NEW APPLICATIONS OF THE PAUSON-KHAND REACTION
AND STUDIES TOWARDS THE SYNTHESIS
OF THE HAMIGERANS

by

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Now unto the King eternal, immortal, invisible and the only wise God be all glory and honor for ever and ever.

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ABSTRACT

NEW APPLICATIONS OF THE PAUSON-KHAND REACTION
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This dissertation is divided into two parts. The first part describes the dicobalt octacarbonyl mediated synthesis of medium sized rings via the intramolecular Pauson-Khand (IMPK) reaction. The cyclization of 1,8-enynes has proved to be difficult via the IMPK reaction due to entropy reasons. To overcome this limitation we attempted this cyclization in the presence of an ortho- buttressing group (t-butyl group) on the aromatic ring so as to reduce the conformationally allowed volume of the alkene arm of the substrate. The construction of the substrates started with O-alkenylation of the commercially available 3,5 di-tert-butyl-2-hydroxylbenzaldehyde and then the O-alkenylation products were alkynylated using ethynyl Grignard reagents to afford the
corresponding enynes. These enynes successfully engaged in the both thermal and oxidative IMPK reaction to afford 5,7,6-tricyclic systems. With the parent enynes we observed diketo-compounds as the major product and traces of the expected PK product. When the alkyne arm of the enynes was substituted, the cyclization gave both the reduced PK product and the expected PK product. In general, the thermal mode gave a better diastereoselectivity when compared to the oxidative mode. Attempts to extend these result to a higher homolog to provide 5,8,6 tricyclic systems unfortunately failed. Thus this work describes a new methodology for the construction of medium (>6) sized rings via IMPK reaction.

A second system was investigated which examined whether highly congested systems, related to those found in the hamigeran benzannulated terpenes, could be constructed. These experiments were successful, setting the stage for the studies described in the second section.

The second part describes approach to the synthesis of the hamigerans by the application of the above developed IMPK methodology. The cyclization substrate was accessed from commercially available salicylic acid. The directed ortho metalation of the amide and treatment with iodine gave the iodo aryl amide. This was subsequently alkynylated using a Sonogashira cross-coupling reaction and then alkenylated via a Grignard reaction. The enyne was the subjected to IMPK reaction to afford the tricyclic core of the hamigerans.
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PART I

MEDIUM Sized RINGS SYNTHESIS VIA
THE PAUSON-KHAND REACTION
CHAPTER 1
INTRODUCTION

In recent years, the use of transition metal complexes in the total synthesis of natural products has attracted a lot of attention, and this area has been thoroughly reviewed in the literature.\textsuperscript{1-4} This increased interest is due to the fact that transition metal-mediated reactions, when compared to their classical organic counterparts, proved to be advantageous when the issues of selectivity and atom economy were considered. As a result, these types of reactions have become powerful tools for the construction of complex cyclic structures from simple and in many cases readily available starting materials. The Pauson-Khand reaction is among such reactions that make use of transition metal complexes to effect C-C bond formation.

1.1 Pauson-Khand Reaction

The Pauson-Khand (PK) reaction is a transition metal-mediated reaction that has attracted substantial interest\textsuperscript{3, 4} in recent years due to its usefulness in total synthesis. The PK reaction is both known intra- and intermolecularly. The synthetic attractiveness of the intramolecular variant is due to the fact that it permits the rapid increase of molecular complexity in a single step. Hence, it offers the opportunity for the rapid
The PK reaction, formally a [2+2+1] cycloaddition reaction, is the cobalt-mediated cyclization between an alkyne, an alkene and carbon monoxide to form a cyclopentenone. Prof. Peter L. Pauson first reported the use of this synthetic method in the early 1970’s and was initially carried out with strained olefins. The reaction proceeded with high regioselectivity in the case of unsymmetrical alkynes, placing the larger substituent of the alkyne in the α–position of the cyclopentenone. On the other hand, the use of an unsymmetrical olefin with a terminal alkyne yields regioisomeric mixtures (1:1) of the cyclopentenones as shown in Scheme 1.1.

![Scheme 1.1](image)

**Scheme 1.1**

1.2 Thermal Pauson-Khand Reaction

Initially, the intermolecular PK reaction was carried out under thermal conditions. The cobalt-alkyne complex was generated first by using a stoichiometric amount of Co₂(CO)₈ in the presence of an alkyne. The cobalt-alkyne complex, in an ethereal solvent, was then heated with a wide variety of alkenes under N₂ or CO atmosphere to afford the corresponding cyclopentenones. One of the disadvantages of
these initial thermal PK reactions is that relatively high temperatures (70 - 110 °C) and long reaction times (hours to days) were required; many times resulting in decomposition of the starting materials and/or product. The intramolecular version of PK reaction was introduced using systems related to 1,6-heptenyne and was most frequently carried out under the thermal conditions described above. Schore, in 1981, was the first to demonstrate the feasibility of an intramolecular PK cycloaddition by connecting the alkene to the alkyne via a carbon tether.\(^8\) Subsequent to the reports of these thermal reactions, a number of experimental variants were introduced which extended the scope of this reaction. In the mid 1980’s, Smit and Caple were the first to report that adsorbing the cobalt complexed enynes onto silica gel or alumina, allows the reaction to proceed at a lower temperature and with shorter reaction time (Scheme 1.2).\(^9\)

**Scheme 1.2**

Moreover, Marie Krafft incorporated a directing and accelerating ligand to an unstrained alkene to get high levels of regiocontrol and high yield in the intermolecular PK reaction.\(^{10}\) The PK cyclization was now regioselective with respect to the olefin and as a result, strained olefins were no longer required, thereby increasing the synthetic utility of the reaction.
1.3 Proposed PK Reaction Mechanism

The mechanism of the Pauson-Khand reaction was initially proposed by Magnus\textsuperscript{11} and has been widely accepted (Scheme 1.3) despite the lack of firm experimental evidence. After this dissertation was completed, this mechanistic pathway was validated by a kinetic studies on the intermolecular PK reaction carried out by Cabot \textit{et al.}\textsuperscript{88} First, the alkyne reacts with a stoichiometric amount of Co\textsubscript{2}(CO)\textsubscript{8} to give the alkyne-cobalt hexacarbonyl complex A. This is then followed by the loss of CO to open up a coordination site on the metal center for the alkene to coordinate. This step follows a dissociative mechanism, thus explaining the need for heat (or additives) that can promote the loss of CO. This step is then followed by the formation of the C-C bond between the alkyne and alkene to give the metallocycle B. This step has been confirmed to be the rate determining and product determining step.\textsuperscript{88} If the alkyne is unsymmetrical, insertion and carbon-carbon bond formation proceeds exclusively at the alkyne carbon with the smaller substituent. Next, CO inserts into the metal-carbon bond leading to the metallocycle C. Then reductive elimination of the Co(CO)\textsubscript{3} fragment followed by the decomplexation of the Co\textsubscript{2}(CO)\textsubscript{6} fragment gives the cyclopentenone D completing the reaction as shown in Scheme 1.3.\textsuperscript{12}
Scheme 1.3

\[
\begin{align*}
R^S & \equiv \equiv R^L & \xrightarrow{\text{Co}_2(\text{CO})_8} & (\text{CO})_3\text{Co-Co(CO)}_3 \xrightarrow{-2 \text{ CO}} A \\
& & & R \equiv \equiv \\
(\text{CO})_2\text{Co-Co(CO)}_3 & + \text{CO} & (\text{CO})_2\text{Co-Co(CO)}_3 & + \text{CO} \\
& & & (\text{CO})_3\text{Co-Co(CO)}_3 \\
& & & R \equiv \equiv \equiv \equiv \\
& & & \xrightarrow{-\text{Co}_2(\text{CO})_8} \xrightarrow{-\text{CO}} D
\end{align*}
\]

The above mechanism was inferred from observations of regio- and stereochemistry results in a large number of cycloadditions; however no intermediate beyond the cobalt-alkyne complex has been isolated in the PK cyclization.

Moreover, theoretical studies have been used to further understand the mechanistic interpretation of the PK reaction. These studies also gave practical models which can be used to predict the diastereoselectivity of the cycloaddition.\textsuperscript{13-23}
1.4 Promoters of the Pauson-Khand Cycloaddition

Originally, the PK reaction was effected using the traditional method of first forming the alkyne-cobalt complex before heating in the presence of the alkene to form the cyclopentenone. The disadvantage of this methodology is that it can require extended reaction times and relatively high temperatures to effect the formation of the cyclopentenone. Consequently, attempts have been made for more than a decade by different groups to find reaction conditions that would accelerate the PK reaction while also reducing the reaction temperature. Smith and Caple\textsuperscript{9} in 1986 were the first to report success in improving the reaction rate for PK reaction by using alumina or silica gel for adsorption of the enyne, thereby reducing the reaction time and temperature. Then in the early 1990’s, the use of various promoters (e.g., $N$-methylmorpholine oxide and trimethylamine $N$-oxide) were reported by Schreiber\textsuperscript{24} and Jeong\textsuperscript{25} respectively. The use of promoters made it possible for the reaction to be carried out at room temperature (or below), thereby allowing the use of sensitive functionality in the cyclization precursors. It is widely accepted that these $N$-oxides act as oxidants creating a vacant coordination site on the cobalt by oxidative removal of the carbon monoxide ligands. This vacant site on the metal center allows for the oxidative addition of the olefin at a faster rate. As mentioned earlier, the oxidative addition of the olefin is considered to be the rate determining step for this reaction.

Sugihara and Yamaguchi\textsuperscript{26} reported that sulfur additives promoted both inter- and intramolecular PK reaction (85% yield in 30 minutes) better than $N$-oxides or the
thermal mode which gave either the decomplexation product or poor yields of the PK product (Scheme 1.4).

**Scheme 1.4**

\[
\text{Co}_2(\text{CO})_6 \quad \text{Ph} \quad + \quad \text{n-Bu-S-CH}_3 \quad \text{1,2-dichloroethane} \quad 83 \ ^\circ\text{C}, \ 30 \ \text{min}, \ 85\%
\]

\[
\text{Decomplexation}
\]

\[
\text{Co}_2(\text{CO})_6 \quad \text{Ph} \quad + \quad \text{NMO (6 eq)} \quad \text{CH}_2\text{Cl}_2, \ 10 \ \text{min}
\]

\[
\text{toluene, reflux} \quad \text{3 days}, \ 23\%
\]

Sugihara and Yamaguchi also showed that 3.5 equivalents of the alkyl or aryl methyl sulfide (R-S-CH$_3$, where R = Ph, i-Pr, n-Bu, t-Bu) afford excellent yields of the cycloadducts.\textsuperscript{26} Also electron donating groups attached to an aromatic ring enhance the yield in comparison to electron withdrawing groups. Moreover, they established that less sterically hindered sulfides functioned as better promoters.

### 1.5 Other Metals that effect the Pauson-Khand Reaction

Apart from cobalt, several other metal complexes such as those of Fe,\textsuperscript{27} Ir,\textsuperscript{28} Rh,\textsuperscript{29} Ti,\textsuperscript{30} Ni,\textsuperscript{31} Zr,\textsuperscript{32} Ru,\textsuperscript{33, 34} etc. have been used in a similar type of transformation. Yet cobalt remains the metal of choice for this type of cycloadditions reactions. These
metal complexes have been used in stoichiometric and catalytic fashion. A few of the
catalytic versions are herewith discussed.

Murai\textsuperscript{34} and Mitsudo\textsuperscript{33} at about the same time reported the use of \ce{Ru2(CO)12} to
effect the intramolecular cycloaddition of enynes to give the cyclopentenones. Both
groups used similar reaction conditions except that their choice of solvent is different
(dioxane versus dimethyl acetamide) as shown in the Scheme 1.5.

\textbf{Scheme 1.5}

\begin{equation*}
\begin{array}{cccc}
\text{EtO}_2\text{C} & \text{EtO}_2\text{C} & \text{Me} \\
\text{EtO}_2\text{C} & \text{EtO}_2\text{C} & \text{Ph} \\
\text{Ru}_2(\text{CO})_{12} & (2 \text{ mol\%}) & \text{CO (10-15 atm)} \\
\text{solvent, 140-150 °C} & & \\
\text{solvent} & \text{yield} \\
\text{Murai} & \text{dioxane} & 86\% \\
\text{Mitsudo} & \text{DMAC} & 78\%
\end{array}
\end{equation*}

Rhodium metal complexes are among the other transition metals that have been
extensively used in PK reaction. Narasaka established that \([\ce{RhCl(CO)2}]_2\) (1-5 mol\%)
promotes the PK cyclization of the 1,6-enynes in CO atmosphere, to give the bicyclic
enones in good yields (Scheme 1.6).\textsuperscript{29}

\textbf{Scheme 1.6}

\begin{equation*}
\begin{array}{cccc}
\text{EtO}_2\text{C} & \text{EtO}_2\text{C} & \text{Ph} \\
\text{EtO}_2\text{C} & \text{EtO}_2\text{C} & \text{Ph} \\
\text{[RhCl(CO)2]_2} & (1 \text{ mol\%}) & \text{CO (1 atm), dibutyl ether} \\
\text{130 °C, 94\%} & & \\
\text{solvent} & \text{yield} \\
\end{array}
\end{equation*}
1.6 Stereoselective Pauson-Khand Reaction

Control of the absolute stereochemistry in the PK reaction has attracted a great deal of attention. Various methods for making the PK reaction stereoselective have been introduced. Approaches aimed at preparing chiral cyclopentenones have involved the use of the following four strategies: (i) chiral precursors, (ii) chiral auxiliaries, (iii) chiral cobalt complexes and (iv) chiral additives.

1.6.1 Chiral Precursors

The most obvious method for promoting stereoselectivity would be to begin with a non-racemic starting material. Incorporation of chirality in the starting material would then make it possible for the transfer of chirality into the Pauson-Khand cycloadduct. Marco-Contelles and co-workers used the ex-chiral pool strategy to obtain the iridoid aglycon (Scheme 1.7). They converted a carbohydrate derived enol ether to a chiral enyne, which then underwent an NMO promoted PK reaction to give the tricycle cyclopentenones. The cyclopentenone was then further functionalized to give the targeted iridoid aglycon.

Scheme 1.7
1.6.2. Chiral Auxiliaries

Chiral auxiliaries can also be used for stereoselective intramolecular PK reaction and they are attached to either the alkene or alkyne arm. Carretero$^{36, 37}$ has shown that chiral sulfinylated enynes can furnish the PK product with excellent diastereoselectivity (Scheme 1.8).

**Scheme 1.8**

Moyano and Perricas$^{38}$ showed that chiral oxazolidin-2-ones are very useful auxiliaries for alkynes (Scheme 1.9).
It was noted through semi-emperical calculations (PM3) on the cobalt-alkyne complexes clearly indicated that the S-configured chiral auxiliary effectively shields the $Re$ face of the tetrahedral cobalt cluster. Therefore, the alkene is directed to an equatorial anti-position of the $Si$ face as depicted in Scheme 1.9. Subsequent insertion of the alkene, followed by CO insertion and cleavage of the cobalt fragment gives the exo-product as the major diastereomer. Both thermal and oxidative mode gave similar yields and diastereoselectivity.\textsuperscript{38}

### 1.6.3. Chiral Cobalt Complexes

Christie\textsuperscript{39, 40} was the first to demonstrate the use of chiral heterobimetallic alkyne complexes in an asymmetric variant of the PK reaction. The chiral mixed metal
complex was prepared by etherification of the cobalt-alkyne complex followed by treatment with Na[CpMo(CO)₃]. This complex was then heated with norbornadiene to afford the cyclopentenone as a single diastereomer (exo-product) as shown in Scheme 1.10 below.

**Scheme 1.10**

![Scheme 1.10](image)

These complexes can be handled under atmospheric conditions for extended periods of time and are also thermally stable. The observed diastereoselectivity is due to the fact that the reaction occurs selectively with one chiral metal site over the other.

Pericas and Moyano,⁴¹, ⁴² while studying heterobimetallic W-Co and Mo-Co systems, found that the PK reaction proceeded diastereoselectively to give the endo product. They attributed the chirality of the C₂MoCo core to be responsible for the diastereoselectivity of the endo-product (Scheme 1.11).
On the other hand, the corresponding [MoCp(CO)2]2 complex did not react with norbornadiene to give the cyclopentenone. This clearly indicates that the cobalt atom is the active species in the heterobimetallic complexes.

**1.6.4 Chiral Amine N-Oxides**

Kerr was the first to report the use of chiral amine N-oxides for the asymmetric variant of the PK reaction. The prochiral cobalt-alkyne complex is desymmetrized by the chiral amine N-oxide which then leads to the preferred decarbonylation of either the Re face or the Si face. This ultimately results in the formation of one of the two enantiomeric cyclopentenones as show in the Scheme 1.12.
Kerr\textsuperscript{43} used brucine \(N\)-oxide as a promoter for the formation of the cycloadduct, disappointingly, this gave the cycloadduct in low enantiomeric excess. Laschat\textsuperscript{44, 45} in an attempt to study the scope and limitation of PK reaction in the presence of chiral amine \(N\)-oxide used different chiral \(N\)-oxides such as (+)-sparteine \(N\)-1-oxide, (-)-sparteine \(N\)-16-oxide, (-)-17-oxosparteine \(N\)-oxide, (-)-nicotine \(N\)-1-oxide and (-)-nicotine \(N\)-1, \(N\)-1'-bisoxide, but they all gave low enantioselectivities (up to 16\% ee) regardless of the alkyne. They were able to increase the enantioselectivity up to 42\% ee by using amine \(N\)-oxides with additional donor functionalities like (-)-quinine \(N\)-oxide, tetracyclic \(N\)-oxide and (-)-brucine \(N\)-oxide (see Fig. 1.1 below).
1.7 Catalytic Pauson-Khand Reaction

Pauson\textsuperscript{5} was one of the first to develop a catalytic PK reaction. At that time, he used strained reactive alkenes like norbornene and norbornadiene with 10 mol% of (acetylene)-Co\textsubscript{2}(CO)\textsubscript{6} in the presence of acetylene and CO at 60-70 °C which gave only 14% of the cyclopentenone (Scheme 1.13).
Rautenstrauch\textsuperscript{46, 47} reported (20 years later) the use of much lower quantities of cobalt (0.22 mol\%) and non-strained alkenes in the presence CO (100 bar) to afford the PK product in 49\% yield (Scheme 1.14). The relatively low yield was attributed to the formation of Co\textsubscript{4}(CO)\textsubscript{12} cluster which may inhibit the catalytic cycle.

Blanco-Urgoiti et al.\textsuperscript{48} were able to improve the catalytic Pauson-Khand Reaction by using molecular sieves and a catalytic amount of Co\textsubscript{2}(CO)\textsubscript{8} at 65 °C. They concluded that this improvement is possible probably due to the ability of molecular sieves to adsorb and keep CO making it possible to effect the reaction even in the absence of CO atmosphere (Scheme 1.15).
In 1996 Buchwald\textsuperscript{49} reported the use of a titanocene complex to catalyze the intramolecular PK reaction. When titanocene (5 mol\%) and CO (1 atm.) was used to effect cyclization, it gave 91\% yield of the tricyclic enone (Scheme 1.16).

Buchwald also reported the synthesis of $\gamma$-butrolactones via a catalytic hetero-PK cyclization using Cp$_2$Ti(PMe$_3$)$_2$ starting from 1,6-enone (Scheme 1.17).\textsuperscript{50}

The catalytic cycle (Scheme 1.18) was proposed to proceed via an oxidative addition of the enyne A to the titanocene dicarbonyl complex to give the titanacyclopropene
complex B. This then undergoes decarbonylation followed by insertion of the alkene to give the titanocyclopentene complex C. The titanocyclopentene complex C then undergoes CO insertion to give the metallocycle D. This then undergoes reductive elimination to give the final PK product.

Scheme 1.18

Buchwald \(^{51, 52}\) also reacted 10 mol% of the titanocene \([\text{Cp}_2\text{Ti}(\text{PMe}_3)_2]\) with a slight excess of (trialkylsilyl)cyanide to give the intramolecular cycloaddition product in 42-
80% yield after hydrolysis of the resultant imine. The use of nickel(0) to catalyze the isocyanide cycloaddition reaction was also investigation (Scheme 1.19).53

**Scheme 1.19**

<table>
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<tr>
<th>Catalyst</th>
<th>Mol%</th>
<th>Yield</th>
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<tr>
<td>Cp2Ti(PMe3)2</td>
<td>10</td>
<td>80%</td>
</tr>
<tr>
<td>Cp2TiCl2/n-BuLi</td>
<td>10</td>
<td>82%</td>
</tr>
<tr>
<td>Ni(COD)2/Ligand</td>
<td>5</td>
<td>60%</td>
</tr>
</tbody>
</table>

Kobayashi et al.29 also reported converting 1,6- and 1,7-enynes having various substituents at the alkenyl or alkynyl moiety to the cyclopentenone products in high yield. Catalytic amounts of [RhCl(CO)2]2 under 1 atmosphere of CO and at 130-160 °C (Scheme 1.20).

**Scheme 1.20**
They also noticed that by reducing the partial pressure of CO to 0.1 atmosphere and using 0.9 atmosphere of argon, the reaction was accelerated and proceeded at a lower temperature (Scheme 1.21).

Scheme 1.21

\[
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad 5 \text{ mol\% } [\text{RhCl(CO)}_2]_2 \quad \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
0.1 \text{ atm CO} + 0.9 \text{ atm Ar} \\
toluene, 0.1 \text{ M, 60 }^\circ\text{C, 12h, 91%}
\]

Mukai and co-workers recently reported the use of a catalytic amount of Co\textsubscript{2}(CO)\textsubscript{8} to effect the hetero-PK reaction of alkynecarbodiimide. They ultimately used this methodology for the synthesis of (+)-physostigmine\textsuperscript{54} They employed 20 mol\% of Co\textsubscript{2}(CO)\textsubscript{8} and tetramethylthiourea (TMTU) in benzene at 70 °C under an atmosphere of CO to effect cyclization in 55% yield (Scheme 1.22).

Scheme 1.22

1.8 PK Reaction in Medium Sized Ring Synthesis

The application of the intramolecular Pauson-Khand (IMPK) reaction is an attractive approach to the synthesis of medium sized rings. The IMPK reaction permits a rapid increase in molecular complexity in one step and also affords the construction of
the carbon skeleton resembling a variety of known polycyclic natural products. The IMPK reaction has proved to be an efficient tool in the synthesis of bicyclo[3.3.0]octenones and bicyclo[4.3.0]nonenones via the corresponding 1,6- and 1,7-enynes as shown in Scheme 1.23

\[ \text{Scheme 1.23} \]

\[
\begin{array}{c}
\text{Co}_2(\text{CO})_6 \quad \text{Ph} \\
n=1, 2 \\
\text{n} \quad \rightarrow \\
\end{array}
\]

Cazes and coworkers were able to construct medium rings via allenic PK reaction. They used 3,3-disubstitued and 1,3-disubstituted allenynes in NMO promoted PK reaction to furnish the bicyclo[5.3.0]octane system, albeit in very low yields (10-23%) (Scheme 1.24).^{55}

\[ \text{Scheme 1.24} \]

Reagents and conditions: (a) \text{Co}_2(\text{CO})_6, \text{NMO}, \text{DCM}, 3 \text{ h, rt.} \]
Later, Brummond greatly improved on the yield of this reaction to approximately 77% by using a catalytic amount of \([\text{Rh(CO)}_2\text{Cl}]_2\)\textsuperscript{56} in place of the \(\text{Co}_2(\text{CO})_8\).

Yet, the construction of bicyclo[5.3.0] decenones and bicyclo[6.3.0] undecenones have proved more difficult via IMPK cyclization of 1,8- and 1,9-enynes, respectively.\textsuperscript{57} Mukai and coworkers attempted to cyclize 1,8-enyne but discovered that instead of leading to the medium ring system, bicyclo[5.3.0]nonenone, it gave bicyclo[4.3.0]nonenone system as a mixture of diastereomers (Scheme 1.25) due to migration of the terminal double bond.\textsuperscript{58}

**Scheme 1.25**

The failure of 1,8- and 1,9-enyne to cyclize to give the corresponding 7- and 8-membered rings may be attributed to the fact that the alkyne and alkene termini need to be close in space as in A before cyclization can take place and this is not entropically favorable. Hence structure B is the preferred conformation, but this conformation cannot lead to cyclization (Figure 1.2).

**Figure 1.2** Preferred conformation of 1,9-enynes.
In an effort to circumvent this problem Krafft and co-workers\textsuperscript{59} reported the use of an aromatic template so as to help in pre-organizing the alkene and alkyne arms of the substrate. As a result, the conformational degrees of freedom which the alkene and alkyne termini can adopt are reduced. The use of an aromatic template enhanced the formation of five or six membered rings annulated to cyclopentenone rings. However, the formation of the medium sized rings still proved difficult or at best gave a very low yield.\textsuperscript{59, 60}

\textbf{Scheme 1.26}

Interestingly, Krafft et al.\textsuperscript{59} reported unusual regioselectivity in the cyclization reaction of 1, 10-enyne to give a 10-membered ring as shown in Scheme 1.27.

\textbf{Scheme 1.27}

All attempts made to improve the yield of this reaction proved futile and in some case lead to decomplexation of the starting material. Lovely and coworkers\textsuperscript{61} using enynes constructed around an aromatic template and by making use of buttressing group effects, reported the unusual cyclization mode of PK reaction leading to medium ring systems (Scheme 1.28).
This unusual cyclization mode was attributed to be caused by both steric and electronic factors. The steric interaction between the internal methylene carbon and the cobalt complex is thought to force the alkene to rotate and orient itself toward the cobalt alkyne complex in order to avoid an unfavorable steric interaction (Fig 1.3). Moreover, electron rich substituents tend to orient $\alpha$-position to the carbonyl function.\textsuperscript{66} Hence the alkene is forced to rotate so as to place the electron rich aromatic ring next to the carbonyl group in the cyclopentenone.
Subsequently, Perez-Castells and coworkers\textsuperscript{62} described the formation of seven membered rings via intramolecular Pauson-Khand reaction in good yield. They made use of the planarity of the indole nucleus and also the effect of heteroatom coupled with the buttressing effect of OTBS group to effect cyclization of the enyne (Scheme 1.29).

**Scheme 1.29**

Reagents and conditions: (A) TMANO -molecular sieves, rt.
(B) molecular sieves, toluene, reflux
(C) refluxing toluene
1.9 Project Strategy

Based on the limitations of existing studies, it is the intent of this project to discover possible experimental solutions to this problem of medium sized ring construction via IMPK reaction. Rigid templates, such as aromatic systems, will be used to pre-organize the alkene and alkyne side chains thus forcing them to be close enough for cyclization to take place.

Also in this study we intend to introduce a buttressing group on the aromatic ring which will further help to reduce the conformational degrees of freedom of the alkene and alkyne termini. This has been previously demonstrated in our research group\textsuperscript{60} to reduce the cyclization time and also improve the yield of the reaction (Scheme 1.30).

\textbf{Scheme 1.30}

\begin{center}
\begin{tikzpicture}
  \node[below] at (0,0) {Reagents and conditions: Co\textsubscript{2}(CO)\textsubscript{8}, NMO, CH\textsubscript{2}Cl\textsubscript{2}, (a) 30 min.; (b) 8 h.};
\end{tikzpicture}
\end{center}
This design paradigm has several advantages. The cyclization precursor is simply and easily assembled. It also includes a heteroatom, which can provide an additional site for the transition metal to coordinate. Kafft and coworkers. showed that the presences of heteroatoms like sulfur and oxygen enhance the rate of the intramolecular cyclization.\textsuperscript{63}

In this study, we are focusing on two types of 1,8-enynes as shown in Figure 1.4 below. For the purposes of this dissertation, the 1,8-enynes will be classified as Type 1 and Type 2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{type1_type2.png}
\caption{Type 1 and Type 2 substrates}
\end{figure}

This dissertation will present the results of both the oxidative and thermal cyclization mode of Type 1 substrates and the result of the thermal cyclizations of type 2 substrates. The oxidative cyclization of several Type 2 substrates has previously been studied and the results of this investigation have been report by Dr. Seshadri in our research group.\textsuperscript{60}
CHAPTER 2
RESULTS AND DISCUSSION

2.1 Preliminary Results

To substantiate our hypothesis that an aromatic template is not sufficient to
effect a good cyclization yield, substrates which contained only an aromatic template
were used to initiate this investigation. These substrates lacked the buttressing group
effect afforded by the presence of an ortho substituent. Preparation of these substrates
involved a straightforward process. O-alkylation of the commercially available 2-
hydroxybenzaldehyde 1 with allyl bromide was achieved in the presence of K₂CO₃ to
furnish 2 in 90% yield. The O-alkylated benzaldehyde 2 was then alkynylated using the
alkynyl Grignard reagent to afford the enynes 3, 4 and 5 in 80, 85 and 86% yield
respectively (Scheme 2.1).

Scheme 2.1

<table>
<thead>
<tr>
<th>1</th>
<th>2, 90%</th>
<th>3; R = H, 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4; R = TMS, 85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5; R = Ph, 86%</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) allyl bromide, DMF, K₂CO₃;
(b) THF, 0 °C, BrMgC≡CR
With these enynes in hand, the PK cyclizations were investigated under standard oxidative conditions in dichloromethane using with N-methylmorpholine (NMO) as the promoter. Disappointingly but not surprisingly, substrates 3 and 4 failed to give the cyclic products 6 and 7. Moreover, substrate 5 gave only 8% of the cyclic product 8. Similar results were obtained under the thermal conditions. Substrates 3 and 4 did not undergo a cyclization reaction, while 5 gave 31% of the cyclized product 8. This result shows that substrate 5 seems to be better PK substrates. A higher yield of the cyclized product 8 was obtained under the thermal activation compared to the oxidative mode. In contrast, both the oxidative and the thermal mode failed to give the cyclized products 6 and 7 (Scheme 2.2).

\[ 
\text{Reagents and conditions: a; Co}_2(\text{CO})_8 (1.1 \text{ eq.}), \text{CH}_2\text{Cl}_2, \text{NMO}; \\
\text{b; Co}_2(\text{CO})_8 (1.1 \text{ eq.}), \text{toluene}, 70^\circ\text{C}. 
\]

Although the aromatic backbone of the enyne provides some reduction in the conformational degrees of freedom of the side chains, preorganization of the alkyne and
alkene is not sufficiently complete for effective cyclization to occur. Hence to further reduce the conformational degrees of freedom of the side chain, it was decided to investigate the introduction of a buttressing group at the propargylic hydroxyl group to see whether this will enhance the cyclization efficiency of the substrate.

Elaboration of the phenyl protected alkyne 5 was further explored based on the results mentioned above which showed higher yields for this substrate under the thermal conditions. The alkyne 5 was treated with tert-butyl-dimethylsilylchloride (TBSCI) to afford the enyne 9 in 98% yield and then 9 was subsequently subjected to the thermal conditions to give the cyclic product 10 in 50% yield as shown in Scheme 2.3.

**Scheme 2.3**

Reagent and conditions: (a). TBSCI, imidazole, DMF, 50 °C, 4.5 h.

(b). Co₂(CO)₈ (1.1 eq.), toluene, 70 °C.

The result above indicates that the steric bulk of the OTBS group helped in increasing the reactive rotamer population of the enyne. Hence, it may be concluded that incorporating a bulky group to the aromatic ring will enhance the cyclization yield of the 1,8-enyne leading to construction of medium size rings.
2.2 Type I Substrates

Type I substrates were prepared via the two step process discussed above, beginning with \( o \)-alkylation and followed by Grignard reaction. Commercially available 3, 5-di-\textit{tert}-butyl-2-hydroxybenzaldehyde (11) was \( O \)-alkylated using allyl bromide, 3-chloro-2-methylpropene, or 4-chloro-2-butene in the presence of \( \text{K}_2\text{CO}_3 \) with DMF as solvent to give the substituted aldehydes 12-14. The yields of these aldehydes range from 93-96\% as shown in the Scheme 2.4 below. The aldehydes 12, 13 and 14 were then subjected to a Grignard reaction using ethynylmagnesium bromide, phenylethynylmagnesium bromide and trimethylsilylethynylmagnesium bromide at 0 \( ^\circ\text{C} \) under a nitrogen atmosphere to afford the enynes 15a-c, 16a-b and 17a-c (Scheme 2.4).

**Scheme 2.4**

![Diagram showing the transformation of substrates and aldehydes](image_url)

Reagents and conditions: (a) alkenyl halides, DMF,rt;
(b) \( \text{BrMg} \longrightarrow 3 \text{, THF, 0 } ^\circ\text{C} \)

The results of the Grignard reaction for the different substrates are summarized in Table 2.1.
Table 2.1: Result of the enyne construction

<table>
<thead>
<tr>
<th>Enynes</th>
<th>% Yield</th>
<th>Mp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>74</td>
<td>95-96</td>
</tr>
<tr>
<td>15b</td>
<td>75</td>
<td>92-93</td>
</tr>
<tr>
<td>15c</td>
<td>75</td>
<td>94-95</td>
</tr>
<tr>
<td>16a</td>
<td>75</td>
<td>oil</td>
</tr>
<tr>
<td>16b</td>
<td>74</td>
<td>oil</td>
</tr>
<tr>
<td>16a</td>
<td>92</td>
<td>49-51</td>
</tr>
<tr>
<td>17b</td>
<td>97</td>
<td>oil</td>
</tr>
<tr>
<td>17c</td>
<td>98</td>
<td>oil</td>
</tr>
</tbody>
</table>

Attempts to prepare the enynes 22a, 22b and 22c containing the o-cinnamyl moiety via this procedure described above gave only a black colored reaction mixture which could not be purified or characterized. Hence, an alternative approach using a Mitsunobu reaction was used to access these enynes. The substituted phenol 19 was prepared in 68% yield by reacting 18 with N-iodosuccinamide. This iodophenol 19 was then subjected to the Mitsunobu protocol utilizing cinnamyl alcohol to afford 20. The O-cinnamyl phenol 20 was then treated with i-PrMgBr at -30 °C and then quenched with 1.0 eq. of DMF to give 21 in 89% yield. Substrate 21 was subsequently treated
with alkynyl Grignard reagents to give 22a-c in 92, 96 and 98% yields respectively (Scheme 2.5).

Scheme 2.5

Reagents and conditions: (a) NIS, THF, 0 °C; (b) Cinnamyl alcohol, DEAD, PPh₃, THF
(c). i-PrMgBr, THF, -30 °C, DMF; (d) BrMg══════R₃, THF, 0 °C

With the enynes 15a–c, 16a–b, 17a–c and 22a–c in hand, the Pauson-Khand reactions were investigated.

The enynes 15a–c were subjected to the Pauson-Khand protocol first. These enynes appeared to undergo reaction to give cyclization products which were anticipated to be PK products, but proved to be difficult to purify due to the formation of multiple products (see below). The multiple products formed were due to the presence of the α-hydroxyl group of the enyne. Consequently, the α-hydroxyl group of
the enynes 15a-c was removed, thereby simplifying the possible products by removing the stereochemical element on the propynyl arm. These reduced materials were obtained from the Co₂(CO)₆-alkyne complex by treatment with trifluoroacetic acid (TFA) and NaBH₄⁶⁴,⁶⁵ and then treating this material with a promoter, NMO, to give the expected PKR product 23 and 24 from 15a and 15b respectively. The combined yield for the two steps, reduction and cyclization, from enynes 15a and 15b is approximately 50% (Scheme 2.6).

Scheme 2.6

![Scheme 2.6](image)

Reagents and conditions: a. (i) Co₂(CO)₆, DCM; (ii). TFA, NaBH₄; (b). NMO

In the case of the enyne 15c, no cyclized product was obtained. Instead, the reduced enyne 26c was isolated as the only product (Scheme 2.7).
Scheme 2.7

Reagents and conditions: a. (i) Co$_2$(CO)$_8$, CH$_2$Cl$_2$, (ii) TFA, NaBH$_4$; (iii) NMO

The inhibition of this cyclization of this substrate can be rationalized by taking alkyne polarization effects into consideration.$^{6}$ Generally, in the reaction of unsymmetrical alkynes, the large and electron rich group is placed α to the carbonyl in the product cyclopentenone. Carbon-carbon bond formation of the alkene occurs with alkyne carbon having a higher electropositive character leading to the metallocycle. With substrate 15c, the C1 carbon has a higher electropositive character than the C2 carbon. Hence for the alkene to insert to form the C-C bond there will be a strain in the intermediate step which will inhibit formation of the metallocycle (Figure 2.1).

Figure 2.1. Alkyne polarization of substrate 25c
Substrates 15a and 15b undergo cyclization reaction due to the presence of the TMS and phenyl groups in the intermediates 25a and 25b which increases the electron density at the C₁ position. With the alkyne C₂ carbon more electropositive than C₁, the carbon-carbon bond formation with the alkene favors the formation of the “normal” metallacycle intermediate, leading to the cyclized products 23 and 24 as shown in Scheme 2.8.

Scheme 2.8

25a; R = TMS
25b; R = Ph

23; R = TMS
24; R = Ph

The above result is similar to those reported by Krafft67 where electron deficient alkynes were used for the Pauson-Khand reaction. She reported that the terminal alkyne did not give any cyclized product whereas substituted alkyne gave the cyclized product under the oxidative conditions (Table 2.2). She also invoked an alkyne polarization model to explain these results.
Table 2.2. Oxidative cyclization result of electron deficient alkynes

<table>
<thead>
<tr>
<th>enyne</th>
<th>condns</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>n = 1</td>
<td>A</td>
<td>n = 1</td>
</tr>
<tr>
<td>O</td>
<td>n = 1</td>
<td>A</td>
<td>n = 1</td>
</tr>
<tr>
<td>O</td>
<td>n = 1</td>
<td>A</td>
<td>n = 1</td>
</tr>
</tbody>
</table>

A : Co$_2$(CO)$_8$, NMO, rt, CH$_2$Cl$_2$, 4-5 h

Further investigation of the PK reaction of 15a-c in scheme 2.6 was carried out in order to find the step that was responsible for the low yield observed. It is conceivable that the reduction step was particularly inefficient for the parent substrate. Hence the isolation of the reduced enynes 26a-c became necessary before subjecting them to the PK conditions to see if the results were consistent with those obtained in Scheme 2.6 and Scheme 2.7 above.
The reduction of the α-hydroxyl group of 15a-c using TFA and triethylsilane (Et₃SiH) gave 96-99% of the reduced enynes, 26a-c. The reduced enyne, after formation of the cobalt complex was then subjected to oxidative PK conditions to afford the cyclized products. The results obtained were similar to those reported in Scheme 2.6 and Scheme 2.7 above. From these observations, it may be concluded that the cyclization step was responsible for the low yield. These results are summarized in Scheme 2.9 below. The reduction of the α-hydroxyl group increases the conformational degrees of freedom of the alkyne termini. As a result, the population of the reactive rotamer was decreased.

**Scheme 2.9**

![Scheme 2.9](image)

<table>
<thead>
<tr>
<th>Reagents and condition: (a) Et₃SiH, TFA, CH₂Cl₂; (b) Co₂(CO)₈, NMO, CH₂Cl₂; (c) Co₂(CO)₈, toluene, 70 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a; R = TMS, 99%</td>
</tr>
<tr>
<td>26b; R = Ph, 98%</td>
</tr>
<tr>
<td>26c; R = H, 96%</td>
</tr>
<tr>
<td>23: TMS, 43% 46%</td>
</tr>
<tr>
<td>24: Ph, 56% 45%</td>
</tr>
<tr>
<td>27: H, 0% 0%</td>
</tr>
</tbody>
</table>

The PK reaction of these substrates was also investigated under the thermal conditions. The yield for the thermal condition reactions were found to be comparable to those obtained under the oxidative conditions including the failure of the parent system to cyclize. These results show that the cyclization of the 1,8-enynes are possible under...
both oxidative and thermal conditions (Scheme 2.9). Although the NMR data for these compounds was completely consistent the expected structures, this was confirmed independently through X-ray crystallography of compound 24 (Figure 2.2).
Fig 2.2. X-ray crystal structure of 24.
Once it was demonstrated that the 1,8-enynes can lead to a cyclized product, the Co$_2$(CO)$_6$ complexes of enynes 15a and 15b were again subjected directly to the oxidative PK condition, without the reduction of the $\alpha$-hydroxyl group. The PK reaction proceeded to give a reasonably complexed mixture of products as shown in Scheme 2.10.

