (C=C aromatic), 1367m, 1256s, 1184s; \( \delta_H \) (500 MHz; C₆D₆) 7.73-7.71 (2H, m, arom.H), 7.19-7.17 (2H, m, arom.H), 7.11-6.99 (1H, m, arom.H), 4.13 (1H, d, \( J = 19.0 \), 1 of CH₂C=CPh), 4.03 (2H, q, \( J = 7.1 \), 2 of OCH₂), 3.85 (1H, dq, \( J = 10.8 \), 7.1, 1 of OCH₂), 3.72 (1H, dq, \( J = 10.8 \), 7.1, 1 of OCH₂), 3.19 (1H, d, \( J = 19.0 \), 1 of CH₂C=CPh), 2.94 (1H, d, \( J = 13.9 \), 1 of CCH₂C(OH)), 2.49 (1H, d, \( J = 17.7 \), 1 of OCCCH₂), 2.22 (1H, d, \( J = 17.7 \), 1 of OCCCH₂), 2.13 (1H, d, \( J = 13.9 \), 1 of CCH₂C(OH)), 0.95 (3H, t, \( J = 7.1 \), OCH₂CH₃), 0.78 (3H, t, \( J = 7.1 \), OCH₂CH₃); \( \delta_C \) (125 MHz; C₆D₆) 205.1 (C=O ketone), 174.8 (C=CPh), 171.9 (C=O ester), 170.9 (C=O ester), 135.1 (C=CPh), 131.1 (arom.C₄), 129.2 (arom.CH), 128.8 (arom.CH), 128.7 (arom.CH), 81.8 (C(OH)), 62.2 (OCH₂), 61.8 (OCH₂), 61.7 (O₂CCCO₂), 49.0 (OCCH₂), 44.5 (CCH₂C(OH)), 35.0 (CH₂C=CPh), 13.9 (OCH₂CH₃), 13.8 (OCH₂CH₃); m/z (FAB pos) 359 (MH⁺, 3%), 338 (25), 307 (26), 289 (12), 154 (100); HRMS calculated for C₂₀H₂₃O₆ (MH⁺) 359.1495; Found 359.1502.
Synthesis of Ethyl 2-(2-oxopropyl)-5-phenylpent-4-ynoate 365

Using the procedure of Krafft et al., a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6-yn-4,4-dicarboxylate (362c, 0.13 g, 0.32 mmol) in dichloromethane (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.16 g, 0.47 mmol) in dichloromethane (1 mL) under nitrogen at rt. The reaction mixture was stirred at rt for 1 h and then concentrated in vacuo to obtain a red residue (0.32 g).

A solution of the above residue in H2O (9.4 mL) and cetyltrimethylammonium bromide (0.10 g, 0.28 mmol) was heated to 70 °C for 2 days. The reaction mixture was cooled to rt, filtered and extracted with diethyl ether (5 x 25 mL). The combined ethereal extracts were successively washed with 2M aqueous HCl (2 x 100 mL) and H2O (100 mL), dried (MgSO4) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO2, Toluene / EtOAc 97 : 3) afforded ethyl 2-(2-oxopropyl)-5-phenylpent-4-ynoate (365, 5 mg, 7%) as a yellow oil.

\[
\text{v}_{\text{max}} (\text{CHCl}_3 \text{ cast})/\text{cm}^{-1} \quad 2908 \text{s} \quad 2856 \text{s} (\text{C-H}), \quad 1717 \text{s} (\text{C=O}), \quad 1599 \text{w} \quad 1490 \text{s} (\text{C=C aromatic}), \quad 1443 \text{s}, \quad 1367 \text{s}, \quad 1181 \text{s}; \quad \delta_{\text{H}} (500 \text{ MHz; C6D6}) \quad 7.45-7.43 (2 \text{H, m, arom.H}), \quad 6.99-6.96 (3 \text{H, m, arom.H}), \quad 4.00-3.95 (2 \text{H, m, OCH2}), \quad 3.16-3.11 (1 \text{H, m CO2CH}), \quad 2.83 (1 \text{H, dd, J 17.0, 8.4, 1 of CH2CO}), \quad 2.67 (1 \text{H, dd, J 17.0, 7.1, 1 of CH2C=CPH}), \quad 2.60 (1 \text{H, dd, J 17.0, 7.1, 1 of CH2C=CPH}), \quad 2.31 (1 \text{H, dd, J 18.0, 8.4, 1 of CH2CO}), \quad 1.65 (3 \text{H, s, CH2CO}), \quad 0.96 (3 \text{H, t, J 7.2, OCH2CH3}); \quad \delta_{\text{C}} (75 \text{ MHz; C6D6}) \quad 204.6 (\text{C=O ketone}), \quad 173.1 (\text{C=O ester}), \quad 131.9 (\text{arom.CH}), \quad 128.5 (\text{arom.CH}), \quad 128.1 (\text{arom.CH}), \quad 124.0 (\text{arom.Cq}), \quad 86.9 \quad 83.3 (\text{C=C}), \quad 60.7 (\text{OCH2}), \quad 43.6 (\text{OCCH2}), \quad 39.6 (\text{CH}), \quad 29.3 (\text{OCCH3}), \quad 22.1 (\text{H2CC=CPH}), \quad 14.1 (\text{OCH2CH3}); \quad m/z (\text{FAB pos}) 281 (\text{MNa}^+, 100\%), \quad 276 (7); \quad \text{HRMS calculated for C16H18O3Na (MNa+) 281.1148 Found 281.1151.}
\]

Synthesis of Diethyl 2-triisopropylsilyloxyhept-1-en-6-yn-4,4-dicarboxylate 367a

\[
\text{n-Butyllithium (1.6 M in hexane, 0.30 mL, 0.47 mmol) was added dropwise to a solution of diisopropylamine (70 \mu L, 0.47 mmol) in THF (2.5 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to -78 °C, a solution of diethylhept-6-yne-2-one-4,4-dicarboxylate (361a, 0.10 g, 0.39 mmol) in THF (1.5 mL) was added dropwise and stirred for 1.5 h. Triisopropylsilyl triflate (0.13 mL, 0.47 mmol) was added dropwise}
\]

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and the reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was warmed to rt over 1 h, quenched with sat. aqueous sodium hydrogen carbonate (3 mL) and extracted with diethyl ether (3 x 10 mL). The combined ethereal extracts were dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Hexane / EtOAc / Et₃N 96 : 3 : 1) afforded diethyl 2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (367a, 18 mg, 11%) as a yellow oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \]
- 3270s (C≡C-H), 2943s & 2867s (C-H), 1739s (C=O), 1634m, 1467m;
- 400 MHz; C₆D₆)
  - 4.30 (1H, d, J0.9, 1 of C≡CH₂), 4.19 (1H, d, J0.8, 1 of C≡CH₂), 4.07 (2H, dq, J10.8, 7.1, 2 of OCH₂), 3.97 (2H, dq, J10.8, 7.1, 2 of OCH₂), 3.35 (2H, d J2.7, CH₂C=C), 3.29 (2H, s, CH₂C=C), 1.74 (1H, t, J2.7, C≡C-H), 1.14-1.10 (21H, m, SiCH(CH₃)₂), 0.94 (6H, t, J7.1, OCH₂CH₃); δC (100 MHz; C₆D₆)
  - 169.6 (C=O), 155.8 (SiOC=CH₂), 93.3 (C=CH₂), 80.0 (C≡CH), 71.8 (C≡CH), 61.5 (OCH₂), 56.7 (O₂C₃CO₂), 39.4 (CH₂C=C), 23.3 (H₂CC≡CH), 18.2 (SiCH(CH₃)₂), 13.9 (SiCH), 13.1 (OCH₂CH₃); m/z (FAB pos) 411 (MH⁺, 100%), 367 (90), 157 (30); HRMS calculated for C₂₂H₃₉O₅Si (MH⁺) 411.2567 Found 411.2570.

