Electrophilic Cyclization of Vinylogous Propargyl-Acetate-Co$_2$(CO)$_6$ Complexes: A Novel Approach Towards The Synthesis of Faveline- and Icetexane-Diterpenes and Related 6,7,n-Ring Systems

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ELECTROPHILIC CYCLIZATION OF VINYLOGOUS
PROPARGYL-ACETATE-Co₂(CO)₆ COMPLEXES: A NOVEL
APPROACH TOWARDS THE SYNTHESIS OF FAVELINE-
AND ICETEXANE-DITERPENES AND RELATED 6,7,n-RING
SYSTEMS

by

Izabela Kołodziej

A Dissertation
Submitted to the Faculty of Graduate Studies
Through the Department of Chemistry and Biochemistry
in Partial Fulfillment
of the Requirements for the Degree of Doctor of Philosophy
at the University of Windsor

Windsor, Ontario, Canada
2014
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ELECTROPHILIC CYCLIZATION OF VINYLOGOUS PROPARGYL-ACETATE-\(\text{Co}_2(\text{CO})_6\) COMPLEXES: A NOVEL APPROACH TOWARDS THE SYNTHESIS OF FAVELINE- AND ICETEXANE-DITERPENES AND RELATED \(6,7,n\)-RING SYSTEMS

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14 July 2014
Declaration of Co-Authorship/Previous Publication

I. Co-Authorship Declaration

I hereby declare that this dissertation incorporates material that is a result of joint research, as follows:

The dissertation also incorporates the outcomes of joint research undertaken under the supervision of Professor Dr. James Green. The collaboration is covered in Chapter 2 of the dissertation. In all cases, the key ideas, primary contributions, experimental designs, data analysis and interpretation, were concepts proposed by both author and co-author, and performed predominately by the author, with oversight and counsel provided by the co-author.

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II. Declaration of Previous Publication

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ABSTRACT

The Nicholas reaction is a Lewis- or Brønsted-acid mediated displacement of dicobalt-hexacarbonyl complexed alcohols, ethers, or acetates, which generates stable cations propargylic to the alkyne-Co$_2$(CO)$_6$ group, that can consequently be trapped by a variety of nucleophiles to form new carbon-carbon or carbon-heteroatom bonds. This reaction features several aspects which makes it especially well-suited for the synthesis of compounds containing cyclic structures by way of annulation reactions. Upon complexation of the alkyne with a Co$_2$(CO)$_6$ unit, the alkyne function bends, and the bond angle is reduced to approximately 140°. This reduced bond angle, coupled with the fact that the generated [(propargylium)Co$_2$(CO)$_6$]$^+$ cations exhibit a relatively high electrophilicity, make participation in ring-formation via electrophilic cyclization by means of Nicholas chemistry a very feasible process. Given the wide occurrence of cycloheptane containing compounds in nature, and the group’s ongoing interest in acetylene-Co$_2$(CO)$_6$ chemistry, the following chapters describe a novel approach to cycloheptyne-Co$_2$(CO)$_6$ synthesis via the preparation and reactivity studies of vinylogous propargyl acetate-Co$_2$(CO)$_6$ complexes. Relying on simple (and commercially available) starting materials, a series of 6,7,6-dibenzocycloheptyne-Co$_2$(CO)$_6$ complexes, and 6,7,5-dibenzocycloheptyne-Co$_2$(CO)$_6$ heterocyclic analogue complexes were synthesized in moderate yields. Treatment of their respective complexed precursors with SnCl$_4$ as Lewis acid generated benzylic-Co$_2$(CO)$_6$ cations which were propargylic by vinylogy, and which were subsequently trapped intramolecularly by electron rich arenes. The remainder of the syntheses focused on the
generation of a plethora of 6,7,n-tricyclic-Co$_2$(CO)$_6$ model substrates ($n = 5, 6, 7$), as outlined in the retrosynthesis below. A series of acetate-Co$_2$(CO)$_6$ complexes were exposed to BF$_3$•OEt$_2$ or SnCl$_4$, which resulted in the formation of their respective allylic/propargylic cation complexes. Intramolecular nucleophilic attack by electron rich arenes (and in one case, a π-excessive heterocycle) led to ring closure to afford the cycloheptyne-Co$_2$(CO)$_6$ complexed systems in excellent yields. A small number of $n$,7-bicyclic-Co$_2$(CO)$_6$ systems ($n = 6, 7$) were synthesized by employing an allylsilane moiety as the nucleophile. These cyclized substrates provided the framework and substitution pattern of a variety of natural products, and hence to establish the broader utility of this process, this procedure was then exemplified by the formal synthesis of some icetexane-diterpenes.
DEDICATION

I would like to dedicate this dissertation to my mother, for all her continued patience and support, and to my brother and my father, who I know will always be looking out for me throughout my journeys in life.

“A ship in port is safe, but that’s not what ships are built for.” - Grace Hopper

“My existence is in a state of quantum indecision.” - Schrodinger’s Cat
ACKNOWLEDGEMENTS

First and foremost, I would like to extend my most sincere thanks to my supervisor and mentor, Dr. James Green. With deepest gratitude, I would like to thank him for having taken me under his supervision, for his incredible patience over the years, for his guidance and his counsel, for fuelling my passion for chemistry with his knowledge, motivation, support, and above all, friendship, and for everything else I cannot seem to find words for. His sound advice and good company will always be remembered and appreciated.

I would like to thank my committee members, Dr. Keith Taylor, Dr. Jan Ciborowski, Dr. Jeremy Rawson, and Dr. Zhuo Wang for all their support, encouragement, and guidance in helping me fulfill my requirements above the requisite standards, and Dr. Michael Kerr for acting as the external examiner. I would also like to thank past and present members of the Green group: Dr. Sheida Amiralaei, Dr. Rafiq Taj, Siniša Đurđević, Mariam Mehdi, Patrick Frias, Rebecca Ngenzi, Michelle Thibodeau, Jake Henkie, Joe Sbrocca, Joey Francisco, and Meriam Hermiz for all their advice, assistance, support, and friendship.

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Finally I would like to give special thanks to my mother for her continued support, encouragement, unconditional love, patience, and tolerance over the years.
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<th>Definition</th>
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<tbody>
<tr>
<td>Ac$_2$O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>BF$_3$•OEt$_2$</td>
<td>Boron trifluoride etherate</td>
</tr>
<tr>
<td>BHA</td>
<td>Butylated hydroxyanisole</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>tert-Butanol</td>
</tr>
<tr>
<td>Bu$_2$BcOTf</td>
<td>Dibutyl boron triflate</td>
</tr>
<tr>
<td>Bu$_3$SnH</td>
<td>Tributyltin hydride</td>
</tr>
<tr>
<td>BTMSA</td>
<td>Bis(trimethylsilyl)acetylene</td>
</tr>
<tr>
<td>n-C$<em>5$H$</em>{11}$</td>
<td>n-Pentyl</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>cm$^{-1}$</td>
<td>Wavenumber</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>Doublet of doublets of doublets</td>
</tr>
<tr>
<td>dH$_2$O</td>
<td>Distilled water</td>
</tr>
<tr>
<td>DIB</td>
<td>(Diacetoxyiodo)benzene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
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</tr>
<tr>
<td>Et₃SiH</td>
<td>Triethylsilane</td>
</tr>
<tr>
<td>EtSNa</td>
<td>Sodium ethylthiolate</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>J</td>
<td>J-coupling</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
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</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
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<td>Dimethyl ether</td>
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<td>Dimethylaluminum trifluoromethanesulphonate</td>
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<tr>
<td>MeSNa</td>
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</tr>
<tr>
<td>Na/Hg</td>
<td>Sodium amalgam</td>
</tr>
<tr>
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<td>Sodium ethoxide</td>
</tr>
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<td>Abbreviation</td>
<td>Full Name</td>
</tr>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NEt₃</td>
<td>Triethylamine</td>
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<td>Nucleophile</td>
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<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
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<tr>
<td>Pd(PPh₃)₂Cl₂</td>
<td>Bis(triphenylphosphine)palladium(II) dichloride</td>
</tr>
<tr>
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xxii
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<td>Tributyltin hydride</td>
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CHAPTER 1: INTRODUCTION

1.1. THE NICHOLAS REACTION

The discovery of new and efficient methods for the construction of carbon-carbon bonds is an advancing, developing, and growing theme in organic synthesis. The use of alkyne chemistry, and in particular, alkyne-Co$_2$(CO)$_6$ complex chemistry, has gained prominence in organic synthesis, with efficient methods developed to perform sophisticated transformations. Acetylene-dicobalt hexacarbonyl (Co$_2$(CO)$_6$) complexes are used primarily for three major applications in organic synthesis\cite{3}: the formation of cyclopentenones by the Pauson-Khand reaction\cite{6,38,49,97,133,144}, the nucleophilic addition to cobalt-complexed propargylic cations, known as the Nicholas reaction\cite{18,30,51,64,65,66,93,137,139,169,185}, and the use of the cobalt moiety as a useful protecting group\cite{143} for acetylenic compounds due to its ease of addition and removal.