**Scheme 2.10**

![Scheme 2.10](image)

Reagents and conditions: (a) Co$_2$(CO)$_6$, CH$_2$Cl$_2$, NMO

The cyclization of the substrates 15a and 15b gave the reduced PK products 23 and 24, as well as the expected PK products 28 and 29 as a mixture of diastereomers. With enyne 15b (R = Ph) the reduced product 24, was isolated as the major product in 55% yield along with the expected PK product 29, as the minor product in 26% yield as a 1:1 mixture of diastereomers. On the other hand, enyne 15a (R = TMS) gave the expected PK products, 28 (2:1 ratio of diastereomers) as the major product in 70% yield of the epimeric mixture along with the reduced PK product 23 as a minor product in 20% yield. We attribute the variation of product constitution is due to the fact that the phenyl
group in 15b stabilizes the carbocation intermediate, through resonance leading to the formation of the reduced product as the major product (Scheme 2.11). This resonance stabilization is not possible with the TMS substrate 15a.

![Scheme 2.11](image)

Attempts were made to establish the appropriate reaction conditions for the thermal PK reaction. Substrates 15a and 15b were used to investigate the optimal thermal condition.

Substrate 15b was stirred and heated to reflux in CH$_2$Cl$_2$ for 4 hours and only the exo epimer of 29 was isolated in 63% yield. Extending the reaction time to 72 hours led to a slight increase in yield of exo isomer of 29 (75%) but also to the appearance of a the reduction product 24 (8%). With the solvent changed to toluene and the reaction mixture heated at 70 °C, the exo-epimer of 29 was isolated exclusively in 99% yield (Scheme 2.12).
Scheme 2.12

<table>
<thead>
<tr>
<th>15b</th>
<th>Solvent</th>
<th>Time</th>
<th>24</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dichloromethane</td>
<td>4 h</td>
<td>0%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72 h</td>
<td>8%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Toluene (70 °C)</td>
<td>18 h</td>
<td>0%</td>
<td>99% (X-ray)</td>
</tr>
</tbody>
</table>

Reagents and condition: (a). Co$_2$(CO)$_8$, solvent, reflux

Also the spectroscopic data for *exo* compound 29 was completely consistent with expected structure and this was confirmed independently through X-ray crystallography of compound 29 (Figure 2.3).
Substrate 15a also showed a similar trend to those of substrate 15b. Substrate 15a was stirred at reflux in dichloromethane for 72 hours, but only starting material, enyne 15a was recovered. When the reaction was carried out in toluene at 70 °C, the \textit{exo} epimer of 28 was isolated in 58% (Scheme 2.13).
Scheme 2.13

A mechanistic rationale depicted in Scheme 2.14 below has been proposed to account for the observed stereochemical outcome of the thermal mode. Once the alkyne-cobalt complex is formed, it can either undergo cyclization via path A or B leading to the exo- or endo-products respectively, since the cobalt complex and the angular H are always syn to each other. The nonbonding (steric) interaction between the OH group and the bulky R-group make pathway B very unfavorable whereas pathway A has little or no such steric interaction. Moreover, the rate of intramolecular cycloadditions is greatly increased by the presence of a heteroatom like oxygen or sulfur at the propargylic or homopropargylic position of the 1,6-enyne, by coordinating to the cobalt metal and thereby stabilizing the complex. Hence, the hydroxyl group at the propargylic position may coordinate to the cobalt metal in the intermediate complex in pathway A. The cobalt-metalloccycle A is stabilized leading to the exo-product. Therefore, the first step (formation of intermediates A and B) would be
considered to be the process determining the reaction’s stereochemical outcome. The scheme also explains why the TMS substrate gives lower yield compared to the phenyl substrate. Since the TMS is a very bulky group, both pathway A and B experience considerable steric interactions. As a result, lower yields of the exo-product, for the TMS substrate, are observed when compared to the phenyl substrate presumably due to competing non-productive pathways \(^{69}\) as shown in Scheme 2.14 which is the possible mechanistic pathway for the thermal PK reaction.
Scheme 2.14

Cobalt Complex

Path A

Exo Product

Path B

Endo Product
The effect of increased steric interaction in these substrates was further investigated. The steric bulk of the \(\alpha\)-hydroxyl function was increased by reacting 15a and 15b with TBSCl to give the silyl ethers 30 and 31 in 97% and 98% yield respectively (Scheme 2.15). With compound 30, when subjected to the oxidative conditions, led to a reversal of the product distribution when compared to the result shown in Scheme 2.9. In this case, the expected PK product 32 became the major product in 60% yield with 5:1 ratio of the stereoisomers, while the reduced PK product 24 was isolated as the minor product in 11%. On the other hand, when the silyl ether 30 was subjected to the thermal PK condition, it gave only 32 in 95% yield with higher diastereoselectivity (10:1) when compared to the oxidative condition. No formation of the reduced product was observed under the thermal reaction conditions (Scheme 2.15).

**Scheme 2.15**

Reagents and conditions: (a) TBSCI, DMF, imidazole, 50 °C; (b) \(\text{Co}_2(\text{CO})_8\), \(\text{CH}_2\text{Cl}_2\), NMO;
(c) \(\text{Co}_2(\text{CO})_8\), toluene, 70 °C
Compound 32 was treated with TBAF in THF to give 29 as the major product identical in all respects to that obtained from 15a. This confirms the stereochemical outcome of the cyclization of 30 as shown in Scheme 2.15.

The slight reduction of diastereoselectivity in the OTBS protected enyne 30 cyclization for the thermal mode may be explained by the fact that the OTBS protection reduces the stabilization due to the coordination of the free hydroxyl group to the cobalt metal as shown in the mechanistic pathway A in Scheme 2.14 above.

With substrate 31, the oxidative PK reaction became completely stereoselective with respect to the epimeric products. The syn-epimer (exo-product) 33 was only cycloadducts, isolated in 61% yield. No cyclized product was formed when 31 was subjected to the thermal PK condition (Scheme 2.15). This may be due to steric hindrance preventing the formation of the intermediate metallocycle and thus decomposition (presumably by decomplexation) becomes the dominant pathway.

With a better idea of some of the products from these reactions, the PK reaction of substrate 15c was then re-investigated. The cyclization products of substrate 15c were different from those observed with 15a and 15b. With substrate 15c, no reduced PKR product was observed. Instead the anticipated PK product 34 was isolated in 11% (1:1 ratio of diastereomers), along with the diketone 35 in 80% yield (6:1 ratio of isomers) as shown in Scheme 2.16. Also, the thermal cyclization of 15c gave 11% (2:1) of 34 and 50% of 35 in 1:1 ratio of the syn- and anti-isomers. The thermal PK of 15c did not show any stereoselectivity (Scheme 2.16).
Scheme 2.16

Reagents and conditions: (a) $\text{Co}_2(\text{CO})_8$, CH$_2$Cl$_2$, NMO;
(b) $\text{Co}_2(\text{CO})_8$, toluene, 70 °C

The diketone, 35, was believed to have been formed from the expected PK product 34 by undergoing transition metal mediated 1,3-hydride shift followed by tautomerization to furnish 35 as shown in Scheme 2.17. 73-75

Scheme 2.17

The TBSCI protection of the $\alpha$-hydroxyl function of 15c gave the silyl ether 36 in 98% yield. Substrate 36 was subjected to both oxidative and thermal Pauson–Khand
conditions. The oxidative mode gave 52% of product 37 as a 2:1 mixture of the epimers. The thermal mode gave 80% of the expected PK product 37 as a 1:1 mixture of epimers (Scheme 2.18). The stereochemical outcome of the thermal reaction is consistent with the thermal mechanistic pathway shown in Scheme 2.14 above. The steric interaction experienced in pathway B does not exist with this substrate since the alkynyl group (R = H) is very small. This makes it possible for the reaction to go through both pathway A and B, leading to the observed reduced diastereoselectivity. This reduction in diastereoselectivity is consistent with small alkyne moiety. Moreover, OTBS group does not coordinate with the cobalt metal center. As a result pathway A for this substrate looses the extra stabilization due to such coordination with the metal center, making it less diastereoselective.

**Scheme 2.18**

![Scheme 2.18](image)

Reagents and conditions: (a) TBSCI, DMF, imidazole, 50 °C; (b) Co₂(CO)₈, CH₂Cl₂, NMO; (c) Co₂(CO)₈, toluene, 70 °C

Although enynes containing terminally substituents participated in the PK reaction, enynes with the internal methyl substituent 16a and 16b did not, only decomplexation of these enynes was observed. This may be attributed to the
unfavorable steric interaction between the internal methyl and the cobalt alkyne complex as shown in Figure 2.3.

![Diagram](image.png)

**Figure 2.4.** Unfavorable steric interaction of enynes with internal Methyl substitution

Interestingly, the terminal alkenyl substituted enynes were found to participate in the PK reaction. Substrates 17a (R = TMS) and 17b (R = Ph), containing an internal alkene, were subjected to both the oxidative and thermal conditions. Under oxidative conditions, substrate 17b gave the reduced PK product 39 as a minor product in 18% yield. It also gave the *endo*-product 40 in 36% yield and the *exo*-product 41 in 45% yield. On the other hand, the thermal mode with substrate 17b gave the *endo*-product 40 in 9% yield and *exo*-product 41 in 90% yield. Thermal conditions were found to lead to diastereoselective cycloadditions providing the *exo*-epimer as shown in the thermal mechanistic pathway. Substrate 17a gave only 7% of *exo*-product 42 under the oxidative conditions while the thermal condition gave 12% of the same product. No reduced PK product was observed. The low yield obtained with substrate 17a may be due to increased steric crowding in the intermediate metallocycle (Scheme 2.19).
The spectroscopic data for the *exo*-compound 41 was completely consistent with expected structure and this was confirmed through X-ray crystallography of compound 41 (Figure 2.5).
For the substrate 17c (R = H), the oxidative mode gave the diketone products 43 in 58% yield (1:3 ratio of the isomers), along with 30% of the reduced product 44. Under thermal PK conditions, 17c gave only 32% of 43 in 1:2 ratios of the syn and anti.
isomers (Scheme 2.20). In addition, substrate 17c showed low stereoselectivity for the thermal conditions compared to the result obtained with substrates 17a and 17b.

Scheme 2.20

![Scheme 2.20](image)

Reagents and conditions: (a) Co\(_2\)(CO)\(_8\), CH\(_2\)Cl\(_2\), then NMO
(b) Co\(_2\)(CO)\(_8\), toluene, 70 °C

The two isomers of the diketo compound were separated by chromatography and a subsequent NOESY experiment confirmed the stereochemistry of the major product to be the cis-isomer (Figure 2.6)

![Figure 2.6](image)

**Figure 2.6.** NOESY confirmation of the stereochemistry of the cis-isomer of 43
Next, steric effects imparted by introducing a bulky group on the $\alpha$-hydroxyl moiety of the substrates, were investigated. Substrate 17a and 17b were reacted with TBSCl to give 45 and 46 in 97% and 98% yield respectively (Scheme 2.21). Then, substrate 45 was subjected to oxidative PK conditions to furnish 47 in 45% yield as 4:1 mixture of epimers. When substrate 45 was subjected to the thermal mode gave 68% yield of the exo-product of compound 47. On the other hand, the TMS-derivative, 46, afforded mainly small amounts of cyclized product along with the recovery of the starting materials when exposed to both NMO and thermal promoted PK conditions. Substrate 46 gave 7% of 48 when subjected to oxidative PK condition. Under thermal condition it gave only 10% of 48 (Scheme 2.21). The low yields obtained from substrate 46 could be due to the steric hindrance formation in the metallocycle from the intermediate alkyne-dicobalt hexacarbonyl complex.
When exo-product 41 was treated with TBSCl and heated to 55 °C for 4 h it gave exclusively exo-product of 47 (Scheme 2.22). This also confirms the stereochemical result of the phenyl substrate in Scheme 2.21 to be mainly exo-product.
Similarly to the previous examples, the $\alpha$-hydroxyl group of the parent substrate 17c was treated with TBSCl to furnish 91% yield of substrate 49. With the cyclization substrate in hand, the oxidative and thermal PK cyclization reactions were investigated. The oxidative PK condition afforded 80% yield of 50 in 1:0.8 ratio of the epimers and thermal condition gave 85% yield of 50 in 4:5 ratio of the diastereomers as shown in Scheme 2.23.

So far the enynes containing a phenyl substituted alkyne have proven to be the best cyclization substrates. Therefore, it was decided to explore the effect of substituting
the alkene arm of the enyne with a phenyl group to see if it will enhance the PK cyclization. Hence, the substrates 22a, 22b and 22c were constructed as previously stated above. These substrates were then subjected to both oxidative and thermal PK conditions. Under the oxidative PK conditions the substrate 22b gave both the reduced PK product 51 in 45% yield and the exo- PK product of 52 in 51% yield. On the other hand, the thermal mode gave 90% yield of 52 in 10:1 ratios of the diastereomers, with the exo-isomer being the major product.\textsuperscript{69, 70} The thermal mode did not give the reduced PK product 51 (Scheme 2.24).

\textbf{Scheme 2.24}

![Scheme 2.24](image)

Reagents and conditions: (a) Co\textsubscript{2}(CO)\textsubscript{8}, dichloromethane, then NMO
(b) Co\textsubscript{2}(CO)\textsubscript{8}, toluene, 70 °C

Once again, the steric effect of increasing the bulkiness of the \(\alpha\)-hydroxyl group was investigated. Substrate 22b was protected with TBSCl to give 53 in 95% yield. Compound 53 was then cyclized under oxidative PK conditions to give the exo- product
54 in 67% yield, while the thermal condition gave 86% of the same product 54 (Scheme 2.25).

**Scheme 2.25**

Reagents and conditions: (a) TBSCI, DMF, imidazole, 50 °C; 
(b) Co$_2$(CO)$_8$, CH$_2$Cl$_2$, NMO; (b) Co$_2$(CO)$_8$, toluene, 70 °C

On the other hand, substrate 22c participated in oxidative PKR to give the diketone 55 in 51% yield in 5:1 ratio of the syn and anti-isomers, with the syn-product as the major product. A somewhat lower yield of 55 was obtained with the thermal PK of this substrate. The thermal reaction of substrate 22c gave 41% yield of 55 in 3:1 ratio of the syn and anti-isomer. The normal PK product 56 was isolated in 5% yield (Scheme 2.26).
Scheme 2.26

The stereochemistry of the major diketone product was confirmed by a NOESY experiment to be the *syn*-isomer as shown in figure 2.7.

**Figure 2.7.** NOESY interaction of cis-isomer of **55**

In addition, TBSCl was used to protect the α-hydroxyl function of substrate **22c** leading to the silyl ether **57** in 93% yield. Then compound **57** was treated under the oxidative PKR conditions to afford 71% yield of **58** in 1:0.8 ratios of the epimers.
Under the thermal condition, substrate 57 gave 86% yield of the PK product 58 in 1:1 ratios of the epimers as shown in Scheme 2.27.

![Scheme 2.27](image)

Reagents and conditions: (a) TBSCI, THF, imidazole, 50 °C; 
(b) Co$_2$(CO)$_8$, CH$_2$Cl$_2$, NMO; (c) Co$_2$(CO)$_8$, toluene, 70 °C

Generally, these results have shown that once the alkyne is substituted, the PK reaction tends to be diastereoselective towards the exo-product. It has been established from the mechanistic rationalization that the substituent on a terminal alkyne provides a greater degree of steric control. Hence, bulky substituents on the on the alkyne arm drives the cyclization to be more stereoselective, leading to the exo-compounds as the major product under the PK conditions.$^{70, 76-78}$ Furthermore, protection of the propargylic hydroxyl group reduces side reaction (reduces isomerization) which led to a reduction of the yield of the expected products.

This work confirms that aromatic ring alone does not sufficiently preorganize the enyne substrate for cyclization leading to medium size rings. However,
incorporation of conformational constraints induced by bulky ortho substituent enhances the efficiency of enyne cyclization.

2.3 Type II Substrates

Substrates that we have designated as Type II have been studied previously under the oxidative PK conditions. Therefore, this part of the project focuses on the thermal PK of Type II of substrates. These substrates were assembled from commercially available 2,4-di-tert-butylphenol (59) by iodination with N-iodosuccinamide to give 60. Compound 60 was subjected to a Sonogashira reaction with TMS-acetylene to afford 61 in 92% yield (Scheme 2.28).79-81

![Scheme 2.28](image_url)

Reagents and conditions: (a) N-iodosuccinamide, 0 °C, DMF, 68%;
(b) HC≡C-TMS, Et3N, dioxane, Pd(PPh3)2Cl2, Cul.

The phenol 61 was then allylated to give 62 followed by a deprotection of the acetylene functionality by stirring in a mixture of THF/MeOH (1:1) in the presence of K2CO3. This reaction gave 63, the cyclization precursor, in quantitative yields (Scheme 2.29).
With both enynes 62 and 63 in hand, they were subjected to the thermal Pauson-Khand reaction protocol. Substrate 62 provided 93% of the six member cyclic product 64. On the other hand, enyne 63 gave 91% of the cyclic product 65 (Scheme 2.30).

Thermal PK conditions for these substrates gave a higher yield compared to the NMO promoted PK reaction. The oxidative PK reactions have been investigated earlier.
by Dr. Seshadri in our laboratory.\textsuperscript{60} Under oxidative conditions, Dr. Seshadri reported the cyclization of 63 to give 70\% yield of the PK product 65.

The influence of substituted alkene moiety on the efficiency of the cyclization was of interest in this investigation. In earlier studies from our group, it had been established that alkene substitution was detrimental to cyclization in substrates which lacked the $o$-tert-butyl group. Hence, the internal methyl alkene substituted enyne was synthesized. Substrate 61 was treated with 2-methylallyl chloride in the presence of NaI and K$_2$CO$_3$ to afford enyne 66. Subsequently, it was desilylated by stirring in THF and methanol mixture in the presence of K$_2$CO$_3$ to give quantitative yield of 67 as shown in Scheme 2.31.

\textbf{Scheme 2.31}

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {61};
\node (2) at (1,0) {66 (98\%)};
\node (3) at (2,0) {67 (quant.)};
\draw[-stealth] (1) -- (2) node[midway,above] {a};
\draw[-stealth] (2) -- (3) node[midway,above] {b};
\end{tikzpicture}
\end{center}

Reagents and conditions: (a) K$_2$CO$_3$, NaI, DMF, BrCH$_2$(CH$_3$)C=CH$_2$; (b) K$_2$CO$_3$, THF, MeOH.

Enynes 66 and 67, upon conversion to the cobalt alkyne complexes, were subjected to the PK conditions to give the corresponding cyclic products. Under the thermal conditions, the enyne 66 furnished the tricyclic compound 68 in 92\% yield. Since enyne 67 was not previously investigated under the oxidative conditions, and so was subjected
to both thermal and oxidative conditions. When enyne 67 was subjected to the thermal PK conditions 91% yield of the tricyclic product 69 was isolated. Under the oxidative mode enyne 67 gave 83% yield of the cyclic product 69 (Scheme 2.32).

Scheme 2.32

![Scheme 2.32](image)

Reagents and conditions: (a) Co$_2$(CO)$_8$, toluene, 70 °C, 91%
(b) Co$_2$(CO)$_8$, NMO, CH$_2$Cl$_2$, 83%

Apparently, these substrates tend to give better yields for the thermal PK reactions when compared to the yields obtained for the oxidative PK reactions.

Enynes with an internal alkene were also investigated. In an attempt to synthesize substrate 71, substrate 20 and TMS protected acetylene were subjected to Sonogashira protocol. Unfortunately, instead of giving the expected Sonogashira product, it gave a cyclized product 70, as shown in the Scheme 2.33 below.
This product 70 was formed via the mechanistic path depicted below in Scheme 2.34. Initially, Pd inserts into the aryl halide bond followed by coordination of the C-C double bond to the metal center. Conjugative addition of the double bond then occurs to give a cyclic compound with an exocyclic double bond. This compound then underwent a transition metal-mediated hydride shift to give product 70 (Scheme 2.34).

A different approach was then taken to prepare substrate 71. From substrate 61, a Mitsunobu protocol with cinnamyl alcohol was followed to afford 71 in 95% yield. Substrate 71 was desilylated to give 93% yield of the enyne 72 (Scheme 2.35).
With substrates 71 and 72 in hand, both the thermal and NMO promoted PKR were investigated. The TMS protected alkynyl enyne 71, under NMO promoted PK condition, gave 81% yield of the cyclic product 73. However, lower yields of the cyclized product 73 were obtained under the thermal PK conditions (71% yield). On the other hand, substrate 72 under oxidative PK condition gave 91% yield of the cyclic product 74. In comparison, 73% yield of the cyclic product 74 was obtained under thermal conditions (Scheme 2.36).
Scheme 2.36

Reagents and conditions: (a) Co$_2$(CO)$_8$, CH$_2$Cl$_2$, the NMO;
(b) Co$_2$(CO)$_8$, toluene, 70 °C

In general, the thermal PK reaction results were viewed extremely encouraging. To utilize this approach for the assembly of larger sized rings, the precursor enynes which upon cyclization would provide seven or eight membered rings was synthesized. Butenyl substituted enyne 75 was constructed by subjecting 61 to a Mitsunobu protocol with 3-buten-1-ol in 95% yield. The TMS group was then cleaved to afford the enyne 76 in 84% yield as shown in Scheme 2.37 below.
When substrate 75 was subjected to thermal PK condition under N\textsubscript{2} atmosphere, the anticipated PK product 77 was obtained in only 14\% yield. The major product was instead the diene 78 (75\% yield), which resulted from a $\beta$-hydride elimination from the intermediate complex. NOESY experiment was used to assign the stereochemistry at the TMS-substituted diene and the indicated NOE was particularly diagnostic. The insertion of CO into the metallocycle was inhibited as a result of the $\beta$-hydride elimination. On the other hand, when the reaction was done under CO atmosphere, the yield of PK product 77 was improved to 20\%. However, 60\% of the starting material 75 was recovered (Scheme 2.38).
Reagents and conditions: (a) Co$_2$(CO)$_8$, toluene, 70 °C

When the desilylated substrate 76 was subjected to thermal PK cyclization, two unique products 79 and 81 were isolated in 17% and 13% yield respectively (Scheme 2.39). Compound 79 is the unusual epoxide product reported earlier by Lovely and coworker.}$^61$
Product 81 seems unusual since it did not resemble any of the anticipated products and its molecular weight is 330 g/mol. The IR showed the presence of a hydroxyl group at $\nu_{\text{OH}} = 3396 \text{ cm}^{-1}$ and carbonyl group at $\nu_{\text{C}=\text{O}} = 1735 \text{ cm}^{-1}$. This absorption is typical for non-conjugated carbonyl groups. Also, the $^1$H NMR showed two additional protons more than was anticipated for the conjugated carbonyl product. Therefore, it was concluded that the cyclized product 81 was a product of Michael addition of H$_2$O on the $\alpha$,$\beta$-unsaturated carbonyl compound 80 (Scheme 2.40).

The epoxidation and hydroxylation products are consistent with the literature reports. It has been demonstrated that strained enones generated from PK reactions undergoes
subsequent processes in order to reduce the inherent strain in the molecule. A molecular model of 80 clearly exhibits strain.

Krafft and coworkers have demonstrated that normal PK reaction takes a different route in the presence of oxygen, leading to interrupted PK reaction resulting in the formation of a non-cyclic enone. Further investigation was carried out in order to explain how the epoxide 79 was formed. Enyne 76 was subjected to the oxidative condition, but in this case instead of carrying out the reaction under the N₂ atmosphere it was done under O₂ atmosphere. The cyclization gave the epoxide 79 exclusively in 63% yield (Scheme 2.41).

Scheme 2.41

![Scheme 2.41](image)

Reagents and conditions: (a) Co₂(CO)₈, CH₂Cl₂, NMO, O₂

This result suggests that oxygen inserts into the cobalt presumably forming a Co=O species. The oxygen is then delivered to the strained bridge head double bond, leading to the formation of the epoxide product 79.

The higher homologue of the butenyl enyne 76 was prepared next to give 82. Then substrate 82 was subjected to the thermal PK to give cyclic compound 83 of identical regiochemistry to that of the butenyl system in 86% yield. The thermal PK
conditions gave a higher yield of compound 83 compared to the NMO promoted PK yield earlier reported by Dr Seshadri (Scheme 2.42).\textsuperscript{61}

\textbf{Scheme 2.42}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\includegraphics[width=0.8\textwidth]{Scheme2.42.png}};
\end{tikzpicture}
\end{center}

Reagents and conditions: (a) $\text{Co}_2(\text{CO})_8$, toluene, 70 °C

This unusual cyclization mode was attributed by Dr. Seshadri\textsuperscript{60,61} to be caused by both steric and electronic factors. The steric interaction between the internal methylene carbon and the cobalt complex probably forced the alkene to rotate and orient itself toward the cobalt alkyne complex in order to avoid an unfavorable steric interaction (Fig 1.3).

Moreover, electron rich substituent tends to orient $\alpha$-position to the carbonyl function. Hence the alkene is forced to rotate placing the electron rich aromatic ring next to the carbonyl group in the cyclopentenone.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\includegraphics[width=0.8\textwidth]{ProposedCyclizationMode.png}};
\end{tikzpicture}
\end{center}

\textbf{Fig. 1.3. Proposed cyclization mode}
Since one of the aims of this study was to establish whether the PK reaction could be used in the total synthesis of the hamigeran family, an attempt was made to prepare enynes that can cyclized to give a product similar to the core of the hamigeran A and B. To accomplish this, the iodophenol 69 was subjected to a Sonogashira protocol with 2-methyl-2-hydroxy-1-butyne. From this reaction, compound 84 was obtained in 94% yield. The compound 84 was then reduced with NaBH₄ in the presence of TFA to give 96% yield of 85 (Scheme 2.43).

Scheme 2.43

\[
\begin{array}{c}
\text{Reagents and conditions: (a) 2-methyl-2-hydroxybut-1-yn-1, Pd(PPh₃)₂Cl₂, Cul, Et₃N, dioxane; (b) NaBH₄, trifluoroacetic acid, dichloromethane, 0 °C)}
\end{array}
\]

Compounds 84 and 85 were then reacted with 2-methylallyl chloride and NaI to afford 86 and 87 in 78% and 92% yields respectively (Scheme 2.44).
Both substrates 86 and 87 were subjected to both the thermal PK and NMO promoted PK conditions to afford cyclic products. Substrate 86, under oxidative condition gave 33% of the cyclized product 88, whereas under the thermal condition, 85% yield of cyclized product 88 was obtained. On the other hand, substrate 87 under the oxidative condition gave 65% of 89, while the thermal condition afforded 84% of the cyclized product 89 (Scheme 2.45).
This result clearly indicates that the P-K methodology will be an effective method for the total synthesis of the hamigeran family and other natural products with 5-membered ring annulated to medium sized rings. Hence with the PK reaction the tricyclic core of the hamigerans will easily be accessed. Our approach to this family of natural products base on this disconnection will be described in the later chapters.

This work clearly confirms our hypothesis that aryl ring could function as a suitable scaffold for the Pauson-Khand cyclization of the enynes. Also, introduction of additional conformational constraints induced by an ortho substituent further restricts
the conformational space available to the enyne arms, thus forcing alkene arm into close proximity with the alkyne group thereby giving access to medium sized rings as well as congested cyclopentenones.
CHAPTER 3

EXPERIMENTAL SECTION

3.1 General Methods

All reagents were purchased from commercial suppliers and were used as received unless otherwise noted. Solvents were dried by distillation over appropriate drying agents: tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl; benzene and dichloromethane were distilled over calcium hydride or purified using Innovative Technologies Inc Pure Solv SPS-400-05 solvent purification system. $^1$H and $^{13}$C NMR (δ in ppm) spectra were recorded in CDCl$_3$ (unless otherwise noted) at 500 and 125.8 MHz, respectively; using a JEOL Eclipse+ 500 spectrometer. Also $^1$H and $^{13}$C NMR (δ in ppm) spectra were recorded sometimes at 300 and 75 MHz respectively; using a JEOL Eclipse 300 spectrometer as otherwise noted using residual CHCl$_3$ (δ = 7.26) as reference for $^1$H NMR and carbon absorption of CDCl$_3$ (δ = 77.0) as internal reference for $^{13}$C NMR. Infrared spectra were recorded either as neat films or as KBr pellets using a Bruker Vector 22 FT-IR spectrometer. All mass spectra data are reported as $m/z$ (relative intensity).

Electrospray ionization (ESI-MS) was obtained from HT labs Inc, San Diego, CA. High resolution mass spectra (HR-MS) were obtained from Dr. Powell’s lab in University of Florida, Gainesville, Florida. Elemental analyses were performed using a Perkin-Elmer 2400 CHN analyzer. Analytical thin layer chromatography (TLC) was
performed on Whatman silica gel 60F_{254} aluminum precoated plates (0.25 mm layer). All chromatographic purifications were performed using ICN silica gel (200-400 mesh).

3.1.1 General procedure for the O-alkylation reaction:
The bromoalkene (11.0 mmol) was added to a suspension of K₂CO₃ (14.4 mmol) and 3,5-di-tert-butyl-2-hydroxybenzaldehyde (11.0 mmol) in DMF (50 mL) and stirred at room temperature for 12 h. The product was extracted with CH₂Cl₂ (25 mL) and washed twice with water, dried using Na₂SO₄ (anhydrous) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂: hexane/EtOAc, 15:1).

3.1.2 General procedure for the reaction of the O-alkylated Product with Grignard reagent.
The Grignard reagent (1.5 eq.) was added to a solution of aldehyde in dry THF (10 mL) under N₂ at 0 °C. The mixture was stirred and gradually allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched with aqueous NH₄Cl and then extracted with CH₂Cl₂. The organic layers were then washed with water, brine and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 80:20).
3.1.3 General procedure for the Pauson-Khand Cyclization

3.1.3.1 General procedure for the reduced PKR (Procedure A)

1.1 eq of Co$_2$(CO)$_8$ was added to a stirred solution of enyne in CH$_2$Cl$_2$ and under N$_2$ at room temperature. The reaction mixture was stirred for 5 h at rt. The reaction mixture was then cooled to 0 °C before adding NaBH$_4$. Subsequently, TFA was added over 10 minutes at 0 °C. The reaction mixture was decanted into 300 mL iced water and the organic layer separated, washed with water and dried (Na$_2$SO$_4$). The organic layers were concentrated and cooled to 0 °C before NMO (12 eq.) was added and stirred for 2 h. The reaction mixture was then poured into a sintered glass funnel with Celite and SiO$_2$ and filtered. The solid packing was washed with EtOAc to extract the remaining product. The filtrates were combined and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 20/1.5).

3.1.3.2 General procedure for the Oxidative Pauson-Khand Method (Procedure B)

1.1 eq of Co$_2$(CO)$_8$ was added to a stirred solution of enyne in CH$_2$Cl$_2$ and under N$_2$ at room temperature. The reaction mixture was stirred for 5 h at rt. The reaction mixture was cooled to 0 °C before NMO (12 eq.) was added in three portions at 30 minutes intervals and then left to stir for 2 h. The reaction mixture was then poured into a sintered glass funnel packed with Celite and SiO$_2$ and washed with EtOAc. The crude product was purified by flash chromatography (hexane/EtOAc, 20/1.5).
3.1.3.3 General procedure for the Thermal Pauson-Khand Method (Procedure C)

1.1 eq of Co$_2$(CO)$_8$ was added to a stirred solution of enyne in toluene and under N$_2$ and stirred for 5 h at room temperature. The reaction mixture was then heated at 70 °C under N$_2$ for overnight. The reaction mixture was then poured into a sintered glass funnel packed with Celite and SiO$_2$ and first washed with hexane to remove the alkyne-Co$_2$(CO)$_6$ remaining and then washed with ethyl acetate to remove any remaining cyclized product. The crude product was purified by flash chromatography (hexane/EtOAc, 20/1.5).

2-(-2-Propenyloxy)benzaldehyde (2)

Allyl bromide (19.8 g, 160 mmol) was added to a suspension of K$_2$CO$_3$ (23.0 g) and 2-hydroxybenzaldehyde (20.0 g, 160 mmol) in DMF (100 mL) and stirred for 12 h according to the general procedure 3.1.1. The crude product was purified by flash chromatography (hexane/EtOAc, 15:1) to give 2 as a brown oil (18.5 g, 70%). $^1$H NMR (500 MHz): $\delta = 10.41$ (s, 1H), 7.70 (dd, $J = 1.4$, 7.8 Hz, 1H), 7.40 (dt, $J = 1.8$, 8.7 Hz, 1H), 6.90 (t, $J = 7.8$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 1H), 6.95 (ddt, $J = 5.5$, 10.5, 17.0 Hz, 1H), 5.33 (dd, $J = 1.4$, 17.4 Hz, 1H), 5.21 (dd, $J = 1.4$, 10.5 Hz, 1H), 4.52 (d, $J = 5.0$ Hz, 2H); $^{13}$C NMR (125 MHz): $\delta = 189.7$, 161.0, 136.1, 132.6, 128.4, 125.1, 120.9, 118.1, 113.1, 69.2; IR (neat, cm$^{-1}$) = 3079, 2866, 1685, 1599, 1483, 1286, 995, 759; HRMS (ESI): Calcd. for C$_{10}$H$_{11}$O$_2$ (m/z): 163.0759. Found 163.0749 [M+H]$^+$. 

83
2-(1-Hydroxy-2-propynyl)-(2-propenyloxy) benzene (3)

0.5 M solution of ethynylmagnesium bromide (55.6 mL, 28.0 mmol) in THF was added at 0 °C to a solution of 2 (3.00 g, 19.0 mmol) in THF (20 mL) under N\textsubscript{2} atmosphere according to the general procedure above. The reaction was worked up according to the general procedure 3.1.2 to give 3 (3.31 g, 95%) as a brown oil after chromatographic purification. \textsuperscript{1}H NMR (500 MHz): δ = 7.57 (dd, J = 1.8, 7.3 Hz, 1H), 7.28 (dt, J = 1.8, 7.3 Hz, 1H), 6.98 (dt, J = 1.0, 7.3 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.05 (ddt, J = 5.5, 10.5, 17.0 Hz, 1H), 5.73 (d, J = 2.3 Hz, 1H), 5.45 (dq, J = 1.8, 17.0 Hz, 1H), 5.30 (dq, J = 1.4, 10.5 Hz, 1H), 4.58 (ddt, J = 1.4, 3.2, 5.0 Hz, 2H), 3.44 (s, 1H), 2.61 (d, J = 2.3, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ = 153.2, 133.0, 129.8, 128.7, 128.0, 121.2, 118.0, 112.3, 83.4, 74.2, 69.2, 60.9; IR (neat, cm\textsuperscript{-1}) = 3392, 3287, 3077, 2870, 2116, 1648, 1601, 1490, 1453; HRMS (CI): Calcd. For C\textsubscript{12}H\textsubscript{12}O\textsubscript{2} (m/z): 188.0837. Found 188.0829 [M\textsuperscript{+}].

2-(1-Hydroxy-3-trimethylsilyl-2-propynyl)-(2-propenyloxy)benzene (4)

Trimethylsilylethynylmagnesium chloride in dry THF was prepared by adding ethynyltrimethylsilane (3.33 g, 34.0 mmol) to 2.0 M solution of iso-propylmagnesium chloride (14.0 mL, 28.0 mmol) under N\textsubscript{2} at 0 °C and the mixture was stirred for 30 minutes before allowing to gradually warm up to room temperature and then stirred further for 10 minutes. To this thus prepared solution of trimethylsilylethynylmagnesium chloride was added a solution of 2 (3.00 g, 19.0 mmol) in dry THF (20 mL) under N\textsubscript{2} atmosphere at -78 °C and then stirred for 2.5 h at
-78 °C. The reaction was then allowed to warm up to room temperature and stirred overnight. The reaction was worked up according to the general procedure 3.1.2 to give 4 (4.97 g, 93%) as a brown oil. $^1$H NMR (300 MHz), $\delta = 7.56$ (dd, $J = 1.7, 7.6$ Hz, 1H), 7.27 (dt, $J = 1.7, 8.3$ Hz, 1H), 6.99 (dt, $J = 1.0, 7.2$ Hz, 1H), 6.89 (d, $J = 8.3$ Hz, 1H), 6.02 (ddt, $J = 4.8, 10.7, 17.2$ Hz, 1H), 5.71 (s, 1H), 5.46 (dq, $J = 1.7, 17.2$ Hz, 1H), 5.31 (dq, $J = 1.4, 10.7$ Hz, 1H), 4.58 (ddt, $J = 1.7, 3.5, 5.2$ Hz, 2H), 3.09 (s, 1H), 0.20 (s, 9H). $^{13}$C NMR (75 MHz), $\delta = 160.0, 132.9, 129.7, 129.0, 128.2, 121.2, 117.8, 112.3, 104.7, 90.9, 69.1, 61.9, -0.1; IR (neat, cm$^{-1}$) = 3403, 2960, 2173, 1601, 1490, 1455, 1249; HRMS (ESI): Calcd. for C$_{15}$H$_{20}$O$_2$Na ($m/z$): 283.1125. Found 283.1124 [M+Na]$^+$.  

2-(1-Hydroxy-3-phenyl-2-propynyl)-(2-propenyloxy)benzene (5)

```
\begin{center}
\includegraphics[width=0.2\textwidth]{structure.png}
\end{center}
```

1.0 M solution of phenylethynylmagnesium bromide (24.6 mL, 25.0 mmol) in THF was added at 0 °C to the solution of 2 (3.00 g, 19.0 mmol) in THF (20 mL) under N$_2$ atmosphere according to the general procedure above. The reaction was worked up according to the general procedure 3.1.2 to give 5 (2.04 g, 47%) as a brown oil. $^1$H NMR (500 MHz): $\delta = 7.64$ (dd, $J = 1.8, 7.8$ Hz, 1H), 7.47 (dd, $J = 2.3, 7.3$ Hz, 2H), 7.32 (m, 4H), 7.02 (dt, $J = 1.0, 7.3$ Hz, 1H), 6.93 (d, $J = 8.3$ Hz, 1H), 6.07 (ddt, $J = 5.0, 10.5, 17.4$ Hz, 1H), 5.96 (d, $J = 6.0$ Hz, 1H), 5.47 (dd, $J = 1.4, 17.4$ Hz, 1H), 5.32 (dq, $J = 1.4, 10.5$ Hz, 1H), 4.65 (ddt, $J = 1.8, 3.7, 5.0$ Hz, 2H), 3.25 (d, $J = 6.0$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 156.0, 133.0, 131.9, 129.7, 129.3, 128.5, 128.4, 128.2, 122.9, 121.2, 117.9, 112.3, 88.7, 86.0, 69.2, 62.0; IR (neat,
(cm$^{-1}$) = 3413, 3079, 2870, 2198, 1560, 1490; HRMS (ESI): Calcd. For C$_{18}$H$_{16}$O$_2$Na ($m/z$): 287.1043. Found 287.1038 [M+Na]$^+$.  

10-Hydroxy-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (8).