Diethyl 7-trisopropylsilyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (367b, 40 mg, 18%) was also isolated from the crude mixture as a yellow oil.
Synthesis of Diethyl 7-phenyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate 367c

n-Butyllithium (1.6 M in hexane, 0.45 mL, 0.73 mmol) was added dropwise to a solution of diisopropylamine (0.10 mL, 0.73 mmol) in THF (2.5 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to −78 °C, a solution diethyl 7-phenylhept-6-yn-2-one-4,4-dicarboxylate (361b, 0.20 g, 0.61 mmol) in THF (2.5 mL) was added dropwise and stirred for 1 h. Triisopropylsilyl triflate (0.20 mL, 0.73 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was warmed to rt over 1 h, quenched with sat. aqueous sodium hydrogen carbonate (5 mL) and extracted with diethyl ether (3 × 20 mL). The combined ethereal extracts were dried (Na₂SO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (Florisil®, Hexane / EtOAc 97 : 3) afforded diethyl 7-phenyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (367c, 0.26 g, 87%) as a yellow oil.

vₘₐₓ (CHCl₃ cast)/cm⁻¹ 2944s & 2867s (C-H), 1739s (C=O), 1623m, 1491m, 1464s; δ₁H (300 MHz; C₆D₆) 7.50-7.44 (2H, m, arom.H), 6.99-6.94 (3H, m, arom.H), 4.33 (1H, s, 1 of C=CH₂), 4.22 (1H, s, 1 of C=CH₂), 4.16 (2H, dq, J 10.8, 7.1, 2 of OCH₂), 3.95 (2H, dq, J 10.8, 7.1, 2 of OCH₂), 3.61 (2H, s, CH₂C=C), 3.38 (2H, s, H₂CC≡CPh), 1.16-1.11 (21H, m, SiCH(CH₃)₂), 0.96 (6H, t, J 7.2, OCH₂CH₃); δC (75 MHz; C₆D₆) 169.9 (C=O), 155.9 (SiOC=CH₂), 131.9 (arom.CH), 128.5 (arom.CH), 127.8 (arom.CH), 124.1 (arom.C₇), 93.4 (C=CH₂), 86.1 & 84.3 (C≡C), 61.5 (OCH₂), 57.3 (O₂CCO₂), 39.7 (CH₂C=CH₂), 24.4 (H₂CC≡CPh), 18.2 (SiCH(CH₃)₂), 17.9 (SiCH), 14.0 (OCH₂CH₃); m/z (CI pos) 488 (10%), 435 (16), 331 (100), 285 (35), 257 (85), 215 (35), 161 (46).

Synthesis of Diethyl 5-triisopropylsilyloxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate 368c

Using the procedure of Mukai et al., a solution of diethyl 7-phenyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (367c, 0.10 g, 0.21 mmol) in acetonitrile (1 mL) was added to a solution of dicobalt octacarbonyl (0.11 g, 0.31
mmol) in acetonitrile (1 mL), at rt under nitrogen, and stirred for 1 h. The resulting reaction mixture was heated to 75 °C overnight.

The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / EtOAc 95: 5) to obtain diethyl 5-triisopropylsilyloxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (368c, 14 mg, 13%) as a yellow oil.

$$\nu_{\text{max}} (\text{CHCl}_3 \text{ cast/cm}^{-1})$$ 2926s & 2867s (C-H), 1738s & 1717s (C=O), 1667m (C=C), 1464s, 1386m, 1367s; $\delta_{\text{H}}$ (500 MHz; C$_6$D$_6$) 7.78-7.76 (2H, m, arom.$\text{H}$), 7.20-7.17 (2H, m, arom.$\text{H}$), 7.08-7.06 (1H, m, arom.$\text{H}$), 4.25 (1H, d, $J$ 18.0, 1 of CH$_2$C=CPh), 4.19 (1H, dq, $J$ 10.8, 7.1, 1 of OCH$_2$), 4.05 (1H, dq, $J$ 10.8, 7.1, 1 of OCH$_2$), 3.80 (1H, dq, $J$ 10.8, 7.1, 1 of OCH$_2$), 3.69 (1H, dq, $J$ 10.8, 7.1, 1 of OCH$_2$), 3.36 (1H, d, $J$ 18.0, 1 of CH$_2$C=CPh), 3.14 (1H, d, $J$ 14.0, 1 of CCH$_2$(OTIPS)), 2.77 (1H, d, $J$ 18.1, 1 of OCH$_2$), 2.41 (1H, d, $J$ 14.0, 1 of CCH$_2$(OTIPS)), 2.36 (1H, d, $J$ 18.1, 1 of OCH$_2$), 1.04-0.99 (24H, m, SiCH(CH$_3$)$_2$) and OCH$_2$CH$_3$, 0.74 (3H, t, $J$ 7.1, OCH$_2$CH$_3$); $\delta_{\text{C}}$ (125 MHz; C$_6$D$_6$) 204.0 (C=O ketone), 175.5 (C=CPh), 171.5 (C=O ester), 170.6 (C=O ester), 135.1 (C=CPh), 131.0 (arom.$\text{C}_q$), 129.3 (arom.$\text{CH}$), 128.8 (arom.$\text{CH}$), 128.7 (arom.$\text{CH}$), 83.6 (C(OTIPS)), 61.88 (OCH$_2$), 61.83 (OCH$_2$), 61.5 (O$_2$CCCO$_2$), 48.5 (OCH$_2$), 47.1 (CCH$_2$(OTIPS)), 35.1 (CH$_2$C=CPh), 18.4 (SiCH(CH$_3$)$_2$), 18.3 (SiCH), 13.9 (OCH$_2$CH$_3$), 13.8 (OCH$_2$CH$_3$); $m/z$ (CI pos) 515 (MH$^+$, 7%), 471 (30), 369 (17), 341 (93), 157 (57), 131 (100); HRMS calculated for C$_{29}$H$_{43}$O$_6$Si (MH$^+$) 515.2829 Found 515.2829.

### 4.2.4 Synthesis of model substrate for ingenol

**Synthesis of Diethyl-2-pent-4-enylmalonate 402**

Using the procedure of Marvel and Hager, diethyl malonate (274, 1.76 mL, 11.6 mmol) was added dropwise to a solution of sodium ethoxide, prepared by addition of sodium (0.23 g, 10 mmol) in small pieces to ethanol (5 mL), under nitrogen. Once the resultant white precipitate dissolved at rt, 5-bromopent-1-ene (403, 1.2 mL, 10 mmol) was added dropwise and the reaction mixture was heated to reflux, overnight.
Ethanol was removed *in vacuo* and the residue was dissolved in H$_2$O (15 mL). The mixture was extracted with EtOAc (5 x 30 mL), the combined organic extracts were washed with brine (150 mL), dried (MgSO$_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO$_2$, Toluene) afforded diethyl-2-pent-4-enylmalonate (402, 1.9 g, 83%) as a clear colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3078w (=C-H$_2$), 2937m & 2864m (C-H), 1732s (C=O), 1641m (C=C), 1447m, 1369m, 1153s; $\delta_H$ (500 MHz; CDCl$_3$) 5.77 (1H, dtt, $J$ 17.0, 10.3, 6.6, HC=CH$_2$), 5.00 (1H, dtt $J$ 17.1, 2.0, 1.7, 1 of HC=CH$_2$ (trans)), 4.95 (1H, dtt $J$ 10.3, 1.9, 1.3, 1 of HC=CH$_2$ (cis)), 4.20 (2H, dq, $J$ 12.5, 7.2, 2 of OCH$_2$), 4.17 (4H, dq, $J$ 12.4, 7.1, 2 of OCH$_2$), 3.31 (1H, t, $J$ 7.6, CO$_2$CHCO$_2$), 2.09-2.05 (2H, m, H$_2$C=CHCH$_2$), 1.92-1.87 (2H, m, H$_2$C=CHCH$_2$CH$_2$H), 1.45-1.38 (2H, m, H$_2$C=CHCH$_2$CH$_2$), 1.25 (6H, t, $J$ 7.1, OCH$_2$CH$_3$); $\delta_C$ (75 MHz; CDCl$_3$) 169.4 (O O), 137.9 (HC=CH$_2$), 115.0 (HC=CH$_2$), 61.3 (OCH$_2$), 51.9 (CO$_2$CHCO$_2$), 33.2 (H$_2$C=CHCH$_2$), 28.1 (H$_2$C=CHCH$_2$CH$_2$H), 26.5 (H$_2$C=CHCH$_2$CH$_2$), 14.0 (CH$_3$); m/z (Cl pos) 229 (MH$^+$, 92%), 183 (100), 137 (75); HRMS calculated for C$_{12}$H$_{21}$O$_4$ (MH$^+$) 229.1434 Found 229.1437.