The Nicholas reaction (Scheme 1.1) is a potent and versatile synthetic tool in organic synthesis, which enables efficient substitution reactions of propargyl alcohols, ethers, and acetates, resulting in the formation of new carbon-carbon and/or carbon-heteroatom bonds. Reported first in 1972 by Nicholas and Petit\cite{141}, the authors, while investigating the use of the Co$_2$(CO)$_6$ unit as a protecting group for the C-C triple bond, detailed the facile nature of the mild, acid-mediated dehydration of dicobalt hexacarbonyl-complexed propargyl alcohols to their corresponding 1,3-enyne derivatives. Propargyl alcohols not complexed to Co$_2$(CO)$_6$ failed to react under the same conditions; dehydration of free propargyl alcohols required forcing conditions, such as considerably high temperatures (80-200 °C) and more strongly
acidic conditions. The Nicholas group soon became interested in the stability of the likely intermediates, [(propargyl)Co$_2$(CO)$_6$]$^+$ cations, based on the hydration/dehydration equilibrium connecting the complexes of progargyl alcohols and their 1,3-ene products$^{139}$.

Scheme 1.1: A) The Nicholas reaction. B) Simplified method of representing the acetylene-Co$_2$(CO)$_6$ bond.

The Nicholas reaction can be best described as an S$_\text{N}1$ process$^{169}$. Prior to the substitution step, the acetylene unit is treated with dicobalt octacarbonyl to yield the triple bond complexed as its $\mu$-$\eta^1$-Co$_2$(CO)$_6$-alkyne adduct (1). The resulting organometallic complex is treated with a Lewis acid (or in some cases, a Brønsted acid) to form the ensuing propargyl carbocation (2), resulting from the loss of an appropriate leaving group. The cation is stabilized by delocalization of the positive charge onto the neighbouring alkyne-
Co$_2$(CO)$_6$ functionality. Subsequent entrapment of the cation by nucleophilic attack furnishes the desired substitution product. The cobalt complex can be oxidatively or reductively removed following nucleophilic attack (3 or 4, respectively), or can be used to further functionalize the Nicholas reaction products in subsequent cobalt-mediated reactions, such as the Pauson-Khand reaction$^{89,155,176}$.

1.1.1. FEATURES OF NICHOLAS REACTION CHEMISTRY

The Nicholas reaction is a resourceful and impressive synthetic application for a variety of reasons: SN$_1$' and SN$_2$' reactions are not possible in the simplest cases, thus eliminating the formation of allenic by-products; buffered systems are possible to use in case acid-sensitive functionalities are present in the substrate; and the reaction can be applied both inter- and/or intramolecularly, in either solution or the solid phase$^{54}$. The reaction also allows for the stereoselective synthesis of chiral products$^{30,137}$ by either: i) the introduction of a chiral ligand into the cobalt complex (i.e., phosphines$^{13}$, tris(1,1,1,3,3,3-hexafluoroisopropyl)phosphate$^{19}$, and phosphoramidites$^{108}$); ii) the use of chiral substrates with well-defined stereocenters at the propargyl position, chiral centres neighbouring the propargyl site, or at the remote acetylenic site (i.e., chiral auxiliary) that control the stereochemistry at the newly created sp$^3$ carbon centre$^{9,10,32,88,134,147}$; iii) the use of chiral nucleophiles$^{138,163}$.

The Nicholas reaction also works well with a wide variety of nucleophiles that are capable of reacting efficiently with the parent cation. Oxygen-centred nucleophiles, such as water and various alcohols, nitrogen nucleophiles comprised of amines and sulphonamides, and activated carbon nucleophiles, such as allyl silanes, allyl stannanes, allyl
boranes, silyl enol ethers, enamines, ketene acetals, and electron rich aromatic rings all react readily with Nicholas cations\textsuperscript{66,102,169,185}. Other nucleophiles include hydrides\textsuperscript{140}, unactivated alkenes\textsuperscript{102} (although a mixture of alkene isomers upon proton loss results, or if a remote oxygenated functional group is in a position to react with the resulting cation, lactones or ethers result), and alkyl dithiols\textsuperscript{57} (with isolation of dimeric by-products along with the intended products). Finally, and most importantly, the reaction can lead to ring formation due to the fact that complexation bends the alkyne unit away from 180° to almost that characteristic of alkenes, allowing for bond geometries not available to their metal-free counterparts (see \textcolor{blue}{Angle Strained Cycloalkynes} section).

Mayr’s group\textsuperscript{105,125,127} have studied the reaction kinetics of some simple \(\text{Co}_2(\text{CO})_6\)-stabilized propargyl cations with a variety of \(\pi\)-nucleophiles (i.e., allyl silanes, allyl stannanes, silylated enol ethers, ketene acetals) and hydride donors (i.e., trialkylsilanes), and quantified their reactivity using their electrophilicity parameter, \(E\). The authors concluded that the studied Nicholas cations (5) are slightly less electrophilic than the dianisylmethylium ion (6), and behave as being roughly equivalent in reactivity to the xanthylium (7) and ferrocenylethylium (8) ions (Figure 1.1A). Their predictions are in good agreement with experimental observations, and confirm the suitability of reactivity of these cations with nucleophiles that inherit a reactivity greater than that of \(m\)-xylene (i.e., electron rich aromatics, simple alkenes, and alkynes)\textsuperscript{66}. In 2000, the Mayr group\textsuperscript{124,126} studied the reactivity of vinyl substituted alkyne-\(\text{Co}_2(\text{CO})_6\) complexes (9) as nucleophiles with a variety of electrophiles in order to generate the propargyl cation. The authors determined that there was no good correlation between the stability of the formed \([(\text{propargylium})\text{Co}_2(\text{CO})_6]^+\)
cation and the reactivity of the precursor alkene. Their nucleophilicities are comparable to 1,3-butadiene (10), and one case in particular, possessed a nucleophilic reactivity parameter equivalent to isobutylene (11) (Figure 1.1B).

Figure 1.1: A) Relative electrophilicity of the [(propargylium)Co$_2$(CO)$_6$]$^+$ cation (R = H, $E = -0.84$; R = Ph, $E = -1.58$) (5) based on the Mayr scale: dianisylmethylium ion ($E = 0.00$) (6), xanthylium ion ($E = -0.99$) (7), and ferrocenylmethylium ion ($E = -2.57$) (8). B) Relative nucleophilicity of the vinyl substituted alkyne-Co$_2$(CO)$_6$ (R = H, $N = -1.1, s = 0.92$; R = Ph, $N = 1.33, s = 0.90$) (9) moiety based on the Mayr scale: 1,3-butadiene ($N = -0.87, s = 1.00$) (10), and isobutylene ($N = 1.11, s = 0.98$) (11).

Facile decomplexation of the cobalt moiety has made Nicholas chemistry an even more attractive synthetic tool. After completion of the Nicholas reaction, the cobalt complex
can be removed using a variety of methods, either oxidatively to yield the parent alkyne, or reductively to yield an alkene or a substituted alkene. Some of the more common oxidative methods include\textsuperscript{185}: Fe(NO\textsubscript{3})\textsubscript{3} in alcohol (ROH), ROH/THF, or CH\textsubscript{2}Cl\textsubscript{2}; CAN in conjunction with a tertiary alcohol in acetone, MeOH, MeOH/H\textsubscript{2}O, MeOH/Et\textsubscript{2}O, or MeCN; I\textsubscript{2} in C\textsubscript{6}H\textsubscript{6} or THF; trimethylamine N-oxide in THF, MeOH, or CHCl\textsubscript{3}; and N-methylmorpholine N-oxide (in conjunction with 1,4-cyclohexadiene) in THF, CH\textsubscript{2}Cl\textsubscript{2}, 'PrOH, DMF, or CCl\textsubscript{4}/tBuOH. Common reductive methods include: lithium in liquid NH\textsubscript{3}; H\textsubscript{2} over Rh/charcoal in EtOH; H\textsubscript{2} over Wilkinson’s catalyst in C\textsubscript{6}H\textsubscript{6}; Bu\textsubscript{3}SnH in C\textsubscript{6}H\textsubscript{6}; NaH\textsubscript{2}PO\textsubscript{2}C\textsubscript{H}\textsubscript{2}O in 2-methoxyethanol; and Et\textsubscript{3}SiH or Ph\textsubscript{3}SiH in C\textsubscript{6}H\textsubscript{6}, which form their respective vinylsilanes. For other, rarer methods, the reader is directed to the Teobald review\textsuperscript{185}.

\textbf{1.1.2. STABILITY OF THE [(PROPARGYLIUM)Co\textsubscript{2}(CO)\textsubscript{6}]\textsuperscript{+} CATION}

The stability of the propargyl carbocation intermediate arises from the benefit of the $\beta$-effect of the cobalt moiety: the complexes are remarkably stable due to significant delocalization of the positive charge onto the Co\textsubscript{2}(CO)\textsubscript{6} unit. In 1973, Seyferth et. al.\textsuperscript{168} studied three carbonium salts, [(CCHR)Co\textsubscript{3}(CO)\textsubscript{9}]PF\textsubscript{6} (\textbf{12}, Figure 1.2), whose stability, they believed, were a direct consequence of their position relative to the triangular arrangement of the three cobalt atoms. The following year, the group\textsuperscript{167} reported the $^1$H- and $^{13}$C-NMR spectra of these carbenium ions, which provided evidence for stabilization through charge delocalization onto the cobalt cluster system. Further experimental evidence for this extensive charge delocalization was reported by Connor and Nicholas\textsuperscript{29} in 1977 (\textbf{13}, Figure 1.2), whose cations provided evidence by an increase in absorption frequencies of the C=O
ligands, $\nu$(CO), in the IR spectrum (+40-60 cm$^{-1}$) compared to those present in the parent alcohols. The shift indicates greater C-O bonding, as would be expected from decreased $d$(Co) $\rightarrow$ $\pi^\ast$(CO) donation in the electron deficient cations. $^1$H-NMR spectra exhibited only small downfield shifts of alkyl groups $\alpha$- to the newly generated cationic centre, suggesting charge dispersal in the generated cations. $^{13}$C-NMR resonances were only mildly deshielded relative to the precursor alcohol complexes; however, they were dramatically shielded compared to the metal-free propargyl cations. The authors also concluded that the organometallic unit possessed powerful electron donating abilities.