The Pauson-Khand cyclization was carried out according to the general procedures 3.1.3.2 and 3.1.3.3. The enyne 5 (200 mg, 0.76 mmol) was dissolved in 10 mL of the appropriate solvent and Co$_2$(CO)$_8$ (285 mg, 0.83 mmol) and NMO (975 mg, 8.30 mmol) were added following the general procedures. The crude product was purified by flash chromatography (silica gel, n-hexane/EtOAc, 90:10) to afford 8 (17.6 mg, 8% using procedure 3.1.3.2 and 70.0 mg, 31% using procedure 3.1.3.3) as a light yellow waxy solid. $^1$H NMR (500 MHz): $\delta$ = 7.57 (m, 4H), 7.09 (m, 5H), 5.59 (d, $J$ = 6.0 Hz, 1H), 4.68 (dd, $J$ = 5.5, 11.5 Hz, 1H), 3.99 (m, 1H), 3.67 (app.t, $J$ = 10.5 Hz, 1H), 2.97 (d, $J$ = 6.0 Hz, 1H), 2.75 (dd, $J$ = 7.0, 19.0 Hz, 1H), 2.09 (d, $J$ = 20.0 Hz, 1H); $^{13}$C NMR (125 MHz): $\delta$ = 205.5, 171.1, 159.8, 140.2, 132.1, 130.6, 130.5, 130.1, 129.4, 128.5, 128.5, 125.1, 123.0, 76.7, 72.3, 39.3, 37.1; IR (neat, cm$^{-1}$) = 3418, 3058, 2953, 1702, 1601, 1486, 1016; HRMS (ESI): Calcd. For C$_{19}$H$_{17}$O$_3$Na ($m/z$): 315.0991. Found 315.0988 [M+Na]$^+$. and Calcd. for C$_{38}$H$_{32}$O$_6$Na ($m/z$): 607.2091. Found 607.2089 [2M+Na]$^+$. Calcd. for C$_{19}$H$_{17}$O$_3$ ($m/z$): 293.1178. Found 293.1166 [M+H]$^+$.  

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2-(1-tert-Butyldimethylsilyloxy -3-phenyl-2-propynyl)-(2-propenyloxy)benzene (9)

Tert-Butyldimethylsilyl chloride (1.51 g, 1.00 mmol) was added at room temperature to a mixture of 5 (880 mg, 3.33 mmol) and imidazole (600 mg, 1.00 mmol) in DMF (10 mL). Then the mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of NaHCO₃ and extracted with Et₂O. The organic layer separated, washed with water, brine and dried with Na₂SO₄ (anhydrous). The organic layer was concentrated to give a dark colored liquid. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 19:1) to give 9 (1.21 g, 96%) as viscous brown liquid. ¹H NMR (500 MHz): δ = 7.76 (dd, J = 1.4, 7.3 Hz, 1H), 7.42 (dd, J = 2.3, 4.1 Hz, 2H), 7.29 (m, 4H), 7.02 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.07 (m, 2H), 5.48 (dq, J = 1.4, 17.4 Hz, 1H), 5.29 (dq, J = 1.4, 10.5 Hz, 1H), 4.63 (app. t, J = 4.6 Hz, 2H), 0.99 (s, 9H), 0.29 (s, 3H), 0.20 (s, 3H). ¹³C NMR (125 MHz): δ = 154.9, 133.5, 131.7, 130.7, 128.8, 128.3, 128.1, 127.6, 123.5, 121.0, 117.3, 111.8, 90.7, 84.2, 69.0, 59.9, 26.0, 18.5, -4.4, -4.7; IR (neat, cm⁻¹) = 3080, 2929, 2857, 2175, 1601, 1490; HRMS (ESI): Calcd. for C₂₄H₃₀O₂SiNa (m/z): 401.1907. Found 401.1902 [M+Na]⁺.
**10-tert-Butyldimethylsilyloxy-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-One (10).**

The Pauson-Khand cyclization was carried out according to the general procedures 3.1.3.2 and 3.1.3.3. The enyne 9 (200 mg, 0.53 mmol) was dissolved in 10 mL of appropriate solvent, Co$_2$(CO)$_8$ (200 mg, 0.58 mmol) and NMO (680 mg, 5.85 mmol) were added following the general procedures. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 10 (110 mg, 50%) using procedure C as a light brown waxy solid. Procedure B gave no cyclized product with only starting material being recovered.

$^1$H NMR (500 MHz): $\delta = 7.36$ (m, 3H), 7.26 (dt, $J = 1.8, 9.2$ Hz, 1H), 7.19 (dd, $J = 1.8, 7.3$ Hz, 1H), 7.10 (m, 2H), 7.08 (d, $J = 7.3$ Hz, 1H), 7.03 (d, $J = 7.8$ Hz, 1H), 5.63 (s, 1H), 4.71 (d, $J = 7.5$ Hz, 1H), 3.86 (m, 2H), 2.79 (dd, $J = 6.4, 18.8$ Hz, 1H), 2.27 (d, $J = 18.8$ Hz, 1H), 0.80 (s, 9H), -0.07 (s, 3H), -0.18 (s, 3H); $^{13}$C NMR (125 MHz): $\delta = 206.1, 172.3, 160.4, 139.0, 131.0, 130.9, 130.7, 130.1, 129.1, 128.4, 123.8, 122.5, 110.9, 72.6, 60.2, 40.2, 38.1, 25.8, 18.1, -4.6, -4.8; IR (neat, cm$^{-1}$) = 2954, 1711, 1486, 1251, 1068, 836; HRMS (ESI): Calcd. For C$_{25}$H$_{31}$O$_3$Si ($m/z$): 407.2037. Found 407.2030 [M+H]$^+$; and Calcd. For C$_{25}$H$_{30}$O$_3$SiNa ($m/z$): 429.1856. Found 429.1858 [M+Na]$^+$. 
3,5-Di-\textit{t}ert-butyl-2-(\textit{2}-propenyloxy)benzaldehyde (12)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {CHO};
\node at (1,0) {O};
\node at (2,0) {CHO};
\end{tikzpicture}
\end{center}

Allyl bromide (1.29 g, 11.0 mmol) was added to a suspension of K$_2$CO$_3$ (2.00 g, 14.4 mmol) and 3,5-di-\textit{t}ert-butyl-2-hydroxybenzaldehyde (2.50 g, 11.0 mmol) in DMF (50 mL) and stirred at room temperature for 12 h according to the general procedure 3.1.1. The crude product was purified by flash chromatography (hexane/EtOAc, 15:1) to give 12 as a light yellow oil (2.72 g, 93%). $^1$H NMR (500 MHz): $\delta = 10.29$ (s, 1H), 7.74 (d, $J = 2.8$ Hz, 1H), 7.65 (d, $J = 2.8$ Hz, 1H), 6.08 (dtt, $J = 4.6$, 11.0, 17.0 Hz, 1H), 5.51 (dq, $J = 1.8$, 17.0 Hz, 1H), 5.31 (dq, $J = 1.4$, 10.5 Hz, 1H), 4.47 (dt, $J = 1.4$, 5.0 Hz, 2H), 1.42 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 190.9$, 159.8, 146.5, 143.1, 140.3, 132.9, 130.9, 129.4, 123.9, 117.5, 79.4, 35.4, 31.4, 30.9; IR (neat, cm$^{-1}$): 2962, 2871, 1690, 1472, 1231, 928; HRMS (ESI): Calcd. for C$_{18}$H$_{26}$O$_2$ ($m/z$): Calcd. For C$_{18}$H$_{27}$O$_2$ ($m/z$): 275.2006. Found 275.1995 [M+H]$^+$. 

3,5-Di-\textit{t}ert-butyl-2-(\textit{2}-methyl-\textit{2}-propenyloxy)benzaldehyde (13)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {CHO};
\node at (1,0) {O};
\node at (2,0) {CHO};
\end{tikzpicture}
\end{center}

3-Chloro-2-methylpropene (1.16 g, 18.0 mmol) was added to a suspension of K$_2$CO$_3$ (2.00 g, 14.4 mmol) and 3,5-di-\textit{t}ert-butyl-2-hydroxybenzaldehyde (1.00 g, 4.26 mmol) in DMF (10 mL) and stirred for 12 h according to the general procedure 3.1.1. The crude product was purified by flash chromatography (hexane/EtOAc, 15:1) to give 13 (1.21 g, 98%) as a light yellow solid: mp. 49-51 $^\circ$C, $^1$H NMR (500 MHz): $\delta = 10.29$ (s, 1H), 7.74 (d, $J = 2.7$ Hz, 1H), 7.65 (d, $J = 2.7$ Hz, 1H), 5.55 (s, 1H), 5.35 (s, 1H), 4.36 (s, 2H), 1.85 (s,
3H), 1.42 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 191.2, 159.6, 146.5, 143.1, 140.4, 130.9, 129.4, 123.6, 110.2, 82.2, 35.4, 34.8, 31.4, 30.9, 19.6; IR (neat, cm$^{-1}$) = 2962, 2869, 1688, 1597, 1478, 993, 896; HRMS (CI): Calcd. For C$_{19}$H$_{28}$O$_2$ $^+$ ($m/z$): 288.2084. Found 288.2082 [M$^+$].

3,5-Di-tert-butyl-2-(3-methyl-2-propenyloxy) benzaldehyde (14)

Crotyl chloride (95% trans, 1.16 g, 18.0 mmol) was added to a suspension of K$_2$CO$_3$ (2.00 g, 14.4 mmol) and 3,5-di-tert-butyl-2-hydroxybenzaldehyde (1.00 g, 4.26 mmol) in DMF (10 mL) and stirred for 12 h according to the general procedure 3.1.1. The crude product was purified by flash chromatography (hexane/EtOAc, 15:1) to give 14 (1.22 g, 99%) as a brown oil. The proton NMR spectrum indicated that it was a 5:1 mixture of the E/Z-isomers. $^1$H NMR of the major isomer (500 MHz): $\delta = 10.29$ (s, 1H), 7.69 (d, $J = 2.7$ Hz, 1H), 7.58 (d, $J = 2.3$ Hz, 1H), 5.88 (m, 1H), 5.80 (m, 1H), 4.39 (dd, $J = 1.4, 6.0$ Hz, 2H), 1.78 (dd, $J = 1.4, 6.4$ Hz, 3H), 1.42 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 191.2, 160.0, 146.4, 143.1, 130.9, 130.7, 129.5, 126.0, 123.8, 79.7, 35.4, 34.8, 31.4, 31.0, 18.0; IR (neat, cm$^{-1}$) = 2958, 1690, 1593, 1460, 1374, 1220, 970; HRMS (ESI): Calcd. For C$_{19}$H$_{28}$NaO$_2$ $^+$ ($m/z$): 311.1981. Found 311.1951 [M+Na$^+$].
4,6-Di-tert-butyl-2-(1-hydroxy-3-trimethylsilyl-2-propynyl)-(-2-propenylxy)benzene (15a)

A solution of trimethylsilylethynylmagnesium chloride in dry THF was prepared by adding ethynyltrimethylsilane (2.47 g, 25.0 mmol) to 3.0 M solution of ethylmagnesium chloride (8.40 mL, 25.0 mmol.) in THF under N₂ at 0 °C and stirred for 30 minutes before allowing the reaction to warm up to room temperature and stirred for additional 10 minutes. To this thus prepared solution of trimethylsilylethynylmagnesium chloride, was added a solution of 12 (3.00 g, 11.0 mmol) in dry THF (20 mL) under N₂ atmosphere at -78 °C. The reaction mixture was stirred for 2.5 h at -78 °C before allowing to warm up to rt. The reaction was then stirred overnight and worked up according to the general procedure 3.1.2 to give 15a (3.05 g, 75%) as a light yellow solid, mp: 94-95 °C. ¹H NMR (500 MHz): δ = 7.61 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 2.3 Hz, 1H), 6.09 (ddt, J = 5.0, 10.5, 17.0 Hz, 1H), 5.73 (d, J = 5.5 Hz, 1H), 5.52 (dq, J = 1.4, 17.0 Hz, 1H), 5.28 (dq, J = 1.4, 10.5 Hz, 1H), 4.64 (ddt, J = 1.8, 5.0, 13.0 Hz, 1H), 4.43 (ddt, J = 1.8, 5.0, 13.0 Hz, 1H), 2.50 (d, J = 5.5 Hz, 1H), 1.41 (s, 9H), 1.30 (s, 9H), 0.19 (s, 9H); ¹³C NMR (125 MHz): δ = 153.4, 146.5, 142.3, 134.0, 133.9, 125.19, 124.1, 116.7, 106.0, 91.1, 76.1, 60.6, 35.6, 34.8, 31.5, 31.3, -0.09; IR (neat, cm⁻¹) = 3454, 2960, 2172; HRMS (ESI): Calcd. for C₂₃H₃₆O₂SiNa (m/z): 395.2377. Found 395.2373 [M+Na]⁺.
4,6-Di-tert-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)-2-propenyloxybenzene (15b)

1.0M solution of phenylethynylmagnesium bromide (15.0 mL, 15.0 mmol) was added at 0 °C to the solution of 12 (3.00 g, 11.0 mmol) in dry THF (20 mL) under N₂ atmosphere according to the general procedure 3.1.2 to give 15b (3.07 g, 75%) as a light yellow solid, mp 92-93 °C. ¹H NMR (500 MHz): δ = 7.69 (d, J = 2.8 Hz, 1H), 7.46 (m, 2H), 7.38 (d, J = 2.8 Hz, 1H), 7.30 (m, 3H), 6.13 (ddt, J = 4.6, 11.0, 17.0 Hz, 1H), 5.98 (s, 1H), 5.58 (dq, J = 1.8, 17.4 Hz, 1H), 5.32 (dq, J = 1.8, 10.5 Hz, 1H), 4.65 (ddt, J = 1.8, 4.6, 13.3 Hz, 1H), 4.50 (ddt, J = 1.8, 4.6, 13.3 Hz, 1H), 2.58 (d, J = 5.5 Hz, 1H), 1.44 (s, 9H), 1.34 (s, 9H); ¹³C NMR (125 MHz): δ = 171.3, 153.3, 146.6, 142.4, 134.4, 133.9 131.8, 128.4, 125.1, 123.9, 122.8, 116.8, 89.7, 86.1, 76.3, 60.6, 35.6, 34.8, 31.6, 31.3; IR (neat, cm⁻¹) = 3414, 2959, 2223, 1479, 1280; HRMS (ESI): Calcd. for C₂₆H₃₃O₂ (m/z): 377.2475. Found 377.2471 [M+H]⁺.

4,6-Di-tert-butyl-2-(1-hydroxy-2-propynyl)-(2-propenyloxy)benzene (15c)

0.5 M solution of ethynylmagnesium bromide (30.0 mL, 15.0 mmol) THF was added to a solution of 12 (2.72 g, 9.92 mmol) in dry THF (20 mL) under N₂ atmosphere at 0 °C according to the general procedure 3.1.2 to give 15c (2.75 g, 92%) as a light yellow solid, mp: 95-96 °C. ¹H NMR (500 MHz): δ = 7.58 (d, J = 2.8 Hz, 1H.), 7.36 (d, J = 2.3 Hz, 1H.), 6.10 (ddt, J = 4.6, 11.0, 17.0 Hz, 1H), 5.76 (d, J = 2.3, 1H), 5.55 (dq, J = 1.8, 17.0, 1H), 5.30 (dq, J = 1.4, 10.5, 1H), 4.59 (ddt, J = 1.8, 4.6, 13.3 Hz, 1H),
4.43 (ddt, $J = 1.8, 5.0, 13.3$ Hz, 1H), 2.62 (d, $J = 1.8$ Hz, 1H), 2.46 (s, 1H), 1.41 (s, 9H), 1.30 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 153.2, 146.7, 142.4, 133.8, 125.3, 123.6, 116.8, 84.6, 76.1, 74.3, 59.8, 35.6, 34.8, 31.6, 31.3$ (only 15 signals out of 16 carbon types were observed); IR (neat, cm$^{-1}$) = 3304, 2960, 2219, 1470, 1281, 989; HRMS (Cl): Calcd. for $C_{20}H_{28}O_2$ ($m/z$): 300.2089. Found 300.2091 [M]$^+$. 

4,6-Di-tert-butyl-2-(-1-hydroxy-3-phenyl-2-propynyl)-(2-methyl-2-propenyloxy)benzene (16b) 

A 1.0 M solution of phenylethynylmagnesium bromide (15.6 mL, 16.0 mmol.) in THF was added to a solution of 13 (3.00 g, 10.0 mmol.) in THF (20 mL) under N$_2$ atmosphere at 0 °C according to the general procedure 3.1.2 to give 16b (4.00 g, 98%) as a light yellow solid, mp: 49-51 °C. $^1$H NMR (500 MHz): $\delta = 7.71$ (d, $J = 2.7$ Hz, 1H), 7.45 (m, 2H), 7.37 (d, $J = 2.7$ Hz, 1H), 7.30 (m, 3H), 6.01 (s, 1H), 5.30 (s, 1H), 5.05 (s, 1H), 4.59 (d, $J = 13.1$ Hz, 1H), 4.41 (d, $J = 13.1$ Hz, 1H), 2.62 (s, 1H), 1.89 (s, 3H), 1.45 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 153.4, 146.6, 142.4, 141.5, 134.3, 131.8, 128.6, 128.4, 125.1, 123.9, 122.8, 111.4, 90.0, 86.1, 78.6, 60.5, 35.6, 34.9, 31.6, 31.3, 19.7; IR (neat, cm$^{-1}$) = 3452, 2963, 2908, 2224, 1658, 1599; HRMS (ESI): Calcd. for $C_{27}H_{34}O_2Na^+$ ($m/z$): 413.2451. Found 413.2442 [M+Na]$^+$; Calcd. for $C_{54}H_{68}O_4Na^+$ ($m/z$): 803.5015. Found 803.5058 [2M+Na]$^+$. 

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4,6-Di-tert-butyl-2-(1-hydroxy-3-trimethylsilyl-2-propynyl)-1-(2-butenyloxy)benzene (17a)

A solution of trimethylsilylethynylmagnesium chloride in dry THF was prepared by adding ethynyltrimethylsilane (2.47 g, 25.0 mmol) to 3.0 M solution of ethylmagnesiumchloride (8.27 mL, 25.0 mmol) THF under N₂ at 0 °C and stirred for 30 minutes before allowing the reaction to warm up to room temperature. The reaction was further stirred for 10 minutes at room temperature. To this aliquot of trimethylsilylethynylmagnesium chloride was added a solution of 14 (2.27 g, 7.87 mmol.) in THF (20 mL) under N₂ atmosphere at -78 °C and stirred for 2.5 h at -78 °C before allowing it to warm up to rt. This was then stirred overnight and then worked up according to the general procedure 3.1.2 to give 17a (3.00 g, 99%) as a light yellow waxy solid; ¹H NMR (500 MHz): δ = 7.54 (d, J = 2.7 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 5.84 (m, 1H), 5.75 (m, 1H), 5.68 (s, 1H), 4.47 (dd, J = 6.0, 11.5 Hz, 1H), 4.35 (dd, J = 6.0, 11.5 Hz, 1H), 1.71 (d, J = 6.4 Hz, 3H), 1.34 (s, 9H), 1.25 (s, 9H), 0.12 (s, 9H); ¹³C NMR (125 MHz): δ = 153.5, 146.3, 142.2, 134.1, 129.6, 126.8, 125.1, 124.0, 106.0, 90.9, 76.2, 60.8, 35.5, 34.7, 31.5, 31.3, 18.0, -0.1; IR (neat, cm⁻¹) = 3361, 2960, 2172, 1462; HRMS (ESI): Calcd. For C₄₈H₇₆O₄Si₂Na⁺ (m/z): 795.5178. Found 795.5212 [2M+Na]⁺.
4,6-Di-tert-butyl-2-(-1-hydroxy-3-phenyl-2-propynyl)-(2-butenyloxy)benzene (17b)

A 1.0 M solution in THF of phenylethynylmagnesium bromide (15.6 mL, 16.0 mmol) was added to the solution of 14 (3.0 g, 10.0 mmol) in dry THF (20 mL) under N₂ atmosphere at 0 °C according to the general procedure 3.1.2 to give 17b (3.00 g, 74%) as a light yellow liquid; ¹H NMR (500 MHz): δ = 7.75 (d, J = 2.3 Hz, 1H), 7.49 (m, 2H), 7.44 (d, J = 2.7 Hz, 1H), 7.32 (m, 3H), 6.03 (d, J = 4.0 Hz, 1H), 5.98 (m, 1H), 5.88 (m, 1H), 4.59 (dd, J = 6.0, 7.3 Hz, 1H), 4.44 (dd, J = 6.0, 7.3 Hz, 1H), 2.85 (d, J = 5.0 Hz, 1H), 1.80 (d, J = 5.5 Hz, 3H), 1.44 (s, 9H), 1.37 (s, 9H); ¹³C NMR (125 MHz): δ = 153.4, 146.5, 142.4, 134.4, 131.8, 129.8, 128.5, 128.4, 126.9, 125.2, 123.8, 122.8, 89.9, 86.1, 76.4, 60.8, 35.6, 34.8, 31.6, 31.4, 18.0; IR (neat, cm⁻¹) = 3357, 2955, 2179, 1463, 1374, 1223; HRMS (ESI): Calcd. for C₂₇H₃₄O₂Na (m/z): 413.2451. Found 413.2461 [M+Na]⁺.

4,6-Di-tert-butyl-2-(-1-hydroxy-2-propynyl)-1-(2-butenyloxy)benzene (17c)

A 0.5 M solution in THF of ethynylmagnesium bromide (12.7 mL, 6.35 mmol.) was added at 0 °C to the solution of 14 (1.22 g, 4.23 mmol.) in dry THF (10 mL) under N₂ atmosphere according to the general procedure 3.1.2 to give 17c as a viscous brown liquid (1.32 g, 99%). ¹H NMR (300 MHz): δ = 7.56 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 2.7 Hz, 1H), 5.91 (q, J = 6.2 Hz, 1H), 5.81 (dt, J = 1.0, 5.5 Hz, 1H), 5.77 (d, J = 2.1 Hz, 1H), 4.51 (ddt, J = 1.0, 5.5, 11.7 Hz, 1H), 4.34 (ddt, J = 1.0, 5.5,
5.9, 11.7 Hz, 1H), 2.61 (d, \( J = 2.4 \) Hz, 1H), 1.78 (d, \( J = 5.2 \) Hz, 3H), 1.40 (s, 9H), 1.32 (s, 9H); \(^{13}\text{C}\) NMR (75 MHz): \( \delta = 153.3, 146.6, 142.4, 133.7, 129.8, 126.7, 125.3, 123.5, 84.4, 76.3, 74.2, 60.1, 35.6, 34.8, 31.5, 31.3, 18.0 \); IR (neat, cm\(^{-1}\)) = 3298, 2958, 2103, 1602, 1277; HRMS (ESI): Calcd. for \( \text{C}_{42}\text{H}_{60}\text{O}_{4}\text{Na}^+ (m/z): 651.4384 \). Found 651.4334 [2M+Na]\(^+\).

**4,6-Di-tert-butyl-2-iodophenol (19)\(^{80,87}\)**

![Structure of 4,6-Di-tert-butyl-2-iodophenol (19)](image)

To a stirred solution of 2,4-di-tert-butylphenol (0.50 g, 2.4 mmol) in DMF (80 mL), a dropwise addition of N-iodosuccinimide (0.66 g, 3.0 mmol) in acetone (20 mL) was done. The reaction mixture was stirred at 0 °C for 8 h. H\(_2\)O (50 mL) was added and the resulting solution was extracted with EtOAc (3x25 mL). The organic phase was combined and treated with 0.1 M HCl (50 mL), washed with saturated NaHCO\(_3\) (50 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. The crude product was purified via flash chromatography (SiO\(_2\), hexane) to afford the **19** (0.55 g, 68%) as a solid: mp: 76-78 °C (lit.\(^{69,76} 77-79 °C\); \(^1\text{H}\) NMR (500 MHz): \( \delta = 7.48 \) (d, \( J = 2.3 \) Hz, 1H), 7.25 (d, \( J = 2.3 \) Hz, 1H), 5.36 (s, 1H), 1.37 (s, 9H), 1.26 (s, 9H); \(^{13}\text{C}\) NMR (125 MHz): \( \delta = 150.5, 145.1, 136.3, 132.7, 125.1, 89.4, 35.7, 34.3, 31.6, 29.4 \).
1,5-Di-tert-butyl-3-iodo-2-(3-phenyl-2-propenyloxy)benzene (E-isomer, 20)

A solution of diethyl azodicarboxylate (15.7 g, 90.4 mmol) in dry THF (50 mL) was added dropwise to a solution of iodophenol 19 (10.0 g, 30.1 mmol), cinnamyl alcohol (8.08 g, 60.2 mmol) and PPh₃ (23.7 g, 90.4 mmol) in dry THF (100 mL) at 0 °C and stirred for 3 h. The solvent was removed in vacuo at the end of the reaction. The crude product was purified by flash chromatography (hexane) to give the product 20 (12.4 g, 92.0 %) as a white solid, mp: 120-122 °C; ¹H NMR (300 MHz): δ = (E-isomer) 7.69 (d, J = 2.41 Hz, 1H), 7.26-7.50 (m, 6H), 6.82 (d, J = 15.8 Hz, 1H), 6.50 (dt, J = 5.5, 16.2 Hz, 1H), 4.69 (d, J = 5.5 Hz, 2H), 1.43 (s, 9H), 1.31 (s, 9H); ¹³C NMR (75 MHz): δ = 155.1, 148.2, 143.9, 136.9, 135.4, 132.6, 128.7, 127.9, 126.7, 125.3, 124.9, 93.4, 73.9, 34.5, 34.0, 31.5, 31.3; IR (neat, cm⁻¹) = 3100, 2960, 2872, 1772, 1434, 1394, 1234, 1087, 963; HRMS (CI): Calcd. for C₂₃H₂₉IO (m/z): 448.1257. Found 448.1218 [M⁺].

3,5-Di-tert-butyl-2-(3-phenyl-2-propenyloxy)benzaldehyde (21)

A solution of 1,5-di-tert-butyl-3-iodo-2-(3-phenyl-2-propenyloxy)benzene 20 (5.00 g, 11.2 mmol) in dry THF (20 mL) was cooled to -30 °C and 2.0 M solution of i-propylmagnesium chloride (1.38 g, 13.5 mmol) in THF was added and the reaction mixture stirred for 20 minutes at -30 °C. The reaction was then allowed to warm up to room temperature and stirred for 20 min. Next the reaction mixture was cooled to 0 °C and DMF (1.30 mL, 16.7 mmol) was added dropwise. The reaction was warmed up to
room temperature and stirred for 2 h. The reaction was quenched with water and extracted with CH$_2$Cl$_2$. The organic layer was separated, concentrated under reduced pressure and dried (MgSO$_4$). The crude product was purified by flash chromatography (SiO$_2$, hexane/EtOAc, 5:1) to give 21 (4.51 g, 98%) as white solid, mp: 123-125 °C; $^1$H NMR (300 MHz): $\delta$ = (E-isomer) 10.37 (s, 1H), 7.73 (d, $J = 2.4$ Hz, 1H), 7.65 (d, $J = 2.4$ Hz, 1H), 7.26-7.47 (m, 5H), 6.80 (d, $J = 15.8$ Hz, 1H), 6.50 (dt, $J = 5.5$, 16.2 Hz, 1H), 4.64 (d, $J = 5.9$ Hz, 2H), 1.46 (s, 9H), 1.33 (s, 9H); $^{13}$C NMR (75 MHz); $\delta$ = 191.0, 159.8, 146.6, 143.2, 136.4, 133.0, 131.0, 129.4, 128.8, 128.1, 126.8, 124.1, 124.0, 79.4, 35.5, 34.8, 31.4, 31.0; IR (neat, cm$^{-1}$) = 3049, 2920, 2150, 1667, 1592, 1485, 1362, 1231, 915, 755, 687; HRMS (ESI): Calcd. for C$_{24}$H$_{31}$O$_2$ (m/z): 351.2319. Found 351.2325 [M+H]$^+$.

4,6-Di-tert-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)-1-(-3-phenyl-2-propenyloxy) benzene (22b)

1.0 M solution of phenylethynylmagnesium bromide (8.59 mL, 8.59 mmol) in THF was added at 0 °C to a solution of 21 (2.00 g, 5.71 mmol) in dry THF (20 mL) under N$_2$ atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched with NH$_4$Cl and extracted with CH$_2$Cl$_2$. The organic extract was washed with water, dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO$_2$, hexane/EtOAc, 10:1) to give 22b (2.0 g, 78%) as a white solid. Mp: 133-134 °C; $^1$H
**4,6-Di-tert-butyl-2-(1-hydroxy-2-propynyl)-1-(3-phenyl-2-propenyloxy) benzene (22c)**

A 0.5 M solution of ethynylmagnesium bromide (17.2 mL, 8.61 mmol) in THF was added at 0 °C to the solution of 21 (2.00 g, 5.71 mmol) in dry THF (20 mL) under N₂ atmosphere. The reaction mixture was allowed to warm up to rt and stirred for 3 h. The reaction was quenched with NH₄Cl and extracted with CH₂Cl₂. The organic extract was washed with water, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 10:1) to give 22c (3.11 g, 99%) as a yellow solid, mp: 136-138 °C; ¹H NMR (300 MHz): δ = 7.26-7.61 (m, 7H), 6.81 (d, J = 15.6 Hz, 1H), 6.46 (dt, J = 5.4, 16.2 Hz, 1H), 5.84 (s, 1H), 4.74 (ddd, J = 1.5, 5.7, 13.2 Hz, 1H), 4.58 (ddd, J = 1.5, 5.7, 13.2 Hz, 1H), 2.64 (d, J = 1.2 Hz, 1H), 2.52 (s, 1H), 1.44 (s, 9H), 1.34 (s, 9H); ¹³C NMR (75 MHz): δ = 153.3, 146.8, 142.4, 136.7, 133.8, 132.2, 128.7, 127.9, 126.7, 125.0, 123.6, 84.5, 76.1, 74.4,
59.9, 35.7, 34.9, 31.6, 31.4; IR (neat, cm\(^{-1}\)) = 3550, 3279, 2962, 2159, 1476, 1362, 1230, 1159, 1118, 1021, 965, 884, 748; HRMS (ESI) Calcd. for C\(_{26}\)H\(_{36}\)O\(_2\)Na\(^+\) (\(m/z\)):

**4,6-Di-tert-butyl-2-(3-trimethylsilyl-2-propynyl)-(2-propenyloxy) benzene (26a)**

Triethylsilane (1.24 g, 10.7 mmol) was added at room temperature to a solution of 15a (1.98 g, 5.30 mmol) in CH\(_2\)Cl\(_2\) (10 mL) under N\(_2\) atmosphere. Then trifluoroacetic acid (2.43 g, 21.3 mmol) was added and the reaction was stirred for 20 minutes. The reaction mixture was quenched with aqueous NaHCO\(_3\) and extracted with dichloromethane (2 x 10mL) to give a yellow liquid after removal of the solvent. The crude product purified by flash chromatography (hexane/EtOAc, 95:5) to give 26a as a light yellow liquid (1.87 g, 99.0%). \(^1\)H NMR (500 MHz): \(\delta\) = 7.47 (d, \(J = 2.5\) Hz, 1H), 7.25 (d, \(J = 2.5\) Hz, 1H), 6.05 (ddt, \(J = 5.0, 10.5, 17.0\) Hz, 1H), 5.49 (dq, \(J = 1.8, 17.0\) Hz, 1H), 5.26 (dq, \(J = 1.8, 10.5\) Hz, 1H), 4.35 (dt, \(J = 1.8, 5.0\) Hz, 2H), 3.64 (s, 2H), 1.39 (s, 9H), 1.32 (s, 9H), 0.18 (s, 9H); \(^{13}\)C NMR (75 MHz): \(\delta\) = 153.6, 145.9, 141.9, 133.9, 129.5, 125.4, 123.1, 116.5, 105.5, 86.8. 73.9, 35.5, 34.8, 31.6, 31.3, 21.4, 0.2; IR (neat, cm\(^{-1}\)) = 2960, 2874, 2177; HRMS (ESI): Calcd. For C\(_{23}\)H\(_{37}\)OSi (\(m/z\)):
357.2608. Found 357.2618 [M+H]\(^+\).
4,6-Di-tert-butyl-2-(-3-phenyl-2-propynyl)-2-propenyloxybenzene (26b)

Triethylsilane (1.24 g, 10.7 mmol) was added at room temperature to a solution of 15b (2.0 g, 5.3 mmol) in CH₂Cl₂ (10 mL) under N₂ atmosphere. Then trifluoroacetic acid (2.43 g, 21.3 mmol) was added and stirred for 20 minutes. The reaction mixture was quenched with aqueous NaHCO₃ and extracted with CH₂Cl₂ (2 x 10mL) to give a yellow liquid. The crude product was purified by flash chromatography (hexane/EtOAc, 95:5) to give 26b as a light yellow liquid (1.87 g, 98%). ¹H NMR (500 MHz): δ = 7.52 (d, J = 2.5 Hz, 1H), 7.44 (m, 2H), 7.30 (d, J = 2.5 Hz, 1H), 7.29 (d, J = 3.0 Hz, 3H), 6.11 (ddt, J = 4.6, 11.0, 17.0 Hz, 1H), 5.55 (dq, J = 1.8, 17.4 Hz, 1H), 5.32 (dq, J = 1.8, 10.5 Hz, 1H), 4.46 (dt, J = 1.8, 4.6 Hz, 2H), 3.83 (d, J = 5.0 Hz, 2H), 1.46 (s, 9H), 1.38 (s, 9H); ¹³C NMR (125 MHz): δ = 153.6, 146.1, 142.0, 134.0, 131.7, 129.9, 128.3, 127.8, 125.5, 124.0, 123.2, 116.5, 88.7, 82.1, 74.1, 35.5, 34.7, 31.6, 31.3, 20.9; IR (neat, cm⁻¹) = 2959, 2870, 1451, 1225, 991, 755; HRMS (ESI): Calcd. For C₂₆H₃₃O (m/z): 361.2526. Found 361.2538 [M+H]⁺, Calcd. For C₂₆H₃₂ONa (m/z): 383.2345. Found 383.2360 [M+Na]⁺.

4,6-Di-tert-butyl-2-prop-2-ynyl-(2-propenyloxy)benzene (26c)

Triethylsilane (1.24 g, 10.7 mmol) was added at room temperature to the solution of 15c (1.60 g, 5.30 mmol) in CH₂Cl₂ (10 mL) under N₂ atmosphere. Then trifluoroacetic acid (2.43 g, 21.3 mmol) was added and stirred for 20 minutes. The reaction mixture was quenched.
with aqueous NaHCO₃ and then extracted with CH₂Cl₂ (2 x 10mL) to give a yellow liquid. The crude product was purified by flash chromatography (hexane/EtOAc 95:5) to give 26c as a light yellow liquid (1.45 g, 96%). ¹H NMR (500 MHz, CDCl₃): δ = 7.39 (d, J = 2.8 Hz, 1H), 7.25 (d, J = 2.8 Hz, 1H), 6.07 (ddt, J = 5.0, 10.5, 17.0 Hz, 1H), 5.51 (dq, J = 1.8, 17.0 Hz, 1H), 5.29 (dq, J = 1.8, 10.5 Hz, 1H), 4.38 (dt, J = 1.4, 5.0 Hz, 2H), 3.58 (d, J = 2.3 Hz, 2H), 2.12 (t, J = 2.8 Hz, 1H), 1.39 (s, 9H), 1.32 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ = 148.9, 142.0, 133.5, 128.9, 125.0, 122.9, 116.6, 83.0, 73.9, 69.7, 35.5, 34.6, 31.6, 31.3, 6.7, 5.9; IR (neat, cm⁻¹) = 3312, 2959, 2872, 2176, 1715, 1507; HRMS (CI): Calcd. For C₂₀H₂₈O⁺ (m/z): 284.2135. Found 284.2132 [M⁺].

6,8-Di-tert-butyl-1-trimethylsilyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (23)

The Pauson-Khand cyclization was carried out according to the general procedures 3.1.3.2 and 3.1.3.3. The enyne 26a (124 mg, 0.35 mmol) was dissolved in 10 mL of the appropriate solvent. Co₂(CO)₈ (200 mg, 0.590 mmol) and NMO (408 mg, 3.48 mmol) were added according to the general procedure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 90:10) to afford 23 (75.0 mg, 56% using procedure 3.1.3.2 and 60.0 mg, 45% using procedure 3.1.3.3) as a yellow solid.

Method II: The cyclization of 15a (500 mg, 1.34 mmol) in 10 mL CH₂Cl₂ was carried out following the general procedures 3.1.3.1. Co₂(CO)₈ (506 mg, 1.47 mmol) was added
under N₂ and stirred at room temperature for 5 h. The reaction mixture was then cooled in an ice bath before adding NaBH₄ (153 mg, 4.03 mmol). Subsequently, TFA (15 mL) was added over 10 minutes at 0 °C. The reaction mixture was decanted into 300 mL of iced water and the organic layer was separated, washed with water and dried (Na₂SO₄). The organic layer was concentrated, redissolved in CH₂Cl₂ (10mL) and cooled to 0 °C before NMO (2.08 g, 17.8 mmol) was added in three portions and then left to stir for 2 h. The reaction mixture was then poured into a sintered glass funnel with Celite and SiO₂ pad and washed with EtOAc to remove any remaining product. The filtrates were combined and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 20:1.5) to afford 23 (240 mg, 48%) as a yellow solid. Mp: 89-91 °C; 

°C: 1H NMR (500 MHz): δ = 7.24 (s, 1H), 7.10 (s, 1H), 4.54 (dd, J = 5.3, 5.6 Hz, 1H), 3.91 (s, 2H), 3.41 (m, 1H), 3.24 (t, J = 11.4 Hz, 1H), 2.52 (dd, J = 7.1, 18.8 Hz, 1H), 1.82 (dd, J = 1.6, 18.8 Hz, 1H), 1.38 (s, 9H), 1.30 (s, 9H), 0.31 (s, 9H); 13C NMR (125 MHz): δ = 211.8, 184.9, 156.5, 146.3, 141.6, 139.2, 129.6, 125.2, 123.0, 76.0, 47.5, 38.4, 38.2, 35.2, 34.6, 31.6, 30.7, -0.03; IR (neat, cm⁻¹) = 2958.3, 1693.5, 1587.2, 1249.7; HRMS (ESI): Calcd. for C₂₄H₃₆O₂SiNa (M+Na): 407.2377. Found 407.2376, Calcd. for C₂₄H₃₆O₂SiK (M+K): 423.2116. Found 423.2108, Calcd. for C₄₈H₇₂O₄Si₂Na (2M+Na): 791.4861. Found 791.4884.
6.8-Di-tert-butyl-1-phenyl-4,4a-dihydro-3\textit{H},10\textit{H}-5-oxabenzo[\textit{f}]azulen-2-one (24)

The Pauson-Khand cyclization was carried out according to the general procedures 3.1.3.2 and 3.1.3.3. The enyne 26b (130 mg, 0.36 mmol) was dissolved in 10 mL of the appropriate solvent. Co$_2$(CO)$_8$ (136 mg, 0.40 mmol) and NMO (460 mg, 3.93 mmol) were added according to the general procedure. The crude product was purified by flash chromatography (silica gel, \textit{n}-hexane/EtOAc, 90:10) to afford 24 (60 mg, 43% using procedure 3.1.3.2 and 64 mg, 46% using procedure C) as a yellow solid.

Method II: The cyclization of 15b (290 mg, 0.77 mmol) in 10 mL CH$_2$Cl$_2$ was carried out following the general procedures 3.1.3.1. Co$_2$(CO)$_8$ (136 mg, 0.40 mmol) was added under N$_2$ and stirred at room temperature for 5 h. The reaction mixture was then cooled in an ice bath before adding NaBH$_4$ (88.0 mg, 2.31 mmol). Subsequently, TFA (10 mL) was added over 10 minutes at 0°C. The reaction mixture was decanted into 300 mL of iced water and the organic layer was separated, washed with water and dried (Na$_2$SO$_4$). The organic layer was then concentrated, redissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0°C before NMO (1.22 g, 10.4 mmol) was added in three portions and then left to stir for 2 h. The reaction mixture was then poured into a sintered glass funnel with Celite and SiO$_2$ pad and washed with EtOAc to remove any remaining product. The filtrates were combined and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 20:1.5) to afford 24 (150 mg, 50%) as a yellow solid.