A side product of the reaction diethyl-2,2-dipent-4-enylmalonate (404, 0.14 g, 5%) was also isolated as a clear colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3077m (=C-H$_2$), 2936s & 2844m (C-H), 1730s (C=O), 1641m (C=C), 1446m, 1193s; $\delta_H$ (400 MHz; CDCl$_3$) 5.76 (2H, dtt, $J$ 16.9, 10.2, 6.7, HC=CH$_2$), 5.00 (2H, dtt $J$ 17.1, 1.9, 1.6, 2 of HC=CH$_2$ (trans)), 4.94 (2H, dtt $J$ 10.2, 2.0, 1.2, 2 of HC=CH$_2$ (cis)), 4.16 (4H, q, $J$ 7.1, OCH$_2$), 2.07-2.05 (4H, m, H$_2$C=CHCH$_2$H), 1.89-1.84 (4H, m, H$_2$C=CHCH$_2$CH$_2$H), 1.30-1.23 (4H, m, H$_2$C=CHCH$_2$CH$_2$), 1.22 (6H, t, $J$ 7.1, OCH$_2$CH$_3$); $\delta_C$ (75 MHz; CDCl$_3$) 171.8 (C=O), 138.1 (HC=CH$_2$), 114.9 (HC=CH$_2$), 61.0 (OCH$_2$), 57.4 (CO$_2$CCO$_2$), 33.8 (H$_2$C=CHCH$_2$), 31.7 (H$_2$C=CHCH$_2$CH$_2$CH$_2$), 23.3
New Substrates for PKR

(H₂C=CHCH₂CH₂), 14.1 (CH₃); m/z (Cl pos) 297 (MH⁺, 100%), 251 (90), 149 (85), 113 (40); HRMS calculated for C₁₇H₂₉O₄ (MH⁺) 297.2060 Found 297.2062.

Synthesis of 6-iodohex-1-yne 406

To a solution of sodium iodide (3.9 g, 26 mmol) in acetone (30 mL), under argon, was added 6-chlorohex-1-yne (405, 0.52 mL, 4.3 mmol) dropwise. The reaction mixture was heated to reflux overnight. Acetone was removed in vacuo at rt, the residue was dissolved in H₂O (6 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (40 mL), dried (MgSO₄) and concentrated in vacuo, at rt, to obtain crude product. Flash chromatography (SiO₂, Hexane) afforded 6-iodohex-1-yne (406, 0.77 g, 86%) as a colourless oil.

Synthesis of Diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate 401

To a suspension of sodium hydride (60% dispersion in oil, 68 mg, 1.7 mmol) in DMF (1.2 mL) at 0 °C, under argon, was added a solution of diethyl-2-pent-4-enylmalonate (402, 0.30 g, 1.3 mmol) in DMF (3.5 mL) and stirred for 30 minutes. A solution of 6-iodohex-1-yne (406, 0.36 g, 1.7 mmol) in DMF (3.5 mL) was added dropwise to reaction mixture, which was stirred at rt for 3 h.

The reaction mixture was quenched with H₂O (200 mL) and extracted with EtOAc (4 x 200 mL). The combined organic extracts were washed with brine (400 mL), dried (MgSO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Petrol 40-60 / EtOAc 98 : 2) afforded diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (401, 0.35 g, 86%) as a colourless oil.
**NEW SUBSTRATES FOR PKR**

\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1} \] 3296s (C=C-H), 3076w (=C-H), 2937s (C-H), 2118w (C=C), 1728s (C=O), 1641s (C=C), 1447s, 1367s, 1175s, 1097s; \( \delta_H \) (500 MHz; CDCl\(_3\)) 5.76 (1H, ddt, \( J = 17.1, 10.2, 6.6 \), \( HC=CH_2 \)), 5.00 (1H, ddt \( J = 17.1, 1.9, 1.6 \), 1 of HC=CH\(_2\) (trans)), 4.95 (1H, ddt \( J = 10.2, 1.9, 1.3 \), 1 of HC=CH\(_2\) (cis)), 4.16 (4H, q, \( J = 7.1, 0.7 \), OCH\(_2\)), 2.18 (2H, td, \( J = 7.1, 2.6 \), HC=CHCH\(_2\)), 2.07-2.02 (2H, m, H\(_2\)=CHCH\(_2\)), 1.91 (1H, t, \( J = 2.6 \), HC=CH\(_2\)), 1.89-1.85 (4H, m, H\(_2\)=CHCH\(_2\)CH\(_2\)CH\(_2\) and HC=CHCH\(_2\)CH\(_2\)CH\(_2\)), 1.55-1.49 (2H, m, HC=CH\(_2\)CH\(_2\)), 1.30-1.23 (4H, m, H\(_2\)=CHCH\(_2\)CH\(_2\) and HC=CHCH\(_2\)CH\(_2\)), 1.23 (6H, t, \( J = 7.1 \), OCH\(_2\)CH\(_3\)); \( \delta_C \) (125 MHz; CDCl\(_3\)) 171.7 (C=O), 138.1 (HC=CH\(_2\)), 114.9 (HC=CH\(_2\)), 84.0 (C=C-H), 68.4 (C=C-H), 57.3 (CO\(_2\)CCO\(_2\)), 33.8 (H\(_2\)=CHCH\(_2\)), 31.62 & 31.57 (H\(_2\)=CHCH\(_2\)CH\(_2\)CH\(_2\) and HC=CHCH\(_2\)CH\(_2\)CH\(_2\)), 28.5 (HC=CHCH\(_2\)CH\(_2\)), 23.4 & 22.9 (H\(_2\)=CHCH\(_2\)CH\(_2\) and HC=CHCH\(_2\)CH\(_2\)), 18.0 (HC=CH\(_2\)), 14.1 (CH\(_3\)); m/z (CI pos) 309 (MH\(^+\), 41%), 263 (100), 217 (60), 189 (50), 161 (58); HRMS calculated for C\(_{18}\)H\(_{29}\)O\(_4\) (MH\(^+\)) 309.2060 Found 309.2062.

A side product of the reaction, Ethylhex-5-ynyl-2-hex-5-ynyl-2-pent-4-enylmalonate (407, 0.02 g, 4%) was also isolated.

\[
\begin{array}{cccc}
\text{O} & \text{O} \\
\text{O} & \text{O}
\end{array}
\]

\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1} \] 3308s (C=C-H), 3078w (=C-H), 2941s (C-H), 2257m (C=C), 2120w (C=C), 1728s (C=O), 1641m (C=C), 1460s, 1252s, 1097s; \( \delta_H \) (500 MHz; CDCl\(_3\)) 5.76 (1H, ddt, \( J = 16.9, 10.2, 6.6 \), \( HC=CH_2 \)), 5.02 (1H, br d \( J = 17.1, 1.7 \), 1 of HC=CH\(_2\) (trans)), 4.96 (1H, br d \( J = 10.2, 1 \) of HC=CH\(_2\) (cis)), 4.19 (2H, q, \( J = 7.1 \), OCH\(_2\)CH\(_3\)), 4.14 (2H, t, \( J = 6.4 \), OCH\(_2\)), 2.21 (2H, td, \( J = 7.1, 2.6 \), HC=CH\(_2\) of hex-5-ynyl ester), 2.19 (2H, td, \( J = 7.1, 2.6 \), HC=CH\(_2\) of hex-5-ynyl ester), 1.92 (1H, t, \( J = 2.6 \), HC=CH\(_2\)), 1.90-1.86 (4H, m, H\(_2\)=CHCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 1.77-1.72 (2H, m, HC=CHCH\(_2\)CH\(_2\)CH\(_2\) of hex-5-ynyl ester), 1.60-1.55 (2H, m, HC=CH\(_2\)CH\(_2\) of hex-5-ynyl ester), 1.55-1.50 (2H, m, HC=CH\(_2\)CH\(_2\)), 1.31-1.20 (4H, m, H\(_2\)=CHCH\(_2\)CH\(_2\) and HC=CHCH\(_2\)CH\(_2\)), 1.24 (3H, t, \( J = 7.1 \), OCH\(_2\)CH\(_3\)); \( \delta_C \) (125 MHz; CDCl\(_3\)) 171.8 & 171.7 (2 x C=O), 138.0
New Substrates for PKR