**Figure 1.2:** Structures studied by the Seyferth group (R = H, CH$_3$, or C$_6$H$_5$) (12), and the Nicholas group (R$_1$ = R$_2$ = CH$_3$, Z = SbF$_6$; R$_1$ = R$_2$ = C$_6$H$_5$, Z = SbF$_6$; R$_1$ = CH$_3$, R$_2$ = H, Z = BF$_4$; R$_1$ = R$_2$ = H, Z = BF$_4$) (13).

### 1.1.3. STRUCTURAL ANALYSIS OF THE [(PROPARYLIUM)Co$_2$(CO)$_6$]$^+$ CATION

The three dimensional structure elucidation of the Nicholas cations awaited some time due to the inability to generate a stable enough crystal suitable for X-ray crystallography. In 1978, *Schilling and Hoffmann*$^{162}$ proposed, on the basis of theoretical calculations, that stabilization occurs in the compound, $[(CCH_3)Co_3(CO)_9]^+$ (14, **Figure 1.3**),
as a result of the formation of tilted -CCH₂ structures towards the -Co₃ plane rather than an upright structure above the tricobalt triangle. In 1982, *Edidin et. al.*⁴³ reported ¹³C-NMR evidence for [(CHCHMe₂)Co₃(CO₉)]⁺ (15, **Figure 1.3**), from which they unambiguously excluded the notion that the transition metal-stabilized cations are true three-coordinate carbenium ions (i.e., upright structures), but are stabilized by direct interactions between the cationic carbon and the metal framework. These cations ultimately provided a model for propargyl-Co₂(CO)₆ complexed cations.

**Figure 1.3:** Structures studied by *Schilling and Hoffmann* (14) and *Edidin et. al* (15).

The most widely and currently accepted model of these organometallic complexes was finally provided by *Schreiber et. al.*¹⁶³, who investigated the dynamic behaviour of several dicobalt hexacarbonyl propargyl cations, and proposed that the cations exist as unsymmetrical structures, and that the charge is delocalized onto the Co₂(CO)₆ moiety. The model (**Figure 1.4**) features a bending of the propargyl carbon towards one of the cobalt atoms, and is fluxional by two processes. Chemical behaviour and stereochemical outcomes can be explained by the consideration of resonance or canonical forms of the Nicholas cations, where the cobalt atoms act as electron donors assisting the electron-deficient carbon atom; the positive charge can be localized formally on carbon (carbocation) or cobalt (cobalt...
cation). These resonance forms allow the existence of a fluxional tautomerism, or equilibria, among four valence or fluxional tautomers, which interconvert to each other by antarafacial and suprafacial migrations. Further studies on cobalt related complexes were conducted by the Nicholas group\textsuperscript{12}, who reported on a (mono)triphenylphosphine complex (i.e., one of the carbonyl ligands was replaced with a triphenylphosphine ligand), and by the Jaouen group\textsuperscript{70,71}, who reported on the X-ray structures and molecular orbital analyses of molybdenum and molybdenum-cobalt clusters.

Figure 1.4: Fluxional model of propargyl-Co\textsubscript{2}(CO)\textsubscript{6} cations as proposed by Schreiber et. al. (Reproduced with permission from Reference 840 Copyright 1987 American Chemical Society).
Melikyan et al.\textsuperscript{131} finally obtained the first X-ray crystal structure of a Nicholas cation in 1998. The carbocation (16, Figure 1.5), doubly stabilized by two adjacent cobalt-complexed alkynyl units to allow for greater thermal stability and greater chances of crystallinity, showed rehybridization of the central $sp^3$ carbon atom to $sp^2$ when comparing the cation to the precursor alcohol complex. The covalent bonds around the central carbon in the cation all shorten, as expected, due to greater $s$ character in hybridized orbitals. The metal complexes became non-equivalent, and a shift of the central carbon atom closer towards one of the metal atoms in each Co-Co pair is also apparent in the cation.

**Figure 1.5:** X-ray crystal structure analysis of the [(propargylium)Co$_2$(CO)$_6$]$^+$ cation (16). (Reproduced with permission from Reference 814 Copyright 1998 Wiley-VCH).

### 1.1.4. VINYLOGOUS NICHOLAS REACTIONS

To probe further the steric and electronic properties of the carbonium ion-stabilizing
alkynyl-Co₂(CO)₆ group, as well as to expand on the synthetic utility made possible by its presence, the Nicholas group studied compounds with propargylic and allylic functionalities. Deemed “second generation complexes”¹³⁹, Padmanabhan and Nicholas¹⁴⁶ reported the reactions of various nucleophiles with vinylogous cations (18) derived from vinyl ethynyl carbinol complexes (17) (Scheme 1.2). The generated cations were attacked regio- and stereoselectively to give (E)-1,3-enyne and 1,4-enyne derivatives (19 and 20, respectively) efficiently. Carbon nucleophiles (anisole, allyl silanes, isopropenyl acetate) reacted extensively at the remote terminus (19 >> 20) and with complete (E) stereoselectivity (a result critically determined by the steric bulk of the Co₂(CO)₆). Ethanol (EtOH), as a nucleophile, however, predominately gave the opposite regioisomer. The authors suggested this to be a result of thermodynamic control. Coupling was likely reversible in the reaction conditions, as the presence of an easily protonated oxygen in the product provided a pathway for cation re-formation.

Scheme 1.2: (E)-1,3-Enyne synthesis via nucleophilic addition to the remote end of the allylic cation.
In 1991, the Nicholas group, in their continuing efforts to explore and exploit the reactivity of propargylic and $\alpha$-vinylpropargylic cations, exposed such cations to three electron rich heterocycles to examine their coupling reactions. The alkylation reactions were carried out by adding a furan derivative to a generated vinylogous cationic species at $-78^\circ$C in CH$_2$Cl$_2$, with the reaction taking place at the remote terminus of the $\alpha$-vinyl cation. Interestingly, they noticed that if alkylation was performed at temperatures above $-45^\circ$C, a significant amount of the internal attack product was isolated as well. The authors, again, suggested that the latter product may actually be thermodynamically favoured.

1.2. ANGLE-STRAINED CYCLOALKYNES

Given the wide occurrence of cyclic compounds in nature, coupled with their structural curiousities, the study of angle strained cyclic compounds and their synthesis has been a provocative theme in many areas of chemistry. Not every ring size, however, is accessible with the same ease. Medium-sized carbocyclic compounds (typically 7-12 carbons) have proven to be synthetically challenging, and in many instances, the most difficult to attain. Cyclization strategies are often inhibited due to entropic factors (probability of the chain ends meeting), and enthalpic factors (increasing strain in the transition state, transannular interactions). One of the most important influences on isolability of carbocycles is ring size.

1.2.1. THE TRIPLE BOND IN A RING SYSTEM

Undistorted triple bonds require four linearly arranged carbon atoms; the
incorporation of such a function into a ring system can only be achieved if the ring size is large enough, since a deviation from 180° is accompanied by strain\textsuperscript{130}. The smallest isolable, unsubstituted cycloalkyne that can be isolated in its free state is cyclooctyne\textsuperscript{103} (24), first synthesized and purified in 1953 by Blomquist & Liu\textsuperscript{11}. The authors reasoned that the ring was probably highly strained due to its explosive reaction with phenyl azide. Smaller homologues, such as cyclopentyne (21), cyclohexyne (22), and cycloheptyne (23) exist as transient, highly reactive molecules, which were finally trapped by Wittig et. al.\textsuperscript{195} seven years later in 1960.

![Cycloalkynes](image.png)

**Figure 1.6:** Small- and medium-sized carbocycles (n = 1, cyclopentyne (21); n = 2, cyclohexyne (22); n = 3, cycloheptyne (23); n = 4, cyclooctyne (24); n = 5, cyclononyne (25); n = 6, cyclodecyne (26); n = 7, cycloundecyne (27); n = 8, cyclododecyne (28)).

Although cyclopentyne, cyclohexyne, and cycloheptyne are capable of existing in solution, they must be generated in fast reactions, at extremely low temperatures, and in the absence of any reactive reagents which could add to the triple bond\textsuperscript{103}. Despite the extra precautions, characterization of such highly reactive intermediates remains elusive due to their limited lifetimes. For example, the half-life of cyclopentyne is estimated to be approximately one second at -78 °C\textsuperscript{61}, and in dilute CH\textsubscript{2}Cl\textsubscript{2} at 25 °C, the half-life of cycloheptyne is less than one minute, although at -78 °C, it can be increased to one hour\textsuperscript{195}.  