Mp: 160-162 °C; $^1$H NMR (500 MHz): $\delta$ = 7.46 (t, \textit{J} = 7.8 Hz, 2H). 7.40 (d, \textit{J} = 2.8 Hz,
1H), 7.34 (d, J = 2.8 Hz, 2H), 7.30 (s, 1H), 7.14 (s, 1H), 4.67 (dd, J = 5.5, 11.5 Hz, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.76 (d, J = 12.8 Hz, 1H), 3.54 (m, 1H), 3.35 (t, J = 11.5 Hz, 1H), 2.75 (dd, J = 7.1, 18.9 Hz, 1H), 2.03 (dd, J = 2.8, 18.8 Hz, 1H), 1.41 (s, 9H), 1.35 (s, 9H); \(^{13}\text{C NMR}\) (125 MHz): \(\delta = 205.5, 172.0, 156.8, 146.7, 141.9, 139.7, 131.3, 129.7, 129.6, 128.3, 125.3, 123.0, 76.2, 44.1, 36.9, 36.7, 35.2, 34.7, 31.6, 30.7; \) IR (neat, cm\(^{-1}\)) = 2958, 1705, 1474, 758; HRMS (ESI): Calcd. for C\(_{27}\)H\(_{32}\)O\(_2\)Na (\(m/z\)): 411.2295. Found 411.2266, Calcd. For C\(_{54}\)H\(_{64}\)O\(_4\)Na (2M+Na): 799.4697. Found 799.4698.

**Cyclization 4,6-Di-tert-butyl-2-(1-hydroxy-3-trimethylsilyl-2-propynyl)-(2-propenyloxy)benzene (15a)**

The Pauson-Khand cyclization of the enyne 15a (102 mg, 0.27 mmol) in 10 mL of the appropriate solvent, was carried out following the general procedures 3.1.3.2 and 3.1.3.3. Co\(_2\)(CO)\(_8\) (103 mg, 0.30 mmol) and NMO (230 mg, 2.74 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO\(_2\). The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford the reduced PK product 23 (21.0 mg, 20%) and the expected PK product 28 (78.0 mg, 70% as a 1:2 mixture of 28 epimers) using the oxidative procedure 3.1.3.2. On the other hand, when the enyne was heated to reflux for 1 day in CH\(_2\)Cl\(_2\) under the thermal procedure 3.1.3.3, it gave the exo- product of 28 (3.3 mg, 3%). However, when enyne 15a was subjected to
procedure 3.1.3.3 conditions at using toluene as the solvent and heated to 70 °C, the yield of the exo- product of 28 (64.0 mg, 58%) was improved.

6,8-Di-tert-butyl-10-hydroxy-1-trimethylsilyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (28)

A light yellow solid, mp: 110-112 °C; 1H NMR (500 MHz):
\[ \delta = 7.32 \text{ (d, } J = 2.3 \text{ Hz, 1H)}, \ 7.17 \text{ (d, } J = 2.3 \text{ Hz, 1H)}, \ 5.68 (d, J = 9.2 \text{ Hz, 1H)}, \ 4.58 (dd, J = 6.0, 11.5 \text{ Hz, 1H)}, \ 3.96 (m, 1H), \ 3.37 (t, J = 11.5 \text{ Hz, 1H)}, \ 3.25 (d, J = 9.2 \text{ Hz, 1H)}, \ 2.55 (dd, J = 7.3, 18.8 \text{ Hz, 1H)}, \ 1.82 (dd, J = 2.8, 18.3 \text{ Hz, 1H)}, 1.37 (s, 9H) 1.30 (s, 9H), 0.29 (s, 9H); \]
13C NMR (125 MHz): \[ \delta = 211.4, 185.1, 155.9, 147.1, 142.5, 140.0, 132.9, 125.0, 124.9, 77.6, 75.0, 41.8, 37.7, 35.3, 34.9, 31.5, 30.7, -0.12; \]
IR (neat, cm\(^{-1}\)) = 3396, 2958, 1710, 1606, 1471, 1367, 1236, 1013; HRMS (ESI): Calcd. for C\(_{24}\)H\(_{37}\)O\(_3\)Si (m/z): 401.2506. Found 401.2500 [M+H]\(^+\);

Cyclization of 4,6-Di-tert-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)-2-propenyloxy benzene (15b)

The Pauson-Khand cyclization of the enyne 15b (250 mg, 0.67 mmol) in 10 mL of the appropriate solvent, was carried out following the general procedures 3.1.3.2 and 3.1.3.3. Co\(_2(CO)\)_8 (250 mg, 0.73 mmol) and NMO (1.22 g, 10.4 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO\(_2\). The crude product was
purified by flash chromatography (silica gel, hexane/EtOAc, 90:10) to afford the reduced PK product 24 (142 mg, 55%) and the expected PK product 29 (70 mg, 26% as a 1:1 mixture of 29 epimers) using the oxidative procedure 3.1.3.2. On the other hand, when the enyne was heated to reflux for 3 days in CH₂Cl₂ under the thermal procedure 3.1.3.3, it gave the reduced PK product 24 (21 mg, 8%) and the exo-product of 29 (193 mg, 75%). However, when procedure 3.1.3.3 was carried out at the same temperature but using toluene as the solvent instead, the reaction only gave the exo-product of 29 (255 mg, 99%).

6,8-Di-tert-butyl-10-hydroxy-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzof[f] azulen-2-one (29)

A light yellow solid, mp: 171-173 °C; ¹H NMR (500 MHz):

δ = 7.46 (m, 3H), 7.35 (d, J = 2.8 Hz, 1H), 7.23 (m, 2H), 7.14 (d, J = 2.8 Hz, 1H), 5.49 (d, J = 9.2 Hz, 1H), 4.61 (dd, J = 5.7, 11.5 Hz, 1H), 4.09 (m, 1H), 3.51 (t, J = 11.9 Hz, 1H), 3.15 (d, J = 8.7 Hz, 1H), 2.76 (dd, J = 6.9, 19.3 Hz, 1H), 2.03 (dd, J = 2.8, 18.8 Hz, 1H), 1.40 (s, 9H), 1.32 (s, 9H); ¹³C NMR (125 MHz); δ = 205.3, 172.3, 156.3, 147.3, 142.8, 139.6, 133.0, 130.7, 129.6, 128.5, 128.3, 125.1, 125.0, 77.9, 73.7, 38.8, 36.7, 35.3, 34.7, 31.5, 30.7; IR (neat, cm⁻¹) = 3435, 2959, 1702, 1598, 756; HRMS (ESI): Calcd. for C₂₇H₃₅O₃ (m/z): 405.2424. Found 405.2425 [M+H]+;
4,6-Di-tert-butyl-2-((1-tert-butyl-dimethylsilyloxy-3-phenyl-2-propynyl)-(2-propenyloxy)benzene (30)

*tert*-Butyldimethylsilyl chloride (0.410 g, 2.71 mmol) was added at room temperature to a mixture of 15b (0.340 g, 0.900 mmol) and imidazole (0.300 g, 2.71 mmol) in DMF (10 mL). The mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of aqueous NaHCO₃ and extracted with Et₂O. The organic layer was separated, washed with water and brine, dried with Na₂SO₄ (anhydrous). The organic layer was concentrated to give a dark colored liquid. The crude product was purified by flash chromatography (hexane/EtOAc; 19:1) to give 30 as viscous brown liquid (0.420 g, 95%).

**1H NMR (500 MHz):** δ = 7.65 (d, J = 2.5 Hz, 1H), 7.41 (d, J = 2.5 Hz, 1H), 7.40 (d, J = 4.0 Hz, 1H), 7.27-7.30 (m, 4H), 6.09 (ddt, J = 4.6, 10.5, 17.4 Hz, 1H), 5.93 (s, 1H), 5.56 (dq, J = 1.8, 17.0 Hz, 1H), 5.29 (dq, J = 1.8, 10.5 Hz, 1H), 4.56 (ddt, J = 1.8, 4.6, 13.8 Hz, 1H), 4.50 (ddt, J = 1.8, 4.1, 13.8 Hz, 1H), 1.42 (s, 9H), 1.33 (s, 9H), 0.86 (s, 9H), 0.14 (s, 3H), 0.02 (s, 3H);

**13C NMR (75 MHz):** δ = 152.5, 146.2, 141.5, 135.8, 134.0, 131.7, 128.3, 124.5, 123.9, 123.3, 116.5, 91.4, 84.7, 75.8, 60.1, 35.5, 34.8, 31.6, 31.2, 25.9, 18.4, -4.4, -4.8 (only 23 signals were observed out of 24 carbon types); IR (neat, cm⁻¹) = 2959, 2864, 1600, 1362, 1063; HRMS (CI): Calcd. for C₃₂H₄₆O₂Si (m/z): 490.3262. Found 490.3277 [M⁺].
4,6-Di-tert-butyl-2-(-1-tert-butyl-dimethylsilyloxy-3-trimethylsilyl-2-propynyl)(-2-propenyloxy)benzene (31)

_tert_-Butyldimethylsilyl chloride (0.500 g, 3.31 mmol) was added at room temperature to a mixture of 15a (0.410 g, 1.10 mmol) and imidazole (0.440 g, 3.31 mmol) in DMF (10 mL). Then the mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of aqueous NaHCO3 and extracted with Et2O. The organic layer was separated, washed with water and brine and dried (Na2SO4). The organic layer was concentrated to give a dark liquid. The crude was purified by flash chromatography (hexane/EtOAc; 19:1) to give 31 as a viscous brown oil (0.510 g, 95%). 

\[ \delta = 7.57 (d, J = 2.3 \text{ Hz}, 1H), 7.28 (d, J = 2.3 \text{ Hz}, 1H), 6.05 \text{ (ddt, } J = 4.6, 10.5, 17.4 \text{ Hz}, 1H), 5.70 \text{ (s, } 1H), 5.51 \text{ (dq, } J = 1.8, 17.4 \text{ Hz}, 1H), 5.29 \text{ (dq, } J = 1.8, 10.5 \text{ Hz}, 1H), 4.48 \text{ (dt, } J = 1.4, 5.0 \text{ Hz}, 2H), 1.39 \text{ (s, } 9H), 1.32 \text{ (s, } 9H), 0.83 \text{ (s, } 9H), 0.15 \text{ (s, } 9H), 0.10 \text{ (s, } 3H), 0.07 \text{ (s, } 3H); \]

\[ \delta = 152.7, 146.0, 141.4, 135.6, 134.1, 124.7, 123.9, 116.0, 107.7, 85.9, 75.7, 60.2, 35.5, 34.8, 31.6, 31.2, 25.9, 18.4, -0.1, -4.4, -4.7; \]

IR (neat, cm\(^{-1}\)) = 2960, 2173, 1470, 1250, 1070; HRMS (Cl): Calcd. for C\(_{29}\)H\(_{50}\)O\(_2\)Si\(_2\) (m/z): 486.3344. Found 486.3355 [M\(^+\)].

Cyclization of 4,6-di-tert-butyl-2-(-1-tert-butyl-dimethylsilyloxy-3-phenyl-2-propynyl)(-2-propenyloxy)benzene (30)

The Pauson-Khand cyclization of the enyne 30 (101 mg, 0.21 mmol) in 10 mL of the appropriate solvent, was carried out following the general procedures 3.1.3.2 and
3.1.3.3. \( \text{Co}_2(\text{CO})_8 \) (141 mg, 0.41 mmol) and NMO (529 mg, 4.52 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel with a short layer of Celite and SiO\(_2\) pad. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford the reduced PK product 24 (11.2 mg, 11%) and the PK product 32 (62.9 mg, 60% as a 1:5 mixture of 32 epimers) using the oxidative procedure 3.1.3.2. On the other hand, when the enyne was heated to 70 °C for 1 day in toluene under the thermal procedure 3.1.3.3, only the PK product of 32 (101 mg, 95% in a 1:10 ratio of epimers) was isolated. The isomers were separated by preparatory thin layer chromatography.

6,8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (32, exo product)

Yellow oil, \(^1\text{H} NMR\) (500 MHz): \(\delta = 7.39\) (m, 3H), 7.31 (d, \(J = 2.3\) Hz, 1H), 7.21 (dd, \(J = 1.8, 7.8\) Hz, 2H), 7.05 (d, \(J = 2.8\) Hz, 1H), 5.55 (s, 1H), 4.62 (dd, \(J = 5.0, 11.9\) Hz, 1H), 4.01 (m, 1H), 3.54 (t, \(J = 10.5\) Hz, 1H), 2.78 (dd, \(J = 7.3, 18.8\) Hz, 1H), 2.10 (d, \(J = 18.8\) Hz, 1H), 1.38 (s, 9H), 1.32 (s, 9H), 0.77 (s, 9H), -0.12 (s, 3H), -0.33 (s, 3H); \(^{13}\text{C} NMR\) (125 MHz): \(\delta = 206.3, 173.9, 157.3, 145.6, 142.4, 138.2, 132.0, 131.0, 129.5, 128.3, 126.1, 126.1, 124.3, 124.2, 74.2, 39.2, 37.3, 35.4, 34.6, 31.5, 30.5, 25.8, 18.2, -4.8\); IR (neat, cm\(^{-1}\)) = 2959, 1709, 849; HRMS (ESI): Calcd. for \(\text{C}_{33}\text{H}_{47}\text{O}_3\text{Si}\) (m/z): 519.3289. Found 519.3295 [M+H].

Yellow liquid, $^1$H NMR (500 MHz): $\delta = 7.69$ (d, $J = 2.5$ Hz, 1H), 7.29-7.23 (m, 6H), 5.90 (s, 1H), 4.62 (dd, $J = 5.5$, 11.5 Hz, 1H), 3.53 (m, 1H), 3.23 (t, $J = 11.5$ Hz, 1H), 2.75 (dd, $J = 6.9$, 18.8 Hz, 1H), 1.94 (dd, $J = 2.3$, 18.8 Hz, 1H), 1.41 (s, 9H), 1.37 (s, 9H), 0.60 (s, 9H), -0.14 (s, 3H), -0.28 (s, 3H); $^{13}$C NMR (125 MHz): $\delta =$ 205.4, 173.7, 146.5, 141.1, 138.2, 134.0, 132.2, 130.4, 127.7, 127.2, 126.2, 123.0, 120.9, 72.2, 61.8, 42.2, 36.6, 35.1, 35.0, 31.6, 30.8, 25.6, 18.1, -5.5; IR (neat, cm$^{-1}$) = 2959, 1709, 1623, 849; HRMS (ESI): Calcd. for C$_{33}$H$_{47}$O$_3$Si ($m/z$): 519.3289. Found 519.3250 [M+H]$^+$. 

Cyclization of 4,6-di-*tert*-butyl-2-(*1-*tert*-butyl-dimethylsilyloxy-3- trimethylsilyl-2-propynyl)-(2-propenyloxy)benzene (31)

The Pauson-Khand cyclization of the enyne 31 (100 mg, 0.21 mmol) in 10 mL of the appropriate solvent, was carried out following the general procedures 3.1.3.2 and 3.1.3.3. Co$_2$(CO)$_8$ (141 mg, 0.41 mmol) and NMO (530 mg, 4.52 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO$_2$ pad. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford only the exo-isomer of the PK product 33 (57.5 mg, 61% yield) using the oxidative procedure.
3.1.3.2. On the other hand, when the enyne 31 was heated to 70 °C for 1 day in toluene under the thermal procedure 3.1.3.3, no cyclized product was isolated.

6,8-Di-tert-butyl-10-t-butyl(dimethyl)silyloxy-1-trimethylsilyl-4,4a-dihydro-3H,10H-5-oxabenzof[\f]azulen-2-one (33)

\[
\begin{align*}
\text{H NMR (500 MHz): } & \delta = 7.26 (d, J = 2.5 \text{ Hz, 1H}), 7.07 (d, J = 2.3 \text{ Hz, 1H}), 5.78 (s, 1H), 4.51 (dd, J = 4.6, 11.9 \text{ Hz, 1H}), 4.18 (dd, J = 4.6, 8.7 \text{ Hz, 1H}), 3.89 (m, 1H), 3.52 (t, J = 11.5 \text{ Hz, 1H}), 2.56 (dd, J = 6.9, 18.8 \text{ Hz, 1H}), 1.94 (d, J = 17.9 \text{ Hz, 1H}) , 1.34 (s, 9H), 1.29 (s, 9H), 0.82 (s, 9H), 0.23 (s, 9H), 0.03 (s, 3H), -0.21 (s, 3H); \\
\text{C NMR (125 MHz): } & \delta = 212.6, 186.9, 157.1, 145.0, 141.9, 138.5, 131.4, 126.3, 124.0, 75.4, 38.8, 38.7, 35.3, 34.5, 31.5, 30.4, 25.8, 18.2, 14.2, 11.0, -0.2, -4.6; \text{ IR (neat, cm}^{-1}) = 3433.6, 2956.3, 2859.6, 1732.2, 1698.8, 1594.5, 1477.2, 1250.8; \text{ HRMS (ESI): Calcd. for C}_{30}H_{51}O_{3}Si_{2} (m/z): 515.3371. Found 515.3389 [M+H]^+.
\end{align*}
\]

Cyclization of 4,6-di-tert-butyl-2-(1-hydroxy-2-propynyl)-(2-propenyloxy)benzene (15c)

The Pauson-Khand cyclization of the enyne 15c (80 mg, 0.27 mmol) in 10 mL of the appropriate solvent, was carried out following the general procedures 3.1.3.2 and 3.1.3.3. Co\(_2\)(CO)\(_8\) (100 mg, 0.29 mmol) and NMO (312 mg, 2.67 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel with a short layer of Celite and SiO\(_2\) pad. The crude product was purified...
by flash chromatography (silica gel, hexane/EtOAc, 90:10) to afford the PK product 34 (14.7 mg, 17% in a 1:1 ratio of 34 epimers) and the diketone product 35 (80 mg, 80% as a 1:6 mixture of the syn- and anti- isomers) using the oxidative procedure 3.1.3.2. On the other hand, when the enyne was heated to 70 °C for 1 days in toluene under the thermal procedure 3.1.3.3, it gave the PK product of 34 (9.6 mg, 11% in a 1:2 ratio of 34 epimers) along with the diketone product 35 (44 mg, 50% as a 1:1 mixture of the syn and anti isomers).

6,8-Di-tert-butyl-10-hydroxyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (34)

Yellow oil, $^1$H NMR (500 MHz): $\delta = 7.56$ (d, $J = 2.3$ Hz, 1H), 7.48 (d, $J = 2.3$ Hz, 1H), 6.29 (s, 1H), 4.71 (dd, $J = 6.0$, 11.5 Hz, 1H), 3.85 (td, $J = 2.8$, 11.5 Hz, 1H), 3.55 (m, 1H), 2.93 (d, $J = 19.3$ Hz, 1H), 2.38 (dd, $J = 8.3$, 17.9 Hz, 1H), 2.04 (dd, $J = 11.0$, 22.5 Hz, 1H), 1.38 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 205.4$, 181.9, 152.6, 147.5, 140.6, 134.3, 128.4, 122.5, 120.6, 77.4, 74.6, 42.3, 36.5, 35.1, 31.6, 30.7, 25.5; HRMS (ESI): Calcd. for C$_{21}$H$_{28}$NaO$_3^+$ (m/z): 351.1931. Found 351.1957 [M+Na]$^+$.  

6,8-Di-tert-butyl-1,1a,4,4a-tetrahydro-3H-5-oxabenzo[f]azulen-2,10-dione (syn isomer 35)

Yellow waxy solid, $^1$H NMR (500 MHz): $\delta = 7.57$ (d, $J = 2.3$ Hz, 1H), 7.49 (d, $J = 2.3$ Hz, 1H), 4.71 (dd, $J = 6.0$, 12.4 Hz, 1H), 2.93 (d, $J = 19.3$ Hz, 1H), 2.38 (dd, $J = 6.0$, 17.9 Hz, 1H), 2.04 (dd, $J = 9.6$, 22.5 Hz, 1H), 1.38 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 205.4$, 181.9, 152.6, 147.5, 140.6, 134.3, 128.4, 122.5, 120.6, 77.4, 74.6, 42.3, 36.5, 35.1, 31.6, 30.7, 25.5; HRMS (ESI): Calcd. for C$_{21}$H$_{28}$NaO$_3^+$ (m/z): 351.1931. Found 351.1957 [M+Na]$^+$.  

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Hz, 1H), 3.85 (dt, $J = 2.8$, 8.7 Hz, 1H), 3.76 (dd, $J = 10.1$, 12.4 Hz, 1H), 3.33 (dddd, $J = 6.0$, 8.7, 10.1, 18.8 Hz, 1H), 2.91 (d, $J = 18.8$ Hz, 1H), 2.41 (dd, $J = 8.3$, 18.3 Hz, 1H), 2.29 (dd, $J = 8.7$, 18.8 Hz, 1H), 2.04 (dd, $J = 10.1$, 17.4 Hz, 1H), 1.40 (s, 9H), 1.30 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 215.3$, 200.9, 160.1, 144.6, 139.9, 128.4, 127.5, 124.3, 51.0, 42.4, 39.5, 39.4, 35.4, 34.7, 31.5, 30.7, 30.2; IR (neat, cm$^{-1}$) = 2960, 2871, 1750, 1678, 1597, 1474, 1439, 1365; HRMS (ESI): Calcd. for C$_{21}$H$_{29}$O$_3$ (m/z): 329.2111. Found 329.2098 [M+H]$^+$.

$\text{6,8-Di-}\text{tert-butyl-1,1a,4,4a-tetrahydro-3H-5-oxabenzo[f]azulen-2,10-dione (anti isomer 35)}$

Yellow waxy solid, $^1$H NMR (500 MHz): $\delta = 7.83$ (d, $J = 2.3$ Hz, 1H), 7.61 (d, $J = 2.3$ Hz, 1H), 4.25 (m, 2H), 3.67 (dd, $J = 11.5$, 19.3 Hz, 1H), 2.87 (dd, $J = 11.5$, 19.3 Hz, 1H), 2.66 (t, $J = 8.3$ Hz, 2H), 2.63 (s, 1H), 2.27 (dt, $J = 3.2$, 14.7 Hz, 1H), 1.43 (s, 9H), 1.32 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 214.4$, 198.7, 167.6, 146.4, 142.8, 130.0, 129.9, 124.8, 74.3, 52.0, 44.3, 39.8, 39.6, 35.6, 34.8, 31.4, 30.8; IR (neat, cm$^{-1}$) = 2960, 2871, 1750, 1678, 1597, 1474, 1439, 1365; HRMS (ESI): Calcd. For C$_{42}$H$_{56}$NaO$_6$ (m/z): 679.3969. Found 679.4005 [2M+Na]$^+$. 

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4,6-Di-<i>tert</i>-butyl-2-(<i>tert</i>-butyl-dimethylsilyloxy-2-propynyl)-(2-propenyl)oxy) benzene (36)

<chemistry>
\[
\begin{align*}
\text{TBSO} & \quad \text{CH}_3 - \text{C} = \text{C} - \text{CH}_2 - \text{C} = \text{C} - \text{Si(CH}_3)_2 \text{O} - \text{C}_6\text{H}_5 \\
\text{TBSO} & \quad \text{CH}_3 - \text{C} = \text{C} - \text{CH}_2 - \text{C} = \text{C} - \text{Si(CH}_3)_2 \text{O} - \text{C}_6\text{H}_5
\end{align*}
\]
</chemistry>

<i>tert</i>-Butyldimethylsilyl chloride (0.750 g, 5.00 mmol) was added at room temperature to a mixture of 15c (0.500 g, 1.67 mmol) and imidazole (0.300 g, 5.00 mmol) in DMF (10 mL). The reaction mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of aqueous NaHCO₃ and extracted with Et₂O. The organic layer was separated, washed with water and brine and dried (Na₂SO₄). The organic layer was concentrated to give a dark liquid. The crude product was purified by flash chromatography (hexane/EtOAc; 19:1) to give 36 as a viscous brown oil, (0.680 g, 99%). ¹H NMR (500 MHz): δ = 7.56 (d, J = 2.8 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 6.06 (ddt, J = 4.6, 11.0, 17.0 Hz, 1H), 5.69 (d, J = 2.3 Hz, 1H), 5.55 (dq, J = 1.8, 17.4 Hz, 1H), 5.29 (dq, J = 1.4, 10.5 Hz, 1H), 4.48 (ddt, J = 1.8, 4.6, 13.8 Hz, 1H), 4.42 (ddt, J = 1.8, 4.6, 13.8 Hz, 1H), 2.49 (d, J = 1.8 Hz, 1H), 1.39 (s, 9H), 1.31 (s, 9H), 0.82 (s, 9H), 0.07 (s, 3H), -0.08 (s, 3H); ¹³C NMR (125 MHz): δ = 152.4, 146.3, 141.5, 135.5, 133.9, 124.2, 124.0, 116.1, 85.9, 75.8, 72.6, 59.3, 35.5, 34.8, 31.6, 31.1, 25.8, 18.3, -4.8, -5.0; IR (neat, cm⁻¹) = 3299, 2956, 2867, 2175, 1466, 1252, 1069; HRMS (ESI): Calcd. for C₂₆H₄₃O₂Si (m/z): 415.3027. Found 415.3045 [M+H]+.
Cyclization of 4,6-di-tert-butyl-2-(1-tert-butyl-dimethylsilyloxy-2-propynyl)-(2-propenyloxy) benzene (36)

The Pauson-Khand cyclization of the enyne 36 (80 mg, 0.19 mmol) in 10 mL of the appropriate solvent, was carried out following the general procedures 3.1.3.2 and 3.1.3.3. Co2(CO)8 (91 mg, 0.27 mmol) and NMO (310 mg, 2.65 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO2. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford the expected PK product 37 (45 mg, 52% as a 2:1 mixture of 37 epimers) using the oxidative procedure 3.1.3.2. On the other hand, when the enyne was heated to 70 °C for 1 day in toluene under the thermal procedure 3.1.3.3, only the PK product of 37 (68.3 mg, 80% in a 1:1 ratio of 37 stereoisomers) was isolated. The stereoisomers of 37 were separated by preparatory thin layer chromatography to give the exo- and endo-products.

6,8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (37, exo-product).

Brown waxy solid, 1H NMR (300 MHz): δ = 7.55 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 6.25 (s, 1H), 5.75 (s, 1H), 4.51 (dd, J = 6.2, 11.4 Hz, 1H), 3.52 (m, 1H), 3.09 (t, J = 11.7 Hz, 1H), 2.58 (dd, J = 6.9, 18.6 Hz, 1H), 1.87 (dd, J = 2.8, 18.6 Hz, 1H), 1.34 (s, 9H), 1.31 (s, 9H), 1.00 (s, 9H), 0.07 (s, 6H), 13C NMR (75 MHz): δ = 206.6, 182.8, 153.8, 146.6, 140.9, 133.0, 127.4, 123.4, 120.5, 75.8, 71.1, 43.1, 37.4,
35.0, 31.7, 30.8, 25.9, 18.4, -4.9, -5.1, only 20 carbons were observed out of 21 carbon types; IR (neat, cm\(^{-1}\)) = 2954, 2862, 1718, 1623, 1475; HRMS (ESI): Calcd. for C\(_{27}H_{43}O_3Si\) \((m/z)\): 443.2976. Found 443.3002 [M+H]\(^+\).

6,8-Di-\textit{tert}-butyl-10-\textit{tert}-butyldimethylsilyloxy-4,4a-dihydro-3\textit{H},10\textit{H}-5-oxabenzo[f]azulen-2-one (37, \textit{endo} product).

Brown waxy solid, \(^1\text{H}\) NMR (300 MHz): \(\delta = 7.29\) (d, \(J = 2.1\) Hz, 1H), 7.11 (d, \(J = 2.4\) Hz, 1H), 6.06 (s, 1H), 5.61 (s, 1H), 4.49 (dd, \(J = 5.2, 11.0\) Hz, 1H), 3.73 (m, 1H), 3.73 (t, \(J = 11.0\) Hz, 1H), 2.62 (dd, \(J = 6.9, 18.9\) Hz, 1H), 1.95 (dd, \(J = 2.1, 18.6\) Hz, 1H), 1.36 (s, 9H), 1.30 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), -0.19 (s, 3H); \(^{13}\text{C}\) NMR (75 MHz): \(\delta = 207.8, 181.2, 155.4, 145.7, 142.2, 132.2, 128.1, 124.9, 124.3, 75.2, 40.7, 38.0, 35.3, 34.6, 31.6, 30.6, 25.8, 18.3, -4.76, -4.8\); IR (neat, cm\(^{-1}\)) = 2952, 2860, 1716, 1620, 1472; HRMS (ESI): Calcd. for C\(_{54}H_{84}NaO_6Si_2\)\(^+\) \((m/z)\): 907.5699. Found 907.5636 [2M+Na]\(^+\).

Cyclization of 4,6-di-\textit{tert}-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)-1-(-3-methyl-2-propenyloxy) benzene (17b)

The Pauson-Khand cyclization of the enyne 17b (630 mg, 0.16 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 5 mL of the appropriate solvent. Co\(_2(CO)_8\) (61 mg, 0.18 mmol) and NMO (189 mg, 1.62 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel.
packed with a short layer of Celite and SiO₂. The crude product was purified by flash chromatography (hexane/EtOAc, 87:13) to afford the reduced PK Product 39 (12 mg, 18%), the *endo-* product 40 (26 mg, 36%) and the *exo-*product 41 (31 mg, 45%) for the oxidative method. The thermal method gave the *endo-*product 40 (6.1 mg, 9%) and the *exo-* PK product 41 (25 mg, 12%) as a light yellow liquid.

**6,8-Di-tert-butyl-1-phenyl-3-methyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (39)**

![Chemical Structure](image.png)

Light yellow solid, mp: 80-82 °C; ¹H NMR (500 MHz): δ = 7.45 (t, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 6.9 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.14 (d, *J* = 1.8 Hz, 1H), 4.72 (dd, *J* = 5.5, 11.5 Hz, 1H), 3.87 (d, *J* = 12.8 Hz, 1H), 3.77 (d, *J* = 12.8 Hz, 1H), 3.37 (t, *J* = 11.5 Hz, 1H), 3.10 (m, 1H), 1.96 (dd, *J* = 2.8, 8.7 Hz, 1H), 1.42 (s, 9H), 1.36 (d, *J* = 7.8 Hz, 3H), 1.34 (s, 9H); ¹³C NMR (125 MHz): δ = 207.7, 169.9, 157.0, 146.7, 141.8, 138.4, 131.5, 129.7, 128.3, 128.1, 125.3, 123.0, 75.5, 52.9, 42.4, 36.5, 35.2, 34.7, 31.6, 30.7, 15.3 (21 carbon was observed out of 22 carbon types); IR (Neat, cm⁻¹) = 2957, 1705, 1466, 752; HRMS (ESI): Calcd. For C₂₈H₃₅O₂ (*m/z*): 403.2632. Found 403.2636 [M+H]⁺.
6,8-Di-tert-butyl-10-hydroxy-3-methyl-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzof[\textit{f}]azulen-2-one (40, endo-product).

Yellow liquid, \( ^1\text{H} \) NMR (500 MHz): \( \delta = 7.37 \) (m, 3H), 7.34 (d, \( J = 2.8 \) Hz, 1H), 7.20 (dd, \( J = 1.8, 8.3 \) Hz, 2H), 7.14 (d, \( J = 2.8 \) Hz, 1H), 5.53 (s, 1H), 4.73 (dd, \( J = 5.5, 11.5 \) Hz, 1H), 4.13 (d, \( J = 7.3 \) Hz, 1H), 4.10 (d, \( J = 7.3 \) Hz, 1H), 3.64 (t, \( J = 11.0 \) Hz, 1H), 2.83 (ddd, \( J = 7.3, 7.8, 11.5 \) Hz, 1H), 1.40 (s, 9H), 1.32 (s, 9H), 1.16 (d, \( J = 7.8 \) Hz, 3H); \(^{13}\text{C} \) NMR (125 MHz): \( \delta = 208.8, 171.5, 156.4, 147.3, 142.7, 138.5, 132.8, 130.9, 129.7, 128.4, 128.3, 125.3, 124.9, 73.5, 42.0, 41.7, 35.3, 34.7, 31.5, 30.7, 14.3, 10.5; IR (Neat, cm\(^{-1}\)) = 3434, 3055, 2960, 2870, 1703, 1477, 1444; HRMS (ESI): Calcd. For C\textsubscript{56}H\textsubscript{68}NaO\textsubscript{6} (\( m/z \)) 859.4908, Found 859.4955 [2M+Na]

6,8-Di-tert-butyl-10-hydroxy-3-methyl-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzof[\textit{f}]azulen-2-one (41, exo product).

Yellow solid, mp 158-160 °C, \( ^1\text{H} \) NMR (500 MHz): \( \delta = 7.42-7.35 \) (m, 3H), 7.34 (d, \( J = 2.8 \) Hz, 1H), 7.23 (d, \( J = 6.5 \) Hz, 2H), 7.18 (d, \( J = 2.8 \) Hz, 1H), 5.53 (d, \( J = 8.3 \) Hz, 1H), 4.76 (dd, \( J = 5.0, 11.0 \) Hz, 1H), 4.12 (dd, \( J = 7.3, 14.2 \) Hz, 1H), 3.60 (m, 1H), 3.54 (t, \( J = 11.0 \) Hz, 1H), 3.14 (d, \( J = 8.7 \) Hz, 1H), 1.41 (s, 9H), 1.38 (d, \( J = 7.3 \) Hz, 3H), 1.32 (s, 9H); \(^{13}\text{C} \) NMR (125 MHz): \( \delta = 207.5, 170.0, 156.5, 147.3, 142.7, 138.5, 132.9, 130.9, 129.6, 128.4, 128.3, 125.2, 124.9, 73.5, 60.5, 47.7, 42.5,
Cyclization of 4,6-di-tert-butyl-2-(1-hydroxy-3-trimethylsilyl-2-propynyl)-1-(3-methyl-2-propenyloxy) benzene (17a)

The Pauson-Khand cyclization of the enyne 17a (200 mg, 0.52 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 5 mL of the appropriate solvent. Co2(CO)8 (195 mg, 0.57 mmol) and NMO (606 mg, 5.18 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO2. The crude product was purified by flash chromatography (hexane/EtOAc, 87:13) to afford the PK Product 42 (15 mg, 7%) for the oxidative method. Thermal method gave 42 (25 mg, 12%) as a light yellow liquid.

6,8-Di-tert-butyl-10-hydroxy-3-methyl-1-trimethylsilyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one 42

Yellow liquid, 1H NMR (500 MHz): δ = 7.32 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 2.8 Hz, 1H), 5.69 (s, 1H), 4.65 (dd, J = 5.0, 11.0 Hz, 1H), 3.50 (ddd, J = 3.2, 5.0, 11.0 Hz, 1H), 3.47 (t, J = 11.0 Hz, 1H), 1.85 (ddd, J = 3.2, 7.3, 14.7 Hz, 1H), 1.38 (s, 9H), 1.29 (s, 9H), 1.23 (d, J = 7.8 Hz, 3H), 0.29 (s, 9H); 13C NMR (125 MHz): δ = 213.5, 182.6, 156.2, 146.9, 142.4, 139.0, 132.7, 125.1, 124.9, 75.0, 60.5, 50.6, 43.6,
35.3, 34.7, 31.5, 30.7, 15.0, -0.09; IR (neat, cm⁻¹) = 3498, 2960, 1697, 1590, 1478;
HRMS (CI): Calcd. for C₂₅H₃₈O₃Si (m/z): 414.2590. Found 414.2593 [M⁺].

**Cyclization of 4,6-di-tert-butyl-2-(-1-hydroxy-2-propynyl)-1-(-2-butenyloxy) benzene (17c)**

The Pauson-Khand cyclization of the enyne 17c (420 mg, 1.34 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 5 mL of the appropriate solvent. Co₂(CO)₈ (500 mg, 1.46 mmol) and NMO (1.72 g, 14.7 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO₂. The crude product was purified by flash chromatography (hexane/EtOAc, 87:13) to afford the reduced PK Product 44 (131 mg, 30%) and the PK product 43 (253 mg, 58.0% as a 1:3 ratio of syn and anti isomers) using the oxidative method. Thermal method only gave 43 (146 mg, 32.0%, 1:2 ratio of syn and anti isomers). Preparatory TLC was used to separate the syn- and anti-products.

**6,8-Di-tert-butyl-3-methyl-1,1a,4,4a-tetrahydro-1H,3H-5-oxabenzo[f]azulen-2,10-Dione (43, syn-product).**

Brown solid, mp: 134-136 °C, ¹H NMR (500 MHz): δ = 7.56 (d, J = 2.8 Hz, 1H). 7.49 (d, J = 2.8 Hz, 1H), 4.84 (dd, J = 6.45, 11.9 Hz, 1H), 3.81 (dt, J = 1.8, 8.7 Hz, 1H), 3.70 (t, J = 11.9 Hz, 1H), 3.16 (dt, J = 1.8, 19.3 Hz, 1H), 2.93 (m, 1H), 2.25 (dd, J = 8.3, 19.3 Hz, 1H), 1.94 (m, 1H), 1.42 (s, 9H), 1.30 (s, 9H), 1.09 (d, J = 6.9
Hz, 3H); $^{13}$C NMR (125 MHz): $\delta$ = 217.0, 200.5, 160.3, 144.4, 139.9, 128.3, 128.0, 124.3, 76.8, 50.0, 48.6, 44.4, 37.4, 35.4, 34.6, 31.5, 30.2, 12.8; IR (neat, cm$^{-1}$) = 2960, 1748, 1680, 1463, 757; HRMS (ESI): Theoretical Calcd. for C$_{22}$H$_{31}$O$_3$ (m/z) 343.2268, Found 343.2272 [M+H]$^+$. 

6,8-Di-tert-butyl-3-methyl-1,1a,4,4a-tetrahydro-1$H$,3$H$-5-oxabenzo[f]azulen-2,10-dione. (43, anti-product)

Yellow waxy solid, $^1$H NMR (500 MHz): $\delta$ = 7.53 (d, $J$ = 2.5 Hz, 1H), 7.39 (d, $J$ = 2.5 Hz, 1H), 4.45 (dd, $J$ = 2.3, 12.8 Hz, 1H), 3.99 (dd, $J$ = 3.7, 12.3 Hz, 1H), 3.59 (dt, $J$ = 8.7, 10.5 Hz, 1H), 2.95 (tt, $J$ = 2.8, 8.7 Hz, 1H), 2.49 (t, $J$ = 8.7 Hz, 1H), 2.41 (ddd, $J$ = 1.8, 8.7, 10.5 Hz, 1H), 2.33 (dd, $J$ = 8.3, 19.3 Hz, 1H), 1.25 (s, 9H), 1.22 (s, 9H), 1.21 (d, $J$ = 2.3 Hz, 3H); $^{13}$C NMR (125 MHz): $\delta$ = 215.9, 202.7, 158.8, 145.1, 140.1, 128.6, 125.2, 125.0, 74.0, 51.1, 45.3, 45.1, 39.8, 35.2, 34.7, 31.5, 30.2, 10.3; IR (neat, cm$^{-1}$) = 2960, 1742, 1678, 1463, 755; HRMS (ESI): Calcd. for C$_{44}$H$_{60}$NaO$_6^+$ (m/z) 707.4282, Found 707.4352 [2M+Na]$^+$. 

6,8-Di-tert-butyl-3-methyl-4,4a-dihydro-3$H$,10$H$-5-oxabenzo[f]azulen-2-one (44)

Light yellow oily waxy solid, $^1$H NMR (500 MHz): $\delta$ = 7.25 (d, $J$ = 2.5 Hz, 1H), 7.06 (d, $J$ = 2.5 Hz, 1H), 6.0 (s, 1H), 4.59 (dd, $J$ = 5.5, 11.5 Hz, 1H), 3.94 (d, $J$ = 13.3 Hz, 1H), 3.73 (d, $J$
=13.3 Hz, 1H), 3.24 (t, J = 11.9 Hz, 1H), 3.03 (m 1H), 1.86 (dd, J = 3.2, 7.3, 14.7 Hz, 1H), 1.38 (s, 9H), 1.29 (s, 9H), 1.23 (d, J = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz): $\delta$ = 210.0, 176.5, 156.6, 146.6, 141.6, 129.2, 128.4, 125.2, 123.3, 75.0, 54.1, 43.6, 38.6, 35.1, 34.6, 31.6, 30.7, 14.9; IR (neat, cm$^{-1}$) = 2959, 1707, 1620, 1468, 1232, 1000; HRMS (ESI): Calcd. for C$_{22}$H$_{31}$O$_2$ (m/z): 327.2319. Found 327.2312 [M+H]$^+$.  