Experimental

(HC=CH2), 115.0 (HC=CH2), 84.0 & 83.6 (2 x C=C-H), 68.8 & 68.4 (2 x C≡C-H), 64.5
(OCH2), 61.1 (OCH2CH3), 57.4 (CO2CCO2), 33.8 (H2C=CHCH2), 31.70 & 31.67
(H2C=CHCH2CH2CH2 and HC≡CCH2CH2CH2CH2), 28.5 (HC≡CCH2CH2), 27.5
(HC≡CCH2CH2 of hex-5-ynyl ester), 24.8 (HC≡CCH2CH2 of hex-5-ynyl ester),
23.3 & 22.7 (H2C=CHCH2CH2 and HC≡CCH2CH2CH2), 18.1 & 18.0 (2 x HC≡CCH2),
14.1 (CH3); m/z (FAB pos) 361 (MH+, 100%), 338 (35), 263 (9); HRMS calculated for
C22H33O4 (MH+) 361.2379 Found 361.2384.

Synthesis of 2-Hex-5-ynyl-2-pent-4-enylmalonic acid 400

Using the procedure of Pugia et al., diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (401, 0.20 g, 0.65 mmol) in 50% aqueous NaOH (4 mL) was heated to reflux for 2 days.

The reaction mixture was cooled, washed with diethyl ether (2 x 20 mL) and ethereal extracts discarded. The aqueous layer was acidified to pH 1 with 2M HCl and extracted with diethyl ether (5 x 50 mL). The combined organic extracts were washed successively with H2O (100 mL) and brine (100 mL), dried (MgSO4) and concentrated in vacuo to obtain crude product. Recrystallisation (ether / hexane) yielded 2-hex-5-ynyl-2-pent-4-enylmalonic acid (400, 55 mg, 34%) as a white crystalline solid.

m.p.: 115 °C; νmax (CHCl3 cast)/cm−1 3296s (C≡C-H), 3000-2610 br s (O-H + C-H),
2130w (C≡C), 1697s (C=O), 1639s (C=C), 1435s, 1300s, 1182s; δH (500 MHz;
CD3OD) 5.79 (1H, ddt, J 17.0, 10.2, 6.7, HC≡CH2), 5.00 (1H, ddt J 17.1, 3.6, 1.6, 1 of
HC≡CCH2 (trans)), 4.94 (1H, ddt J 10.2, 2.2, 1.2, 1 of HC≡CH2 (cis)), 2.19 (1H, t, J 2.6,
HC≡C), 2.18-2.16 (2H, m, HC≡CH2), 2.08-2.04 (2H, m, H2C=CHCH2), 1.87-1.83
(4H, m, H2C=CHCH2CH2CH2 and HC≡CCH2CH2CH2CH2), 1.53-1.48 (2H, m,
HC≡CCH2CH2), 1.36-1.27 (4H, m, HC≡CCH2CH2CH2 and H2C=CHCH2CH2); δC (125
MHz; CD3OD) 175.6 (C=O), 139.4 (HC≡CH2), 115.3 (HC≡CH2), 84.7 (C≡C-H), 69.7
(C≡C-H), 58.4 (CO2CCO2), 35.0 (H2C=CHCH2), 33.26 & 33.25 (H2C=CHCH2CH2CH2 and
HC≡CCH2CH2CH2CH2), 29.8 (HC≡CCH2CH2), 24.7 & 24.2 (H2C=CHCH2CH2 and
HC≡CCH2CH2CH2), 18.8 (HC≡CCH2).
Synthesis of Ethyl-2-pent-4-enyl-2-hex-5-ynoate 408

Using the procedure of Krapcho et al.\textsuperscript{105}, a solution of diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (401, 2.32 g, 7.52 mmol), lithium chloride (0.64 g, 15 mmol) and H\textsubscript{2}O (0.14 mL, 7.5 mmol) in DMSO (12.5 mL) was heated to reflux overnight.

The reaction mixture was cooled, diluted with H\textsubscript{2}O (60 mL) and extracted with EtOAc (5 x 150 mL). The combined organic extracts were washed with brine (600 mL), dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} to obtain crude product. Flash chromatography (Si\textsubscript{0}2, Petrol 40-60 / EtOAc 98 : 2) afforded ethyl-2-pent-4-enyl-2-hex-5-ynoate (408, 1.41 g, 79%) as a colourless oil.

\[ \nu_{\text{max}} \text{ (neat)} / \text{cm}^{-1} \]

- 3312s (C=H), 3078s (=C-H\textsubscript{2}), 2739 br s (C-H), 2120m (C=C), 1734s (C=O), 1641s (C=C); \( \delta \)\textsubscript{H} (500 MHz; CDCl\textsubscript{3}) 5.73 (1H, ddt, J 17.1, 10.2, 6.7, HC=CH\textsubscript{2}), 4.95 (1H, ddt J 17.1, 2.0, 1.6, 1 of HC=CH\textsubscript{2} (trans)), 4.90 (1H, ddt J 10.2, 2.0, 1.2, 1 of HC=CH\textsubscript{2} (cis)), 4.10 (2H, q, J 7.2, OCH\textsubscript{2}), 2.29 (1H, tt, J 8.9, 5.1, HCCO\textsubscript{2}), 2.13 (2H, td, J 7.1, 2.6, HC=CH\textsubscript{2}), 2.03-1.98 (2H, m, H\textsubscript{2}C=CHCH\textsubscript{2}), 1.89 (1H, t, J 2.7, HC=CH), 1.56-1.54 (2H, m, H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2} and HC=CCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.51-1.46 (2H, m, HC=CHCH\textsubscript{2}CH\textsubscript{2}), 1.43-1.38 (4H, m, HC=CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2} and HC=CCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.37-1.30 (2H, m, H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.22 (3H, t, J 7.2, OCH\textsubscript{2}CH\textsubscript{2}), \( \delta \)\textsubscript{C} (125 MHz; CDCl\textsubscript{3}) 176.1 (C=O), 138.3 (HC=CH\textsubscript{2}), 114.5 (HC=CH\textsubscript{2}), 84.2 (C=C-H), 68.2 (C=C-H), 59.9 (OCH\textsubscript{2}), 45.3 (HCCO\textsubscript{2}), 33.5 (H\textsubscript{2}C=CHCH\textsubscript{2}), 31.79 \& 31.76 (H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2} and HC=CCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 28.2 (HC=CHCH\textsubscript{2}CH\textsubscript{2}), 26.5 \& 26.4 (H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2} and HC=CCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 18.1 (HC=CH\textsubscript{2}), 14.2 (CH\textsubscript{3}); \( m/z \) (CI pos) 237 (MH\textsuperscript{+}, 100%), 209 (11), 163 (14); HRMS calculated for C\textsubscript{16}H\textsubscript{25}O\textsubscript{2} (MH\textsuperscript{+}) 237.1855 Found 237.1853.

Synthesis of Dimethyl-2-pent-4-enylmalonate 412

Using the procedure of Marvel and Hager et al.\textsuperscript{89}, dimethyl malonate (409, 1.2 mL, 11.6 mmol) was added dropwise to a solution of sodium methoxide, prepared by addition of sodium (0.23 g, 10.1 mmol) in small pieces to methanol (5 mL) under...
nitrogen. Once the resultant white precipitate dissolved at rt, 5-bromopent-1-ene (403, 1.2 mL, 10.1 mmol) was added dropwise and the reaction mixture was heated to reflux, overnight.