13
Experimental evidence for cyclobutyn and cyclopropyne has not yet been established\textsuperscript{103,130}.

Strained cyclic alkynes show a strongly enhanced reactivity in comparison to their acyclic counterparts. Deformed triple bonds react with a variety of reagents in order to relieve their geometrical strain\textsuperscript{130}. For example, cyclohexyne (22), generated in a flash pyrolysis and frozen in an inert matrix, still exhibited a short lifetime due to a retro-Diels-Alder cleavage to butatriene (29) and ethene (30) (\textbf{A, Scheme 1.3}). Steric shielding of the triple bond by four methyl groups helped prolong the lifetime of the cyclohexyne, however, the retro-Diels-Alder reaction was still possible. Dimerization and isomerization reactions are other lifetime-reducing factors. Cycloheptyne (23) underwent a [2+2] cycloaddition reaction to yield the cyclobutadiycycloheptene compound (31) (\textbf{B, Scheme 1.3}).

\begin{center}
\begin{tikzpicture}[scale=0.8]

\node[draw, shape=circle, minimum size=1cm] (A) at (0,0) {$22$};
\node[draw, shape=rectangle, minimum size=1cm] (B) at (4,0) {$23$};
\node[draw, shape=rectangle, minimum size=1cm] (C) at (8,0) {$29$};
\node[draw, shape=rectangle, minimum size=1cm] (D) at (12,0) {$30$};
\node[draw, shape=rectangle, minimum size=1cm] (E) at (16,0) {$31$};

\draw[->, thick] (A) -- node[above] {\textbf{A}} (B);
\draw[->, thick] (B) -- node[above] {\textbf{B}} (E);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.3}: A) Retro-Diels-Alder of cyclohexyne. B) Dimerization of cycloheptyne.
1.2.2. STABILIZATION OF CYCLOALKYNES VIA TRANSITION METALS OTHER THAN COBALT

Transition metals present unique and appealing opportunities for stabilization of highly reactive organic and inorganic fragments, and for activation of such fragments towards selective attack by a variety of chemical reagents, including highly selective cyclization reactions. Complexation of a metal to functional groups such as unactivated olefins, dienes, or acetylenes modifies the reactivity of these groups and, therefore, new reactivities are possible. Such processes provide medium-sized rings from simple fragments and offer an alternative pathway to previous conventional methods.

Small- and medium-sized cycloalkynes that are short-lived, transient molecules or are unknown in their free state can be stabilized by coordination to various transition metal fragments. In 1978, Bennett and Yoshida\textsuperscript{8} reported on the \textit{in situ} construction of stable bis(triphenylphosphine)platinum complexes of cyclohexyne and cycloheptyne. Generated by the reduction of the appropriate 1,2-dibromocycloalkene (32) with 1% sodium amalgam in the presence of Pt(PPh\textsubscript{3})\textsubscript{2}, the cyclohexyne complex, Pt(C\textsubscript{6}H\textsubscript{8})(PPh\textsubscript{3})\textsubscript{2} (33a), and the cycloheptyne complex, Pt(C\textsubscript{7}H\textsubscript{10})(PPh\textsubscript{3})\textsubscript{2} (33b), were isolated in good yields (A, Scheme 1.4). In 1989, Bennett reported on the synthesis of what they formulated to be the cyclopentyne complex, Pt(PPh\textsubscript{3})\textsubscript{2}(C\textsubscript{5}H\textsubscript{6}), a colourless, very reactive solid\textsuperscript{7}. As was expected, the cycloalkyne-Pt(PPh\textsubscript{3})\textsubscript{2} complexes became increasingly reactive as the ring became smaller. In the same paper, they also reported on the first dinickel(0) complex of 1,4-benzdiyne (34, Scheme 1.4B). Throughout the years, Buchwald et. al. reported on the preparation, characterization, and reactions of the trimethylphosphine adduct of the
zirconocene-cyclohexyne complex\textsuperscript{17}, the zirconocene complexes of benzyne\textsuperscript{16}, and the diziriconium complexes of benzdiyne\textsuperscript{15}.

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (a) at (0,0) {A};
  \node[anchor=west] (b) at (0,-2) {B};

  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (1) at (0,0) {$n=0$, 59\%};
  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (2) at (0,-0.8) {$n=1$, 81\%};
  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (3) at (1,0) {33};
  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (4) at (1,-0.8) {32};

  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (5) at (2,0) {33a};
  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (6) at (2,-0.8) {33b};

  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (7) at (3,0) {34};

  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (8) at (4,0) {1\% Na/Hg, Pt(PPh\textsubscript{3})\textsubscript{3}};
  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (9) at (4,-0.8) {THF, RT, 4 h};

  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (10) at (5,0) {$n=0$, 59\%};
  \node[draw,shape=circle,fill=black,inner sep=1pt,minimum size=1.5mm] (11) at (5,-0.8) {$n=1$, 81\%};

\end{tikzpicture}
\end{center}

Scheme 1.4: A) Bennett’s cyclohexyne-platinum ($n=1$) (33\textit{a}) and cycloheptyne-platinum ($n=2$) (33\textit{b}) complexes. B) Bennett’s dinickel complex of 1,4-benzdiyne (34) (Cy = cyclohexyl).

1.2.3. STABILIZATION OF CYCLOALKYNES WITH COBALT

Dicobalt hexacarbonyl fragments have been used commonly as protecting groups to allow geometrically disfavoured cyclization reactions by bending and stabilizing the alkyne moiety\textsuperscript{159}. Sly\textsuperscript{175} reported, in as early as 1959, the dramatic modification in the geometry of the linear acetylenic -C≡C- upon complexation by an M\textsubscript{2}L\textsubscript{6} unit. Complexation of diphenylacetylene by Co\textsubscript{2}(CO)\textsubscript{6} reduced the alkynyl angles of Ph-C≡C-Ph from 180$^\circ$ to 137$^\circ$ and 138$^\circ$. In 1986, Schreiber \textit{et. al.}\textsuperscript{164} reported on the use of the Nicholas reaction in the form of a Lewis acid-mediated intramolecular cyclization reaction of propargyl ether.
complexes tethered to an allylsilane (35) in their preparation of the first cycloheptyne unit (36) complexed to a dicobalt hexacarbonyl fragment with an exocyclic vinyl fragment (Scheme 1.5). Using this method, the group also succeeded in synthesizing six- and eight-membered ring systems.

Scheme 1.5: Schreiber’s synthesis of the first cycloheptyne-Co$_2$(CO)$_6$ complex (36).

The Magnus group, in their attempts to synthesize the bicyclo[7.3.0]dodecadiyne core structure of various antitumor agents, observed an unexpected homologous ene reaction to yield a cyclopentadienylallene cyclohexenyne-Co$_2$(CO)$_6$ (37, Figure 1.7) compound as a 1:1 mixture of epimers$^{111,112}$. Iwasawa et. al. reported the first examples of isolated naphthalyne-Co$_2$(CO)$_6$ complexes (38, Figure 1.7), along with X-ray analysis, and study of their unique reactivity$^{87}$. The three complexes isolated (R = H, OMe, or Br) showed no naphthalene character, but substituted benzene character, as reasoned based on bond lengths of the non-complexed benzene part of the moiety. The complexes, however, did exhibit limited stability to air (as is common to cycloheptyne-Co$_2$(CO)$_6$ complexes).
Figure 1.7: Cyclopentadienylallene-cyclohexenyne-Co$_2$(CO)$_6$ (37) synthesized by Magnus et. al., and the naphthalyne-Co$_2$(CO)$_6$ complex (R = H, OMe, or Br) (38) isolated by Iwasawa et. al.

1.3. APPLICATIONS OF THE NICHOLAS REACTION IN SYNTHESIS

Lewis acid-mediated inter- and intramolecular C-C bond formations represent a major class of reactions adaptable to the synthesis of acyclic and cyclic compounds, in particular, by way of alkyne-Co$_2$(CO)$_6$ complexes through Nicholas reaction chemistry. This chemistry has proven to be very reliable in the construction of a plethora of simple and complex units, with some very intricate and well-conceived syntheses reported thus far.

1.3.1. CYCLOHEPTYNE-Co$_2$(CO)$_6$ SYNTHESIS VIA INTRAMOLECULAR NICHOLAS REACTION

The Green group has been very active in the application of the Nicholas reaction towards seven-membered ring construction and in the study of their structural and electronic properties, with the hopes of expanding the scope of the Nicholas reaction and its synthetic applicability. In a 1998 report, Green$^{68}$ was able to demonstrate the synthesis of various cycloheptyne-Co$_2$(CO)$_6$ complexes (39, Figure 1.8) by way of a BF$_3$•OEt$_2$ Lewis acid-
mediated 7-endo trig cyclization of suitably constructed allylsilanes onto the generated [(propargyl)Co₂(CO)₆]⁺ cation. Allylsilane cyclizations on the formed cations could also be made to result in the formation of exo-methylene systems (40) by choosing the appropriate allylsilane (Figure 1.8).

![Figure 1.8: Cycloheptyne-Co₂(CO)₆ complexes generated by intramolecular Nicholas reactions of allylsilanes with Nicholas cations (R₁ = R₂ = H; R₁ = Ph, R₂ = H; R₁ = Me, R₂ = H; R₁ = H, R₂ = Me).](Image)

Ding and Green detailed a series of benzocycloheptenyne dicobalt complexes, which they obtained by intramolecular Nicholas reactions of neutral and electron rich arenes, and their heterocyclic analogues³⁴ (Scheme 1.6). Treatment of aryl (Z)-enyne propargyl acetate-Co₂(CO)₆ complexes (41) (prepared from their corresponding benzaldehydes) with BF₃•OEt₂ mediated an intramolecular nucleophilic attack by the arene to afford the benzo-fused cycloheptenyne-Co₂(CO)₆ complexes (42).
Scheme 1.6: Benzocycloheptyne-Co$_2$(CO)$_6$ complexes (42) via intramolecular Nicholas reactions (R$_1$ = H, OMe, or (OMe)$_3$; R$_2$ = H, Me, or Ph).