4,6-Di-tert-butyl-2-(1-tert-butyl-dimethylsilyloxy-3-phenyl-2-propynyl)-(-2-butenyloxy)benzene (45)  

![Chemical Structure](image)  

tert-Butyldimethylsilyl chloride (1.16 g, 7.69 mmol) was added at room temperature to a mixture of 17b (1.00 g, 2.60 mmol) and imidazole (0.460 g, 7.69 mmol) in DMF (10 mL). The reaction mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of aqueous NaHCO$_3$ and extracted with Et$_2$O. The organic layer was separated, washed with water and brine and dried (Na$_2$SO$_4$). The organic layer was concentrated to give a dark liquid. The crude product was purified by flash chromatography (hexane/EtOAc, 19:1) to give 45 as viscous brown liquid (1.28 g, 98.0%). $^1$H NMR (500 MHz): $\delta$ = 7.67 (d, 1H, J = 3.0 Hz), 7.47 (m, 2H), 7.31 (d, 1H, J = 3.0 Hz), 7.29 (m, 3H), 6.01 (m, 1H), 5.98 (s, 1H), 5.86 (m, 1H), 4.46 (dd, 2H, J = 5.5, 11.0 Hz), 1.83 (d, 3H, J = 6.5 Hz), 1.42 (s, 9H), 1.34 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (125 MHz): $\delta$ = 152.7, 146.1, 141.5, 135.9, 131.7, 128.9, 128.3, 127.1, 124.5, 123.8, 123.4, 91.5, 84.6, 76.0, 60.2, 35.6, 34.8, 31.6, 31.2, 25.9,
25.8, 18.4, 18.1, -4.4, -4.7, IR (neat, cm\(^{-1}\)) = 2960, 2300, 1560, 1475, 1252, 1064; HRMS (ESI): Calcd. for C\(_{33}\)H\(_{48}\)O\(_2\)SiNa (\(m/z\)): 527.3316. Found 527.3345 [M+Na]\(^+\).

4,6-Di-\(\text{-tert}\)-butyl-2-(\(\text{-1-tert}\)-butyl-dimethylsilyloxy-3- trimethylsilyl -2-propynyl)-(2-butenyloxy)benzene (46)

\(\text{\textit{tert}}\)-Butyldimethylsilyl chloride (0.940 g, 6.22 mmol) was added at room temperature to a mixture of 17\(a\) (0.800 g, 2.07 mmol) and imidazole (0.400 g mL). The reaction mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of aqueous NaHCO\(_3\) and extracted with Et\(_2\)O. The organic layer was separated, washed with water and brine and dried (Na\(_2\)SO\(_4\)). The organic layer was concentrated to give a dark colored liquid. The crude product was purified by flash chromatography (hexane/EtOAc, 19:1) to give 46 as viscous brown oil, (1.02 g, 98%). \(^1\)H NMR (500 MHz) \(\delta = 7.58\) (d, \(J = 3.0\) Hz, 1H), 7.28 (d, \(J = 3.0\) Hz, 1H), 5.94 (dq, \(J = 6.4, 15.5\) Hz, 1H), 5.81 (dt, \(J = 6.0, 15.6\) Hz, 1H), 5.73 (s, 1H), 4.52 (d, \(J = 4.5\) Hz, 2H), 1.81 (d, \(J = 6.5\) Hz, 3H), 1.40 (s, 9H), 1.30 (s, 9H), 0.85 (s, 9H), 0.16 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H); \(^{13}\)C NMR (125 MHz): \(\delta = 152.9, 145.6, 141.4, 135.7, 128.7, 127.2, 124.6, 123.8, 107.8, 89.4, 76.0, 60.3, 35.5, 34.8, 31.6, 31.2, 25.8, 18.4, 18.1, -0.1, -4.4, -4.6; IR (neat, cm\(^{-1}\)) = 2959, 2216, 1469, 1251; HRMS (ESI): Calcd. For C\(_{30}\)H\(_{52}\)O\(_2\)Si\(_2\)Na (\(m/z\)): 523.3398. Found 523.3412 [M+Na]\(^+\).
6, 8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-3-methyl-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (47)

The Pauson-Khand cyclization of the enyne 45 (210 mg, 0.400 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 5 mL of the appropriate solvent. Co₂(CO)₈ (150 mg, 0.440 mmol) and NMO (510 mg, 4.36 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO₂. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 87:13) to afford the PK Product 45 (99.8 mg, 45.0%, 1:4 ratio of the diastereomers) for the oxidative method. Thermal method gave 45 (151 mg, 68.0%) as a brown waxy solid. 

1H NMR (500 MHz): δ = 7.36 (m, 3H), 7.31 (d, J = 2.5 Hz, 1H), 7.21 (d, J = 7.0 Hz, 2H), 7.09 (d, J = 2.5 Hz, 1H), 5.60 (s, 1H), 4.68 (dd, J = 5.0, 12.0 Hz, 1H), 3.68 (t, J = 9.5 Hz, 1H), 3.51 (d, J = 3.5 Hz, 1H), 2.15 (d, J = 5.0 Hz, 1H), 1.40 (s, 9H), 1.38 (d, J = 5.0 Hz, 3H), 1.33 (s, 9H), 0.78 (s, 9H), -0.11 (s, 3H), -0.27 (s, 3H); 13C NMR (125 MHz): δ = 208.4, 171.5, 157.4, 145.4, 142.1, 137.2, 131.7, 131.1, 129.4, 128.2, 126.3, 124.2, 75.1, 73.8, 48.4, 43.2, 35.4, 34.6, 31.7, 31.6, 30.5, 25.8, 18.2, 15.1, -4.75, -4.79; IR (neat, cm⁻¹) = 2957, 1709, 1465, 1066, 841; HRMS (ESI): Calcd. for C₃₄H₄₉O₃Si (m/z): 533.3445. Found 533.3468.
6.8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-3-methyl-1-trimethylsilyl-4,4a-
dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (48)

The Pauson-Khand cyclization of the enyne 46 (100 mg, 0.200 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 5 mL of the appropriate solvent. Co2(CO)8 (75 mg, 0.22 mmol) and NMO (260 mg, 2.20 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO₂. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 87:13) to afford only the exo PK Product 48 (7.8 mg, 7.0%) for the oxidative method. Thermal method gave also the exo-product 48 (10.4 mg, 10.0%) as a brown waxy solid, ¹H NMR (500 MHz): δ = 7.26 (d, J = 2.5 Hz, 1H), 7.06 (d, J = 2.5 Hz, 1H), 5.78 (s, 1H), 4.58 (dd, J = 4.6, 11.5 Hz, 1H), 3.71 (t, J = 9.5 Hz, 1H), 3.34 (m, 1H), 2.06 (m, 1H), 1.34 (s, 9H), 1.30 (s, 9H), 1.23 (d, J = 5.0 Hz, 3H), 0.83 (s, 9H), 0.21 (s, 9H), 0.06 (s, 3H), -0.14 (s, 3H); ¹³C NMR (125 MHz) δ = 214.6, 177.1, 168.7, 163.0, 155.4, 138.6, 121.7, 114.5, 82.2, 71.8, 44.5, 35.4, 34.5, 33.2, 31.5, 30.4, 30.3, 29.8, 25.8, 18.2, 6.1, -0.2, -4.5; IR (neat, cm⁻¹) = 2957, 1709, 1465, 1066, 841; HRMS (ESI): Calcd. for C₃₁H₅₃O₃Si₂ (m/z): 529.3528. Found 529.3500 [M+H]⁺.
**4,6-Di-tert-butyl-2-(1-tert-butyl-dimethylsilyloxy-2-propynyl)-(2-butenyloxy)benzene (49)**

* tert-Butyldimethylsilyl chloride (2.20 g, 14.3 mmol) was added at room temperature to a mixture of 17c (1.50 g, 4.78 mmol) and imidazole (0.980 g, 14.3 mmol) in DMF (10 mL). The reaction mixture was heated at 50 °C for 4.5 h. The reaction was quenched by the addition of aqueous NaHCO₃ and extracted with Et₂O. The organic layer was separated, washed with water and brine and dried (Na₂SO₄). The organic layer was concentrated to give a dark liquid. The crude product purified by flash chromatography (hexane/EtOAc; 19:1) to give 49 as viscous brown oil, (2.03 g, 99.0%).

**¹H NMR (500 MHz):** δ = 7.58 (d, J = 2.8 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 5.94 (dq, J = 6.4, 15.1 Hz, 1H), 5.81 (dt, J = 6.0, 15.1 Hz, 1H), 5.73 (d, J = 2.3 Hz, 1H), 4.28 (ddt, J = 1.4, 5.5, 10.5 Hz, 1H), 4.21 (ddt, J = 1.4, 5.5, 12.4 Hz, 1H), 2.49 (d, J = 2.3 Hz, 1H), 1.81 (dd, J = 6.5, Hz, 3H), 1.41 (s, 9H), 1.33 (s, 9H), 0.85 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); **¹³C NMR (125 MHz):** δ = 152.6, 146.2, 141.5, 135.6, 128.8, 126.9, 124.1, 124.0, 86.0, 76.0, 72.6, 59.5, 35.5, 34.8, 31.6, 31.2, 25.8, 18.3, 18.0, -4.8, -5.0; **IR (neat, cm⁻¹):** 3311, 2960, 2934, 2118, 1649, 1474; **HRMS (ESI):** Calcd. for C₂₇H₄₄O₂SiNa (m/z): 451.3003. Found 451.3010 [M+Na]^+.
6,8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-3-methyl-4,4a-dihydro-3H,10H-5-oxa benzof[f]azulen-2-one (50)

The Pauson-Khand cyclization of the enyne 49 (200 mg, 0.470 mmol) was carried out following the general procedures B and C in 5 mL of the appropriate solvent. Co₂(CO)₈ (180 mg, 0.530 mmol) and NMO (620 mg, 5.30 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO₂. The crude product was purified by flash chromatography (hexane/EtOAc, 87:13) to afford the PK product 50 (170 mg, 80%, with the ratio of the epimers being 1:0.8) for the oxidative method. Thermal method gave also the PK product 50 (180 mg, 85%, 5:4 mixture of isomers) as a brown waxy solid; ¹H NMR (300 MHz): δ = 7.29 (d, J = 2.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 6.06 (s, 1H), 5.63 (s, 1H), 4.59 (dd, J = 5.1, 11.4 Hz, 1H), 3.72 (app. t, J = 10.2 Hz, 1H), 3.20 (d, J = 3.5 Hz, 1H), 2.07 (d, J = 3.9 Hz, 1H), 1.31 (s, 9H), 1.30 (s, 9H), 1.23 (d, J = 3.9 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz): δ = 210.2, 178.9, 153.9, 145.5, 142.0, 131.9, 127.1, 124.3, 120.6, 75.4, 71.1, 49.6, 44.1, 35.3, 34.6, 31.6, 30.7, 25.8, 18.3, 14.6, -4.7, -4.8; IR (neat, cm⁻¹) = 2957, 1712, 1624, 1474; HRMS (ESI): Calcd. for C₂₈H₄₅O₃Si (m/z): 457.3132. Found 457.3131 [M+H]⁺.
Cyclization of 4,6-di-tert-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)-1-(3-phenyl-2-propenyl oxygenoxo) benzene (22b)

The Pauson-Khand cyclization of the enyne 22b (110 mg, 0.240 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 5 mL of the appropriate solvent. Co2(CO)8 (92 mg, 0.27 mmol) and NMO (310 mg, 2.65 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO2. The crude product was purified by flash chromatography (SiO2, hexane/EtOAc, 87:13) to afford the reduced product 51 (50 mg, 45%) as a yellow waxy solid and exo-PK products of 52 (60 mg, 51%) for the oxidative method. The thermal method gave only the PK product 52 (110 mg, 90%, 1:10 ratio of the epimers) as a yellow solid. No reduced PK product 51 was isolated.

6,8-Di-tert-butyl-1,3-diphenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one

Yellow waxy solid, 1H NMR (300 MHz): δ = 7.27-7.51 (m, 10H), 7.25 (d, J = 2.1 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 4.78 (dd, J = 4.5, 10.2 Hz, 1H), 3.96 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 12.9 Hz, 1H), 3.55 (m, 1H), 3.48 (t, J = 11.4 Hz, 1H), 3.13 (d, J = 3.0 Hz, 1H), 1.42 (s, 9H), 1.37 (s, 9H), 13C NMR (75 MHz): δ = 204.7, 170.7, 157.0, 146.8, 141.9, 138.8, 138.6, 131.3, 129.8, 129.5, 129.1, 128.4, 128.3, 128.2, 127.4, 125.3, 123.1, 75.4, 54.2, 53.8, 36.6, 35.2, 34.7, 31.6, 30.7; IR (neat,
\(\text{cm}^{-1}\) = 3059, 3029, 2961, 2869, 1707, 1638, 1599, 1476; HRMS (ESI): Calcd. For \(\text{C}_{33}\text{H}_{36}\text{O}_{2}\text{Na}(m/z): 487.2608. \text{Found} 487.2625 \{M+Na\}^+.

6,8-Di-tert-butyl-10-hydroxy-1,3-diphenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (52)

Yellow solid, mp: 173-175 °C. \(^1\)H NMR (500 MHz): \(\delta = 7.36\) (m, 6H), 7.25 (m, 5H), 7.22 (d, \(J = 2.3\) Hz, 1H), 5.60 (s, 1H), 4.81 (dd, \(J = 5.5, 11.5\) Hz, 1H), 4.10 (m, 1H), 3.68 (t, \(J = 11.5\) Hz, 1H), 3.17 (d, \(J = 2.8\) Hz, 1H), 1.41 (s, 9H), 1.35 (s, 9H);

\(^{13}\)C NMR (75 MHz): \(\delta = 204.5, 170.9, 156.4, 147.4, 142.8, 138.7, 138.2, 132.7, 130.7, 129.7, 129.1, 128.6, 128.3, 128.2, 127.5, 125.2, 125.1, 73.5, 60.5, 54.2, 48.6, 35.4, 34.8, 31.5, 30.7; IR (neat, \(\text{cm}^{-1}\)) = 3450, 3058, 2956, 1700, 1638, 1600, 1477, 1361, 1266; HRMS (ESI): Calcd. For \(\text{C}_{33}\text{H}_{36}\text{O}_{3}\text{Na}(m/z): 503.2557. \text{Found} 503.2548 \{M+Na\}^+.

4,6-Di-tert-butyl-2-(1-tert-butyldimethylsilyloxy-3-phenyl-2-propynyl)-1-(3-phenyl-2-propenyloxy) benzene (53)

tert-Butyldimethylsilyl chloride (1.00 g, 6.64 mmol) was added at room temperature to a mixture of 22b (1.00 g, 2.21 mmol) and imidazole (450 mg, 6.64 mmol) in DMF (10 mL). The reaction mixture was then heated at 50 °C for 4.5 h. The reaction was quenched with aqueous NaHCO₃ and extracted with Et₂O. The organic layer separated, washed with water and brine, dried (\(\text{Na}_2\text{SO}_4\)) and concentrated.
to give a dark liquid. The crude product was purified by flash chromatography (hexane/EtOAc, 19:1) to give 53 (1.23 g, 98%) as dark brown oil. $^1$H NMR (500 MHz): \( \delta = 7.73 \) (d, \( J = 2.8 \text{ Hz}, 1\text{H} \)), 7.29-7.51 (m, 11H), 6.92 (d, \( J = 16.0 \text{ Hz}, 1\text{H} \)), 6.53 (dt, \( J = 5.0, 15.6 \text{ Hz}, 1\text{H} \)), 6.06 (s, 1H), 4.77 (ddd, \( J = 1.8, 5.5, 15.0 \text{ Hz}, 1\text{H} \)), 4.70 (ddd, \( J = 1.8, 5.5, 15.0 \text{ Hz}, 1\text{H} \)), 1.49 (s, 9H), 1.40 (s, 9H), 0.92 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (125 MHz): \( \delta = 152.6, 146.3, 141.6, 137.0, 135.9, 131.8, 131.6, 128.7, 128.3, 128.3, 127.8, 126.7, 125.5, 124.6, 124.0, 123.3, 91.5, 84.9, 75.8, 60.4, 35.6, 34.9, 31.7, 31.3, 26.0, 18.4, -4.3, -4.6; IR (neat, \( \text{cm}^{-1} \)) = 3102, 2928, 2709, 2223, 1946, 1659, 1599, 1472; HRMS (ESI): Calcd. for $\text{C}_{38}\text{H}_{50}\text{O}_{2}\text{SiNa} (m/z)$: 589.3472. Found 589.3505 [M+Na]$^+$. 

6,8-Di-tert-butyl-10-t-butylidemthysilyloxy-1,3-diphenyl-4,4a-dihydro-3\(H\),10\(H\)-5-oxabenzo[f]azulen-2-one (54)

The Pauson-Khand cyclization of the enyne 53 (200 mg, 0.35 mmol) was carried out following the general procedures 3.1.3.2 and 3.1.3.3 in 10 mL of the appropriate solvent. $\text{Co}_2(\text{CO})_8$ (140 mg, 0.41 mmol) and NMO (490 mg, 4.19 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO$_2$. The crude product was purified by flash chromatography (hexane/EtOAc, 87:13) to afford only the \textit{exo}-PK products of 54 (140 mg, 67.0%) for the oxidative method. The thermal method gave also the \textit{exo}-PK product 54 (180 mg, 86%) as a yellow viscous liquid. $^1$H
NMR (500 MHz): δ = 7.16-7.42 (m, 12H), 4.71 (s, 1H), 4.75 (dd, J = 4.6, 11.5 Hz, 1H), 4.10 (m, 1H), 3.83 (t, J = 10.0 Hz, 1H), 3.31 (s, 1H), 1.42 (s, 9H), 1.37 (s, 9H), 0.81 (s, 9H), -0.05 (s, 3H), -0.24 (s, 3H); 13C NMR (75 MHz); δ = 205.3, 172.5, 157.4, 145.6, 142.3, 138.7, 137.2, 131.9, 130.9, 129.6, 129.1, 128.4, 128.3, 128.2, 127.3, 126.3, 124.3, 73.9, 60.5, 54.6, 49.2, 35.5, 34.6, 31.6, 30.5, 25.8, 18.2, 14.3, -4.8; IR (neat, cm^-1) = 3098, 2955, 1712, 1600, 1477, 1361, 1254; HRMS (ESI): Calcd. For C_{39}H_{51}O_{3}Si (m/z): 595.3602. Found 595.3605 [M+H]^+.

Cyclization of 4,6-di-tert-butyl-2-(1-hydroxy-2-propynyl)-1-(3-phenyl-2-propenyl)oxy benzene. (22c)

The Pauson-Khand cyclization of the enyne 22c (200 mg, 0.530 mmol) was carried out following the general procedures B and C in 5 mL of the appropriate solvent. Co_2(CO)_8 (200 mg, 0.590 mmol) and NMO (680 mg, 5.85 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO_2. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc, 87:13) to afford the diketone product 55 (130 mg, 51%, 1:5 ratio of the syn- and trans-isomers) as a yellow waxy solid, for the oxidative method. The thermal method gave the 55 (90 mg, 41%, 3:1 ratio of the syn and trans-isomers) and the normal PK product 56 (10 mg, 5.0%).
6,8-Di-tert-butyl-3-phenyl-1,1a,4,4a-tetrahydro-3H-5-oxabenzo[f]azulen-2,10-dione (55)

For the major Isomer (obtained pure). \(^1\)H NMR (300 MHz): \(\delta = 7.62 \text{ (d, } J = 2.4 \text{ Hz, } 1\text{H}), 7.50 \text{ (d, } J = 2.4 \text{ Hz, } 1\text{H}), 7.29 \text{ (m, } 3\text{H}), 7.08 \text{ (d, } J = 6.9 \text{ Hz, } 2\text{H}), 4.67 \text{ (dd, } J = 6.2, 12.0 \text{ Hz, } 1\text{H}), 3.94 \text{ (dt, } J = 1.2, 8.6 \text{ Hz, } 1\text{H}), 3.73 \text{ (t, } J = 12.0 \text{ Hz, } 1\text{H}), 3.53 \text{ (ddt, } J = 6.2, 8.6, 19.2 \text{ Hz, } 1\text{H}), 3.29 \text{ (d, } J = 19.2 \text{ Hz, } 1\text{H}), 3.12 \text{ (d, } J = 12.9 \text{ Hz, } 1\text{H}), 2.40 \text{ (dd, } J = 8.4, 18.9 \text{ Hz, } 1\text{H}), 1.39 \text{ (s, } 9\text{H}), 1.32 \text{ (s, } 9\text{H}); ^{13}\text{C NMR (75 MHz): } \delta = 214.0, 200.4, 160.5, 144.5, 140.0, 136.0, 129.1, 128.4, 128.1, 127.8, 124.3, 76.7, 56.4, 49.7, 48.4, 38.2, 35.4, 34.7, 31.5, 30.2, 29.8; \text{IR (neat, cm}^{-1}) = 3099, 2959, 2869, 2360, 1750, 1676, 1597, 1438; \text{HRMS (ESI): Calcd. for } \text{C}_{27}\text{H}_{33}\text{O}_{3}^+ (m/z): 405.2424. \text{Found 405.2432 [M+H]^+}. 

6,8-Di-tert-butyl-10-hydroxy-3-phenyl-4,4a-dihydro-3H,10H-5-oxabenzo[f] azulen-2-one (56)

It gave yellow waxy solid, \(^1\)H NMR (300 MHz): \(\delta = 7.19-7.36 \text{ (m, } 7\text{H}), 6.20 \text{ (s, } 1\text{H}), 5.56 \text{ (s, } 1\text{H}), 4.69 \text{ (dd, } J = 5.40, 11.4 \text{ Hz, } 1\text{H}), 4.21 \text{ (dd, } J = 3.6, 5.4 \text{ Hz, } 1\text{H}), 3.96 \text{ (m, } 1\text{H}), 3.57 \text{ (t, } J = 10.8 \text{ Hz, } 1\text{H}), 3.08 \text{ (d, } J = 3.3 \text{ Hz, } 1\text{H}), 1.38 \text{ (s, } 9\text{H}), 1.32 \text{ (s, } 9\text{H); } ^{13}\text{C NMR (75 MHz): } \delta = 206.4, 177.8, 147.4, 142.6, 129.1, 128.9, 128.4, 128.1, 127.5, 125.4, 125.0, 111.2, 89.8, 77.3, 75.6, 50.4, 35.3, 34.8, 31.5, 30.7, 29.8; \text{IR (neat, cm}^{-1}) = 3451, 2959, 2926, 2869, 2360, 1712, 1476, 1362, 1269; \text{HRMS (ESI): Calcd. For } \text{C}_{27}\text{H}_{32}\text{NaO}_{3} (m/z): 427.2244. \text{Found 427.2216 [M+Na]^+.}
4,6-Di-tert-butyl-2-(1-tert-butyldimethylsilyloxy -2-propynyl)-1-(3-phenyl -2-propenyloxy) benzene (57)

*tert*-Butyldimethylsilyl chloride (1.20 g, 7.98 mmol) was added at room temperature to a mixture of the 22c (1.0 g, 2.66 mmol) and imidazole (0.54 g, 7.98 mmol) in DMF (10 mL). Then the mixture was heated at 50 °C for 4.5h. The reaction was quenched by the addition of aqueous NaHCO₃ and extracted with Et₂O. The organic layer separated, washed with water and brine, dried with anhydrous Na₂SO₄ and then concentrated to give a dark liquid. Purification was by flash chromatography (hexane/EtOAc; 19:1) to give 57 (1.29 g, 99%) as dark red oil. ¹H NMR (500 MHz): δ = 7.59 (d, J = 2.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 6.44 (dt, J = 5.1, 16.0 Hz, 1H), 5.76 (s, 1H), 4.62 (dd, J = 5.1, 13.8 Hz, 2H), 2.52 (s, 1H), 1.42 (s, 9H), 1.33 (s, 9H), 0.82 (s, 9H), 0.07 (s, 3H), -0.06 (s, 3H); ¹³C NMR (75 MHz): δ = 152.44, 146.4, 141.6, 136.9, 135.6, 131.5, 128.7, 127.8, 126.7, 125.3, 124.2, 124.1, 85.9, 75.7, 72.8, 59.5, 34.8, 31.6, 31.2, 25.8, 18.3, -4.7, -4.9; IR (neat, cm⁻¹) = 3308, 3027, 2963, 2223, 1601, 1472, 1362, 1289, 1159, 1119, 1068, 965; HRMS (ESI): Calcd. For C₃₂H₄₇O₂Si (m/z): 491.3340. Found 491.3343 [M+H]⁺; Calcd. For C₃₂H₄₆O₂SiNa (m/z): 513.3159. Found 513.3155 [M+Na]⁺.
6,8-Di-tert-butyl-10--t-butyldimethylsilyloxy -3-phenyl-4,4a-dihydro-3H,10H-5-oxa benzo[f]azulen-2-one (58)

The Pauson-Khand cyclization of the enyne 57 (200 mg, 0.410 mmol) was carried out following the general procedures B and C in 10 mL of the appropriate solvent. Co2(CO)8 (153 mg, 0.450 mmol) and NMO (525 mg, 4.49 mmol) were added according to the general procedures. The reaction mixture was filtered using a sintered glass funnel packed with a short layer of Celite and SiO2. The crude product was purified by flash chromatography (SiO2, hexane/EtOAc, 87:13) to afford the PK products of 58 (150 mg, 71%, 1:0.8 ratio of the epimers) for the oxidative method. Thermal method gave also the PK product 58 (180 mg, 86%, 1:1 ratio of the epimers) as a yellow viscous liquid.

1H NMR (500 MHz): δ = ( 1:1 mixture of exo- and endo-compound) 7.62 (d, J = 2.3 Hz, 1H), 7.27-7.36 (m, 8H), 7.19-7.15 (m, 5H), 6.38 (s, 1H), 6.17 (s, 1H), 5.83 (s, 1H), 5.69 (s, 1H), 4.67 (dd, J = 6.4, 11.5 Hz, 1H), 4.59 (dd, J = 6.4, 11.9 Hz, 1H), 3.82 (broad s, 2H), 3.62 (m, 1H), 3.32 (t, J = 11.9 Hz, 1H), 3.24 (s, 1H), 3.02 (d, J = 3.2 Hz, 1H), 1.41 (s, 9H), 1.38 (s, 9H), 1.35 (s, 9H), 1.34 (s, 9H), 1.06 (s, 9H), 0.89 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), -0.10 (s, 3H); 13C NMR (125 MHz): δ = 207.0, 205.8, 181.6, 179.5, 155.8, 155.7, 153.9, 146.7, 145.6, 142.1, 141.0, 138.4, 138.3, 132.7, 131.6, 129.1, 129.0, 128.2, 127.9, 127.4, 127.3, 127.2, 126.3, 125.5, 124.4, 123.5, 120.6, 75.1, 71.1, 55.9, 54.9, 52.8, 50.8, 35.4, 35.1, 34.6, 31.7, 31.6, 30.9, 30.6, 26.0, 25.8, 18.5, 18.3, 14.3, -4.7, -4.7, -4.8, -5.1; IR (neat, cm⁻¹) = 3105, 2955, 1710,
4,6-Di-tert-butyl-2-iodophenol (60)\textsuperscript{80,87}

To a stirred solution of 2,4-di-tert-butylphenol (0.50 g, 2.4 mmol) in DMF (80 mL), a dropwise addition of N-iodosuccinimide (0.66 g, 3.0 mmol) in acetone (20 mL) was done. The reaction mixture was stirred at 0 °C for 8 h. H₂O (50 mL) was added and the resulting solution was extracted with EtOAc (3x25 mL). The organic phase was combined and treated with 0.1 M HCl (50 mL), washed with saturated NaHCO₃ (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified via flash chromatography (SiO₂, hexane) to afford the 60 (0.55 g, 68%) as a solid: mp: 76-78 °C (lit.\textsuperscript{69,76} 77-79 °C); \(^1\)H NMR (500 MHz): \(\delta = 7.48 \text{ (d, } J = 2.3 \text{ Hz, } 1\text{H}), 7.25 \text{ (d, } J = 2.3 \text{ Hz, } 1\text{H}), 5.36 \text{ (s, } 1\text{H}), 1.37 \text{ (s, } 9\text{H}), 1.26 \text{ (s, } 9\text{H}); \(^{13}\)C NMR (125 MHz): \(\delta = 150.5, 145.1, 136.3, 132.7, 125.1, 89.4, 35.7, 34.3, 31.6, 29.4.

4,6-Di-tert-butyl-2-trimethylsilylethynylphenol (61)\textsuperscript{61}

To a stirred solution of 60 (3.54 g, 10.7 mmol) and Et₃N (5.9 mL) in dioxane (5.9 mL), was added trimethylsilylacetylene (1.37 g, 13.9 mmol), PdCl₂(PPPh₃)₂ (78 mg, 0.12 mmol) and CuI (41 mg, 0.24 mmol). The reaction mixture was stirred at 55 °C (oil bath temperature) under N₂ for 5 h. At the end of reaction time, Et₂O (50 mL) and 1 M HCl
(20 mL) were added and the organic layer was separated, neutralized with a saturated NaHCO₃ (30 mL) solution, washed with H₂O and dried (Na₂SO₄). The organic layer was concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, hexane) to afford 61 (3.03 g, 93.0%), as a solid. mp: 114-116 °C (lit.⁵⁰ 114-116 °C). ¹H NMR (500 MHz): δ = 7.27 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 6.08 (s, 1H), 1.39 (s, 9H), 0.27 (s, 9H); ¹³C NMR (125 MHz): δ = 153.6, 142.1, 134.8, 125.7, 109.2, 102.5, 100.3, 76.8, 35.0, 34.3, 31.5, 29.5, 0.1.

4,6-Di-tert-butyl-2-trimethylsilylethynyl-(2-propenyoxy)benzene (62)

Allyl bromide (1.35 g, 14.9 mmol) was added to a suspension of K₂CO₃ (2.06 g, 14.9 mmol) and 61 (1.50 g, 4.97 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 8 h. This was then quenched with excess water (100 mL) and extract with CH₂Cl₂. The organic layer was then separated, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, hexane/EtOAc, 91:9) to furnish 62 (1.74 g, 98.0%) as a light yellow oil. ¹H NMR (300 MHz): δ = 7.30 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 6.07 (ddt, J = 5.2, 10.7, 17.2 Hz, 1H), 5.41 (dd, J = 1.7, 17.2 Hz, 1H), 5.22 (dd, J = 1.4, 10.7 Hz, 1H), 4.77 (dd, J = 1.4, 5.2 Hz, 2H), 1.37 (s, 9H), 1.28 (s, 9H), 0.24 (s, 9H); ¹³C NMR (75 MHz): δ = 157.5, 145.2, 142.0, 134.4, 129.2, 125.3, 116.6, 116.4, 103.2, 98.5, 73.2, 35.3, 34.5, 30.5, 30.7, 0.1; IR (neat, cm⁻¹) = 3082, 2963, 2864, 2151, 1466, 1361, 1303, 1229,
1203, 1123; HRMS (ESI): Calcd. For C_{22}H_{35}OSi (m/z): 343.2452. Found 343.2446 [M+H]^+.

**4,6-Di-tert-butyl-2-ethynyl-(2-propenloxy)benzene (63)**

K$_2$CO$_3$ (0.49 g, 3.6 mmol) was added to a solution of 62 (0.62 g, 1.7 mmol) in 1:1 mixture of MeOH/THF (10 mL). The reaction mixture was stirred at rt for 4 h. At the end of the reaction time, the reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel plug (EtOAc). The crude product was purified by flash chromatography (SiO$_2$, hexane/ether, 83:17) to furnish 63 (0.50 g, quantitative) as colorless liquid: $^1$H NMR (500 MHz), $\delta$ = 7.38 (d, $J$ = 2.5 Hz, 1H), 7.36 (d, $J$ = 2.5 Hz, 1H), 6.17 (m, 1H), 5.49 (dd, $J$ = 1.3, 10.4 Hz, 1H), 5.29 (dd, $J$ = 1.3, 17.2 Hz, 1H), 4.81 (d, $J$ = 5.3 Hz, 2H), 3.31 (s, 1H), 1.42 (s, 9H), 1.32 (s, 9H); $^{13}$C NMR (125 MHz), $\delta$ = 157.7, 145.4, 142.2, 134.2, 129.5, 125.6, 116.8, 115.5, 81.9, 81.5, 73.6, 35.3, 34.5, 31.4, 30.7.

**6,8-Di-tert-butyl-1-trimethylsilyl-3a,4-dihydro-3H-cyclopenta[c]chromen-2-one (64)**

The enyne 62 (100 mg, 0.29 mmol) was cyclized in toluene (5 mL) following the general thermal PK procedures 3.1.3.3 in the presence of Co$_2$(CO)$_8$ (110 mg, 0.32 mmol). The reaction was
worked up as indicated in the general procedure. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 90:10) to afford 64 (100 mg, 93%) as a light yellow solid, mp: 132-134 °C; ¹H NMR (500 MHz), δ = 7.41 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 4.67 (dd, J = 5.7, 10.4 Hz, 1H), 3.87 (dd, J = 10.4, 13.4 Hz, 1H), 3.15 (m, 1H), 2.62 (dd, J = 7.0, 17.8 Hz, 1H), 1.95 (dd, J = 4.5, 17.8 Hz, 1H), 1.39 (s, 9H), 1.31 (s, 9H), 0.33 (s, 9H); ¹³C NMR (125 MHz), δ = 210.7, 177.3, 152.5, 141.1, 137.4, 133.3, 128.0, 124.5, 119.0, 70.2, 38.2, 37.2, 35.3, 34.7, 31.6, 29.8, 0.1; IR (neat, cm⁻¹) = 2960, 1693, 1578, 1440, 1248, 844; HRMS (ESI): Calcd. For C₂₃H₃₅O₂Si (m/z): 371.2401. Found 371.2402 [M+H]+; Anal. Calcd. for C₂₃H₃₄O₂Si: C, 74.54; H, 9.25. Found: C, 74.13; H, 9.33.

**6,8-Di-tert-butyl-3a,4-dihydro-3H-cyclopenta[c]chromen-2-one (65)**₆⁰,₆¹

![Chemical Structure](image)

The enyne 63 (100 mg, 0.37 mmol) was cyclized in toluene (5 mL) following the general thermal PK procedures 3.1.3.3 in the presence of Co₂(CO)₈ (140 mg, 0.41 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 65 (100 mg, 91%) as a solid, m.p: 178-179 °C (lit.₆⁰,₆¹ 179-180 °C). ¹H NMR (500 MHz): δ = 7.44 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 6.35 (d, J = 1.7 Hz, 1H), 4.64 (dd, J = 5.5, 10.7 Hz, 1H), 3.80 (dd, J = 10.3, 13.4 Hz, 1H), 3.28 (m, 1H), 2.67 (dd, J = 6.9, 17.9 Hz, 1H), 2.04 (dd, J = 4.1, 17.9 Hz, 1H), 1.39 (s, 9H), 1.32 (s, 9H); ¹³C NMR (125 MHz): δ = 206.3,
3-Chloro-2-methylpropene (1.35 g, 14.9 mmol) was added to a suspension of K$_2$CO$_3$ (2.06 g, 14.9 mmol), NaI (2.34 g, 14.9 mmol), and 61 (1.50 g, 4.97 mmol) in DMF (20 mL). The reaction mixture was stirred for 12 h. The reaction was then quenched with water (100 mL) and extracted with CH$_2$Cl$_2$. The organic layers were combined, dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO$_2$, hexane/EtOAc, 91:9) to furnish 66 (1.74 g, 98.0%) as yellow liquid. $^1$H NMR (500 MHz): $\delta$ = 7.32 (d, $J$ = 2.3 Hz, 1H), 7.30 (d, $J$ = 2.8 Hz, 1H), 5.20 (s, 1H), 4.97 (s, 1H), 4.69 (s, 2H), 1.86 (s, 3H), 1.37 (s, 9H), 1.29 (s, 9H), 0.24 (s, 9H); $^{13}$C NMR (125 MHz): $\delta$ = 157.4, 145.2, 142.1, 141.5, 129.4, 125.3, 116.4, 111.1, 103.2, 98.6, 75.5, 35.2, 34.5, 31.4, 30.7, 19.7, 0.02; IR (neat, cm$^{-1}$) = 2961, 2151, 1436, 1249, 960; HRMS (ESI): Calcd. For C$_{23}$H$_{37}$OSi (m/z): 357.2608. Found 357.2613 [M+H]$^+$. 
4,6-Di-tert-butyl-2-ethynyl-(2-methylallyloxy)benzene (67)

K$_2$CO$_3$ (0.49 g, 3.55 mmol) was added to a solution of 66 (0.62 g, 1.7 mmol) in MeOH/THF (10 mL/1:1). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel plug (EtOAc). The residue was purified by flash chromatography (SiO$_2$, hexane/ether, 83:17) to furnish 67 (0.50 g, quantitative) as yellow liquid. $^1$H NMR (300 MHz): $\delta = 7.38$ (d, $J = 2.4$ Hz, 1H), 7.36 (d, $J = 2.4$ Hz, 1H), 5.20 (s, 1H), 5.00 (s, 1H), 4.70 (s, 2H), 3.30 (s, 1H), 1.90 (s, 3H), 1.41 (s, 9H), 1.32 (s, 9H); $^{13}$C NMR (75 MHz): $\delta = 157.7$, 145.3, 142.2, 141.7, 129.6, 125.6, 115.5, 111.8, 81.9, 81.6, 76.0, 35.3, 34.5, 31.5, 30.7, 19.8; IR (neat, cm$^{-1}$) = 3313, 3108, 2974, 2107, 1658, 1438, 1233, 1165, 1123, 1042; HRMS (ESI): Calcd. For C$_{20}$H$_{28}$ONa ($m/z$): 307.2032. Found 307.2037, and Calcd. for C$_{20}$H$_{29}$O ($m/z$): 285.2213. Found 285.2211 [M+Na]$^+$. 

6,8-Di-tert-butyl-1-trimethylsilyl-3a-methyl-4-hydro-3H-cyclopenta[c]chromen-2-one (68):

The enyne 66 (240 mg, 0.64 mmol) was cyclized in toluene (10 mL) following the general thermal PK procedures 3.1.3.3 in the presence of Co$_2$(CO)$_8$ (240 mg, 0.74 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 68 (240 mg, 92%) as a solid, m.p: 156-157 °C; $^1$H NMR (500 MHz), $\delta = 7.40$ (d, $J = 2.3$ Hz, 1H),
7.24 (d, $J = 2.3$ Hz, 1H), 6.23 (s, 1H), 4.32 (d, $J = 10.7$ Hz, 1H), 3.96 (d, $J = 10.7$ Hz, 1H), 2.31 (d, $J = 17.2$ Hz, 1H), 2.02 (d, $J = 17.5$ Hz, 1H), 1.39 (s, 9H), 1.32 (s, 9H), 1.19 (s, 3H), 0.30 (s, 9H); $^{13}$C NMR (125 MHz), δ = 210.1, 181.4, 151.3, 141.2, 137.1, 132.1, 127.9, 124.8, 117.8, 74.6, 47.3, 39.0, 35.2, 34.6, 31.6, 29.7, 22.9, 0.2; IR (neat, cm$^{-1}$) = 2959, 1691, 1529, 1255, 1028, 938; HRMS (ESI): Calcd. For C$_{24}$H$_{37}$O$_2$Si ($m/z$): 385.2557. Found 385.2559 [M+H]$^+$. Anal. Calcd. for C$_{24}$H$_{36}$O$_2$Si: C, 74.94; H, 9.43. Found: C, 74.77; H, 9.23.