Methanol was removed in vacuo, the residue was dissolved in H$_2$O (15 mL) and extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO$_4$) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO$_2$, Toluene) afforded dimethyl-2-pent-4-enylmalonate (412, 1.15 g, 57%) as a clear colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3080w (=C-H$_2$), 2955s (C-H), 1734s (C=O), 1641s (C=C), 1437s, 1344s, 1155s; $\delta_H$ (500 MHz; CDCl$_3$) 5.72 (1H, ddt, J 17.0, 10.2, 6.7, HC=CH$_2$), 4.97 (1H, ddt J 17.1, 1.7, 1.7, 1 of HC=CH$_2$ (trans)), 4.91 (1H, ddt J 10.2, 1.9, 1.2, 1 of HC=CH$_2$ (cis)), 3.68 (6H, s, OCH$_3$), 3.32 (1H, t J 7.5, CO$_2$CHCO$_2$), 2.06-2.01 (2H, m, H$_2$C=CHCH$_2$), 1.89-1.84 (2H, m, H$_2$C=CHCH$_2$CH$_2$), 1.40-1.34 (2H, m, H$_2$C=CHCH$_2$CH$_2$); $\delta_C$ (125 MHz; CDCl$_3$) 169.7 (C=O), 137.7 (HC=CH$_2$), 114.9 (HC=CH$_2$), 52.3 (OCH$_3$), 51.4 CO$_2$CHCO$_2$, 33.1 (H$_2$C=CHCH$_2$), 28.1 (H$_2$C=CHCH$_2$CH$_2$CH$_2$), 26.4 (H$_2$C=CHCH$_2$CH$_2$); m/z (CI pos) 201 (MH$^+$, 100%), 169 (80), 137 (90), 108 (50); HRMS calculated for C$_{10}$H$_{17}$O$_4$ (MH$^+$) 201.1127 Found 201.1122.

A side product of the reaction, dimethyl-2,2-dipent-4-enylmalonate (413, 0.05 g, 12%), was also isolated as a clear colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3077w (=C-H$_2$), 2953s & 2927m (C-H), 1733s (C=O), 1641m (C=C), 1460m, 1436m, 1259s, 1197s; $\delta_H$ (500 MHz; CDCl$_3$) 5.75 (2H, ddt, J 17.2, 10.2, 6.7, HC=CH$_2$), 5.00 (2H, ddt J 17.2, 2.1, 1.7, 1 of HC=CH$_2$ (trans)), 4.95 (2H, ddt J 10.2, 2.1, 1.3, 1 of HC=CH$_2$ (cis)), 3.70 (6H, s, OCH$_3$), 2.06-2.02 (4H, m, H$_2$C=CHCH$_2$), 1.89-1.85 (4H, m, H$_2$C=CHCH$_2$CH$_2$CH$_2$), 1.27-1.20 (4H, m, H$_2$C=CHCH$_2$CH$_2$); $\delta_C$ (125 MHz; CDCl$_3$) 172.2 (C=O), 137.8 (HC=CH$_2$), 115.0 (HC=CH$_2$), 57.5 (CO$_2$CHCO$_2$), 214.
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52.3 (OCH₃), 33.7 (H₂C=CHCH₂), 31.9 (H₂C=CHCH₂CH₂CH₂), 23.4 (H₂C=CHCH₂CH₂); m/z (Cl pos) 269 (MH⁺, 100%), 237 (50), 205 (20), 149 (10); HRMS calculated for C₁₀H₁₇O₄ (MH⁺) 269.1753 Found 269.1758.

Synthesis of Dimethyl-2-hex-5-ynyl-2-pent-4-enylmalonate 414

To a suspension of sodium hydride (60% dispersion in oil, 0.21 g, 5.2 mmol) in DMF (2 mL) at 0 °C, under argon, was added a solution of dimethyl-2-pent-4-enylmalonate (412, 0.80 g, 4.0 mmol) in DMF (8 mL). A solution of 6-iodohex-1-yne (406, 1.0 g, 4.8 mmol) in DMF (10 mL) was added dropwise to the reaction mixture, which was stirred at rt overnight.

The reaction mixture was quenched with H₂O (100 mL) and extracted with EtOAc (4 x 150 mL). The combined organic extracts were washed with brine (450 mL), dried (MgSO₄) and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Petrol 40-60 / EtOAc 98 : 2) afforded dimethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (414, 1.09 g, 98%) as a colourless oil.

ν_max (neat)/cm⁻¹ 3296s (O=C-H), 3077w (=C-H₂), 2951s & 2702s (C-H), 2116w (C=C), 1736s (C=O), 1639m (C=C), 1435s, 1171s, 1099m; δ_H (500 MHz; CDCl₃) 5.71 (1H, ddt, 17.1, 10.3, 6.5, HC=CH₂), 4.96 (1H, ddt, J 17.2, 1.9, 1.6, 1 of HC=CH₂ (trans)), 4.91 (1H, ddt, J 10.3, 1.9, 1.2, 1 of HC=CH₂ (cis)), 3.66 (6H, s, OCH₃), 2.14 (2H, td, J 7.1, 2.7, HC=CH₂H₂), 2.02-1.98 (2H, m, H₂C=CHCH₂), 1.88 (1H, t, J 2.7, HC=CH₂), 1.85-1.81 (4H, m, H₂C=CHCH₂CH₂CH₂ and HC=CHCH₂CH₂CH₂H₂), 1.51-1.45 (2H, m, HC=CHCH₂H₂), 1.25-1.17 (4H, m, H₂C=CHCH₂CH₂ and HC=CHCH₂CH₂CH₂); δ_C (125 MHz; CDCl₃) 172.0 (C=O), 137.9 (HC=CH₂), 114.9 (HC=CH₂), 83.8 (C=C-H), 68.4 (C=C-H), 57.3 (CO₂CCO₂), 52.2 (OCH₃), 33.6 (H₂C=CHCH₂), 31.8 & 31.7 (H₂C=CHCH₂CH₂CH₂ and HC=CHCH₂CH₂CH₂H₂), 28.3 (HC=CHCH₂H₂), 23.2 & 22.9 (H₂C=CHCH₂CH₂ and HC=CHCH₂CH₂H₂), 17.9 (HC=CH₂); m/z (Cl pos) 281 (MH⁺, 48%), 249 (100), 217 (50), 189 (45), 161 (40), 95 (41); HRMS calculated for C₁₆H₂₅O₄ (MH⁺) 281.1753 Found 281.1758.
Synthesis of Methyl-2-pent-4-enyl-2-hex-5-ynoate 415

Using the procedure of Krapcho et al.\textsuperscript{105}, a solution of dimethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (414, 0.70 g, 2.5 mmol), lithium chloride (0.21 g, 5.0 mmol) and H\textsubscript{2}O (50\mu L, 2.50 mmol) in DMSO (4.2 mL) was heated to reflux for 7 h. The reaction mixture was cooled, diluted with H\textsubscript{2}O (20 mL) and extracted with EtOAc (6 x 80 mL). The combined organic extracts were washed with brine (350 mL), dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} to obtain crude product. Flash chromatography (SiO\textsubscript{2}, Petrol 40-60 / EtOAc 98 : 2) afforded methyl-2-pent-4-enyl-2-hex-5-ynoate (415, 0.26 g, 48\%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm\textsuperscript{-1}: 3306s (C=CH\textsubscript{2}), 3077w (=C-H\textsuperscript{2}), 2943s & 2864s (C-H), 2118w (C≡C), 1736s (C=O), 1641m (C=C), 1435m, 1159s; $\delta_{\text{H}}$ (500 MHz; CDCl\textsubscript{3}) 5.75 (1H, ddt, $J$ 17.0, 10.2, 6.70, HC=CH\textsubscript{2}), 4.97 (1H, ddt $J$ 17.1, 1.9, 1.7, 1 of HC=CH\textsubscript{2} (trans)), 4.92 (1H, dtt $J$ 10.2, 2.0, 1.2, 1 of HC=CH\textsubscript{2} (cis)), 3.65 (3H, s, OCH\textsubscript{3}), 2.34 (1H, tt, $J$ 8.9, 5.2, HCCO\textsubscript{2}), 2.15 (2H, td, $J$ 7.2, 2.6, HC=CHCH\textsubscript{2}), 2.05-2.01 (2H, m, H\textsubscript{2}C=CHCH\textsubscript{2}), 1.91 (1H, t, $J$ 2.6, HC=C), 1.65-1.58 (2H, m, H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.50-1.37 (4H, m, HC=CH\textsubscript{2}CH\textsubscript{2} and HC=CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.36-1.32 (4H, m, H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2} and HC=CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}); $\delta_{\text{C}}$ (125 MHz; CDCl\textsubscript{3}) 176.6 (C=O), 138.3 (HC=CH\textsubscript{2}), 114.6 (HC=CH\textsubscript{2}), 84.2 (C=C-H), 68.3 (C=C-H), 51.5 (OCH\textsubscript{3}), 45.3 (HCCO\textsubscript{2}), 33.5 (H\textsubscript{2}C=CHCH\textsubscript{2}), 31.81 & 31.79 (H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2} and HC=CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 28.3 (HC=CH\textsubscript{2}CH\textsubscript{2}), 26.6 & 26.5 (H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2} and HC=CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 18.2 (HC=CH\textsubscript{2}); $m/z$ (Cl pos) 223 (MH\textsuperscript{+}, 100\%), 163 (55), 81 (25); HRMS calculated for C\textsubscript{14}H\textsubscript{23}O\textsubscript{2} (MH\textsuperscript{+}) 223.1698 Found 223.1696.
Synthesis of 2-Pent-4-enyloct-7-ynoic acid 399