1.3.2. CYCLOHEPTYNE-Co$_2$(CO)$_6$ SYNTHESIS VIA CYCLOADDITION AND RING CLOSING METATHESIS METHODS

The Green group$^{151}$ has also shown that it is possible to gain entry into cycloheptenyne complexes by way of a [4+3] cycloaddition reaction based on tandem Nicholas reactions (Scheme 1.7). [(Propargyl)Co$_2$(CO)$_6$]$^+$ cations, generated from their respective butyne-1,4-diol/diether complexes (43) upon treatment with BF$_3$•OEt$_2$, reacted with allyltin (44) to generate presumed intermediate (45), which then underwent the final bond-forming process by an allylsilane-propargyl cation condensation. The reaction selectivity depended on the substitution pattern at the propargylic sites: the predominant product (46) became the one resulting from the initial Nicholas reaction occurring at the less substituted end of the diol/diether complex (43). The use of a larger ether function vs. a methyl ether function at the more substituted propargylic site, however, increased the selectivity.
Scheme 1.7: Nicholas reaction based on a [4+3] cycloaddition to generate cycloheptyne-Co$_2$(CO)$_6$ complexes (46 and 46') (R$_1$ = H, Me, or Ph; R$_2$ = Bn, Me, Et TBDMS, or iPr; R$_3$ = Bn, Me, or Et).

The group was also able to isolate the exo-methylcycloheptyne-Co$_2$(CO)$_6$ complex (40) via this type of chemistry by using an appropriate version of the allylsilane (47, Figure 1.9). Finally, slow addition of the Lewis acid (over 12 h) under high dilution afforded fluorocycloheptyne-Co$_2$(CO)$_6$ complexes (48, Figure 1.9).
Figure 1.9: Allylsilane (47) employed to generate the exo-methylene system (40) using a [4+3] cycloaddition reaction; and fluorocycloheptyne-Co$_2$(CO)$_6$ complexes (48) generated from a slight change in reaction conditions ($R_1 = R_2 = R_3 = H$; $R_1 = Me$, $R_2 = R_3 = H$; $R_1 = Ph$, $R_2 = R_3 = H$; $R_1 = R_2 = Me$, $R_3 = H$; $R_1 = R_2 = H$, $R_3 = Me$).

The group reported further progress in using [4+3] cycloaddition reactions employing unactivated alkene functions and Nicholas cations, formed from (43), to generate [(cycloheptyne)Co$_2$(CO)$_6$]$^+$ cations, which were trapped by a fluoride, chloride, or bromide nucleophile (depending on the Lewis acid) to give (48) with a wider range of $X$.

The Tanino group reported a series of cycloaddition reactions using alkyne-Co$_2$(CO)$_6$ complexes to afford seven- ([5+2] cycloaddition$^{183}$), eight- ([6+2] cycloaddition$^{132}$), and ten-membered ([6+4] cycloaddition$^{39}$) ring systems. In a 2000 publication$^{184}$, the group expressed their interest in a [5+2] cycloaddition reaction using a vinylogue of the allyl cationic species (Scheme 1.8). Pentadienyl cations were unappealing as substrates due to the need to control the geometry of the cation as a “U” shape, and the potential for the formation of cyclopentene derivative as a side-product. Instead, the group opted for use of an acetylene-Co$_2$(CO)$_6$ complex (49) as their equivalent of a pentadienyl cation. The
reaction proceeded step-wise, involving a silyloxonium ion intermediate (52) arising from nucleophilic attack of the silyl enol ether (51) onto the Nicholas cation (50). Ring closure afforded the cycloheptyne-Co$_2$(CO)$_6$ product (53) in good yield, with the stereochemistry arising during the intramolecular cyclization step as a result of the large bond angles and rigid conformation of the acetylene-Co$_2$(CO)$_6$ complex.

Scheme 1.8: Tanino’s [5+2] cycloaddition employing the Nicholas cation.

The Green group$^{67}$ found that the alkyne-Co$_2$(CO)$_6$ unit is not affected by most metathesis pre-catalysts, and hence these pre-catalysts could be used in the synthesis of cycloheptyne-Co$_2$(CO)$_6$ compounds via ring closing metathesis (Scheme 1.9). Acyclic 1,8-nonadiene-4-yne-Co$_2$(CO)$_6$ complexes (54) cleanly underwent RCM in the presence of Grubbs’ (I) catalyst to afford their corresponding cycloheptyne-Co$_2$(CO)$_6$ product complexes (55). One cyclooctyne-Co$_2$(CO)$_6$ ring system was also prepared using the -5-yne-Co$_2$(CO)$_6$
complex as the starting substrate under the same reaction conditions. The author hypothesized that the alkyne-Co$_2$(CO)$_6$ facilitated the cyclization by acting as a conformational restraint.

![Scheme 1.9](image)

**Scheme 1.9:** Ring closing metathesis in the synthesis of cycloheptyne-Co$_2$(CO)$_6$ substrates (55) ($R_1 = \text{OAc or H; } R_2 = H, n\text{-Pr, } n\text{-C}_5\text{H}_{11}, \text{ or OAc; } (\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=$CHPh $= \text{Grubbs’ (I) catalyst).}$

*Young et. al.*$^{201}$ also explored the use of Co$_2$(CO)$_6$ complex linked alkenes to help facilitate RCM in their assembly of medium-sized rings (7-9) using very similar chemistry. Metathesis of dienes linked by an alkyne-Co$_2$(CO)$_6$ unit (56) was attained with the use of either Grubbs’ (I) or Schrock’s catalysts at room temperature to generate their respective seven- ($n = 1$), eight- ($n = 2$) or nine-membered ($n = 3$) rings (57) in fair to good yields (Scheme 1.10). A variety of functional groups were also well tolerated under their metathesis conditions. Attempted synthesis of a six-membered ring with either catalyst, at any temperature, only met with a lack of success.
Scheme 1.10: Young et. al’s RCM using $\text{Co}_2(\text{CO})_6$ complex linked alkenes ($R = \text{H, Ac, TBS, } \equiv \text{O}$; Grubbs’ (I) catalyst: $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$; Schrock’s catalyst: 2,6-diisopropylphenyl-imidoneophylidene-molybdenum (VI) bis(hexafluoro-tert-butoxide).

1.3.3. MACROCYCLIC CYCLOALKYNE SYNTHESIS

Diaz et. al.$^{31}$, in their study of formal propargylic dications, generated from treatment of alkyne-$\text{Co}_2(\text{CO})_6$ diols with $\text{BF}_3\cdot\text{OEt}_2$, were able to synthesize cyclodecadiyne ether complexes by employing 2-butyne-1,4-diol as both the cationic and nucleophilic source. At a low concentration, the complexed diol (58) was treated with $\text{BF}_3\cdot\text{OEt}_2$ to generate, what the authors believed to be, the dicationic species (59), which was trapped with an uncomplexed diol to generate the 1,6-dioxacyclodec-3,8-diyn-$\text{Co}_2(\text{CO})_6$ complex (60). Treatment with CAN afforded the all-organic compound (61) in good yield (Scheme 1.11).
Scheme 1.11: Diaz et al.’s report of macrocyclic ring synthesis through a dicationic alkyne-Co$_2$(CO)$_6$ species (59).

Green and co-workers have made use of acetylene-Co$_2$(CO)$_6$ complexes to construct a variety of macrocycles. Guo and Green$^{72}$ found that bis(propargyl ether) tetracobalt complexes (62) are capable of reacting with electron rich arenes and some $\pi$-excessive heterocycles to rapidly assemble [7]metacyclophanediyne tetracobalt complexes (63) (A, Scheme 1.12). Inserting an aryl group as a spacer between propargyl cation units, using more dilute conditions, a lesser amount of the trimethoxybenzene, and a large excess of the Lewis acid afforded the [3.3.3.3]$m,p,m,p$-cyclophanetetrayne complex (64), albeit in low yields (B, Scheme 1.12)$^{60}$. Similar complexes were also reported using indole instead of the trimethoxybenzene moieties$^{59}$. 
Scheme 1.12: A) Guo and Green’s synthesis of [7]metacycphanadiyne(dodecacarbonyl)-tetracobalt complexes (63). B) Insertion of a spacer, and a slight change in reaction conditions affords a cyclophanetetrayne-octacobalt complex (64).

1.3.4. SELECTIVITY IN THE NICHOLAS REACTION

The Tyrrell group, in their report of a diastereoselective one-pot procedure (complexation, cyclization, and decomplexation), have detailed the use of non-activated alkenes in trapping Co$_2$(CO)$_6$ cations in an intramolecular Nicholas reaction to yield a range of functionalized benzopyrans bearing exocyclic alkynes after decomplexation$^{121}$ (Scheme 1.13). The complexed precursor (65), upon treatment with tetrafluoroboronic acid (HBF$_4$), afforded the Nicholas cation (66), which underwent concomitant intramolecular cyclization to afford the corresponding complexed benzopyran derivative (68). The formation of the
second product (69) was reasoned to occur by the generation of the second cation (67), a consequence of the intramolecular Nicholas reaction, which was then quenched by a fluoride ion. Subsequent decomplexation using CAN afforded an equimolar mixture of the benzopyrans (70) and (71), separable by chromatography, in a 25% overall yield over the three steps. Extensive ¹H-NMR spectroscopy studies showed a trans stereochemical relationship between the two chiral centres.

Scheme 1.13: Tyrrell’s one-pot synthesis of benzopyran derivatives bearing an exo-alkyne functionality.
The group followed up with a report of another diastereoselective one-pot tandem series of reactions, which featured an intermolecular Nicholas reaction followed by a tandem intramolecular Nicholas reaction, and finally an *in situ* decomplexation reaction to afford a series of tricyclic ring systems\(^{187}\).