6,8-Di-tert-butyl-3a-methyl-3a,4-dihydro-3$H$-cyclopenta[c]chromen-2-one (69);

The enyne 67 (110 mg, 0.39 mmol) was cyclized in toluene (5 mL) following the general oxidative and thermal PK procedures 3.1.3.2 and 3.1.3.3 in the presence of Co$_2$(CO)$_8$ (130 mg, 0.380 mmol) and NMO (453 mg, 3.87 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 69 (97.9 mg, 81.0%) for the oxidative mode. The thermal condition also gave 69 (110 mg, 91%) as a solid, m.p: 130-132 °C; $^1$H NMR (300 MHz): δ = 7.43 (d, $J = 2.4$ Hz, 1H), 7.36 (d, $J = 2.1$ Hz, 1H), 6.23 (s, 1H), 4.33 (d, $J = 10.4$ Hz, 1H), 3.87 (d, $J = 10.7$ Hz, 1H), 2.39 (d, $J = 17.5$ Hz, 1H), 2.20 (d, $J = 17.5$ Hz, 1H), 1.40 (s, 9H), 1.31 (s, 9H), 1.30 (s, 3H); $^{13}$C NMR (75 MHz): δ = 205.8, 174.9, 151.7, 143.2, 138.3, 128.4, 121.5, 120.0, 116.2, 73.9, 47.0, 38.8, 35.2, 34.4, 31.4, ., 29.7, 23.8; IR (neat, cm$^{-1}$) = 3098, 2962, 1700, 1594, 1463, 1183, 1011; HRMS (ESI): Calcd. For C$_{21}$H$_{29}$O$_2$ ($m/z$): 313.2162. Found 313.2164 [M+H]$^+$. 142
4,6-Di-tert-butyl-2-ethynyl-(3-phenyl-2-propenyloxy)benzene (71)

DEAD (3.46 g, 19.9 mmol) in THF (10 mL) was added dropwise to a solution of 61 (2.0 g, 6.60 mmol), cinnamyl alcohol (1.78 g, 13.3 mmol) and PPh₃ (5.21 g, 19.9 mmol) in THF (20 mL) and stirred at 0 °C for 6 h. The solvent was removed in vacuum. The crude product was purified by flash chromatography (hexane) to give the product 71 (2.70 g, 95%) as a white solid, mp. 123-125 °C; ¹H NMR (500 MHz): δ = 7.45 (d, J = 7.3 Hz, 2H), 7.33-7.36 (m, 4H), 7.25-7.28 (m, 1H), 6.82 (d, J = 16.0 Hz, 1H), 6.50 (dt, J = 6.0, 15.8 Hz, 1H), 4.97 (dd, J = 1.8, 5.5 Hz, 2H), 1.42 (s, 9H), 1.31 (s, 9H), 0.27 (s, 9H); ¹³C NMR (125 MHz): δ = 157.5, 145.3, 142.1, 137.0, 132.0, 129.3, 128.6, 127.7, 126.6, 125.8, 125.4, 116.5, 103.3, 98.7, 73.2, 35.3, 34.5, 31.5, 30.8, 0.15; IR (neat, cm⁻¹) = 3109, 2960, 2152, 1434, 1371, 1229, 1120; HRMS (ESI): Calcd for C₂₈H₃₉OSi (m/z): 419.2765. Found 419.2767 [M+H]⁺. Calcd for C₂₈H₃₉NaOSi (m/z): 441.2584. Found 441.2589 [M+Na]⁺.

4,6-Di-tert-butyl-2-trimethylsilylethynyl-(3-phenyl-2-propenyloxy)benzene (71)

K₂CO₃ (1.32 g, 9.57 mmol) was added to a solution of 71 (1.0 g, 2.4 mmol) in 1:1 mixture of MeOH/THF (10 mL). The reaction mixture was stirred at room temperature for 4 h. At the end of the reaction time, the reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel plug (EtOAc). The residue was purified by flash chromatography (hexane/ether, 83:17) to furnish 72 (0.77 g, 93%) as colorless
liquid which later solidified to give a purple solid. mp: 100-102 °C; \(^1\)H NMR (500 MHz): \(\delta = 7.45\) (d, \(J = 7.3\) Hz, 2H), 7.24-7.38 (m, 5H), 6.78 (d, \(J = 16.0\) Hz, 1H), 6.51 (dt, \(J = 5.5\), 15.6 Hz, 1H), 4.94 (dd, \(J = 1.8\), 6.0 Hz, 2H), 3.34 (s, 1H), 1.42 (s, 9H), 1.31 (s, 9H); \(^{13}\)C NMR (125 MHz): \(\delta = 157.8, 145.5, 142.3, 137.0, 132.2, 129.5, 128.6, 127.8, 127.6, 125.7, 115.6, 82.0, 81.6, 73.6, 35.3, 34.5, 31.5, 30.8\); LRMS (ESI): for C\(_{25}\)H\(_{31}\)O: 347 (M+H), for C\(_{25}\)H\(_{30}\)ONa: 369 (M+Na); IR (neat, cm\(^{-1}\)) = 3298, 2959, 2103, 1658, 1578, 1435, 1368, 1230, 1121; Anal. Calcd. for C\(_{25}\)H\(_{30}\)O: C, 86.66; H, 8.73. Found: C, 86.40; H, 8.86.

\textbf{6,8-Di-\textit{tert}-butyl-3-phenyl-1-trimethylsilyl-3a,4-dihydro-3\textit{H}-cyclopenta[c]chromen-2-one (73)}

The enyne 71 (200 mg, 0.48 mmol) was cyclized in (10 mL) of the appropriate solvent following the general oxidative and thermal PK procedures 3.1.3.2 and 3.1.3.3 in the presence of Co\(_2\)(CO)\(_8\) (180 mg, 0.53 mmol) and NMO (620 mg, 5.26 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 73 (170 mg, 81%) for the oxidative mode. The thermal condition also gave 73 (150 mg, 71%) as a light yellow solid, m.p: 129-131 °C; \(^1\)H NMR (500 MHz): \(\delta = 7.46\) (d, \(J = 2.3\) Hz, 1H), 7.42 (d, \(J = 2.3\) Hz, 1H), 7.34 (t, \(J = 7.3\) Hz, 2H), 7.28 (d, \(J = 7.3\) Hz, 1H), 7.19 (d, \(J = 6.9\) Hz, 2H), 4.77 (dd, \(J = 5.5\), 10.5 Hz, 1H), 4.01 (dd, \(J = 10.5\), 13.3 Hz, 1H), 3.30 (dt, \(J = 5.5\), 12.8 Hz, 1H), 3.14 (d, \(J = 5.0\) Hz, 1H), 1.39 (s, 9H), 1.36 (s, 9H), 0.39 (s,
9H); $^{13}$C NMR (125 MHz): $\delta = 209.5, 174.7, 153.0, 141.5, 138.2, 137.7, 132.2, 128.9, 128.7, 128.3, 127.2, 124.7, 118.7, 69.6, 56.1, 46.2, 35.4, 34.8, 31.7, 29.8, 0.1; IR (neat, cm$^{-1}$) = 3106, 2961, 1687, 1581, 1441, 1249, 1007, 939; LRMS (ESI): for C$_{29}$H$_{39}$SiO$_2$: 447 [M+H$^+$], for C$_{29}$H$_{38}$SiO$_2$Na: 469 [M+Na$^+$], for C$_{29}$H$_{37}$SiO$_2$: 445 [M-H]; HRMS (ESI): Calcd. For C$_{29}$H$_{38}$SiO$_2$Na ($m/z$): 469.2533. Found 469.2579 [M+Na$^+$].

6,8-Di-tert-butyl-3-phenyl-3a,4-dihydro-3H-cyclopenta[c]chromen-2-one (74);

The enyne 72 (200 mg, 0.58 mmol) was cyclized in (10 mL) of the appropriate solvent following the general oxidative and thermal PK procedures 3.1.3.2 and 3.1.3.3 in the presence Co$_2$(CO)$_8$ (220 mg, 0.64 mmol) and NMO (740 mg, 6.40 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 74 (200 mg, 91.0%) for the oxidative mode. The thermal condition also gave 74 (160 mg, 73%) as a light yellow solid, m.p: 155-157 °C; $^1$H NMR (500 MHz): $\delta = 7.49$ (d, $J = 2.3$ Hz, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.36 (t, $J = 7.3$ Hz, 2H), 7.30 (d, $J = 7.3$ Hz, 1H), 7.21 (d, $J = 7.3$ Hz, 2H), 6.47 (d, $J = 1.8$ Hz, 1H), 4.74 (dd, $J = 5.5$, 10.5 Hz, 1H), 3.96 (dd, $J = 10.5$, 13.3 Hz, 1H), 3.36 (ddt, $J = 1.8$, 5.5, 12.5 Hz, 1H), 3.26 (d, $J = 4.6$ Hz, 1H), 1.39 (s, 9H), 1.35 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 205.6, 168.2, 153.4, 143.5, 138.7, 137.9, 129.0, 128.8, 128.6, 127.4, 121.3, 119.9, 116.8, 69.2, 56.0, 45.6, 35.3, 34.5, 30.4, 29.7; IR (neat, cm$^{-1}$) = 3105, 2959, 2864, 1712, 1607, 1476, 1214, 1151, 1005; LRMS
(ESI): for C\textsubscript{26}H\textsubscript{30}O\textsubscript{2}K: 413 [M+K], for C\textsubscript{26}H\textsubscript{30}O\textsubscript{2}Na: 397 [M+Na], for C\textsubscript{26}H\textsubscript{31}O: 375 [M+H]; Anal. Calcd. for C\textsubscript{26}H\textsubscript{30}O\textsubscript{2}: C, 83.38; H, 8.07. Found: C, 83.25; H, 8.18.

3-Butenyloxy-4,6-di-\textit{tert}-butyl-2-trimethylsilyl-ethynylbenzene (75)

A solution of diethyl azodicarboxylate (3.46 g, 19.9 mmol) in THF (20 mL) was added dropwise to a stirred solution of 61 (2.0 g, 6.6 mmol), 3-buten-1-ol (0.96 g, 13.3 mmol) and PPh\textsubscript{3} (5.22 g, 19.9 mmol) in THF (50 mL) at 0 °C. The reaction mixture was then stirred for 6 h. At the end of the reaction, the solvent was removed in vacuo. The crude product was purified by flash chromatography (hexane) to give the product 75 (2.35 g, 99%) as a clear liquid. \(^1\)H NMR (300 MHz): \(\delta = 7.31 \text{ (d, } J = 2.8 \text{ Hz, 1H), 7.30 \text{ (d, } J = 2.8 \text{ Hz, 1H), 5.92 \text{ (ddt, } J = 6.9, 10.3, 17.2 \text{ Hz, 1H), 5.15 \text{ (dd, } J = 3.1, 17.2 \text{ Hz, 1H), 5.09 \text{ (dd, } J = 3.1, 10.3 \text{ Hz, 1H), 4.29 \text{ (t, } J = 6.9 \text{ Hz, 2H), 2.61 \text{ (dt (app, q), } J = 6.9, 6.9 \text{ Hz, 2H), 1.38 \text{ (s, 9H), 1.29 \text{ (s, 9H), 0.27 \text{ (s, 9H), 13}}\text{C NMR (75 MHz): } \delta = 157.8, 145.0, 141.9, 134.9, 129.4, 125.3, 116.8, 116.4, 103.5, 98.3, 71.8, 35.3, 34.7, 34.5, 31.5, 30.8, 0.13; IR (neat, cm}^{-1} = 3106, 2959, 2151, 1437, 1235, 1123, 960, 912; HRMS (ESI): Calcd. For C\textsubscript{23}H\textsubscript{37}OSi (m/z): 357.2608. Found 357.2613.
3-Butenyloxy-4,6-di-tert-butyl-2-ethynylbenzene (76)\textsuperscript{60, 61}

\[
\text{K}_2\text{CO}_3 (1.13 \text{ g, 8.20 mmol) was added to a solution of 75 (1.41 g, 4.10 mmol) in 1;1 mixture of MeOH/THF (10 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel using EtOAc. The crude product was purified by flash chromatography (hexane/ether, 83:17) to furnish 76 (0.75 g, 80\%) as a colorless liquid. }^{1} \text{H NMR (500 MHz): } \delta = 7.34 (d, J = 2.4 \text{ Hz, 1H}), 7.33 (d, J = 2.4 \text{ Hz, 1H}), 5.98 (ddt, J = 6.8, 10.3, 17.0 \text{ Hz, 1H}), 5.16-5.20 (m, 1H), 5.09-5.11 (m, 1H), 4.30 (t, J = 7.0 \text{ Hz, 2H}), 3.30 (s, 1H), 2.62-2.67 (m, 2H), 1.39 (s, 9H), 1.29 (s, 9H); ^{13} \text{C NMR (125 MHz): } \delta = 158.1, 145.1, 142.0, 134.9, 129.5, 125.5, 116.8, 115.4, 82.1, 81.3, 72.2, 35.3, 34.8, 34.5, 31.5, 30.8; \text{IR (neat, cm}^{-1}): 3304, 2959, 2107, 1656, 1122, 727.\]

Thermal cyclization of 3-butenyloxy-4,6-di-tert-butyl-2-trimethylsilylethynyl benzene (75)

The enyne 75 (0.20 g, 0.56 mmol) was cyclized in toluene (10 mL) following the general thermal PK procedure 3.1.3.3 in the presence Co\textsubscript{2}(CO\textsubscript{8}) (0.21 g, 0.62 mmol) and heated at 70 °C. The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (SiO\textsubscript{2}, hexane/EtOAc, 90:10) to afford the expected PK product 77 (30 mg, 14\%) as a brown waxy solid and a diene 78 (150 mg, 75\%) as a yellow solid. When the reaction was carried out under CO (1 atm)
conditions, the yield of the product 77 increased to 22% and also starting material was recovered.

7,9-Di-tert-butyl-1-trimethylsilyl-4,4a-dihydro-3H,5H-6-oxabenzo[f]azulen-2-one (77);

\[
\begin{align*}
^1H \text{ NMR (300 MHz): } & \delta = 7.33 (d, J = 3.0 \text{ Hz}, 1H), 6.90 (d, J = 2.4 \text{ Hz}, 1H), 4.37 (dt, J = 3.3, 9.0 \text{ Hz}, 1H), 3.76 (dt, J = 1.2, 11.4 \text{ Hz}, 1H), 2.98 (p, J = 5.1 \text{ Hz}, 1H), 2.70 (dd, J = 6.6, 18.6 \text{ Hz}, 1H), 2.18 \text{ m, 1H}, 2.12 (dd, J = 1.8, 18.6 \text{ Hz}, 1H), 1.76 (dq, J = 3.0, 10.2 \text{ Hz}, 1H), 1.39 (s, 9H), 1.30 (s, 9H), -0.03 (s, 9H); \\
^{13}C \text{ NMR (75 MHz): } & \delta = 212.5, 189.4, 154.6, 144.7, 141.5, 132.6, 125.5, 125.2, 125.2, 72.7, 43.8, 43.7, 35.2, 31.6, 34.7, 31.6, 30.4, -0.7; \text{ IR (neat, cm}^{-1}\text{) = 2954, 1692, 1587, 1560, 1432, 1360, 1248, 1224, 1123, 1068, 1025, 936; \text{ HRMS (ESI): Calcd. For } C_{24}H_{36}O_2SiNa (m/z): 407.2377. \text{ Found } 407.2397 \text{ [M+Na]^+.}
\end{align*}
\]

(7,9-Di-tert-butyl-4-methylene -3,4-dihydro-2H-benzo[b]oxepin-5-ylidenemethyl)-trimethylsilane (78)

Mp. 105-107 °C \(^1H \text{ NMR (500 MHz): } \delta = 7.23 (d, J = 1.8 \text{ Hz}, 1H), 7.19 (d, J = 1.8 \text{ Hz}, 1H), 5.77 (s, 1H), 4.94 (d, J = 6.4 \text{ Hz}, 2H), 4.16 (t, J = 5.1 \text{ Hz}, 2H), 2.76 (t, J = 5.1 \text{ Hz}, 2H), 1.37 (s, 9H), 1.32 (s, 9H), 0.5 (s, 9H); \(^{13}C \text{ NMR (125 MHz): } \delta = 159.1, 153.5, 148.9, 144.4, 139.7, 134.9, 130.5, 123.5, 123.4, 111.8, 70.4, 39.8, 35.3, 34.6, 31.7, 30.6,
0.6; IR (neat, cm$^{-1}$) = 2955, 1639, 1571, 1468, 1433, 1361, 1245, 1166; HRMS (Cl): Calcd. For C$_{23}$H$_{36}$SiO ($m/z$): 356.2530. Found 356.2533 [M$^+$].

**Thermal cyclization of 3-butenyloxy-4,6-di-tert-butylethynylbenzene (76)**

The enyne 76 (200 mg, 0.70 mmol) was cyclized in 10 mL of toluene following the general thermal PK procedure 3.1.3.3 in the presence Co$_2$(CO)$_8$ (270 mg, 0.78 mmol) and heated at 70 °C. The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford epoxide 79 (40 mg, 17%) and Michael addition product 81 (30 mg, 13%) as a colorless solid.

**Oxidative cyclization of 3-butenyloxy-4,6-di-tert-butylethynylbenzene (76) under oxygen atmosphere.**

The enyne 76 (300 mg, 1.06 mmol) was dissolved in 10 mL of CH$_2$Cl$_2$ and Co$_2$(CO)$_8$ (400 mg, 1.16 mmol) was added under N$_2$ and stirred for 2 h. The reaction mixture was then purged with O$_2$ and then NMO (1.24 g, 10.6 mmol) was added in three portions at 0 °C and the reaction was left to stir to room temperature under oxygen atmosphere. The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford only the epoxide 79 (220 mg, 63%).
4,6-Di-tert-butyl-8-13-dioxatetracyclo[9.2.2.02,7.01,12]tetradeca-2,4,6-triene-14-one

(79)\(^{61}\)

\(^1\)H NMR (500 MHz): \(\delta = 7.40\) (d, \(J = 3.0\) Hz, 1H), 7.37 (d, \(J = 3.0\) Hz, 1H), 4.46 (d, \(J = 13.5\) Hz, 1H), 4.05 (s, 1H), 3.41 (t, \(J = 13.5\) Hz, 1H), 2.96 (s, 1H), 2.74 (ddd, \(J = 1.0, 6.5, 18.5\) Hz, 1H), 2.52 (t, \(J = 15.5\) Hz, 1H), 1.97 (d, \(J = 18.5\) Hz, 1H), 1.91 (d, \(J = 15.0\) Hz, 1H), 1.34 (s, 9H), 1.32 (s, 9H).

\(^{13}\)C NMR (125 MHz): \(\delta = 207.9, 157.7, 145.5, 141.3, 125.5, 125.1, 70.1, 67.5, 37.5, 36.6, 35.2, 34.7, 32.4, 31.6, 31.6, 31.3, 30.7\).

4,6-Di-tert-butyl-14-hydroxy-8-oxa-tricyclo[9.2.1.0^2,7]tetradeca-2,4,6-triene-13-one

(81)

Mp. 192-194 °C \(^1\)H NMR (500 MHz): \(\delta = 7.23\) (d, \(J = 2.3\) Hz, 1H), 7.07 (d, \(J = 2.3\) Hz, 1H), 4.18 (d, \(J = 11.9\) Hz, 1H), 3.51 (t, \(J = 10.5\) Hz, 1H), 3.27 (s, 1H), 3.06 (dd, \(J = 8.7, 18.3\) Hz, 1H), 2.66 (s, 1H), 2.38 (m, 1H), 2.16 (d, \(J = 18.3\) Hz, 1H), 1.96 (s, 1H), 1.72 (d, \(J = 14.7\) Hz, 1H), 1.33 (s, 9H), 1.31 (s, 9H); \(^{13}\)C NMR (125 MHz): \(\delta = 219.2, 145.5, 142.0, 129.0, 123.4, 71.1, 63.0, 43.0, 41.2, 35.5, 35.2, 34.5, 31.6, 31.2; IR (neat, cm\(^{-1}\)) = 3396, 2957, 1734; LRMS (ESI): for C\(_2\)H\(_{30}\)O\(_3\)Na: 353 [M+Na], for C\(_2\)H\(_{30}\)O\(_3\)Cl: 365 [MCl\(^-\)], for C\(_2\)H\(_{29}\)O\(_3\): 329 [M-H]; Anal. Calcd. for C\(_2\)H\(_{30}\)O\(_3\): C, 76.33; H, 9.15. Found: C, 76.17; H, 9.31.
4,6-Di-tert-butyl-8-oxa-tricyclo[10.2.1.02,7]pentadeca-1(15),2,4,6-tetraene-14-one \(^{60,61}\) (83)

The enyne \(82\) (130 mg, 0.44 mmol) was cyclized in 10 mL of toluene following the general thermal PK procedure \(3.1.3.3\) in the presence \(\text{Co}_2(\text{CO})_8\) (164 mg, 0.48 mmol) and heated at 70 °C. The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford the cyclization compound \(83\) (120 mg, 86%) as a colorless solid, m.p:190-192 °C (lit.\(^{49}\), mp. 191-192 °C); \(^1\)H NMR (300 MHz): \(\delta = 7.28 (d, J = 2.5 \text{ Hz}, 1\text{H}), 7.52 (s, 1\text{H}), 7.07 (d, J = 2.5 \text{ Hz}, 1\text{H}), 4.37 (t, J = 10.3 \text{ Hz}, 1\text{H}), 3.34-3.35 (m, 1\text{H}), 3.20-3.22 (m, 1\text{H}), 2.67 (dd, J = 5.8, 18.0 \text{ Hz}, 1\text{H}), 2.27 (d, J = 18.0 \text{ Hz}, 1\text{H}), 1.93-2.04 (m, 1\text{H}), 1.80-1.89 (m, 1\text{H}), 1.42-1.47 (m, 1\text{H}), 1.34 (s, 9\text{H}), 1.30 (s, 9\text{H}), \(^{13}\)C NMR (75 MHz), \(\delta = 208.5, 166.5, 153.3, 145.3, 141.5, 141.1, 127.8, 123.9, 123.6, 76.3, 40.5, 39.3, 35.0, 34.6, 33.7, 31.6, 31.2, 25.6\); IR (KBr, cm\(^{-1}\)) 2956, 1706, 1594, 1441, 1110, 750; HRMS (ESI): Calcd. For \(\text{C}_{22}\text{H}_{30}\text{O}_2\text{Na} (m/z)\): 349.2138. Found 349.2159 [M+Na]\(^+\); Calcd. For \(\text{C}_{44}\text{H}_{60}\text{O}_4\text{Na} (m/z)\): 675.4384. Found 675.4326 [2M+Na]\(^+\).
2,4-Di-tert-butyl-6-(-3-hydroxy-3-methylbut-1-ynyl)phenol (84)

To a stirred solution of 60 (2.82 g, 8.50 mmol) and Et₃N (5.9 mL) in dioxane (5.9 mL) was added 2-hydroxy-2-methylbut-1-ynyl (2.14 g, 25.5 mmol), PdCl₂(PPh₃)₂ (0.30 g, 0.43 mmol) and CuI (0.16 g, 0.84 mmol). The reaction mixture was stirred at 55 °C (oil bath temperature) under N₂ for 5 h. At the end of reaction time, Et₂O (50 mL) and 1 M HCl (20 mL) were added and the organic layer was separated, neutralized with a saturated NaHCO₃ (30 mL) solution, washed with H₂O and dried (Na₂SO₄). The organic layer was concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, hexane) to afford 84 (2.30 g, 94%), as a golden yellow solid. mp: 97-99 °C. ¹H NMR (300 MHz): δ = 7.27 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.02 (s, 1H), 2.31 (s, 1H), 1.66 (s, 6H), 1.40 (s, 9H), 1.28 (s, 9H); ¹³C NMR (75 MHz): δ = 153.0, 142.1, 134.9, 125.8, 125.3, 108.6, 100.7, 77.7, 66.0, 35.0, 34.3, 31.7, 31.5, 29.5; IR (neat, cm⁻¹) = 3358, 2959, 2223, 1443, 1415, 1363, 1197; HRMS (ESI): Calcd. for C₁₉H₂₆O₂Na (m/z): 311.1982. Found 311.1985 (M+Na)⁺.
2,4-Di-tert-butyl-6-(-3-methylbut-1-ynyl)phenol (85)

To a stirred solution of 84 (0.10 g, 0.35 mmol) and NaBH₄ (0.13 g, 3.5 mmol) in dichloromethane (5.0 mL) at 0 °C, was added TFA (3 mL) over a period of 10 minutes. The reaction mixture was then decanted into 300 mL of iced water and extracted with CH₂Cl₂ (20 mL). The organic layer was separated, neutralized with a saturated NaHCO₃ (30 mL) solution, washed with H₂O and dried (Na₂SO₄). The organic layer was then concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, n-hexane) to afford 85 (0.90 g, 96%), as a golden yellow oil. ¹H NMR (500 MHz): δ = 7.23 (d, J = 2.8 Hz, 1H), 7.17 (d, J = 2.8 Hz, 1H), 6.03 (s, 1H), 1.28 (s, 9H), 2.86 (sept, J = 6.9 Hz, 1H), 1.40 (s, 9H), 1.30 (d, J = 6.9 Hz, 6H); ¹³C NMR (125 MHz): δ = 152.8, 141.9, 134.5, 125.6, 124.4, 109.9, 102.8, 74.8, 35.0, 34.3, 31.6, 29.5, 23.3, 21.5; IR (neat, cm⁻¹) = 3497, 2959, 1443, 1363, 1234, 880; HRMS (ESI): Calcd. for C₁₉H₂₉O (m/z), 273.2213. Found 273.2221.

4,6-Di-tert-butyl-2-(-2-methylbut-3-yn-2-ol)-(2-methylallyloxy)benzene (86)

3-Chloro-2-methylpropene (1.26 g, 13.9 mmol) was added to a suspension of K₂CO₃ (1.92 g, 13.9 mmol), NaI (2.08 g, 13.9 mmol), and 84 (1.0 g, 3.47 mmol) in DMF (20 mL). The reaction mixture was stirred for 12 h. The was then quenched with excess of water (100 mL) and extract with CH₂Cl₂. The organic layers were combined and dried (Na₂SO₄). The organic layer was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, n-hexane) to afford 86 (1.30 g, 94%), as a golden yellow oil. ¹H NMR (500 MHz): δ = 7.28 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 2.8 Hz, 1H), 6.03 (s, 1H), 1.28 (s, 9H), 2.86 (sept, J = 6.9 Hz, 1H), 1.40 (s, 9H), 1.30 (d, J = 6.9 Hz, 6H); ¹³C NMR (125 MHz): δ = 152.8, 141.9, 134.5, 125.6, 124.4, 109.9, 102.8, 74.8, 35.0, 34.3, 31.6, 29.5, 23.3, 21.5; IR (neat, cm⁻¹) = 3497, 2959, 1443, 1363, 1234, 880; HRMS (ESI): Calcd. for C₁₉H₂₉O (m/z), 273.2213. Found 273.2221.
pressure. The residue was then purified by flash chromatography (SiO₂, hexane/EtOAc, 91:9) to furnish **86** (0.88 g, 74%) as a light yellow solid, mp: 91-93 °C. ¹H NMR (500 MHz): δ = 7.31 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 2.7 Hz, 1H), 5.25 (s, 1H), 4.99 (s, 1H), 4.63 (s, 2H), 2.12 (s, 1H), 1.85 (s, 3H), 1.60 (s, 6H), 1.38 (s, 9H), 1.29 (s, 9H); ¹³C NMR (75 MHz); δ = 157.0, 145.3, 142.1, 141.9, 128.8, 125.0, 116.1, 110.7, 97.9, 80.1, 75.5, 65.8, 35.3, 34.5, 31.7, 31.4, 30.7, 29.7, 19.7; IR (neat, cm⁻¹) = 3331, 2956, 2866, 1657, 1467, 1436, 1410, 1361, 1229, 1200, 1166, 1125, 1038; HRMS (ESI): Calcd. for C₂₃H₃₄NaO₂⁺ m/z, 365.2451, found m/z, 365.2450 [M+Na]⁺; Anal. Calcd. for C₂₃H₃₄O₂: C, 80.65; H, 10.01. Found: C, 80.11; H, 9.89.

**4,6-Di-tert-butyl-2-(2-methylbut-3-ynyl)-(2-methylallyloxy)benzene (87)**

3-Chloro-2-methylpropene (0.15 g, 1.7 mmol) was added to a suspension of K₂CO₃ (0.11 g, 0.81 mmol), NaI (0.25 g, 1.7 mmol) and **85** (0.11 g, 0.40 mmol) in DMF (20 mL). The reaction mixture was stirred for 12 h. The reaction was then quenched with water (100 mL) and extracted with CH₂Cl₂. The organic layers were separated, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 91:9) to furnish **87** (0.12 g, 92%) as a light yellow oil. ¹H NMR (300 MHz): δ = 7.27 (d, J = 2.7 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 5.21 (t, J = 1.0 Hz, 1H), 4.98 (t, J = 1.4 Hz, 1H), 4.67 (s, 2H), 2.74-2.88 (sept, J = 6.9 Hz, 1H), 1.87 (s, 3H), 1.38 (s, 9H), 1.29 (s, 9H), 1.26 (d, J = 7.2 Hz, 6H); ¹³C NMR (75 MHz): δ = 156.8, 145.1, 141.9, 141.7, 128.9, 124.2, 117.2, 110.9, 99.9,
75.2, 35.2, 34.5, 31.5, 30.7, 29.4, 23.0, 21.6, 19.7; IR (neat, cm⁻¹) = 2964, 2871, 2229, 1660, 1595, 1437, 1362, 1260; HRMS (CI): Calcd. For C₂₃H₃₄O⁺ (m/z): 326.2604. Found 326.2585 [M]+.

6,8-Di-tert-butyl-1-(-1-hydroxy-1-methylethyl)-3a-methyl-3a,4-dihydro-3H-cyclopenta[c]chromen-2-one (88);

The enyne 86 (110 mg, 0.32 mmol) was cyclized in the appropriate solvent (10 mL) following the general oxidative and thermal PK procedures 3.1.3.2 and 3.1.3.3 in the presence Co₂(CO)₈ (120 mg, 0.35 mmol) and NMO (410 mg, 3.51 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 88 (40 mg, 33%) for the oxidative mode. The thermal condition also gave 88 (91 mg, 75%) as a light yellow liquid. ^1H NMR (300 MHz): δ = 7.39 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 4.72 (s, 1H), 4.32 (d, J = 10.7 Hz, 1H), 3.96 (d, J = 11.0 Hz, 1H), 2.38 (d, J = 18.2 Hz, 1H), 2.16 (d, J = 18.2 Hz, 1H), 1.69 (s, 3H), 1.56 (s, 3H), 1.38 (s, 9H), 1.31 (s, 9H), 1.16 (s, 3H); ^13C NMR (75 MHz): δ = 207.9, 166.4, 151.1, 141.0, 138.5, 136.7, 127.4, 125.8, 116.6, 74.7, 71.4, 46.0, 36.2, 35.2, 34.5, 31.5, 31.4, 29.6, 27.8, 22.6; IR (neat, cm⁻¹) = 3393, 2956, 2869, 1680, 1603, 1467, 1438, 1025; HRMS (ESI): Calcd. for C₂₄H₃₅O₃ (m/z): 371.2581. Found 371.2587 [M+H]^+. 

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6,8-Di-tert-butyl-1-isopropyl-3a-methyl-3a,4-dihydro-3H-cyclopenta[c]chromen-2-one (89)

The enyne 87 (110 mg, 0.34 mmol) was cyclized in (10 mL) of the appropriate solvent following the general oxidative and thermal PK procedures 3.1.3.2 and 3.1.3.3 in the presence Co₂(CO)₈ (130 mg, 0.370 mmol) and NMO (395 mg, 3.37 mmol). The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford 89 (77.6 mg, 65%) for the oxidative mode. The thermal condition also gave 89 (100 mg, 84%) as a solid: mp: 147-149 °C; ¹H NMR (300 MHz): δ = 7.40 (d, J = 2.3 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 4.31 (d, J = 10.5 Hz, 1H), 3.90 (d, J = 10.5 Hz, 1H), 3.14 (m, 1H), 2.28 (d, J = 17.9 Hz, 1H), 2.04 (d, J = 17.9 Hz, 1H), 1.40 (s, 9H), 1.38 (d, J = 6.8 Hz, 3H), 1.32 (s, 9H), 1.26 (d, J = 6.8 Hz, 3H), 1.19 (s, 3H); ¹³C NMR (75 MHz): δ = 206.2, 164.9, 150.9, 142.0, 138.8, 137.3, 126.9, 123.0, 117.1, 74.9, 46.2, 35.8, 35.3, 34.4, 31.5, 29.6, 25.9, 22.9, 20.6, 19.7; IR (neat, cm⁻¹) = 3375, 2962, 1698, 1611, 1474, 1386, 1363, 1307, 1231, 1166, 1129, 1021; HRMS (ESI): Calcd. for C₂₄H₃₅O₂ (m/z): 355.2632. Found 355.2635 [M+H]⁺.
PART II

APPROACH TO THE TOTAL SYNTHESIS OF HAMIGERAN

VIA THE PAUSON-KHAND REACTION
CHAPTER 4
TOTAL SYNTHESIS OF HAMIGERANS

4.1 Introduction

Total synthesis of natural products is one of the most vigorous research frontiers in chemistry of our times. It is considered by most people as the engine that drives organic synthesis forward, this endeavor combines elements of art, science, and technology and provides a strong and indispensible foundation for drug discovery. The pharmaceutical and biotechnology sectors are the driving force behind this field of study. Apparently this is due to its potential applications in these industries and by the discovery of naturally occurring novel bioactive molecules that are relevant to disease. The examples of aspirin, penicillin, and paclitaxel come to mind, but these are only a few of the myriad of naturally occurring lead compounds that provided us with medical breakthroughs. With recent progress made in molecular and cell biology, the science of chemical synthesis do promise to become even more effective in the hands of medicinal chemists who are poised to synthesize the next generation of drugs against disease.

Since the discovery of the Pauson-Khand (PK) reaction (formally a [2+2+1] cycloaddition) in the early 70’s,¹ a great deal of work has transpired to increase the synthetic value of this method and it is now regarded as a method of choice when preparing cyclopentenones.² The synthetic utility of the PK reaction has been
demonstrated by the utilization of this cyclopentenone forming reaction, in the total synthesis of numerous natural products including pentalene, coriolin and hirsutic acid, among others.

![Chemical structures of pentalene, Coriolin, and Pentalenic acid.](image)

**Fig 4.1.** Some natural products synthesized via PK reaction.

### 4.1.1 Hamigerans

It was demonstrated earlier in this work that it is possible to construct highly congested cyclopentenones via the PK reaction. Given this success, we intend to explore the application of this strategy in the total synthesis of hamigeran family of natural products. Hamigerans are halogenated marine natural products isolated by Cambie and co-workers.

![Chemical structures of Hamigeran A, Debromohamigeran A, Hamigeran B, 4-Bromohamigeran B, Hamigeran C, and Hamigeran D.](image)

**Fig 4.2.** The hamigeran family
The hamigerans are benzannulated terpenes isolated from the marine sponge *Hamigerans tarangaensis* Bergquist and Fromont (family Anchinoidae, syn. Phorbasidae) collected from the Hen and Chicken Islands in New Zealand. These natural products contain a carbon skeleton with a polysubstituted aromatic ring fused to [4.3.0] or [5.3.0] bicyclic system containing three to four stereogenic centers and an isopropyl group.

Evaluation of these compounds for biological activity showed hamigeran D having the strongest in-vitro antitumor activity against P-388 (a murine leukemia) with an IC$_{50}$ of 8 μM. Similar biological activity was described for both hamigeran B and 4-bromohamigeran B with IC$_{50}$s of 13.5 and 13.9 μM respectively against P-388. Hamigeran C had IC$_{50}$ of 16.0 μM. Hamigeran A has low cytotoxicity with IC$_{50}$ of 31.6 μM. Furthermore when screened against the Gram-positive bacterium *Bacillus subtilis*, hamigeran C and D showed a 3-mm inhibition zone outside the disk at assay loadings of 96 and 150 μg respectively.

### 4.1.2 Synthetic Approaches

These natural products have attracted attention from the synthetic community leading to the report of several synthetic approaches. Nicolaou reported a rather lengthy synthetic route to hamigeran A and B via an intramolecular Diels-Alder reaction of $o$-enolquinodimethane that was generated in situ. A photoenolization of the substituted aldehyde and subsequent Diels-Alder (PEDA) trapping of the generated hydroxyl-$o$-
quinodimethanes to get to the hamigeran A and B core. Upon further functionalization, the natural products were obtained (Scheme 4.1).

Scheme 4.1

Clive and Wang\textsuperscript{9,10} used free radical processes to annulate the five membered ring onto a tetralone derivative. They began their synthesis by conversion of commercially available \textit{m}-cresol to phenolic acid with succinic acid. The phenolic acid was further functionalized and then cyclized to give the tetralone. The tetralone was then alkylated before using a free radical method to annulate the five membered ring.
onto the tetralone. This reaction gave the undesired stereochemistry at C-1 position as shown in the Scheme 4.2 below.

Scheme 4.2

Trost and coworkers\textsuperscript{11} used a palladium catalyzed coupling strategy in an asymmetric synthesis of Hamigeran B. While Mehta and Shende\textsuperscript{12} synthesized 6-epi-hamigeran B by using a Heck cyclization as the key step. Limonene was converted to the cyclopentane aldehyde containing an appropriately positioned quaternary methyl and isopropyl group. The cyclopentane aldehyde was subsequently functionalized to give the cyclopentane aldehyde which was then coupled to the aromatic ring to give the aryl ketone. The aryl triflate derivative was subjected to the Heck reaction to furnish the
tricyclic framework of the Hamigeran B. This tricyclic core was then converted to the 6-epi-(-)-hamigeran B through a few more steps (Scheme 4.3).

**Scheme 4.3**

Reagents and conditions: (a) BTSE, TMSOTf (0.01 eq.), DCM, -78 °C; (b) O₃, MeOH, -78 °C; (c) NaBH₄, MeOH, 0 °C; (d) POCl₃, pyridine, 0 °C-rt; (e) HCl, THF, rt. 6 h; (f) t-BuLi, hexane, 0 °C, 1 h, then -78 °C to 0 °C; (g) PDC, 4 A mol. sieves, DCM, 10 h; (h) 20% HCl, THF, 5 h; (i) Tf₂O, pyridine, rt, 10 h (j) Pd(OAc)₂ (20 mol%), DPPP (20 mol%), NEt₃, DMF, 90 °C, 10 h; (k) 10% Pd/C, H₂, 5 h; (l) SeO₂, AcOH (cat.), aq. dioxane, reflux, 24 h; (m) BBr₃, DCM, -20 °C, 5 h; (n) NBS, DIPA (cat.), DCM, 0 °C, 3 h.

Wright and Sperry⁰¹ were able to obtain the hamigeran core through a two-step electrochemical benzannulation reaction. The annulation was effected by an initial conjugate addition of a phenethyl cuprate to 3-methylcyclopentenone with *in situ* silylation of the resulting enolate. An anodic oxidation was employed to effectively couple the pendant arene and the silyl enol ether to produce the key intermediate for the synthesis of the natural product. Hence this method allowed the preparation of the
tricyclic core of hamigeran A and B in just four steps from the commercially available starting materials (Scheme 4.4).

**Scheme 4.4**

4.2 Project Strategy

As mentioned earlier in this dissertation the intramolecular mode of the Pauson-Khand (IMPK) reaction is a particularly attractive tool as it permits the rapid increase of molecular complexity in a single synthetic step. It has been extensively used in the synthesis of bicyclo[3.3.0]octanes and bicyclo[4.3.0]nonanes ring system via the IMPK cyclization of 1,6- and 1,7-enynes respectively (Figure 4.3).

**Figure 4.3.** Rings assembled via the IMPK reaction
In this study we believe that the IMPK cyclization method will be an effective way to access the tricyclic core of the hamigerans. The tricyclic cores of both hamigeran A, B and hamigeran C, D can be obtained from the PK products of 1,7- and 1,8-enynes respectively (Figure 4.4). It should be noted that the core of hamigeran C and D can be obtained from the lower homolog via a ring expansion.

![Diagram of Hamigeran core assembly via IMPK reaction](image)

**Figure 4.4.** Hamigeran core assembly via IMPK reaction

From our previous studies, where we used steric buttressing elements to enhance the IMPK reaction to cyclize successfully 1,7- and 1,8-enynes leading to benzo[c]bicyclo[4.3.0] and benzo[c]bicyclo[5.3.0] systems. These appeared to provide ample precedence for application of this tactic in a total synthesis of the hamigerans. (Scheme 4.5).
Scheme 4.5

Reagents and conditions: (a) Co$_2$(CO)$_8$, toluene, 70 °C
CHAPTER 5

RESULTS AND DISCUSSIONS

5.1 IMPK Reaction in Total Synthesis of the Hamigerans

To date, no total synthesis has been reported in the literature for the larger hamigeran C and D. We intend to employ a synthetic approach to hamigerans with an identical starting material to that used in the Nicolaou approach (Scheme 4.1). Also, we intend to use a similar ortho lithiation method to obtain the tetrasubstituted aryl derivative.