Method 1
Using the procedure of Rosini et al.\(^{129}\), a solution of ethyl-2-pent-4-enyl-2-hex-5-ynoate (408, 0.20 g, 0.85 mmol) in 2M potassium hydroxide in ethanol (0.55 mL, 1.1 mmol) was heated to reflux overnight. Ethanol was removed \textit{in vacuo} and the residue dissolved in \(\text{H}_2\text{O}\) (8 mL). The solution was washed with diethyl ether (3 x 20 mL) to remove traces of unreacted ester. The aqueous layer was acidified to pH 1 with 6M HCl and then extracted with diethyl ether (5 x 20 mL). The combined organic extracts were successively washed with \(\text{H}_2\text{O}\) (80 mL) and brine (80 mL), dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo} to obtain crude product. Flash chromatography (SiO\(_2\), Hexane / Acetone 4 : 1) afforded 2-pent-4-enyloct-7-ynoic acid (399, 0.16 g, 96%) as a colourless oil.

Method 2
Using the procedure of Rosini et al.\(^{129}\), a solution of methyl-2-pent-4-enyl-2-hex-5-ynoate (415, 0.2 g, 0.9 mmol) in 2M potassium hydroxide in methanol (0.58 mL, 1.2 mmol) was heated to reflux overnight. Methanol was removed \textit{in vacuo} and the residue dissolved in \(\text{H}_2\text{O}\) (8 mL). This solution was washed with diethyl ether (3 x 20 mL) to remove traces of unreacted ester. The aqueous layer was acidified to pH 1 with 6M HCl and then extracted with diethyl ether (5 x 20 mL). The combined organic extracts were successively washed with \(\text{H}_2\text{O}\) (100 mL) and brine (100 mL), dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo} to obtain crude product. Flash chromatography (SiO\(_2\), Hexane / Acetone 4 : 1) afforded 2-pent-4-enyloct-7-ynoic acid (399, 0.14 g, 75%) as a colourless oil.

\(v_{\text{max}}\) (neat)/\(\text{cm}^{-1}\): 3304s (C=C-H), 3100br (O-H), 2855s (C-H), 2118w (C=O), 1705s (C=O), 1641s (C=O), 1418s, 1232s; \(\delta_{\text{H}}\) (500 MHz; CDCl\(_3\)) 11.73 (1H, br s, OH), 5.76
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(1H, ddt, J 17.0, 10.3, 6.7, HC=CH₂), 4.99 (1H, ddt J 17.1, 1.9, 1.6, 1 of HC=CH₂ (trans)), 4.94 (1H, ddt J 10.3, 2.0, 1.3, 1 of HC=CH₂ (cis)), 2.35 (1H, tt, J 8.6, 5.0, HCCO₂), 2.17 (2H, td, J 7.0, 2.7, HC=CH₂), 2.07-2.02 (2H, m, H₂C=CHCH₂), 1.92 (1H, t, J 2.7, HC=CH), 1.67-1.60 (2H, m, H₂C=CHCH₂H₂, HC=CH₃CH₂CH₂CH₂, HC=CH₂CH₂CH₂ and HC=CH₂CH₂); δC (125 MHz; CDCl₃) 183.0 (C=O), 138.2 (HC=CH₂), 114.7 (HC=CH₂), 84.1 (C=C-H), 68.4 (C=C-H), 45.2 (HCCO₂), 33.5 (H₂C=CHCH₂), 31.43 & 31.40 (H₂C=CHCH₂H₂ and HC=CH₂CH₂CH₂), 28.2 (HC=CH₂CH₂), 26.4 & 26.3 (H₂C=CHCH₂ and HC=CH₂CH₂CH₂), 18.1 (HC=CH₂); m/z (CI pos) 209 (MH⁺, 96%), 191 (48), 163 (100), 123 (73); HRMS calculated for C₁₃H₂₁O₂ (MH⁺) 209.1542 Found 209.1538.

Synthesis of 5-Hex-5-ynyl-bicyclo[3.2.0]heptan-6-one 396

Using the procedure of Sinder et al.¹³⁰, a solution of 2-pent-4-enyloct-7-ynoic acid (399, 0.57 g, 2.7 mmol) in benzene (5.7 mL) was added slowly to a suspension of sodium hydride (60% dispersion in oil, 0.16 g, 4.1 mmol) in benzene (7.0 mL) at 0 °C under argon and stirred for 15 min. Oxalyl chloride (1.20 mL, 13.7 mmol) was added dropwise and the resultant reaction mixture warmed to rt and then heated at 60 °C for 1 h. The reaction mixture was cooled and concentrated in vacuo. The resultant mixture of acid chloride and sodium chloride was taken up in toluene (7.3 mL) and added dropwise to a solution of triethylamine (3.8 mL, 27 mmol) in toluene (27 mL) at reflux and heated to reflux, under argon, overnight. The reaction mixture was cooled to rt, filtered through Celite® and concentrated in vacuo to obtain the crude product. Flash chromatography (SiO₂, Hexane / Toluene 3 : 2) afforded 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (396, 0.34 g, 65%) as a colourless oil.

ν_max (neat)/cm⁻¹ 3292s (C=C-H), 2978s (C-H), 2100w (C=C), 1771s (C=O), 1450m, 1387m, 1240m, 1067m; δH (500 MHz; CDCl₃) 3.09 (1H, dd, J 18.5, 9.7, 1 of OCCH₂), 2.58-2.54 (1H, m, OCCH₂CH₂), 2.41 (1H, dd, J 18.5, 4.6, 1 of OCCH₂), 2.16 (2H, td, J 7.1, 2.7, HC=CH₂), 1.98 (1H, dd, J 12.9, 6.3, 1 of OCCCH₂), 1.92 (1H, t, J 2.7, HC=CH), 1.85-1.75 (3H, m, 1 of OCCH₂CH₂CH₂H₂, HC=CH₂CH₂CH₂CH₂), 1.70-1.48

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(6H, m, 1 of OCCH₂CH₂CH₂CH₂, 1 of OCCH₂CHCH₂, HC≡CCH₂CH₂, HC≡CCH₃CH₂H₂), 1.41-1.33 (2H, m, 1 of OCCCH₂, 1 of OCCH₂CHCH₂); δC (125 MHz; CDCl₃) 218.0 (C=O), 84.2 (C≡C-H), 75.7 (OCC), 68.3 (C≡C-H), 49.2 (OCCH₂), 35.3 (OCCCH₂), 33.9 (OCCH₂CH), 32.6 (HC≡CCH₂CH₂CH₂), 32.5 (HC≡CCH₂CH₂H₂), 28.8 (HC≡CCH₂H₂), 24.9 (OCCH₃CH₂CH₂H₂), 24.7 (OCCH₂CHCH₂), 18.2 (HC≡CCH₂); m/z (Cl pos) 257 (100%), 243 (35), 191 (MH⁺, 31), 173 (41), 149 (70), 121 (40); HRMS calculated for C₁₃H₁₉O (MH⁺) 191.1436 Found 191.1437.