*Nakamura et. al.*\(^{138}\), in their use of stereochemically defined carbon centres, reported that a *trans*-decalin system possessing an exocyclic alkylidene and a propargyl acetate-Co\(_2\)(CO)\(_6\) complex (72) underwent one of two cyclization reactions via a common cationic intermediate (73). Highly Lewis acidic organoaluminum reagents gave a 7,6,6-ring system (74) predominantly via cyclization followed by proton loss. Less Lewis acidic organoaluminum reagents afforded a 7,7,5-ring system (75) as the major product that is characteristic of the ingenol skeleton via cyclization followed by a pinacol-type rearrangement (Scheme 1.14).
Scheme 1.14: Intramolecular cyclization of the trans-decalin system possessing an exocyclic alkylidene and a propargyl acetate-Co$_2$(CO)$_6$ (72) to afford either a 7,6,6-ring system (74) or a 7,5,5-ring system (75). Lewis acid, MX$_n$ = Me$_2$AlCl, Me$_2$Al(OTf), MeAl(OTf)$_2$, MeAl(OCOCF$_3$)$_2$, or MeAl(OCOCF$_3$)(OAr); Ar = 2,6-(CH$_3$)$_2$-4-(NO$_2$)C$_6$H$_2$ or 4-NO$_2$C$_6$H$_4$.

1.3.5. THE NICHOLAS REACTION IN THE SYNTHESIS OF NATURAL PRODUCTS

The Green group has made extensive use of the Nicholas reaction in the synthesis of several natural products and/or related targets. In 2010, Djurdjevic et. al.$^{35}$ reported the formal synthesis of (-)-allocolchicine (Scheme 1.15), building on from previous work in the synthesis of NSC 51046.$^{36}$ Treatment of the biaryl-alkyne-Co$_2$(CO)$_6$ complex 76 with Lewis acid BF$_3$•OEt$_2$, in the presence of $N$-$N$-diisopropylethylamine, resulted in the intramolecular
nucleophilic attack of the electron rich aromatic ring onto the propargylic cation formed to yield the dibenzocycloheptyno-Co$_2$(CO)$_6$ complex (77). Reductive decomplexation was achieved by use of triethylsilane in the presence of bis(trimethylsilyl)acetylene (BTMSA, a trapping reagent used to minimize olefin isomerization), followed by desilylation with trifluoroacetic acid (TFA) to afford the alkene (78). Hydroboration-oxidation converted the alkene to a ketone, and further transformations, including an asymmetric reduction of the ketone, produced (-)-allocolchicine (79)$^{189}$.

Scheme 1.15: Formal synthesis of (-)-allocolchicine (79) as reported by Djurdjevic and Green.

*Taj and Green*$^{180}$ reported the first total synthesis of (±)-microstegiol that same year (Scheme 1.16). Having demonstrated the viability of Nicholas reaction-based γ-carbonyl
cation chemistry in the assembly of cycloheptade[naphthalene rings, and in the construction of the rearranged abietane framework of microstegiol\textsuperscript{181}, the authors arrived at the racemic product a year later. The reaction of protected 3-isopropyl-2,7-naphthalenediol (80) with the alkyne-Co\textsubscript{2}(CO)\textsubscript{6} complex (81) under acidic conditions afforded the monosubstitution product (82) following decomplexation with iodine. Upon arriving at alcohol (83), cyclization was initiated with H\textsubscript{2}SO\textsubscript{4} to give the seven-membered ring, with simultaneous tautomerization of the naphthol to the ketone. Aerobic oxidation in the presence of sodium hydride completed the synthesis and afforded (±)-microstegiol (84) in an overall yield of 7.2\% in 15 steps from 2,7-dihydroxynaphthalene.

Scheme 1.16: First total synthesis of (±)-microstegiol (84) as reported by Taj and Green.

The potential use of the Nicholas reaction in natural product synthesis was realized in the much earlier work of Saha et. al.\textsuperscript{160}, who reported a total synthesis of the guiane, (±)-
cyclocolorenone (Scheme 1.17).

Scheme 1.17: Total synthesis of (-)-cyclocolorenone (89) reported by Saha et. al.

Tropone (85) was converted to silyl enol ether (86) in several steps, which featured the use of Fe₂(CO)₉ as both a protecting and activating group for the diene unit. This silyl enol ether acted as the nucleophile in a Nicholas reaction to give the corresponding α-propargylated complex (87) (3:1 diastereomeric mixture). Demetallation with subsequent conversion of the pendant side chain to a ketone afforded the product (88) as an 8:1 diastereomeric mixture. Separation of the diastereomers by preparative TLC, and subjection of the major diketone isomer to basic conditions at ambient temperature yielded the desired product (89) as a single isomer in good yield.
Isobe and co-workers have spent more than 25 years pursuing the total synthesis of ciguatoxin (90, **Figure 1.10**), and in 2009, reported the final total synthesis of the marine toxin. Their numerous processes relied heavily on the Nicholas reaction for ring construction, with one of the key reactions being a cyclization to form the F ring in the final total synthesis73.

![Figure 1.10: Structure of ciguatoxin (90).](image)

One example86 of the many processes that the group reported in the mid 1990's featured the synthesis of a series of medium sized bicyclic ethers (7-, 8-, and 9-membered rings) via an intramolecular Nicholas reaction under moderately acidic conditions. Treatment of the propargylic pivaloate (91) with BF$_3$•OEt$_2$ resulted in the nucleophilic attack of the hydroxy group of the dihydropyranyl ring onto the generated propargylic cation. The cation was further stabilized by virtue of being allylic. The cyclization afforded the 7,6-bicyclic ring system (92), and selectively the syn-trans diastereomer, characteristic of ciguatoxin.
Scheme 1.18: Isobe’s intramolecular Nicholas cyclization to generate a 7,6-bicyclic ring system (92).

1.3.6. VINYLOGOUS NICHOLAS REACTIONS IN THE SYNTHESIS OF NATURAL PRODUCT RING STRUCTURES

*Shibuya and Isobe*\(^\text{170,171}\) reported on the synthesis of the bicyclo[9.3.1]pentadecatriene skeleton seen in taxachitiene natural products. Their application of the vinylogous Nicholas reaction featured a Hosomi-Sakurai type reaction as the key step in the Lewis acid-mediated intramolecular cyclization between the enyne-CO\(_2\)(CO)_6 complex electrophile and allytrimethylsilane nucleophile (93) to generate the twelve-membered ring (94) (Scheme 1.19).
Scheme 1.19: Intramolecular vinylogous Nicholas reaction in the generation of macrocycle (94), as reported by Shibuya & Isobe.

Alvaro et. al.\(^4\) also exploited such “second generation” complexes (95, Figure 1.11) in their synthesis of terpene-aromatic hybrids by way of the Nicholas reaction between easily available propargyl derivatives and different aromatic nucleophiles. Attack was observed at C-3, with subsequent double bond isomerization to between C-2 and C-10.

Figure 1.11: Alvaro’s complexed precursor (95) for vinylogous Nicholas chemistry.
1.4. FAVELINE- AND ICETEXANE-DITERPENE NATURAL PRODUCTS

The icetexanes are a family of diterpenoid natural products which have been isolated from a variety of terrestrial plant sources\textsuperscript{172}. They encompass a variety of structurally unique and interesting features, and exhibit a broad spectrum of attractive bioactive properties (i.e., anti-cancer, anti-bacterial, anti-fungal, anti-Chagasic activities)\textsuperscript{172}. The 6,7,6-tricyclic framework (96, Figure 1.12), representative of this family, possesses a cyclohexane ring, a central seven-membered ring, and an aromatic ring (or a quinone).

\textbf{Figure 1.12:} 6,7,6-tricyclic skeleton of an icetexane diterpenoid (96).

Biosynthetically, the architecture of the icetexane is hypothesized to arise from a ring-expanding rearrangement of the more common abietane (97, Figure 1.13), giving rise to the 6,7,6-tricyclic skeleton that bears the systematic name 9(10→20)-abeo-abietane. In accordance with this hypothesis, the majority of icetexane natural products that have been isolated and characterized to date have been found in plant species which also produce abietane diterpenoids as secondary metabolites\textsuperscript{172}. 

\[ \text{Figure 1.13:} \]
Icetexone (98, Figure 1.14) was the first 9(10→20)-abeo-abietane natural product to be isolated and structurally characterized; accordingly, the icetexane family derives its name from this compound\textsuperscript{172}. The icetexanes that have been discovered so far vary widely in the degree of oxygenation and oxidation in each ring.

The simplest subclass of icetexanes are the pisiferins, with pisiferin (99, Figure 1.15) the parent compound. Pisiferin was first isolated from the leaves of \textit{Chamaeyparis pisifera} in 1980\textsuperscript{199}. The authors originally proposed a 7,6,6-tricyclic skeleton as the structure for pisiferin; however, following its re-isolation in 1984 along with isopisiferin (100, Figure
The second subclass of icetexanes is exemplified by barbatusol (101, Figure 1.16), which was isolated from the bark and heartwood of the Brazilian plant, *Coleus barbatus*, in 1983, and found to possess *in vivo* hypotensive activity in rats\(^6\). Rosmaridiphenol (102, Figure 1.16) was identified in the leaves of *Rosmarinus officinalis* in 1984, and was found to possess antioxidant activity superior to that of BHA, and approaching that of BHT\(^8\). The original structure was proposed as having the carbonyl functional group at C-20 (refer to compound 96 for the numbering schematic); however, in 2010, *Pertino et al.*\(^{154}\) showed, through examination of spectroscopic data and chemical reactions, that the carbonyl actually resides on C-1 instead of C-20. Other members of this subclass include salviasperanol, grandione, and przewalskin, among others\(^{172}\).
1.4.1. EXAMPLES OF TOTAL SYNTHESSES OF FAVELINE- AND ICETEXANE-DITERPENES

The unique structural architecture and intriguing biological activities of the icetexanes have made them attractive targets for synthetic chemists and biologists, respectively. It is no surprise then, that numerous synthetic chemists have reported creative and elegant approaches to the total syntheses of these compounds.