5.2 Retrosynthesis

The proposed retrosynthesis is given below (Scheme 5.1). From our retrosynthesis hamigeran A and B have a common tricyclic core, while hamigeran C and D also has a same tricyclic core. These cores can be obtained from the functionalization of the PK product 94 for hamigeran A and B core and the hamigeran C and D core from PK product 97. The PK products 94 and 97 can be obtained from the IMPK cyclization of the 1,7-enyne 93 and 1,8-enyne 96 respectively. Both enynes 93 and 96 can be accessed by the alkenylation of a common precursor, benzaldehyde 92. This benzaldehyde 92 in turn can be obtained in several steps from the aryl iodide 91. This iodo aryl amide 91 can be accessed from commercially available salicylic acid 90 by subjecting the acid to
functional group interconversion to give amide before treating it with $t$-BuLi / I$_2$ to afford 91.

Scheme 5.1

5.3 Total Synthesis
The total synthesis will be done in three different stages. The first stage was to prepare the aryl iodide 91 which is the precursor to substrate 92. The second stage will be to get to the hamigeran core which can be accessed through the PK cyclization reaction. The final stage will be the functionalization of the core to provide the various hamigeran natural products.

**Stage 1**

The first stage of the total synthesis started with the protection of the hydroxyl function of the commercially available 4-methyl salicylic acid 91 by treating it with Me₂SO₄ in the presence of KOH to give 99 (Scheme 5.2). The 2-methoxy-4-methylbenzoic acid 99 was subjected to functional group interconversion by reacting it with oxalyl chloride and t-butylamine to give the amide 100.⁶-⁸ A directed ortho metalation reaction was carried out on compound 100 using 2.2 equivalents of t-BuLi and then quenched with I₂ to compound 91 in 70% yield (Scheme 5.2).

**Scheme 5.2**
Initially, attempts were made to convert the amide 91 to an ester function 103 but these were not successful. When 91 was heated to reflux for 2 hours with \( p \)-TsOH, an approach we had found successful in another context in our group,\(^6\)\(^-\)\(^8\),\(^9\) no reaction was observed. The starting material was recovered as shown in Scheme 5.3.

**Scheme 5.3**

\[
\begin{align*}
91 & \xrightarrow[p-TsOH, MeOH, reflux, 2 h]{X} \text{No reaction (NR)} \\
\end{align*}
\]

Under more acidic conditions, the amide 91 gave only a primary amide 106 with the loss of \( i \)-butene as shown in Scheme 5.4 below. The amide 91 was also heated to reflux in concentrated \( H_2SO_4 \) for 2 days, but the expected product was not obtained, instead, the primary amide 106 was isolated.

**Scheme 5.4**

\[
\begin{align*}
91 & \xrightarrow[CF_3CO_2H, reflux, 2 h]{X} 106 \\
91 & \xrightarrow[Conc. H_2SO_4, MeOH, reflux, 2 days]{X} 106 \\
\end{align*}
\]

Furthermore, an attempt to convert the secondary amide to the carboxylic acid by heating to reflux in a mixture of conc. \( H_2SO_4/H_2O \) (1:2 v/v) for just one day only led to the recovery of the starting material. However when the mixture was heated to reflux for 3 days it led to a complete loss of the amide function to give the anisole 107
(Scheme 5.5). Compound 107 may be formed by initial conversion of the secondary amide to the carboxylic acid and subsequent decarboxylation.\textsuperscript{15,16}

\textbf{Scheme 5.5}

\[\begin{align*}
\text{Conc. } \text{H}_2\text{SO}_4/ \text{H}_2\text{O} &\quad \text{reflux, 1 days} \\
\text{Conc. } \text{H}_2\text{SO}_4/ \text{H}_2\text{O} &\quad \text{reflux, 3 days}
\end{align*}\]

At this point, we decided to reduce the primary amide 106 formed in the reaction shown in Scheme 5.4 to the aldehyde functionality using DIBAL-H or LiAlH\textsubscript{4}. Under both conditions, only the starting material was recovered as shown in Scheme 5.6.

\textbf{Scheme 5.6}

\[\begin{align*}
\text{DIBAL-H} &\quad \text{toluene, -78 }^\circ\text{C} \\
\text{LiAlH}_4, \text{THF} &\quad \text{Et}_2\text{NH, rt}
\end{align*}\]

Therefore, an alternative route to the aldehyde 112 was devised. We brominated the commercially available 2,5-dimethylphenol 108 in the presence of aluminum and Br\textsubscript{2} to give the perbrominated product 109.\textsuperscript{17,18} The perbromophenol 109 was debrominated
compound 106 by heating to reflux in 45% aqueous hydroiodic acid to give the 3-bromo-2,5-dimethyl phenol 110. The protection of the phenolic function using dimethyl sulfate gave the 3-bromo-2,5-dimethylanisole 111. This compound was then subjected to a free radical reaction with NBS using AIBN as the initiator followed by oxidation with DMSO and NaHCO₃ to give the aldehyde 112 in 45% yield as shown in Scheme 5.7.

At this point we came across a report by Keck et al. that helped to explain the difficulties encountered in amide 91 conversion to the ester 103 (Scheme 5.2). They reported a two-step, one pot procedure, in which a tertiary amide is first treated with trimethyloxonium tetrafluoroborate to generate an imidate intermediate. This imidate intermediate was then hydrolyzed, generally by the addition of saturated aqueous sodium bicarbonate solution. Interestingly, it was reported that if the two ortho
positions of the aromatic amide were substituted, the conversion does not take place. However if one of the two ortho substituent is a free hydroxyl group the conversion proceeds smoothly. It was also reported that if this hydroxyl function is protected, the conversion to the ester will be hindered, except when protected with TBS group. Their results show that in the presence of trimethyloxonium tetrafluoroborate, the OTBS function was deprotected first before the conversion to a free phenolic ester takes place (Scheme 5.8).

![Scheme 5.8](image)

Based on these results, we decided to investigate the procedure using our compound 91. Deprotection of compound 91 using BBr$_3$ gave compound 101. Then 101 was reacted with the trimethyloxonium tetrafluoroborate to give the imidate ester which was hydrolyzed with NaHCO$_3$ to give the ester 102 (Scheme 5.2). With 102 in hand, the
free hydroxyl group was protected with \( \text{Me}_2\text{SO}_4 \) and then the ester was reduced with DIBAL-H to the benzylic alcohol 104. Pyridinium chlorochromate (PCC) was then used to oxidize the benzylic alcohol to benzaldehyde 105 in good yield as shown in Scheme 5.9.

### Scheme 5.9

![Scheme 5.9](image)

**Stage 2**

This stage of the total synthesis focuses on the construction of the enyne 93 and the cyclization of this enyne to give the PK cyclization product 94. Initially the substrate 105 was subjected to palladium catalyzed Sonogashira reaction with 3-methyl-1-butyne. However, only the starting material was recovered. Several conditions reported for effecting the Sonogashira reaction were employed to promote this coupling, but with no success. We attributed this failure to the volatility of the alkyne which has a boiling point of 23 °C; hence under the Sonogashira conditions the alkyne evaporates before the coupling reaction takes place (Scheme 5.10).
The substrate 105 was then subjected to the Sonogashira reaction with 3-hydroxy-3-methyl-1-butyne, which has a higher boiling point. From this reaction, the Sonogashira product 92 was isolated in excellent yield.\(^\text{21}\) A Grignard reaction was then carried out with compound 92 and 2-methylallylmagnesium chloride to give the enyne 93. Disappointingly when substrate 93 was subjected to the thermal PK conditions, the reaction did not give the expected PK product, rather only starting material was recovered (Scheme 5.11).
The cyclization method used by Blanco-Urgoiti et al.\textsuperscript{22} was attempted next. Preheated 4Å molecular sieves were used in an attempt to cyclize the enyne 93 in the presence of 10 mol\% of the catalyst in toluene at 65 °C. However, this reaction did not give the cyclization product either, again only the starting material was recovered (Scheme 5.12).

**Scheme 5.12**

Also the cyclization of enyne 93 was attempted by adsorbing the alkyne-dicobalt hexacarbonyl complex of 93 to SiO\textsubscript{2} before heating it at 65 °C for 3 h.\textsuperscript{23} In this case also only the starting material was also recovered (Scheme 5.12).

**Scheme 5.12**

The reason for the failure of this cyclization may be due to the facile free rotation of the alkene arm of enyne 93. This free rotation of the alkene arm makes it
difficult for the alkene and alkyne arms to come in close proximity for the cyclization to occur. Hence the reactive rotamer is not the most stable one. The most stable rotamer places the alkene and alkyne moieties far apart from each other as shown in Figure 5.1. Thus, heating the Co2(CO)8 complex simply leads to thermal decomplexation and recovery of starting material.

![Figure 5.1. Rotational isomers of substrate 93](image)

We have shown in the earlier chapter that the presence of a large o-substituent can promote cyclization. However, the buttressing effect of the aromatic methoxy group is very minimal, so increasing the steric bulk of the phenolic group may increase the population of the reactive rotamer leading to cyclization. Alternatively, deprotection of the phenolic group and then locking up the phenolic and the benzylic hydroxyl group will reduce the rotational degree of freedom of the alkene arm. Hence, the population of the reactive rotamer of the substrate 93 will be increased.

Initial attempts to deprotect the methoxy group of compound 93 with BBr3 did not give the expected enyne 121. Instead it gave a dark complex mixture which could not be purified or characterized (Scheme 5.14).
At this point, a slight modification of the synthetic scheme became necessary so as to permit the incorporation of a bulkier buttressing group at the phenolic function. Hence, $t$-butyldimethylsilyl group was used instead of using the methyl group to protect the phenol function. The commercially available 4-methylsalicylic acid 90 was converted to acid chloride with oxalyl chloride. The formed acid chloride was then reacted with $N$, $N$-diethylamine to give the amide 114. The hydroxyl moiety of compound 114 was then protected by reacting it with $t$-butyldimethylsilyl chloride in the presence of imidazole as a base to give compound 115. Since tertiary amides have been known to be good ortho directing metatation groups,\textsuperscript{24} iodination of compound 115 was then carried out by subjecting it to directed ortho metatation reaction using tert-butyllithium and the reaction was subsequently quenched with iodine to afford the aryl iodide 116. With 116 in hand, the amide was subjected to the Sonogashira reaction with 3-hydroxy-3-methyl-1-butyne in the presence of Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} and CuI as catalysts to give the alkynylated aryl amide 117. Trimethylloxonium tetrafluoroborate was then used to convert the amide 117 to the salicylate derivative 118 as shown in Scheme 5.15. The methyl salicylate 118 was then reduced to a benzyl alcohol 119 in the presence of DIBAL-H. Finally, the
benzyl alcohol 119 was oxidized to salicylaldehyde 120 using manganese (IV) oxide (Scheme 5.15).

Scheme 5.15

With compound 120 in hand, the aldehyde was treated with t-butyldimethylsilyl chloride in the presence of imidazole in an attempt to protect the phenolic function. This reaction did not give the expected product, instead the imidazole reacted with the aldehyde group to give compound 122 (Scheme 5.16).
Meanwhile compound 120 was reacted with a Grignard reagent, 2-methylallyl magnesium chloride to give the 1,7-enyne 121 (Scheme 5.17).

Cyclization of the 1,7-enyne 121 was attempted by adsorbing the alkyne-dicobalt hexacarbonyl complex of 121 to SiO₂ before heating it at 65 °C for 3 h. In this case also only the starting material was also recovered (Scheme 5.18).
The alkynylated methyl salicylate 118 was subjected to protection with TBSCI at 55 °C, but this did not give the expected product. Instead, the starting material was recovered. This result was explained to be due to the fact that TBS protected phenols can easily be deprotected at elevated temperature. Hence, the reaction was then carried out at room temperature to give the phenolic silyl ether 124 in excellent yield (Scheme 5.19).

**Scheme 5.19**

![Scheme 5.19](image)

The TBS-protected methyl salicylate 124 was reduced with DIBAL-H to give the benzylic alcohol 125 in 99% yield. Then the alcohol was oxidized with pyridinium chlorochromate to the benzaldehyde 126 in 85% yield (Scheme 5.20).

**Scheme 5.20**

![Scheme 5.20](image)

When the benzaldehyde 126 was reacted with 2-methylallylmagnesium chloride it gave a complex mixture. This may have been due to the easy migration of the silyl group to
the benzylic hydroxyl group after the Grignard reaction. Moreover the reaction mixture was difficult to purify by SiO₂ chromatography.

This problem was then resolved by using the enyne 121 and then carrying out silylene protection of both hydroxyl groups to give 86% of enyne 128 (Scheme 5.21).

**Scheme 5.21**

Silylene protected enyne 128 is believed to be rigid enough to reduce the free rotation of the alkene arm, hence making it possible for the enyne to participate in PK reaction. With enyne 128 at hand it was subjected to thermal PK conditions to give the expected cyclized product 129 (Scheme 5.22)

**Scheme 5.22**
Hence the silylene protection effectively preorganized and reduced the degree of free rotation of the alkene arm thereby forcing it to cyclize to give the tricycle core of the hamigerans. Further functionalization of this core will give hamigeran A and B.
CHAPTER 6
EXPERIMENTAL

6.1 General Methods

See Page 83 for general methods used earlier.

2-Methoxy-4-methylbenzoic acid (99)\textsuperscript{6-8}

Dimethyl sulfate (37.3 mL, 0.395 mol) in acetone (100 mL) was added dropwise to a mixture of KOH (22.2 g, 395 mmol) and 2-hydroxy-4-methylbenzoic acid 90 (20.0 g, 132 mmol) in acetone (100 mL) and heated to reflux for 3 h at 60 °C. The reaction mixture was then filtered through a pad of Celite and washed with acetone to remove the remaining product. The organic phase was washed with water, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue was then dissolved in 60% methanol and KOH (20.0 g, 0.357 mmol) was added. The reaction mixture was heated to reflux for 2 h. The reaction mixture was then allowed to cool to rt, acidified to pH \textless 1 with conc HCl and extracted with EtOAc. The organic phase was washed with water and brine, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo. Purification was done by flash chromatography (hexane/EtOAc, 10:3) to afford the pure product 99 (20.4 g, 93%). \textsuperscript{1}H NMR (500 MHz): \(\delta = 10.75\) (broad s, 1H), 8.03 (d, \(J = 7.5\) Hz, 1H), 6.92 (d, \(J = 7.5\) Hz, 1H), 6.84 (s, 1H), 4.07 (s, 1H), 2.41 (s, 3H); \textsuperscript{13}C NMR (125 MHz): \(\delta = 165.6, 158.1, 146.6, 133.8, 123.2, 114.9, 112.3, 56.7, 22.1\); IR (neat,
\text{cm}^{-1} = 2974, 1677, 1612, 1464, 1414, 1300, 1251, 1151, 1093, 784, 587; \text{HRMS (ESI)}: \text{Calcd. for C}_9\text{H}_{11}\text{O}_3 (m/z): 189.0522. \text{Found 189.0514 [M+Na]}^+.

\textit{N-tert-Butyl-2-methoxy-4-methylbenzamide (100)}^{6-8}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

Oxalyl chloride (31.5 g, 0.368 mmol) was added to a solution of 99 (20.4 g, 0.122 mmol) in CH$_2$Cl$_2$ (100 mL) followed by the addition of catalytic amount of DMF. The reaction mixture was then stirred at rt for 4 h. At the end of the reaction period the excess oxalyl chloride and solvent were removed under aspirator pressure. The crude benzoyl chloride product was dissolved in benzene (120 mL) and cooled to 0 °C. \textit{N-tert}-butylamine (25.3 mL, 0.246 mol) was then added dropwise with evolution of gas. The reaction temperature was then allowed to warm up to rt and stirred for 12 h. At the end of the reaction period, the mixture was then washed with 1N HCl, brine and dried (Na$_2$SO$_4$). The organic layer was concentrated and purified by flash chromatography (hexane/EtOAc, 10:3) to give a viscous liquid 100 (27.1 g, 99.9 %); $^1$H NMR (500 MHz): $\delta = 8.00 (d, J = 7.5 \text{ Hz, 1H}), 7.79 (\text{broad s, 1H}), 6.79 (d, J = 8.0 \text{ Hz, 1H}), 6.67 (s, 1H), 3.85 (s, 3H), 2.30 (s, 3H), 1.40 (s, 9H); $^{13}$C NMR (125 MHz), $\delta = 164.3, 157.2, 143.1, 131.8, 122.1, 120.0, 112.1, 55.9, 50.9, 29.0, 21.7; \text{IR (neat, cm}^{-1}) = 3398, 2967, 1661, 1613; \text{HRMS (ESI)}: \text{Calcd. for C}_{26}\text{H}_{39}\text{N}_2\text{O}_4^+ (m/z): 443.2904. \text{Found 443.2881 [2M+H]}^+; \text{Anal. Calcd. for C}_{13}\text{H}_{19}\text{NO}_2: C, 70.56; H, 8.65; N, 6.33. \text{Found: C, 70.17; H, 8.64; N, 6.30.
**N-tert-Butyl-6-iodo-2-methoxy-4-methylbenzamide (91)**

A solution of benzamide 100 (20.0 g, 90.5 mmol) in anhydrous THF (20 mL) was added dropwise to a mixture of tert-butyllithium (117 mL, 100 mmol) and N,N,N,N-tetramethylethylenediamine (27.3 mL, 181 mmol) in anhydrous THF (100 mL) at -78 °C under N₂ and stirred for 1 h. At the end of the reaction period, the reaction mixture was quenched with a solution of iodine (29.9 g, 118 mmol) in THF (80 mL). The reaction was then allowed to warm up to ambient temperature and stirred overnight. The reaction was then quenched with NH₄Cl solution (100 mL) and the mixture decolorized with Na₂S₂O₃ solution and extracted with CH₂Cl₂. The organic layer was washed with water, dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude product. Purification was done by flash chromatography using gradient elution (hexane/EtOAc, 10:1 - 10:3) to give a light yellow liquid 91 (22.0 g, 70%) ¹H NMR (300 MHz):  δ = 7.21 (s, 1H), 6.65 (s, 1H), 5.41 (s, 1H), 3.77 (s, 3H), 2.28 (s, 3H), 1.46 (s, 9H) ; ¹³C NMR (75 MHz) δ = 166.9, 156.4, 141.5, 131.6, 130.8, 111.9, 94.0, 56.1, 52.1, 28.9, 21.2; IR (neat, cm⁻¹) = 3301, 2959, 2918, 1648, 1619; HRMS (ESI): Calcd. for C₂₆H₃₆I₂N₂O₄Na⁺ (m/z): 717.0657. Found 717.0596 [2M+Na]⁺; Anal. Calcd. for C₁₆H₁₈INO₂: C, 44.97; H, 5.23; N, 4.03. Found: C, 45.17; H, 5.17; N, 4.03.
**N-tert-Butyl-6-iodo-2-hydroxy-4-methylbenzamide (101)**

1.0 M solution of BBr₃ (23.1 mL, 23.1 mmol) in CH₂Cl₂ was added dropwise to a solution of 91 (2.00 g, 5.76 mmol) in CH₂Cl₂ (20 mL) at -78 °C under N₂. The solution was then stirred at room temperature overnight. The mixture was cooled to -78 °C and quenched with methanol and washed with water. The organic layer was separated, dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product 101. Purification was done by flash chromatography with gradient elution (hexane/EtOAc, 10:3 -1:1) to give a white solid (1.89 g, 99.5 %) mp: 185-187 °C ¹H NMR (300 MHz): δ = 10.93 (s, 1H), 7.26 (s, 1H), 6.75 (s, 1H), 6.51 (s, 1H), 2.23 (s, 3H), 1.49 (s, 9H); ¹³C NMR (75 MHz): δ = 168.4, 160.2, 141.2, 133.3, 119.6, 118.8, 91.9, 53.0, 28.7, 20.8; IR (neat, cm⁻¹) = 3321, 2962, 2991, 1609, 1549; HRMS (ESI): Calcd. for C₂₄H₃₂I₂N₂O₄Na⁺ (m/z): 689.0344. Found 689.0300 [2M+Na]⁺.

**2-Hydroxy-6-iodo-4-methyl-methylbenzoate (102)**

NaHPO₄ (1.22 g, 8.60 mmol) and (CH₃)₃OBF₄ (2.53 g, 17.1 mmol) was added at rt to a solution of 101 (1.90 g, 5.70 mmol) in CH₃CN (50 mL) and stirred for 18 h. Saturated aqueous NaHCO₃ solution (20 mL) was then added slowly followed by the addition of solid NaHCO₃ (1.44 g, 17.1 mmol) and stirred for another 18 h at rt. The product was extracted with EtOAc (3 x 20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 10:1) to give a white solid 102 (1.51 g, 90%); mp: 80-82 °C; ¹H NMR (500 MHz): δ = 10.95 (s, 1H), 7.44 (d, J = 1.0 Hz, 1H), 6.76 (d, J =
0.5 Hz, 1H), 3.95 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (125 MHz): $\delta$ = 169.1, 162.5, 146.6, 135.3, 118.6, 113.9, 93.8, 51.8, 21.0. IR (neat, cm$^{-1}$) = 3030, 3002, 2948, 1652, 1434, 1345; HRMS (ESI): Calcd. for C$_9$H$_9$IO$_3$Na$^+$ (m/z): 314.9489. Found 314.9459 [M+Na]$^+$; Calcd. for C$_9$H$_{10}$IO$_3$ $^+$ (m/z): 292.9669. Found 292.9638 [M+H]$^+$.

**2-Methoxy-6-iodo-4-methyl-methylbenzoate (103)**

Dimethyl sulfate (9.18 g, 72.9 mmol) was added to a mixture of 102 (9.49 g, 32.5 mmol) and benzyltributylammonium chloride (1.36 g, 4.34 mmol) in CH$_2$Cl$_2$ (150 mL). Then 1.4 M aqueous NaOH (100mL) was added and stirred vigorously for 4 h at rt. The organic layer was the separated and the aqueous layer was extracted twice with CH$_2$Cl$_2$. The combined organic layers were washed with water, dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/hexane, 1:9) gave **103** (9.61 g, 97%) as a white solid, mp: 77-79 °C. $^1$H NMR (500 MHz): $\delta$ = 7.16 (s, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (125 MHz): $\delta$ = 168.0, 156.7, 142.4, 131.4, 127.5, 111.9, 92.4, 56.1, 52.7, 21.3, IR (neat, cm$^{-1}$) = 1732, 1597, 1556, 1272, 1039; HRMS (ESI): Calcd. For C$_{20}$H$_{22}$I$_2$O$_6$Na$^+$ (m/z): 634.9398. Found 634.9337 [2M+Na]$^+$.
2-iodo-4-methyl-6-Methoxy-benzylalcohol (104)\textsuperscript{16}

DIBAL (1.0 M in hexane, 55.5 mL) was added dropwise to a stirred solution of 103 (8.50 g, 27.8 mmol) in dry toluene (250 mL) at -78 °C.

The mixture was stirred at -78 °C for 2 h and then stirred at 0 °C (iced bath) for 1 h. The reaction was stirred for 6 h while gradually allowing the temperature to warm up to rt. The solution was then cooled to -78 °C and MeOH (10 mL), Na\textsubscript{2}SO\textsubscript{4}.10H\textsubscript{2}O (4.0 g), Celite (6.0 g) and water (2 mL) were added successively. The cold bath was then removed and stirring was continued for 30 min before filtering the slurry through a sintered glass funnel. The organic layer was washed with water, dried (Na\textsubscript{2}SO\textsubscript{4}) and the concentrate under reduced pressure to give 104 as a milky solid (7.45 g, 97%); Mp: 68 -70 °C; \textsuperscript{1}H NMR (500 MHz): \(\delta = 7.28\) (s, 1H), 6.67 (s, 1H), 4.80 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 2.31 (s, 3H); \textsuperscript{13}C NMR (125 MHz): \(\delta = 157.7, 141.0, 132.2, 128.8, 112.0, 101.0, 65.0, 55.8, 21.1\); IR (neat, cm\textsuperscript{-1}) = 3395, 2959, 2938, 1598, 1557, 1457, 1402, 1270, 1043; HRMS (ESI): Calcd. for C\textsubscript{18}H\textsubscript{22}I\textsubscript{2}NaO\textsubscript{4}S (m/z): 578.9500. Found 578.9449 [2M+Na]\textsuperscript{+}.

2-Iodo-4-methyl-6-methoxy-benzaldehyde (105)\textsuperscript{16}

A mixture of pyridinium chlorochromate (8.07 g, 37.4 mmol) and powdered 4 Å molecular sieves (3.0 g) was added to a stirred solution of 104 (7.43 g, 26.7 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (200mL). Stirring was continued at room temperature for 10 h by which time the oxidation was completed. The solvent was evaporated to approximately 50 mL and the slurry was filtered through
a pad of SiO₂ and washed with 1:1 EtOAc-hexane. The filtrate was concentrated and purified by flash chromatography (SiO₂, EtOAc/hexane 2:3) to give the aldehyde 105 as a yellow solid (5.43 g, 74%). mp: 86- 88 °C. ¹H NMR (300 MHz): δ = 10.19 (s, 1H), 7.43 (s, 1H), 6.77 (s, 1H), 3.89 (s, 3H), 2.34 (s, 3H); ¹³C NMR (75 MHz): δ = 191.5, 161.9, 146.9, 134.8, 122.2, 112.9, 97.0, 56.0, 21.6; IR (Neat, cm⁻¹) = 2986, 1739, 1681, 1589, 1036; HRMS (ESI): Calcd. for C₁₈H₁₈I₂NaO₄ (m/z): 574.9187. Found 574.9153 [2M+Na]⁺.

3,4,6-Tribromo-2,5-dimethylphenol (109)¹⁸

Aluminum (0.50 g, 18.5 mmol) was cautiously added in small portions to Br₂ (12.5 mL, 243 mmol) cooled to 0 °C. The mixture was stirred until the sparks ceases (50 min). A solution of the 2,5-dimethylphenol (5.0 g, 41 mmol) in dry CH₂Cl₂ (12.5 mL) was added dropwise and the mixture stirred for an additional 2h (The HBr gas evolved during the reaction was trapped by a water trap connected to an aqueous Na₂CO₃ scrubber). The solvent and excess Br₂ were removed at reduced pressure using a water aspirator (with the trap still in place). The residue was then stirred overnight with 10% HCl. Then sodium thiosulfate was added to decolorize the solution and filtered to give a yellow precipitate which can be recrystallized from hot ethanol to give pure white needles of 3,4,6-tribromo-2,5-dimethylphenolin 109 (12.51 g, 85%); mp = 176-177 °C (lit¹⁷ mp = 175-177 °C). ¹H NMR (300 MHz): δ = 5.81 (s, 1H), 2.63 (s, 3H), 2.44 (s, 3H), ¹³C NMR (75 MHz): δ =
3-Bromo-2,5-dimethylphenol (110) \(^{19}\)

The de la Mare’s procedure was followed. A suspension of the perbromophenol 109 (2.31 g, 6.43 mmol) in aqueous HI (57 wt %, 25 mL) was heated at reflux under N\(_2\) for 3 h. At the end of the reaction period, the reaction mixture was cooled to rt before adding CHCl\(_3\) (20 mL). Na\(_2\)S\(_2\)O\(_3\) was then added to decolorize and extracted with CHCl\(_3\) (3 x 20 mL). The organic layers were combined, dried (Na\(_2\)SO\(_4\)) and concentrated to give a yellow powder. Recrystallization from hexane and charcoal was used to decolorize the product to give white crystal of the product 110 (1.28 g, 99%). Mp: 90-92 °C (lit\(^{18}\) mp: 90-92 °C). \(^1\)H NMR (300 MHz): \(\delta = 6.98\) (s, 1H), 6.54 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H). \(^{13}\)C NMR (75 MHz): \(\delta = 154.0, 137.8, 125.8, 120.9, 115.0, 71.5, 20.8, 15.2\); IR (neat, cm\(^{-1}\)) = 3316, 2918, 1602; HRMS (CI): Calcd. for C\(_8\)H\(_7\)Br\(_3\)O\(^+\) (\(m/z\)): 355.8079. Found 355.8096 [M\(^+\)].

3-Bromo-2, 5-dimethylanisole (111)

Dimethyl sulfate (0.94 mL, 9.95 mmol) was added to a mixture of the bromophenol 110 (1.0 g, 5.0 mmol), benzyltributylammonium chloride (0.19 g, 0.60 mmol) in CH\(_2\)Cl\(_2\) (10 mL) and 1.4 M aqueous NaOH (20 mL). The reaction mixture was stirred vigorously for 4 h. The organic layer separated
and the aqueous layer was further extracted with CH$_2$Cl$_2$. The combined organic layers were then washed with water, dried (Na$_2$SO$_4$) and concentrated to give yellow oil. Flash chromatography (SiO$_2$, hexane/EtOAc, 9:1) was used for purification to give **111** (1.01 g, 94%) as a colorless oil. $^1$H NMR (300 MHz): $\delta$ = 6.99 (s, 1H), 6.59 (s, 1H), 3.80 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H). $^{13}$C NMR (75 MHz): $\delta$ = 158.1, 137.4, 125.5, 124.9, 123.7, 110.3, 55.8, 21.2, 15.4; IR (neat, cm$^{-1}$) = 2927, 2863, 1607, 1567; HRMS (Cl): Calcd. For C$_9$H$_{11}$BrO$^+$ ($m/z$): 213.9997. Found 213.9981 [M$^+$].

**2-Bromo-6-methoxy-4-methylbenzaldehyde (112).**

3-Bromo-2,5-dimethylanisole **111** (23.4 g, 110 mmol) was dissolved in CCl$_4$ (100 mL) and thoroughly purged with N$_2$ by repeated evacuation. N-Bromosuccinimide (19.6 g, 110 mmol) and AIBN (540 mg, 0.33 mmol) was added in one portion. The reaction mixture was heated to reflux until the NBS was converted to succinimide, which then floated on the surface of the CCl$_4$. The reaction mixture was then cooled to room temperature and then filtered through a Celite pad to remove the residual succinimide. The filtrate was concentrated under reduced pressure. The crude product was then redissolved in dry DMSO (100 mL) and then NaHCO$_3$ (54.0 g, 660 mmol) was added, and the mixture was heated at 110 °C for 15 h and cooled to rt. The reaction mixture was quenched with ice water (400 mL) and extracted with Et$_2$O. The combined organic extracts were washed with brine (400 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Purification was done by flash chromatography using gradient elution (SiO$_2$, hexane/EtOAc, 19:1 to
3:1) to give the aldehyde 112 (12.2 g, 49%) as a yellow waxy solid. Mp: 50- 52 °C; 
$^1$H NMR (300 MHz): $\delta = 10.36$ (s, 1H), 7.07 (s, 1H), 6.73 (s, 1H), 3.89 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (75 MHz): $\delta = 190.1$, 162.1, 146.6, 127.3, 125.3, 120.9, 112.0, 56.2, 21.9; IR (neat, cm$^{-1}$) = 2942, 2852, 2784, 1730, 1690, 1602, 1562; HRMS (ESI): Calcd. for C$_9$H$_{10}$BrO$_2$ $^{16+}$ ($m/z$): 228.9859. Found 228.9835 [M+H]$^+$. 

2-(3-Hydroxy-3-methyl-1-butynyl)-4-methyl-6-methoxy-benzaldehyde (91)$^{16}$

A solution of 105 (5.00 g, 18.1 mmol) in Et$_3$N (20 mL) was purged with N$_2$ for about 30 min. The solution was then cooled to 0 °C. To the purged solution of 105 was added PdCl$_2$(PPh$_3$)$_2$ (0.25 g, 0.36 mmol) and CuI (35.0 mg, 0.18 mmol) and stirred at 0 °C for 10 minutes. To the reaction mixture was added 2-hydroxy-2-methylbut-1-yne (2.29 g, 18.1 mmol) and stirred at 55 °C (bath temperature) under N$_2$ for 5 h. Et$_2$O (50 mL) and 1.0 M HCl (20 mL) were added and the organic layer was separated. The reaction was neutralized with a saturated NaHCO$_3$ (30 mL) solution, washed with H$_2$O, dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, hexane) to afford 91 (4.14 g, 99%) as a yellow waxy solid. $^1$H NMR (300 MHz): $\delta = 10.44$ (s, 1H), 6.76 (s, 1H), 6.56 (s, 1H), 3.90 (s, 3H), 2.38 (s, 3H), 1.52 (s, 6H); $^{13}$C NMR (75 MHz): $\delta = 190.2$, 161.2, 146.1, 127.0, 126.2, 122.5, 112.5, 100.1, 82.1, 65.4, 55.9, 31.2, 21.1; IR (neat, cm$^{-1}$) = 3446, 2981, 2936, 2359, 1715, 1681, 1609; HRMS (ESI): Calcd. For C$_{14}$H$_{17}$O$_3$$^{16+}$ ($m/z$): 233.1171. Found 233.1141 [M+H]$^+$. 

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2-(1-Hydroxy-3-methyl-3-butenyl)-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl anisole (93)

0.5 M solution of 2-methylallylmagnesiumchloride (4.48 mL, 2.24 mmol) in THF was added dropwise to a solution of 91 (0.26 g, 1.1 mmol) in THF (10 mL) at 0 °C under N₂ atmosphere and stirred to warm up to room temperature. The mixture was further stirred at room temperature for 3 h. The reaction mixture was quenched with NH₄Cl, extracted with dichloromethane and washed severally with water and brine solution. The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure. Purification was by flash chromatography (hexane/EtOAc; 1:2) to afford compound 93 (0.3 g, 94%) as a light yellow liquid. 

1H NMR (500 MHz): δ = 6.85 (s, 1H), 6.68 (s, 1H), 5.31 (m, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 3.84 (s, 3H), 3.52 (d, J = 11.0 Hz, 1H), 2.62 (dd, J = 9.2, 13.7 Hz, 1H), 2.42 (dd, J = 5.0, 13.7 Hz, 1H), 2.36 (s, 1H), 2.27 (s, 3H), 1.81 (s, 3H), 1.58 (s, 6H); 

13C NMR (125 MHz): δ = 157.2, 143.1, 137.9, 130.5, 125.9, 121.6, 112.8, 112.6, 98.2, 80.4, 70.6, 65.6, 55.6, 45.7, 31.5, 22.6, 21.3; IR (neat, cm⁻¹) = 3404, 3071, 2979, 1717, 1676, 1607, 1575, 1459; HRMS (ESI): Calcd. For C₃₆H₄₈NaO₆ (m/z): 599.3343. Found 599.3342 [2M+Na]⁺.
**N,N-Diethyl-2-hydroxy-4-methylbenzamide (114)**

Oxalyl chloride (5.1 g, 40.2 mmol) was added to a solution of 90 (3.0 g, 19.7 mmol) in CH$_2$Cl$_2$ followed by the addition of a catalytic amount of DMF (3 drops). The reaction mixture was stirred at room temperature for 4 h. The excess oxalyl chloride and solvent were removed and the residue was dried under vacuum pump to give the crude acid chloride. The crude benzoyl chloride was dissolved in benzene (120 mL) and cooled to 0 °C. Next, N,N-diethylamine (4.10 mL, 55.8 mmol) was added dropwise with the evolution of gas. The reaction temperature was then warmed up to rt and stirred for 12 h. The reaction mixture was washed with 1N HCl and brine solution. The organic layer was separated, dried (Na$_2$SO$_4$) and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 10:3) to give 114 (3.81 g, 93%) as a brown viscous liquid. $^1$H NMR (300 MHz): $\delta = 7.14$ (d, $J = 7.8$ Hz, 1H), 6.81 (s, 1H), 6.63 (dd, $J = 1.2$, 7.8 Hz, 1H), 3.47 (q, $J = 7.2$ Hz, 4H), 2.31 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 6H); $^{13}$C NMR (75 MHz): $\delta = 171.8$, 159.1, 143.2, 127.3, 119.4, 118.4, 115.2, 42.3, 21.6, 13.5; IR (neat, cm$^{-1}$) = 3166, 2976, 1599, 1439, 1297, 1130; HRMS (ESI): Calcd. For C$_{12}$H$_{17}$NaNO$_2$ ($m/z$): 230.1152. Found 230.1145 [M+Na]$^+$. 
**N,N-Diethyl-2-(tert-butyl-dimethylsilyloxy)-4-methylbenzamide (115)**

To a solution of 114 (3.30 g, 15.9 mmol) and imidazole (3.26 g, 47.8 mmol) in DMF (50 mL) was added TBSCl (7.21 g, 47.8 mmol) at rt. The reaction mixture was heated at 50 °C for 4.5 h. The reaction was then quenched with saturated aqueous NaHCO₃ (50 mL) and extracted twice with Et₂O (20 mL). The combined organic layers were washed with water and brine, dried (Na₂SO₄) and concentrated under reduced pressure. Purification was done by flash chromatography (SiO₂, hexane/EtOAc, 10:2) to give 115 (5.1g, 99%) as a light yellow liquid. ¹H NMR (500MHz): δ = 7.01 (d, J = 7.3 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.57 (s, 1H), 3.53 (p, J = 6.4 Hz, 1H), 3.41 (p, J = 6.9 Hz, 1H), 3.18 (p, J = 6.9 Hz, 1H), 3.06 (p, J = 6.9 Hz, 1H), 2.25 (s, 3H), 1.17 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ¹³C NMR (125 MHz): δ = 169.2, 151.0, 139.7, 127.7, 127.0, 122.2, 120.0, 42.9, 39.2, 25.8, 25.7, 21.4, 18.1, 14.2, 13.3, -4.1, -4.05; IR (neat, cm⁻¹) = 2930, 1636, 1427, 1291, 1165, 1133, 1084, 971; HRMS (ESI): Calcd. for C₃₂H₆₂N₂O₄Si₂Na⁺ (m/z): 665.4140. Found 665.4068 [2M+Na]⁺; Anal. Calcd. for C₁₈H₃₁NO₂Si: C, 67.24; H, 9.72; N, 4.36. Found: C, 66.96; H, 9.46; N, 4.39.