**Synthesis of 7-(4-Toluenesulfonyloxycarbonyl)dodec-11-en-1-yne 416**

Using the procedure of Corey *et al.*¹³¹, triethylamine (0.40 mL, 2.9 mmol) was added to a solution of 2-pent-4-enyl-oct-7-ynoic acid (399, 0.10 g, 0.48 mmol) and para-toluenesulfonyl chloride (0.28 g, 1.4 mmol) in benzene (6.7 mL) under argon and heated to reflux for 3 h.

The reaction mixture was cooled, filtered through Celite® to remove the white precipitate and concentrated in vacuo to obtain crude product. Flash chromatography (SiO₂, Hexane / Acetone 95 : 5) afforded 7-(4-toluenesulfonyloxycarbonyl)dodec-11-en-1-ylene (416, 0.17 g, 99%) as a yellow oil.

ν_max (neat)/cm⁻¹ 3304 s (C≡C-H), 3170 w (=C-H₂), 2941 s & 2862 s (C-H), 2190 w (C≡C), 1809 s (C=O), 1705 s (C=O of carboxylic acid 399), 1641 w (C=O), 1595 w (C=O), 1379 m, 1026 m; δH (400 MHz; CDCl₃) 7.92 (2H, d, J8.4, PhC-tf), 7.40 (2H, d, J8.4, PhC-H), 5.76 (1H, ddt, J17.0, 10.2, 6.6, HC=CH₂), 5.03-4.98 (1H, m, 1 of HC=CH₂), 4.97-4.94 (1H, m, 1 of HC=CH₂), 2.48 (3H, s, CH₃), 2.43 (1H, tt, J8.9, 5.3, HCCO₂), 2.19 (2H, td, J6.7, 2.5, HC≡CCH₂), 2.09-2.03 (2H, m, H₂C=CHCH₂), 1.94 (1H, t, J2.6, HC≡C), 1.73-1.61 (2H, m, H₂C=CHCH₂CH₂CH₂), 1.57-1.40 (8H, m, H₂C=CHCH₂CH₂, HC≡CCH₂CH₂CH₂CH₂, HC≡CCH₂CH₂H₂ and HC=CH=CH₂H₂); δC (100 MHz; CDCl₃) 171.6 (C=O), 146.8 (arom.C₉), 141.6 (arom.C₉), 138.0 (HC≡CCH₂), 130.2 (arom.CH), 127.0 (arom.CH), 115.0 (HC=CH₂), 84.1 (C≡C-H), 68.5 (C≡C-H), 46.3 (HCCO₂), 33.5 (H₂C=CHCH₂), 31.1 & 31.0 (H₂C=CHCH₂CH₂CH₂ and HC≡CCH₂CH₂CH₂CH₂), 28.2 (HC≡CCH₂CH₂), 26.3 & 26.2 (H₂C=CHCH₂CH₂.
and HC=CCH₂CH₂CH₂), 21.8 CH₃), 18.2 (HC=CCH₂); m/z (El pos) 333 (8%), 277 (14), 217 (13), 191 (91), 173 (82), 155 (ArSO₂⁺, 94), 121 (100).

New Substrates for PKR

**Synthesis of 1-Hex-5-ynyl-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene 417**

Using the procedure of Wu et al., lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.55 mL, 0.55 mmol) was added dropwise to a stirred solution of 5-hex-5-ynylbicyclo[3.2.0]heptan-6-one (396, 0.10 g, 0.53 mmol) in THF (1 mL) at -78 °C under argon and stirred for 45 minutes, then trimethylchlorosilane (80 µL, 0.63 mmol) was added dropwise.

The reaction mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. The reaction mixture was concentrated in vacuo and dissolved in hexane (5 mL), to precipitate out lithium salts, filtered through cotton wool and concentrated in vacuo at rt to obtain 1-hex-5-ynyl-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (417, 0.13 g, 93%) as a pale yellow oil, contaminated with trimethylsilyl impurities, which was used without further purification.

ν max (neat)/cm⁻¹ 3313m (C=CH), 3080w (=C-H), 2938s (C-H), 1619s (C=C), 1351m, 1254s, 1194s; δH (500 MHz; CD₆) 4.34 (1H, s, C=CH), 2.41 (1H, d, J₆.₂, C=CHCH), 1.99 (2H, td, J 7.1, 2.7, HC=CCH₂), 1.94-1.84 (1H, m, 1 of C=CHCH₂CH₂), 1.79 (1H, t, J 2.7, HC=CH), 1.76-1.74 (1H, m, 1 of C=CHCH₂CH₂CH₂), 1.69-1.65 (1H, m, 1 of C=CHCH₂CH₂CH₂), 1.62-1.45 (5H, m, 1 of C=CHCH₂CH₂CH₂ and HC=CHCH₂CH₂), 1.40-1.39 (2H, m, HC=CHCH₂CH₂), 1.28-1.20 (1H, m, 1 of C=CHCH₂CH₂), 0.99-0.93 (1H, m, 1 of C=CHCH₂CH₂CH₂), 0.16 (9H, s, OSi(CH₃)₃); δc (125 MHz; CD₆) 152.0 (OC=CH), 100.8 (C=CH), 84.5 (C=CH), 68.7 (C=C=H), 61.7 (SiOCC), 43.1 (C=CCHCH), 34.2 & 25.5 (HC=CHCH₂CH₂CH₂), 29.7 (C=CHCH₂CH₂CH₂), 29.5 (HC=CHCH₂CH₂), 27.5 (C=CHCH₂CH₂), 24.2 (C=CHCH₂CH₂), 18.6 (HC=CHCH₂), -0.2 (OSi(CH₃)₃); m/z (ES pos) 285 (MNa⁺, 100%), 213 (35); HRMS calculated for C₁₆H₂₆ONa (MNa⁺) 285.1645 Found 285.1648.
Synthesis of 1-(6-Trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one 419

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\text{Si(CH}_3\text{)}_3
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Method 1

Using the procedure of Sugihara et al.\textsuperscript{29}, a solution of 1-hex-5-ynyl-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (417, 0.13 g, 0.51 mmol) in 1,2-dichloroethane (3.1 mL) was added to a solution of dicobalt octacarbonyl (0.25 g, 0.73 mmol) in 1,2-dichloroethane (2 mL), under argon at rt. The reaction mixture was stirred at rt for 1 h. \textit{n}-Butyl methyl sulfide (0.22 mL, 1.8 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled, a solution of \textit{para}-toluenesulfonic acid monohydrate (0.19 g, 1.02 mmol) in methanol (4 mL) was added and the mixture was stirred at rt for 2 h.

The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, gradient elution, EtOAc / Hexane 5 : 95 to 50 : 50) to afford 1-(6-Trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one (419, 9.4 mg, 5% (from cyclobutanone 396) as a colourless oil.

Method 2

Using the procedure of Wu et al.\textsuperscript{132}, lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.28 mL, 0.28 mmol) was added dropwise to a stirred solution of 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (396, 50 mg, 0.26 mmol) in THF (0.5 mL) at -78 °C under argon and stirred for 40 min, then trimethylchlorosilane (40 \textmu L, 0.32 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 40 min and then allowed to warm to rt over 40 min.

The reaction mixture was again cooled to -78 °C and lithium(bistrimethyl)silyl amide (1.0 M, 0.30 mL, 0.30 mmol) was added dropwise, followed by stirring at -78 °C for 30 minutes and then dropwise addition of trimethyl chlorosilane (40 \textmu L, 0.32 mmol). The reaction mixture was stirred at -78 °C for 30 minutes and then warmed to rt.

The reaction mixture was concentrated \textit{in vacuo} and then dissolved in hexane (5 mL) to precipitate out lithium salts, filtered through cotton wool and concentrated \textit{in vacuo} at rt.
to obtain 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (420, 0.15 g) as a pale yellow oil, contaminated with trimethylsilyl impurities, which was used without further purification.