The first total synthesis of (±)-pisiferin was reported by Matsumoto et al. in 1986\textsuperscript{123} (Scheme 1.20). Starting with racemic $\alpha$-cyclocitrinal (103) and a benzylic Wittig reagent (104), a series of reactions were preformed which ultimately afforded the $\alpha,\beta$-unsaturated ketone (105). Next, an intramolecular cyclization was achieved by heating with polyphosphoric acid (PPA) at 80-85 °C to give a separable mixture of stereoisomers (106). The cis (α-H) isomer was reduced with LiAlH$_4$, and the methyl ether moiety of the resulting alcohol was cleaved with AlCl$_3$ and EtSH. Bismesylation and subsequent elimination of the secondary mesylate provided the alkene, which, upon treatment with LiAlH$_4$, readily converted to (±)-pisiferin (99) with an overall yield 16.2\%.
**Scheme 1.20:** First total synthesis of (±)-pisiferin (99) reported by Matsumoto et. al.

The second total synthesis of (±)-pisiferin and the first total synthesis of (±)-isopisiferin was reported by Kametani et. al. in 199092.

In 2010, Jan et. al. reported the first enantioselective synthesis of (-)-isopisiferin90 (Scheme 1.21). 4,4-Dimethyl-2-cyclohexenone (107) was converted to aldehyde (-)-108 in 98% ee through a sequence of iodination, asymmetric reduction, Claisen rearrangement, and oxidation reactions. Aldehyde (-)-108 was then added to an aryllithium reagent, generated in situ from aryl bromide 109 and nBuLi by lithium-halogen exchange, to afford the alcohol (110) as a pair of diastereomers. Further reactions involving a dehydration, lithium-halogen exchange, hydrogenation, and hydrolysis effectively led to carboxylic acid (-)-111. The central seven-membered ring was constructed by an intramolecular Friedel-Crafts acylation mediated by trifluoroacetic anhydride (TFAA) to afford (-)-112. The keto carbonyl was reduced via treatment with NaBH₄, followed by mesylation in the presence of NEt₃, and
finally, deprotection with EtSNa, which converted 112 to the target compound, (-)-isopisiferin, in 15 steps with an overall yield of 11.4%.

Scheme 1.21: First asymmetric total synthesis of (-)-isopisiferin as reported by Jan et. al.

The first total synthesis of (±)-barbatusol was reported in 1987 by Kroft\textsuperscript{104} (Scheme 1.22). Enone (107) underwent Hosomi-Sakurai addition of allyltrimethylsilane in the presence of titanium tetrachloride (TiCl\textsubscript{4}), with the resulting ketone being protected as the ketal. Ozonolysis yielded the aldehyde (113). Metallation of the amide (114) (prepared separately) with “BuLi, followed by treatment with the aldehyde (113), and the subsequent
treatment of the resulting adduct with anhydrous acid, provided the lactone (115) as an inseparable mixture of diastereomers. The alcohol (116) was then generated via saponification of (115) with NaOH, methylation with MeI, and treatment with LiAlH₄. Oxidation of (116) with PDC provided the aldehyde, which underwent intramolecular aldol condensation upon treatment with NaOEt in ethanol. The resulting diastereomers (117) were subjected to ionic reduction to remove the benzylic methyl ether moieties using Et₃SiH/BF₃•OEt₂, followed by reductive transposition of the enone with TsNHNH₂ and NaBH₃CN. Lastly, demethylation of the phenolic methyl ethers with EtSNa afforded (±)-barbatusol (101) in an overall yield of 4.5%.
Scheme 1.22: First total synthesis of (±)-barbatusol (101) reported by Krost.

The second total synthesis of (±)-barbatusol was reported by Majetich et. al. in 1993\textsuperscript{120} (Scheme 1.23), which featured a TiCl\textsubscript{4} induced Friedel-Crafts intramolecular alkylation between a functionalized arene and a conjugated dienone, in eight steps with a 14.6\% overall yield. Majetich’s group, very active in the synthesis of compounds from the icetexane family, have reported superb syntheses of (±)-pisiferin, (±)-deoxofaveline, (±)-xochitlolone, and (±)-faveline\textsuperscript{117}; (-)-barbatusol, (+)-demethylsalvicanol, (-)-brussonol, and (+)-grandione\textsuperscript{116}; as well as related natural products, including diterpene (±)-nimbidiol\textsuperscript{118}, and triterpene (±)-perovskone and (+)-perovskone\textsuperscript{115}. In their 1993 synthesis of (±)-
barbatusol, 4,4-dimethylcyclohexane-1,3-dione (118) was alkylated with benzyl bromide (119) (synthesized from 3-isopropylveratrole) to generate product (120). Once converted to the dienone (121), treatment with TiCl₄ in CH₂Cl₂ at -78 °C effected a cycloalkylation reaction to generate tricycle (122). Reductive transposition of the generated enone moiety (122) with TsNHNH₂ and NaBH₃CN, followed by demethylation of the methyl ethers under basic conditions using EtSNa, resulted in the isolation of racemic barbatusol (101) without isomerization of the C-1, C-10-trisubstituted double bond.

**Scheme 1.23:** Total synthesis of (±)-barbatusol (101) as reported by Majetich et. al.

**Simmons and Sarpong** reported the first total synthesis of (±)-salviasperanol in 2006 via a cycloisomerization of an alkynyl indene using gallium trichloride (GaCl₃)¹⁷⁴ (Scheme
1.24). Starting from 3-isopropylveratrole (123), the generated indanone (124) (synthesized via a Friedel-Crafts acylation), underwent alkylation with iodide (125). Saponification, decarboxylation, reduction, and dehydration followed to afford indene (126). Treatment of 126 with GaCl₃ at 40 °C in the presence of 4 Å molecular sieves effected an enyne cycloisomerization to deliver (127). Chemoselective epoxidation of the tetrasubstituted double bond was achieved using m-CPBA, followed by treatment with catalytic trifluoroacetic acid, which isomerized the vinyl epoxide moiety to the corresponding dihydrofuran, and finally cleavage of the methyl ether groups with EtSNa provided (±)-salviasperanol (128) in an overall yield of 5.4%. Sarpong’s group have also reported total syntheses of (±)-5,6-dihydro-6α-hydroxysalviasperanol, (±)-brussonol, and (±)-abrotanone as part of their ongoing interest in icetexane diterpenoid synthesis¹⁷₃.
Scheme 1.24: First total synthesis of (±)-salviasperanol (128) as reported by Simmons and Saprong.

Other notable successful approaches to such related compounds include radical cyclization chemistry^63^, epoxide ring-opening reactions^20^, Barbier-type reactions^191^, and palladium-catalyzed Heck reactions^166^.

1.5. RESEARCH OBJECTIVES

The Green group’s ongoing interest in the synthesis of seven-membered rings has led to the expansion of the scope of reaction methods for ring construction in conjunction with Nicholas chemistry: cycloadditions, ring closing metathesis reactions, and Umpolung
chemistry, among others. The main goal of this research project was to expand the scope of the vinylogous Nicholas reaction to include the synthesis of a variety of tricyclic-ring systems possessing a central seven-membered ring, and ultimately apply it towards the synthesis of natural products.

1.5.1. SYNOPSIS OF DISSERTATION

Attack by nucleophiles at the allyl terminus remote to cobalt is known; however, vinylogous Nicholas reactions have yet to be employed in the formation of cycloheptyne-Co$_2$(CO)$_6$ ring systems. The goals were thus set as:

i) Given the normal reactivity pattern of vinylogous propargyl-Co$_2$(CO)$_6$ cations, and the fact that cyclopentyne-Co$_2$(CO)$_6$ complexes (129) appear to be prohibitively strained and sustainable only at extreme environmental conditions, it was considered that intramolecular vinylogous Nicholas reaction chemistry would readily give access to 6,7,6-tricyclic ring systems (130), and other 6,7,$n$-systems (Scheme 1.25). This approach would also lead to the core structure of the faveline- and icetexane-diterpenes. A few examples were also prepared in which the double bond was part of an aromatic and nominally aromatic ring system.
ii) As the idea was to formulate a general and modular entry into this class of compounds, the reaction was then expanded to include the synthesis of a few bicyclic \( n,7\)-ring systems under similar reaction conditions.

iii) Given the interesting biological activities and unique structural features of the icetexanes, coupled with the fact that they possess a central seven-membered ring, and as part of the group’s continuing synthetic studies in naturally occurring compounds, it was envisioned that the developed chemistry would be applied towards the synthesis of compounds from the pisiferin subclass, as well as the barbatusol subclass.