**2-(tert-Butyl-dimethylsilyloxy)-6-iodo-4-methyl-N,N-diethylbenzamide (116)**

A solution of benzamide 115 (13.4 g, 41.8 mmol) in dried Et₂O (100 mL) was added dropwise to a mixture of tert-butyllithium (26.6 mL, 45.2 mmol) at -78 °C under N₂ and stirred for 1 h. After 1h at -78 °C, the reaction mixture was quenched by adding a solution of iodine
(11.3 g, 44.4 mmol) in THF dropwise. The resulting solution was then allowed to warm up to ambient temperature overnight. Saturated NH₄Cl solution (100 mL) was added followed by Na₂S₂O₃ solution to decolorize the reaction mixture. The reaction was then extracted with CH₂Cl₂. The organic layer was separated, washed with water, dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude product. Purification was done by flash chromatography using gradient elution (hexane/EtOAc, 10:1 - 10:3) to give 116 (16.34 g, 87%) as a light yellow solid, mp: 66- 68 °C. ¹H NMR (300 MHz), δ = 6.97 (s, 1H), 6.55 (s, 1H), 3.72 (m, 1H), 3.25 (m, 1H), 3.12 (qd, J = 2.8, 7.2 Hz, 2H), 2.28 (s, 3H), 1.21 (t, J = 6.9 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), ¹³C NMR (75 MHz): δ = 166.4, 152.5, 140.4, 128.4, 125.9, 120.1, 118.8, 42.9, 39.2, 25.6, 21.2, 18.2, 14.0, 12.8, -3.9, -4.6; IR (neat, cm⁻¹) = 2932, 2859, 1638, 1472, 1292, 1255; HRMS (ESI): Calcd. For C₁₈H₃₁INO₃Si (m/z): 448.1163. Found 448.1167 [M+H]+;

2-(3-Hydroxy-3-methyl-1-butynyl)-4-methyl-6-(tert-butyl-dimethylsilyloxy)-N,N-diethylbenzamide (117)

A solution of 116 (5.33 g, 11.9 mmol) in Et₃N (30 mL) was purged with N₂ for about 30 min and then cooled to -78 °C. To the purged solution of 116 was added PdCl₂(PPh₃)₂ (0.17 g, 0.24 mmol) and CuI (23.0 mg, 0.12 mmol) and stirred at -78 °C for 10 min. To the reaction mixture, was then added 2-hydroxy-2-methylbut-1-yne (1.72 g, 20.5 mmol) and stirred at 55 °C for 5 h. Next, Et₂O (50 mL) and 1 M HCl (20 mL) were
added. The organic layer was separated, neutralized with saturated NaHCO₃ (30 mL) solution, washed with H₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, n-hexane) to afford 117 (3.50 g, 73%) as a yellow waxy solid. ¹H NMR (500 MHz): δ = 6.86 (s, 1H), 6.58 (s, 1H), 3.68 (sext, J = 7.0 Hz, 1H), 3.42 (sext, J = 7.0 Hz, 1H), 3.21-3.08 (m, 2H), 2.26 (s, 3H), 1.71 (s, 1H), 1.53 (s, 6H), 1.28 (t, J = 7.5 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H), 0.94 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H); ¹³C NMR (75 MHz): δ = 167.5, 151.3, 139.1, 129.5, 125.7, 120.3, 107.4, 65.4, 43.2, 39.4, 31.4, 31.3, 25.6, 21.3, 18.1, 14.0, 13.4, -3.9, -4.6; IR (neat, cm⁻¹) = 3382, 2931, 2859, 1619, 1568, 1428, 1285, 1075; HRMS (ESI): Calcd. for C₂₃H₃₈NO₃Si⁺ (m/z): 404.2615. Found 404.2616 [M+H]⁺;

2-(3-Hydroxy-3-methyl-1-butynyl)-6-hydroxy-4-methyl-methylbenzoate (118)

NaHPO₄ (1.67 g, 11.8 mmol) and (CH₃)₃OBF₄ (3.48 g, 23.5 mmol) were added at rt to a solution of 117 (3.16 g, 7.80 mmol) in CH₃CN (50 mL) and stirred for 18 h. Then saturated NaHCO₃ solution (20 mL) was added slowly followed by addition of solid NaHCO₃ (3.29 g, 39.2 mmol) and stirred for another 18 h at rt. The product was extracted using EtOAc (3 x 20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 10:1) to give 118 (1.76 g, 90 %) as a viscous brown waxy solid. ¹H NMR (500 MHz): δ = 11.17 (s, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 3.78 (s, 3H), 2.07 (s, 3H), 1.50 (s, 6H); ¹³C NMR (125 MHz): δ = 170.7, 162.0, 145.0, 127.3, 123.7, 118.3,

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110.3, 98.3, 81.5, 65.4, 51.8, 31.4, 21.2; IR (neat, cm⁻¹) = 3435, 2982, 1663, 1605, 1571, 1440, 1164; HRMS (TOF-MS): Calcd. For C₁₄H₁₆O₄Na⁺ (m/z): 271.0946. Found 271.0939 [M+Na]⁺.

2-(3-Hydroxy-3-methyl-1-butynyl) -6-hydroxy -4-methyl -benzylalcohol (119)

DIBAL (1.0M in hexane, 5.16 mL, 5.16 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of 118 (640 mg, 2.58 mmol) in dry toluene (10 mL). The mixture was then stirred at -78 °C for 2 h and then stirred at 0 °C for 1 h. The stirring was continued for 6 h without recharging the ice bath. The solution was then recooled to -78 °C and MeOH (10mL), Na₂SO₄.10H₂O (2.0 g), Celite (3.0 g) and water (2 mL) were added successively. The cold bath was then removed and stirring continued for 30 minutes before filtering the slurry through a sintered glass funnel and washed with EtOAc. The organic layer was then concentrate under reduced pressure to give 119 (560 mg, 98%) as a yellow liquid. ¹H NMR (500 MHz): δ = 6.76 (s, 1H), 6.65 (s, 1H), 5.01 (s, 2H), 2.22 (s, 3H), 1.59 (s, 6H); ¹³C NMR (125 MHz): δ = 156.3, 139.0, 124.9, 122.9, 121.1, 118.1, 79.9, 65.8, 62.1, 31.5, 21.1; IR (neat, cm⁻¹) = 3345, 2981, 2935, 2222, 1611, 1582, 1141; HRMS (ESI): Calcd. For C₁₃H₁₆NaO₃ (m/z): 243.0992. Found 243.1012 [M+Na].
2-(3-Hydroxy-3-methyl-1-butynyl)-6-hydroxy-4-methyl-benzaldehyde (120)

Manganese (IV) oxide (360 mg, 4.02 mmol) was added to a stirred solution of 119 (300 mg, 1.36 mmol) in dry CH₂Cl₂ (10 mL). The reaction mixture was then heated to reflux for 10 h by which time oxidation was completed. The solvent was evaporated to approximately 50 mL and the slurry was filtered through a pad of SiO₂ and washed with CH₂Cl₂. The filtrate was concentrated and purified by flash chromatography (SiO₂, EtOAc-hexane 2:3) to give the aldehyde 120 (280 mg, 94%) as a viscous brown waxy solid. ¹H NMR (500 MHz): δ = 11.58 (s, 1H), 10.23 (s, 1H), 6.75 (s, 1H), 6.63 (s, 1H), 3.25 (broad s, 1H), 2.23 (s, 3H), 1.59 (s, 6H); ¹³C NMR (125 MHz): δ = 196.2, 162.4, 148.5, 126.8, 125.8, 118.4, 117.6, 100.8, 77.4, 65.6, 31.3, 21.9; IR (neat, cm⁻¹) = 3352, 2983, 2935, 2221, 1652, 1616, 1567, 1411; HRMS (ESI): Calcd. for C₁₃H₁₄NaO₃ (m/z): 241.0835. Found 241.0833 [M+Na]+.

2-(1-Hydroxy-3-methyl-3-butenyl)-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl phenol (121)

2-Methylallylmagnesium chloride (6.90 mL, 3.44 mmol) was added dropwise to a solution of 120 (0.25 g, 1.15 mmol) in THF (10 mL) at 0 °C under N₂ atmosphere. The reaction mixture was then allowed to warm up to rt and stirred for 3 h. The reaction mixture was quenched with NH₄Cl, extracted with dichloromethane and washed with water and brine solution. The organic layer was the dried (Na₂SO₄) and concentrated under reduced pressure.
Purification was done by flash chromatography (SiO₂, hexane/EtOAc; 1:2) to afford compound 121 (300 mg, 97%) as a light yellow liquid. \(^1\)H NMR (500 MHz): \(\delta = 8.79\) (broad s, 1H), 6.74 (s, 1H), 6.63 (s, 1H), 5.40 (dd, \(J = 3.7, 10.1\) Hz, 1H), 4.95 (s, 1H), 4.88 (s, 1H), 3.47 (broad s, 1H), 2.64 (broad s, 1H), 2.53 (dd, \(J = 10.5, 14.2\) Hz, 1H), 2.44 (dd, \(J = 2.8, 14.2\) Hz, 1H), 2.19 (s, 3H), 1.84 (s, 3H), 1.57 (s, 6H); \(^1\)C NMR (125 MHz): \(\delta = 155.8, 142.3, 138.5, 125.1, 124.9, 120.3, 118.8, 114.5, 97.9, 79.9, 71.6, 65.7, 45.2, 31.6, 22.3, 20.9;\) IR (neat, cm\(^{-1}\)) = 3311, 3073, 2980, 2221, 1650, 1614, 1577, 1162; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{22}\)NaO\(_3\) (m/z): 297.1512. Found 297.1502 [M+Na]⁺.

2-(3-hydroxy-3-methyl-1-butynyl)-6-(\(\tau\)-butyldimethylsilyloxy)-4-methyl-methylbenzoate (124)

A solution of 2-(3-hydroxy-3-methyl-1-butynyl)-6-Hydroxy-4-methyl-methylbenzoate 118 (3.00 g, 12.1 mmol), imidazole (2.47 g, 36.3 mmol) and t-butyldimethylsilyl chloride (2.19 g, 14.5 mmol) in dry DMF (30 mL) was stirred for 18 h. The reaction mixture was diluted with water and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine, dried (Na\(_2\)SO\(_4\)) and evaporated to yield oil. The crude product was purified by flash chromatography (SiO₂, hexane/EtOAc, 10:3) to give 124 (4.35 g, 99%) as a light yellow oil. \(^1\)H NMR (500 MHz): \(\delta = 6.85\) (s, 1H), 6.58 (s, 1H), 3.84 (s, 3H), 2.25 (s, 3H), 1.55 (s, 6H), 0.94 (s, 9H), 0.18 (s, 6H); \(^1\)C NMR (125 MHz): \(\delta = 167.8, 152.4, 140.7, 125.7, 121.6, 120.6, 97.0, 65.4, 52.2, 31.4, 25.7, 21.3, 201
18.1, 14.3; IR (neat, cm\(^{-1}\)) = 3456, 2953, 2859, 2237, 1738, 1567; HRMS (ESI): Calcd. For C\(_{20}\)H\(_{30}\)SiO\(_4\)Na\(^+\) (\(m/z\)): 385.1806. Found 385.1816 [M+Na]\(^+\).

2-(3-Hydroxy-3-methyl-1-butynyl) -6-(\(t\)-butyldimethylsilyloxy) -4-methyl –benzyl alcohol (125)

DIBAL (1.0 M in hexane, 24.4 mL, 24.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of 124 (4.42 g, 12.2 mmol) in dry toluene (10 mL). The mixture was then stirred at -78 °C for 2 h and then stirred at 0 °C (iced bath) for 1 h. The stirring was continued for 6 h without recharging the ice bath. The solution was then recooled to -78 °C and MeOH (10 mL), Na\(_2\)SO\(_4\).10H\(_2\)O (2.0 g), Celite (3.0 g) and water (2 mL) were added successively. The cold bath was then removed and stirring continued for 2 h before filtering the slurry through a sintered disk funnel and wash with EtOAc. The organic layer was then concentrate under reduced pressure to give 125 (3.67 g, 90%) as a yellow liquid. \(^1\)H NMR (300 MHz): \(\delta = 6.86\) (d, \(J = 0.7\) Hz, 1H), 6.58 (d, \(J = 0.7\) Hz, 1H), 4.75 (s, 2H), 2.23 (s, 3H), 1.59 (s, 6H), 1.00 (s, 9H), 0.22 (s, 6H); \(^{13}\)C NMR (75 MHz): \(\delta = 153.9, 138.7, 130.0, 126.2, 123.8, 120.4, 97.9, 80.0, 65.4, 58.6, 31.5, 25.9, 21.2, 18.3, -4.1;\) IR (neat, cm\(^{-1}\)) = 3364, 2956, 2931, 2246, 1600, 1572, 1326, 1253; HRMS (ESI): Calcd. For C\(_{19}\)H\(_{30}\)NaO\(_3\)Si (\(m/z\)): 357.1856. Found 357.1873 [M+Na]\(^+\).
2-(3-Hydroxy-3-methyl-1-butynyl)-6-(t-butyl(dimethyl)silyloxy)-4-methyl-benzaldehyde (126)

Pyridinium chlorochromate (2.54 g, 11.8 mmol) and powdered 4A molecular sieves (3.0 g) was added to a stirred solution of 125 (2.81 g, 8.41 mmol) in dry CH₂Cl₂ (10mL). The reaction mixture was then stirred at rt for 10 h by which time oxidation was completed. The solvent was evaporated to approximately 50 mL and the slurry was filtered through a pad of SiO₂ and washed with CH₂Cl₂. The filtrate was concentrated and purified by flash chromatography (SiO₂, EtOAc-hexane 2:3) to give the aldehyde 126 (2.35 g, 84%) as a yellow waxy solid. ¹H NMR (300 MHz): δ = 10.40 (s, 1H), 6.88 (s, 1H), 6.56 (s, 1H), 2.23 (s, 3H), 1.59 (s, 6H), 0.95 (s, 9H), 0.19 (s, 6H); ¹³C NMR (75 MHz): δ = 189.7, 158.3, 145.4, 128.1, 125.2, 124.9, 121.3, 99.5, 80.1, 65.5, 31.3, 25.8, 21.7, 18.4, -4.2; IR (neat, cm⁻¹) = 3442, 2981, 2931, 2860, 2246, 1696, 1593, 1562; HRMS (ESI): Calcd. For C₁₉H₂₈NaSiO₃ (m/z): 355.1699. Found 355.1716 [M+Na]⁺.

4-[2,2-Di-tert-butyl-7-methyl-4-(2-methyl-allyl)-4H-benzo[1,3,2]dioxasilin-5-yl]-2-methyl-but-3-yn-2-ol (128)

Pyridine (0.21 mL, 2.63 mmol) and tBu₂Si(SO₃CF₃)₂ (0.23 mL, 0.70 mmol) were added to ice-cooled solution of 121 (0.10g, 0.37 mmol) in dry CH₂Cl₂ (10 mL) under N₂ atmosphere and stirred to warm up to room temperature. The mixture was
further stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (hexane/EtOAc; 10:2) to afford compound \( \text{128} \) (0.13 g, 86%) as a colorless liquid. \(^1\)H NMR (300 MHz): \( \delta = 6.84 \) (s, 1H), 6.72 (s, 1H), 5.49 (dd, \( J = 2.4, 10.7 \) Hz, 1H), 4.92 (s, 1H), 4.90 (s, 1H), 2.61 (d, \( J = 15.1 \) Hz, 1H), 2.42 (dd, \( J = 10.7, 15.5 \) Hz, 1H), 2.24 (s, 3H), 1.88 (s, 3H), 1.59 (s, 6H), 1.10 (s, 9H), 0.91 (s, 9H); \(^13\)C NMR (75 MHz, CD\(_3\)Cl): \( \delta = 153.3, 143.3, 137.9, 128.9, 126.4, 121.2, 120.1, 112.1, 98.9, 80.0, 72.7, 65.7, 47.0, 31.6, 31.5, 27.5, 26.9, 22.7, 22.2, 20.8, 19.8); IR (neat, cm\(^{-1}\)) = 3366, 2967, 2934, 2860, 2221, 1651, 1607, 1569; HRMS (ESI): Calcd. For C\(_{25}\)H\(_{38}\)NaO\(_3\)Si (\( m/z \)): 437.2482. Found 437.2481 [M+Na];

5,5-Di-tert-butyl-10-(1-hydroxy-1-methyl-ethyl)-2,7a-dimethyl-6a,7,7a,8-tetrahydro-4,6-dioxa-5-sila-cyclopenta\([a]\)phenalen-9-one (129)

\( \text{Co}_2(\text{CO})_8 \) (82 mg, 0.24 mmol) was added to the solution of enyne \( \text{128} \) (90 mg, 0.22 mmol) in toluene (10 mL) under N\(_2\) and stirred for 2 h at room temperature. The reaction mixture was then heated at 70 °C under N\(_2\) for overnight. The reaction mixture was then poured into a sintered glass funnel packed with Celite and SiO\(_2\) and first washed with hexane to remove the alkyne-Co\(_2(CO)_6\) remaining and then washed with ethyl acetate to remove any remaining cyclized product. The crude product was purified by flash chromatography (hexane/EtOAc, 20/1.5) to give 129 (67 mg, 70%) as a colorless liquid.
$^1$H NMR (500 MHz): $\delta = 6.84 \text{ (s, 1H)}, 6.78 \text{ (s, 1H)}, 5.01 \text{ (dd, } J = 4.6, 7.8 \text{ Hz, 1H)}, 4.78 \text{ (s, 1H)}, 2.48 \text{ (AB q, } J = 18.6 \text{ Hz, 2H)}, 2.34 \text{ (s, 3H)}, 2.25 \text{ (dd, } J = 7.3, 14.2 \text{ Hz, 1H)}, 2.02 \text{ (dd, } J = 5.04, 13.8 \text{ Hz, 1H)}, 1.61 \text{ (s, 3H)}, 1.34 \text{ (s, 3H)}, 1.10 \text{ (s, 9H)}, 1.06 \text{ (s, 3H)}, 0.97 \text{ (s, 9H)}; ^{13}$C NMR (125 MHz): $\delta = 210.1, 170.6, 153.6, 140.7, 138.1, 131.0, 124.1, 122.1, 121.6, 77.3, 71.3, 66.4, 51.3, 45.3, 39.1, 31.7, 28.1, 27.6, 27.1, 21.8, 21.4, 20.9; IR (neat, cm$^{-1}$) = 3452, 2964, 2934, 2861, 1730, 1684, 1569, 1473, 1331, 1285, 1009, 828; HRMS (ESI): Calcd. For $\text{C}_{26}\text{H}_{38}\text{SiO}_4\text{Na (m/z)}$: 465.2432. Found 465.2470 [M+Na]$^+$; Calcd. For $\text{C}_{52}\text{H}_{76}\text{Si}_2\text{O}_8\text{Na (m/z)}$: 907.4971. Found 907.4991 [2M+Na]$^+$. 

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APPENDIX 1

$^1$H and $^{13}$C NMR SPECTRA OF

2-(-2-Propenylxy)benzaldehyde (2)
APPENDIX 2

$^1$H and $^{13}$C NMR SPECTRA OF

2-(1-Hydroxy-2-propynyl)-(2-propenyloxy) benzene (3)
APPENDIX 3

$^1$H and $^{13}$C NMR SPECTRA OF

2-(1-Hydroxy-3-trimethylsilyl-2-propynyl)-(2-propenylxy) benzene (4)
APPENDIX 4

$^1$H and $^{13}$C NMR SPECTRA OF

2-(1-Hydroxy-3-phenyl-2-propynyl)-(2-propenyl)oxybenzene (5)
APPENDIX 5

$^1$H and $^{13}$C NMR SPECTRA OF

10-hydroxy-1-phenyl-4,4a-dihydro-3$H$,10$H$-5-oxabenzof]azulen-2-one (8)
APPENDIX 6

$^1$H and $^{13}$C NMR SPECTRA OF

2-(1-tert-butyl-dimethylsilyloxy -3-phenyl-2-propynyl)-(2-propenylxy)benzene (9)
229

**Experiment**
- single pulse dec

**Sample id**
- #2252457

**Solvent**
- CHLOROFORM-D

**Creation time**
- 6-CT-2004 03:55:16

**Revision time**
- 28-APR-2006 21:1:0:09

**Content**
- Single Pulse with Br

**Data Format**
- 10 COMPEx

**Dim size**
- 65536

**Dim size**
- 13C

**Dim units**
- [ppm]

**Site**
- Eclipse+ SQG

**Spectrometer**
- INEPT HR

**Field strength**
- 11.7472575 Tesla [500 MHz]

**X.acq.duration**
- 1.726704 [s]

**X.domain**
- 13C

**X.freq**
- 125.76529766 MHz

**X.offset**
- 100 [ppm]

**X.points**
- 65536

**X.precision**
- 4

**X.resolution**
- 0.57580336 MHz

**X.vee**
- 27.73944906 kHz

**Irr.0.main**
- 500.15991551 MHz

**Irr.0.freq**
- 51 ppm

**Mod.setups**
- 1

**Scans**
- 302

**X.90.width**
- 141.05 [ms]

**X.acq.time**
- 1.726704 [s]

**X angle**
- 300.0 [deg]

**X.pulse**
- 4.666666667 [us]

**Initial.wait**
- 1 [us]

**Phase preset**
- 1 [us]

**Recpr gain**
- 10

**Relaxation delay**
- 4 [s]

**Temp.set**
- 24 [°C]

**Unblank time**
- 2 [us]
APPENDIX 7

$^1$H and $^{13}$C NMR SPECTRA OF

10-$/t$-butyldimethylsilyloxy-1-phenyl-4,4a-dihydro-

$3H,10H$-5-oxabenzo[$f$]azulen-2-one (10)
APPENDIX 8

$^1$H and $^{13}$C NMR SPECTRA OF

3,5-Di-tert-butyl-2-(2-propenloxy)benzaldehyde (12)
APPENDIX 9

$^1$H and $^{13}$C NMR SPECTRA OF

3,5-Di-<i>tert</i>-butyl-2-(3-methyl-2-propenyloxy) benzaldehyde (14)
APPENDIX 10

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-hydroxy-2-propynyl)-(2-propenyl)benzene (15c)
APPENDIX 11

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)-2-propenylxybenzene (15b)
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- 3.95: 1.00 ppm
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**X**: parts per Million (ppm)
APPENDIX 12

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-hydroxy-3-trimethylsilyl-2-propynyl)-

(-2-propenyloxy) benzene (15a)
APPENDIX 13

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-hydroxy-2-propynyl)-1-(2-butenyloxy)benzene (17c)
APPENDIX 14

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-((1-hydroxy-3-phenyl-2-propynyl)-1-(2-butenyloxy) benzene (17b)
APPENDIX 15

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-((1-hydroxy-3-trimethylsilyl-2-propynyl)

-1-(-2- butenyloxy)benzene (17a)
APPENDIX 16

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-iodophenol (19)
APPENDIX 17

$^1\text{H}$ and $^{13}\text{C}$ NMR SPECTRA OF

1,5-Di-tert-butyl-3-iodo-2-(3-phenyl-2-propenyloxy)benzene (20)
APPENDIX 18

\(^1\)H and \(^{13}\)C NMR SPECTRA OF

3,5-Di-\(\text{tert}\)-butyl-2-(3’-phenyl-2’-propenyoxy) benzaldehyde (21)
APPENDIX 19

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-hydroxy-2-propynyl)

-1-(3-phenyl -2-propenyl)benzene (22c)
APPENDIX 20

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-hydroxy-3-phenyl-2-propynyl)

-1-(3-phenyl-2-propenylxy) benzene (22b)

280
APPENDIX 21

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(3-trimethylsilyl-2-propynyl)

-(-2-propenylxy) benzene (26a)
APPENDIX 22

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(-3-phenyl-2-propynyl)-2-propenylbenzene (26b)
APPENDIX 23

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-prop-2-ynyl-(2-propenyloxy)benzene (26a)
APPENDIX 24

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1-trimethylsilyl-4,4a-dihydro

-3H,10H-5-oxabenzo[f]azulen-2-one (23)
APPENDIX 25

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1-phenyl-4,4a-dihydro-3H,10H-5-oxabenzof[7]azulen-2-one (24)
APPENDIX 26

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-1-trimethylsilyl-4,4a-dihydro

-3H,10H-5-oxabenzo[f] azulen-2-one (28)
APPENDIX 27

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-1-phenyl-4,4a-dihydro

-3$H$,10$H$-5-oxabenzo[f] azulen-2-one (29)
APPENDIX 28

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1,1a,4,4a-tetrahydro-3H-5-oxabenzo[f]azulen-2,10-dione (syn isomer, 35)
APPENDIX 29

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1,1a,4,4a-tetrahydro-3H-5-
oxabenzo[f]azulen-2,10-dione (anti-isomer, 35)
APPENDIX 30

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(-1-tert-butyl-dimethylsilyloxy -3-phenyl-2-propynyl)

-(-2-propenyloxy)benzene (30)
APPENDIX 31

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(-1-tert-butyl-dimethylsilyloxy-3-trimethylsilyl-2-propynyl)
-(-2-propenyloxy)benzene (31)
APPENDIX 32

$^1$H and $^{13}$C NMR SPECTRA OF

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-(-2-propenylxyloxy) benzene (36)
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$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-/-butyldimethylsilyloxy-1-phenyl-4,4a-dihydro

$^3H,10^H$-5-oxabenzo[f]azulen-2-one (32)
APPENDIX 34

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-t-butyldimethylsilyloxy-1-trimethylsilyl-4,4a-dihydro

-3H,10H-5-oxabenzo[f]azulen-2-one (33)
APPENDIX 35

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-tert-butyl(dimethyl)silyloxy-4,4a-dihydro
-3H,10H-5-oxabenzo[f]azulen-2-one (exo product, 37)
APPENDIX 36

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (endo product, 37)
APPENDIX 37

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1-phenyl-3-methyl-4,4a-dihydro

-3$H,10H$-5-oxabenzo[f]azulen-2-one (39)
APPENDIX 38

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-3-methyl-1-phenyl-4,4a-dihydro

-$3H,10H$-oxabenzo[f]azulen-2-one (endo product, 40)
APPENDIX 39

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-3-methyl-1-phenyl-4,4a- dihydro

$\text{-}3H,10H$-5-oxabenzo[f]azulen-2-one (exo product, 41)
APPENDIX 40

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-3-methyl-1-trimethylsilyl
-4,4a- dihydro-3$H$,10$H$-5-oxabenzof[3]azulen-2-one (42)
APPENDIX 41

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-3-methyl-1,1a,4,4a-tetrahydro-$1^H,3^H$-5-oxabenzof[azulen-2,10-dione (anti-product, 43)
APPENDIX 42

\(^1\text{H} \text{ and } ^{13}\text{C} \text{ NMR SPECTRA OF}

6,8-Di-tert-butyl-3-methyl-1,1a,4,4a-tetrahydro-1\text{H},3\text{H}-5-

oxabenzo[f]azulen-2,10-dione (syn-product, 43)
APPENDIX 43

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-3-methyl-4,4a-dihydro-3$H,10H$-5-oxabenzof[\textit{f}]azulen-2-one (44)
APPENDIX 44

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-tert-butyl-dimethylsilyloxy

-3-phenyl-2-propynyl)-(2-butenyloxy)benzene (45)
APPENDIX 45

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(-1-tert-butyl dimethylsilyloxy
-3-trimethylsilyl-2-propynyl)-(2- butenloxy) benzene (46)
APPENDIX 46

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1'-tert-butyl dimethylsilyloxy

-2-propynyl)-(-2- butenyloxy) benzene (49)
APPENDIX 47

$^1$H and $^{13}$C NMR SPECTRA OF

6, 8-Di-tert-butyl-10-tert-butyldimethylsilyloxy-3-methyl-1-phenyl
-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (47)
APPENDIX 48

$^1$H and $^{13}$C NMR SPECTRA OF

6, 8-Di-tert-butyl-10-tert-butylidimethylsilyloxy-3-methyl-1-trimethylsilyl
-4,4a-dihydro-3H,10H-5-oxabenzo[f]azulen-2-one (48)
APPENDIX 49

$^1$H and $^{13}$C NMR SPECTRA OF

6, 8-Di-$t$-butyl-10-$t$-butyldimethylsilyloxy-3-methyl
-4,4a-dihydro-3$H$,10H-5-oxabenzo[f]azulen-2-one (50)
APPENDIX 50

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1,3-diphenyl-4,4a-dihydro

$-3H,10H$-5-oxabenzo[f]azulen-2-one (51)
APPENDIX 51

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-1,3-diphenyl-4,4a-dihydro

-3H,10H-5-oxabenzo[f] azulen-2-one (52)
APPENDIX 52

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-tert-butyldimethylsilyloxy-3-phenyl-2-propynyl)
-1-(3-phenyl-2-propenyloxy) benzene (53)
APPENDIX 53

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-$t$-butyl-10--$t$-butyldimethylsilyloxy-1,3-diphenyl
-4,4a-dihydro-3$H,10H$-5-oxabenzo[f]azulen-2-one (54)
APPENDIX 54

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-3-phenyl-1,1a,4,4a-tetrahydro-3$^H$-5-oxabenzof[fl]azulen-2, 10-dione (55)
APPENDIX 55

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10-hydroxy-3-phenyl-4,4a-dihydro

$-3H,10H$-5-oxabenzo[f] azulen-2-one (56)
APPENDIX 56

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(1-tert-butyldimethylsilyloxy -2-propynyl) -1-(-3-phenyl -2-propenyloxy) benzene (57)
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- Labels for peaks

**Notes:**

- Parts per Million (ppm)
- Natural reading of the data
- No hallucination
APPENDIX 57

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-10--$t$-butyldimethylsilyloxy -3-phenyl
-4,4a-dihydro-3$H,10H$-5-oxa benzo[f]azulen-2-one (58)
APPENDIX 58

$^1$H and $^{13}$C NMR SPECTRA OF

Di-tert-butyl-2-trimethylsilylethynyl

-(-2-propenyloxy)benzene (62)
APPENDIX 59

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1-trimethylsilyl-3a,4-dihydro

-3$H$- cyclopenta[c]chromen-2-one (64)
APPENDIX 60

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-trimethylsilylethynyl

-(-2-methylallyloxy)benzene (66)
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APPENDIX 61

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-ethynyl

-(-2-methylallyloxy)benzene (67)
APPENDIX 62

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-$^\text{tert}$-butyl-1-trimethylsilyl -3a-methyl

-4-hydro-$^3$H-cyclopenta[c]chromen-2-one (68)
APPENDIX 63

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-3a-methyl-3a,4-dihydro

-3$H$-cyclopenta[c]chromen-2-one (69)
APPENDIX 64

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-trimethylsilylethynyl

-(-3-phenyl-2-propenloxy)benzene (71)
APPENDIX 65

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-ethynyl

-(-3-phenyl-2-propenylxyloxy)benzene (72)
APPENDIX 66

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-3-phenyl-1-trimethylsilyl-3a,4-dihydro

-3$H$- cyclopenta[c]chromen-2-one (73)
APPENDIX 67

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-3-phenyl-3a,4-dihydro

-3H- cyclopenta[c]chromen-2-one (74)
APPENDIX 68

$^1$H and $^{13}$C NMR SPECTRA OF

3-Butenyl-oxy-4,6-di-tert-butyl

-2-trimethylsilylethynylbenzene (75)
APPENDIX 69

$^1$H and $^{13}$C NMR SPECTRA OF

7,9-Di-tert-butyl-1-trimethylsilyl

-4,4a-dihydro-$3H,5H$-6-oxabenzo$[f]$azulen-2-one (77)
APPENDIX 70

$^1$H and $^{13}$C NMR SPECTRA OF

(7,9-Di-\textit{tert}-butyl-4-methylene -3,4-dihydro

-2$\textit{H}$-benzo[\textit{b}]oxepin-5-ylidenemethyl)-trimethylsilane (78)
APPENDIX 71

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-14-hydroxy-8-oxa

-tricyclo[9.2.1.0]tetradeca-2,4,6-triene-13-one (81)
APPENDIX 72

$^1$H and $^{13}$C NMR SPECTRA OF

2,4-Di-tert-butyl-6-(-3-hydroxy-3-methylbut-1-ynyl)phenol (84)
APPENDIX 73

$^1$H and $^{13}$C NMR SPECTRA OF

2,4-Di-$\text{-}t\text{ert}-$butyl-6-($\text{-}3$-methylbut-$\text{1}$-ynyl)$phenol (85)
APPENDIX 74

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(-2-methylbut-3-yn-2-ol)-(-2-methylallyloxy)benzene (86)
APPENDIX 75

$^1$H and $^{13}$C NMR SPECTRA OF

4,6-Di-tert-butyl-2-(2-methylbut-3-ynyl)

-(-2-methylallyloxy)benzene (87)
APPENDIX 76

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1-(1-hydroxy-1-methylethyl)-3a-methyl
-3a,4-dihydro-3H-cyclopenta[c]chromen-2-one (88)
APPENDIX 77

$^1$H and $^{13}$C NMR SPECTRA OF

6,8-Di-tert-butyl-1-isopropyl-3a-methyl-3a,4-dihydro

-3H-cyclopenta[c]chromen-2-one (89)
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<tr>
<td>Noe time</td>
<td>2 [s]</td>
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<td>Sec. gain</td>
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<td>Relaxation time</td>
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<tr>
<td>Repetition time</td>
<td>4.004120300[s]</td>
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<td>Temp. set</td>
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</table>

![Image of a spectral analysis graph]
APPENDIX 78

$^1$H and $^{13}$C NMR SPECTRA OF

2-Methoxy-4-methylbenzoic acid (99)
Filename = 1_psa_1h-7.5GF
Experiment = single_pulse.exp
SAMPLE ld = 25929411
Solvent = CH3CN:MeOH=9:1
Creation time = 9-FEB-2006 12:41:00
Revision time = 21-OCT-2006 16:38:29
Current time = 21-OCT-2006 16:38:29
Content = Single Pulse Experiment
Data format = 10 COMPLEX
Dim_title = CH
Dim units = ppm
Dimensions = X
Site = Eclipse 500
Spectrometer = DELTA NMR
Field strength = 11.7435759 [T] [1000 MHz]
X_acq duration = 2.182468 [s]
X_domain = 500.15991521 [MHz]
X_freq = 5 [ppm]
X_points = 14384
X_points = 0
X_resolution = 0.45822189 [MHz]
X_sweep = 7.57750975 [kHz]
Mod_return = 1
Zoom = 32
X90 width = 15 [us]
X_acq time = 5.252446 [s]
X_angle = 45 [deg]
X_pulse = 7.5 [us]
Initial wait = 1 [s]
Phase preset = 9 [us]
Recur gain = 19
Relaxation delay = 4 [s]
Temp qst = 22 [øC]
Usb time = 2 [us]

X : parts per Million : H1
APPENDIX 79

$^1$H and $^{13}$C NMR SPECTRA OF

$N$-tert-buty1-2-methoxy-4-methylbenzamide (100)
APPENDIX 80

$^1$H and $^{13}$C NMR SPECTRA OF

$N$-tert-butyl-6-iodo-2-methoxy-4-methylbenzamide (91)
APPENDIX 81

$^1$H and $^{13}$C NMR SPECTRA OF

$N$-tert-butyl-6-iodo-2-hydroxy-4-methylbenzamide (101)
APPENDIX 82

$^1$H and $^{13}$C NMR SPECTRA OF

2-Hydroxy-6-iodo-4-methyl-methylbenzoate (102)
APPENDIX 83

$^1$H and $^{13}$C NMR SPECTRA OF

2-Methoxy-6-iodo-4-methyl-methylbenzoate (103)
APPENDIX 84

$^1$H and $^{13}$C NMR SPECTRA OF

2- Iodo-4-methyl-6-methoxy-benzylalcohol (104)
APPENDIX 85

$^1$H and $^{13}$C NMR SPECTRA OF

2- Iodo-4-methyl-6-methoxy-benzylaldehyde (105)
APPENDIX 86

$^1$H and $^{13}$C NMR SPECTRA OF

3,4,6-Tribromo-2,5-dimethyphenol (109)
APPENDIX 87

$^1$H and $^{13}$C NMR SPECTRA OF

3-Bromo-2,5-dimethylphenol (110)
APPENDIX 88

$^1$H and $^{13}$C NMR SPECTRA OF

3-Bromo-2,5-dimethylanisole (111)
Filename = 1_cmr120crude_r-3.pdf
Author = delta
Experiment = single_pulse.ex2
Sample id = 08479743
Solvent = CHLOROFORM-D
Creation time = 21-05-2020 21:15:03
Revision_time = 21-05-2020 19:43:34
Current time = 21-05-2020 19:44:07
Content = single_pulse
Data format = 1D COMPLEX
Dim size = 13107
Dim title = H
Dim units = ppm
Dimensions = X
Site = EXC 300
Spectrometer = DELTA_2 MRS

Field strength = 7.0506012[T] (300)MHz
X_arg_duration = 2.90717696[s]
X_domain = 1
X_freq = 300.52855592[MHz]
X_offset = 0[ppm]
X_points = 16384
X_resolution = 0.3497631[Hz]
X_sweep = 0.00707084[kHz]
Trc_domain = 10
Trc_freq = 500.52855592[MHz]
Trc_offset = 0[ppm]
Trc_points = 16384
Trc_resoluion = 0.3497631[Hz]
Trc_sweep = 0.00707084[kHz]
Clipped = FALSE
Mod return = 1
Scans = 24
Total_scans = 24
X90_width = 13.01[us]
X_arg_time = 2.90717696[s]
X_angle = 45[deg]
X_att = 4[db]
X_pulse = 6.5055[us]
Trc_mode = Off
Tri_mode = Off
Dantel_preset = FALSE
Initial_wait = 1[s]
Nseg gain = 40
Balderon delay = 0[ms]
Repetition_time = 7.95717696[s]
Temp goto = 23.7[°C]

X : parts per Million : HH
APPENDIX 89

$^1$H and $^{13}$C NMR SPECTRA OF

2-Bromo-6-methoxy-4-methylbenzaldehyde (112)
APPENDIX 90

$^1$H and $^{13}$C NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)-

4-methyl-6-methoxy-benzaldehyde (91)
APPENDIX 91

$^1$H and $^{13}$C NMR SPECTRA OF

2-(1-Hydroxy-3-methyl-3-butenyl)

-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl anisole (93)
APPENDIX 92

$^1$H and $^{13}$C NMR SPECTRA OF

$N$,$N$-Diethyl-2-hydroxy-4-methylbenzamide (114)
APPENDIX 93

$^1$H and $^{13}$C NMR SPECTRA OF

$N,N$-Diethyl-2-(tert-butyl-dimethylsilyloxy)-4-methylbenzamide (115)
APPENDIX 94

$^1$H and $^{13}$C NMR SPECTRA OF

2-(tert-Butyl-dimethylsilyloxy)

- 6-ido-4-methyl- $N,N$-diethylbenzamide (116)
APPENDIX 95

\(^1\)H and \(^{13}\)C NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)-4-methyl-6-

(\textit{tert}-butyl-dimethylsilyloxy)-N,N-diethylbenzamide (117)
APPENDIX 96

$^1$H and $^{13}$C NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)

-6-hydroxy-4-methyl-methylbenzoate (118)
APPENDIX 97

$^{1}H$ and $^{13}C$ NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)

-6-hydroxy -4-methyl -benzylalcohol (119))
APPENDIX 98

$^1$H and $^{13}$C NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)

-6-hydroxy -4-methyl -benzaldehyde (120)
APPENDIX 99

$^1$H and $^{13}$C NMR SPECTRA OF

2-(1-Hydroxy-3-methyl-3-butenyl)-3-

(3-hydroxy-3-methyl-1-butynyl)-5-methyl phenol (121)
APPENDIX 100

$^1$H and $^{13}$C NMR SPECTRA OF

2-(3-hydroxy-3-methyl-1-butynyl)

$\sim$6-(\textit{t}-butyldimethylsilyloxy)$\sim$4-methyl-methylbenzoate (124)
APPENDIX 101

$^1$H and $^{13}$C NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)

-6-(t-butyldimethylsilyloxy) -4-methyl –benzyl alcohol (125)
APPENDIX 102

$^1$H and $^{13}$C NMR SPECTRA OF

2-(3-Hydroxy-3-methyl-1-butynyl)

-6-(t-butyldimethylsilyloxy)-4-methyl-benzaldehyde (126)
APPENDIX 103

$^1$H and $^{13}$C NMR SPECTRA OF 4-[2,2-Di-tert-butyl-7-methyl-4-(2-methyl-allyl)-4$H$-benzo[1,3,2]dioxasilin-5-yl]-2-methyl-but-3-yn-2-ol (128)
APPENDIX 104

$^1$H and $^{13}$C NMR SPECTRA OF

5,5-Di-tert-butyl-10-(1-hydroxy-1-methyl-ethyl)
-2,7a-dimethyl-6a,7a,8-tetra hydro-4,6-dioxa
-5-sila-cyclopenta[a]phenalen-9-one (129)
SUPPORTING INFORMATION
FOR CRYSTAL STRUCTURE

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Table S2. Crystal, data collection, and refinement parameters for 29
Table S3. Crystal, data collection, and refinement parameters for 41
<table>
<thead>
<tr>
<th>Table S1. Crystal data and structure refinement for 24</th>
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<td>Density (calculated)</td>
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<td>100(2) K</td>
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<td></td>
<td>b = 12.1017(5) Å, γ = 90°</td>
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<td></td>
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<td>Space group</td>
<td>P2(1)/n</td>
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<td>Volume</td>
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</table>
REFERENCES

PART I


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\textbf{PART II}


BIOGRAPHICAL INFORMATION

Christian E. Madu, born in Aba, Nigeria, obtained his B.Sc. and M.S. from the University of Lagos, Nigeria in 1997. He worked as a research associate under the guidance of Professor Oluwole B. Familoni at the University of Lagos, Nigeria from 1999 to 2001. He then began his doctoral studies at the University of Texas at Arlington in Fall semester, 2001. As a graduate student he worked with Professor Carl Lovely. He obtained his doctorate in 2007.