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\text{Si(CH}_3\text{)}_3
\]

\[
\text{OSi(CH}_3\text{)}_3
\]

\[\nu_{\text{max}} (\text{neat}) / \text{cm}^{-1}: 2940 \text{s} (\text{C-H}), 2176 \text{m} (\text{C=C}), 1619 \text{s} (\text{C=C}), 1253 \text{s}, 1195 \text{s}; \delta_H (500 \text{ MHz}; \text{C}_6\text{D}_6) 4.40 (1\text{H}, \text{s}, \text{C}=\text{CH}), 2.43 (1\text{H}, \text{d}, J 6.3, \text{C}=\text{CH}_2\text{)}\text{H}), 2.11 (2\text{H}, \text{t}, J 6.8, \text{SiC}=\text{CCH}_2\text{)}, 1.95-1.86 (1\text{H}, \text{m}, 1 \text{ of } \text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 1.79-1.75 (1\text{H}, \text{m}, 1 \text{ of } \text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 1.71-1.65 (1\text{H}, \text{m}, 1 \text{ of } \text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 1.63-1.39 (7\text{H}, \text{m}, 1 \text{ of } \text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, \text{SiC}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{H}, \text{SiC}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{H} \text{ and SiC}=\text{CCH}_2\text{CH}_2\text{)}, 1.28-1.22 (1\text{H}, \text{m}, 1 \text{ of } \text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 1.01-0.95 (1\text{H}, \text{m}, 1 \text{ of } \text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 0.16 (9\text{H}, \text{s}, \text{OSi(CH}_3\text{)}_3\text{)}, \text{CSi(CH}_3\text{)}_3\text{ obscured by impurities}; \delta_C (125 \text{ MHz}; \text{C}_6\text{D}_6) 152.0 (\text{OC}=\text{CH}), 108.1 (\text{CH}_2\text{C}=\text{CSi(CH}_3\text{)}_3\text{)}, 100.8 (\text{C}=\text{CH}), 84.4 (\text{CH}_2\text{C}=\text{CSi(CH}_3\text{)}_3\text{)}, 61.8 (\text{SiOCC}), 43.1 (\text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 34.2 \text{ & } 25.6 (\text{SiC}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{)}, 29.7 (\text{C}=\text{CHCHCH}_2\text{CH}_2\text{CH}_2\text{)}, 29.6 (\text{SiC}=\text{CCH}_2\text{CH}_2\text{)}, 27.5 (\text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 24.3 (\text{C}=\text{CHCHCH}_2\text{CH}_2\text{)}, 20.1 (\text{SiC}=\text{CCH}_2\text{)}, -0.16 (\text{OSi(CH}_3\text{)}_3\text{)}, \text{CSi(CH}_3\text{)}_3\text{ obscured by impurities}; m/z (\text{Cl pos}) 335 (\text{MH}^+, 51\%), 319 (100), 261 (45), 173 (50), 73 (65); \text{HRMS calculated for } \text{C}_{19}\text{H}_{34}\text{OSi}_2 (\text{MH}^+) 335.2226 \text{ Found 335.2227.}

Using the procedure of Sugihara et al. \textsuperscript{29}, a solution of 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (420, 0.16 g, 0.26 mmol) in 1,2-dichloroethane (1.63 mL) was added to a solution of dicobalt octacarbonyl (0.16 g, 0.48 mmol) in 1,2-dichloroethane (1 mL), under argon at rt. The reaction mixture was stirred at rt for 1 h. \textit{n}-Butyl methyl sulfide (0.11 mL, 0.92 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled, a solution of \textit{para}-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, gradient elution, EtOAc / Hexane 5 : 95 to 50 : 50) to
afford 1-(6-trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one (419, 23 mg, 34%) as a colourless oil.

Method 3
Using the procedure of Wu et al.\textsuperscript{132}, lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.28 mL, 0.28 mmol) was added dropwise to a stirred solution of 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (396, 50 mg, 0.26 mmol) in THF (0.5 mL) at -78 °C under argon and stirred for 40 min, then trimethylchlorosilane (40 μL, 0.32 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 40 min and then allowed to warm to rt over 40 min.

The reaction mixture was again cooled to -78 °C and lithium(bistrimethyl)silyl amide (1.0 M, 0.30 mL, 0.30 mmol) was added dropwise, followed by stirring at -78 °C for 30 minutes and then dropwise addition of trimethyl chlorosilane (40 μL, 0.32 mmol). The reaction mixture was stirred at -78 °C for 30 minutes and then warmed to rt.

The reaction mixture was concentrated \textit{in vacuo} and then dissolved in hexane (5 mL) to precipitate out lithium salts, filtered through cotton wool and concentrated \textit{in vacuo} at rt to obtain 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (420, 0.15 g) as a pale yellow oil, contaminated with trimethylsilyl impurities, which was used without further purification. (see Method 2 for characterisation)

Using the procedure of Sugihara et al.\textsuperscript{29}, a solution of 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (420, 0.15 g, 0.26 mmol) in toluene (1.3 mL) was added to a solution of dicobalt octacarbonyl (0.13 g, 0.39 mmol) in toluene (1 mL), under argon at rt. The reaction mixture was stirred at rt for 1 h and then heated to reflux overnight.

The reaction mixture was cooled, a solution of \textit{para}-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated \textit{in vacuo} and the residue was purified by flash chromatography (SiO\textsubscript{2}, gradient elution, EtOAc / Hexane 5 : 95 to 50 : 50) to afford 1-(6-trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one (419, 2 mg, 3%) as a colourless oil.

v\textsubscript{max} (neat)/cm\textsuperscript{-1} 2940s (sp\textsuperscript{3} C-H), 2174m (C≡C), 1772s (C=O), 1249m, 1066m; δ\textsubscript{H} (500 MHz; CDCl\textsubscript{3}) 3.11 (1H, dd, J 18.4, 9.5, 1 of OCCH\textsubscript{2}), 2.59-2.54 (1H, m, OCCH\textsubscript{2}CH),
NEW SUBSTRATES FOR PKR

2.43 (1H, dd, $J$ 18.5, 4.5, 1 of OCH$_2$), 2.22 (2H, t, $J$ 7.0, SiC=CH$_2$), 2.00 (1H, dd, $J$ 12.9, 6.3, 1 of 1 of OCCC$_2$), 1.85-1.77 (3H, m, 1 of OCH$_2$CHCH$_2$CH$_2$, HC=CH$_2$CH$_2$CH$_2$CH$_2$), 1.73-1.48 (6H, m, 1 of OCH$_2$CHCH$_2$CH$_2$, 1 of OCH$_2$CHCH$_2$CH$_2$, HC=CH$_2$CH$_2$CH$_2$CH$_2$, 1.43-1.35 (2H, m, 1 of OCCC$_2$, 1 of OCH$_2$CHCH$_2$), 0.14 (9H, s, CSi(CH$_3$)$_3$); $\delta_C$ (125 MHz; CDCl$_3$) 218.1 (C=O), 107.2 (CH$_2$C=CSi(CH$_3$)$_3$), 84.7 (CH$_2$C=CSi(CH$_3$)$_3$), 75.8 (OCC), 49.2 (OCH$_2$), 35.3 (OCCC$_2$), 33.9 (OCH$_2$CH), 32.7 (HC=CH$_2$CH$_2$CH$_2$CH$_2$), 32.4 (HC=CH$_2$CH$_2$CH$_2$CH$_2$), 28.9 (SiC=CH$_2$CH$_2$), 25.0 (OCH$_2$CHCH$_2$CH$_2$), 24.7 (OCH$_2$CHCH$_2$), 19.6 (SiC=CH$_2$), 0.13 (Si(CH$_3$)$_3$); $m/z$ (CI pos) 263 (MH$^+$, 35%), 247 (39), 173 (26), 131 (30), 83 (50), 73 (100); HRMS calculated for C$_{16}$H$_{27}$OSi (MH$^+$) 263.1831 Found 263.1832.
5. Bibliography


Billington, D. C.; Pauson, P. L. Organometallics **1982**, *1*, 1560.


Jeong, N.; Chung, Y. K.; Lee, B.U.; Lee, S. H.; Yoo, S. E. Synlett, **1991**, 204.


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BIBLIOGRAPHY

New Substrates for PKR

New Substrates for PKR

BIBLIOGRAPHY


96 P. Garner Personal communication. Case Western Reserve University. Cleveland


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