**Scheme 1.25:** Anticipated mode of cyclization by intramolecular Nicholas reaction.
CHAPTER 2: DISCUSSION

2.1. VINYLLOGOUS NICHOLAS REACTIONS IN THE SYNTHESIS OF TRICYCLIC RING SYSTEMS BEARING A CENTRAL CYCLOHEPTYNE-Co$_2$(CO)$_6$

Allylic cations of the form 18 are known to undergo Nicholas reaction chemistry, and more importantly, they prefer to react at the remote site relative to the alkyne-Co$_2$(CO)$_6$ function. Initial work by Padmanabhan and Nicholas$^{146}$ reported the regioselective attack of nucleophiles at the remote terminus of the cation to afford its corresponding enyne-complexed product (with the exception of ethanol) (Scheme 1.2). Subsequent work by DiMartino and Green$^{33}$ (Scheme 2.1) also showed that cations derived from cyclic allylic acetate alkyne-Co$_2$(CO)$_6$ complexes (131) kinetically favoured reaction at the remote site ($\gamma$) (132) for most nucleophiles, ultimately driving the alkene and alkyne-Co$_2$(CO)$_6$ functions of the cycloheptyne-Co$_2$(CO)$_6$ complexes into conjugation. The $\alpha$-site (133) was preferred by nucleophiles with the greatest nucleophilicity, based on the Mayr scale$^{105,125,127}$. 
Despite the fact that vinylogous Nicholas reaction chemistry has been demonstrated to be useful in the synthesis of cyclic compounds \(^{170,171}\), it has never been employed in the formation of cycloheptynedicobalt ring systems, and given the reactivity pattern of vinylogous propargyl-Co\(_2\)(CO)\(_6\) cations, alongside the fact that cyclopentyn-Co\(_2\)(CO)\(_6\) complexes appear to be prohibitively strained, it was rationalized that this type of chemistry could be applied to cycloheptyne-Co\(_2\)(CO)\(_6\) ring synthesis.

### 2.1.1. INITIAL ATTEMPTS WITH AROMATIC AND NOMINALLY AROMATIC ELECTROPHILIC RING SYSTEMS

Initial attempts involved compounds in which the double bond was part of an aromatic ring (Scheme 2.2). The initial substrates were prepared as follows: 2-bromobenzaldehyde (134) was subjected to standard Sonogashira conditions with (trimethyl)silylacetylene to afford the silylated alkynyl benzaldehyde (135). Desilylation was carried out using KF\(\cdot\)2H\(_2\)O in DMF to afford the terminal acetylene function (136), which was subsequently exposed to another round of Sonogashira chemistry with another
aromatic halide bearing at least one methoxy group. The coupled products (137) were then subjected to a reduction reaction using DIBAL-H, and subsequent acetylation with acetic anhydride in the presence of DMAP and pyridine afforded the acetate products (138). These products were then complexed with dicobalt octacarbonyl in a straightforward fashion, generating the precursors (139) necessary for attempted cyclization.

Scheme 2.2: Synthetic route towards complexed acetate-Co$_2$(CO)$_6$ precursors (139).

Early attempts to cyclize compounds 139 proved unsuccessful. Treatment of 139 with three equivalents of BF$_3$•OEt$_2$ in CH$_2$Cl$_2$ at 0 °C under nitrogen, in both the presence and absence of diisopropylethylamine, resulted in almost immediate decomposition of the reactant, and no cyclized product was recovered. Using a Brønsted acid, such as H$_2$SO$_4$, also
did not afford any product. In 2004, the Mayr group reported a scale comparing the nucleophilicity parameter, $N$, of solvents with the $N$ parameter of typical $\pi$ systems. They predicted that solvolytically generated cations should be trapped by $\pi$ nucleophiles if the $N$ parameter of the corresponding $\pi$ nucleophile is greater than the $N$ of the solvent under consideration (i.e., the nucleophile is located above the solvent on the scale). Based on the reported scale, the best solvent for a situation where anisole is the nucleophile would be $1,1,1,3,3,3$-hexafluoro-2-propanol due to its low $N$ and high polarity (to support cation formation). In other words, hexafluoro-2-propanol would help facilitate stabilization of the generated cation without out-competing anisole as the nucleophile. Attempts at substituting dichloromethane solvent with hexafluoro-2-propanol, in the presence of $\text{BF}_3\cdot\text{OEt}_2$, only afforded starting material. Given that the starting material did not decompose when hexafluoro-2-propanol was used instead of dichloromethane could suggest that the Lewis acid was being complexed by the solvent rather than the acetate leaving group on the cobalt complex, making it unavailable for formation of the cation. In an attempt to determine whether the cation was even being generated, and perhaps ring closure was just not favourable, hence leading to decomposition, an external nucleophile (furan) was added to the reaction, which was recommenced in $\text{CH}_2\text{Cl}_2$, to determine whether the intended cation could be trapped. That experiment, however, proved unsuccessful as well, and also led to decomposition. At this point, attempts to cyclize benzylic acetates were abandoned.

In much later chemistry that employed simpler compounds (i.e., where the double bond was part of a cycloalkene), successes were realized with $\text{SnCl}_4$ as a Lewis acid in place of $\text{BF}_3\cdot\text{OEt}_2$, and hence this set of reactions was returned to in order to decipher whether...
such successes would be observed with SnCl₄ in cyclizing (139). Sure enough, treatment of 139a (R = H) with three equivalents of SnCl₄ under the same reaction conditions as initially attempted (dry CH₂Cl₂, 0 °C, N₂) gave products 140a (R₁ = H, R₂ = OMe) and 140a’ (R₁ = OMe, R₂ = H) as a separable pair of regioisomers in a 3.7:1 ratio of para:ortho, in a combined yield of 66%. The reaction was complete after 15 h, as monitored by TLC, and after allowing the reaction to warm up to room temperature (Scheme 2.3). Compound 140b (R₁ = R₂ = OMe) was also obtained under these experimental conditions from 139b (R = OMe), and as a single isomer (the second methoxy group removes the ability for regioisomers) in 51% yield.

**Scheme 2.3:** Cyclization of benzyl acetate-Co₂(CO)₆ complexes (139) using SnCl₄ (when R = H, R₁ = H, R₂ = OMe or R₁ = OMe, R₂ = H; when R = OMe, R₁ = R₂ = OMe).

One advantage of working with cobalt complexes is the case of visualizing the characteristic colour of the cobalt components in the reaction mixture by TLC. Both the starting complexed precursors (139) and their cyclized products (140), dark brown and maroon in colour, respectively, coupled with their significant Rₜ differences (the product
having the higher $R_f$), made monitoring the reaction quite easy and convenient. Another advantage of working with such compounds is that both the complexed precursors and their cyclized products can be stored and handled in air, under standard laboratory conditions, and can survive traditional chromatography techniques, making their purification also quite convenient. Their intense colour facilitated the location on a chromatography column without staining or a UV light. The complexes were also amenable to spectroscopic analysis, and as such, all have been characterized by $^1$H-NMR, $^{13}$C-NMR, IR, and MS spectra. A broad peak was observed near the 200 ppm region of the $^{13}$C-NMR spectra, indicative of the carbonyl carbons of the ligands, and several absorptions around 2000 cm$^{-1}$ in the IR spectra, also indicative of the C=O ligands. $^{13}$C-NMR chemical shift differences have been taken to give an indication of the change in electron density in a compound$^{109}$, although, upon complexation, the alkynyl carbon peaks made no significant changes in the $^{13}$C spectra. Interestingly, nevertheless, the protons on the carbon bearing the acetate leaving group shifted upfield by approximately 0.2-0.3 ppm in the $^1$H spectra upon complexation.

It is unclear why the reaction proceeds with the tin Lewis acid, but not with the boron trifluoride. In fact, Childs et. al.$^{22}$ analyzed the complexation of a variety of Lewis acids with a handful of unsaturated carbonyl bases by $^1$H-NMR and $^{13}$C-NMR techniques, and showed BF$_3$$\cdot$OEt$_2$ to be the stronger Lewis acid. Kobayashi et. al.$^{100}$ studied a plethora of Lewis acids, and classified them based on their activity and selectivity in an addition reaction to a carbonyl or an imine. The group reported that the boron and tin Lewis acids studied were both classified as “active” and carbonyl-selective. Despite also using the aid of the Hard/Soft Acid/Base (HSAB) theory$^{196}$, it appears that until a more concise Lewis acid
scale is developed, the choice of Lewis acid will continue to depend on the trial-and-error concept, where reactions are screened with a variety of Lewis acids to determine the optimum type and stoichiometry. Several groups have reported improved conditions and/or increased yields when switching from BF$_3$•OEt$_2$ to SnCl$_4$, TiCl$_4$, HBF$_4$, or B(C$_6$F$_5$)$_3$. It may be possible that the molecule of Et$_2$O has an influential role in the diminished reactive ability of the boron trifluoride Lewis acid under these conditions.

When the cyclizations of (139) did not initially work with BF$_3$•OEt$_2$, it was reasoned that perhaps the generated benzyl cation gained no additional stabilization from the Co$_2$(CO)$_6$ moiety, or perhaps that the rate of decomposition was faster than the rate of cyclization under the reaction conditions. It was, therefore, decided that a switch to a system where the double bond was part of an only nominally aromatic ring might prove more fruitful. It was believed that the cation might be more readily formed if the ring was less than fully aromatic (i.e., the minimally aromatic furan).
**Scheme 2.4:** Synthetic route towards complexation precursors (146) using a less than fully aromatic system. A) Coupling of 3-[(trimethylsilyl)ethynyl]furan-2-carbaldehyde (142) to 3-iodoanisole. B) Coupling of 3-bromo-2-formylfuran (141a) or 3-bromothiophene-2-carbaldehyde (141b) to [(3,5-dimethoxyphenyl)ethynyl]trimethylsilane (156c). C) Continued synthesis towards complexed precursors (146).
The synthetic route follows an analogous scheme (Scheme 2.4) as outlined in both Scheme 2.2 and Scheme 2.3. 3-Bromo-2-formylfuran (141a) was subjected to Sonogashira coupling with (trimethylsilyl)acetylene to afford the coupled product (142). Tandem desilylation and Sonogashira coupling with 3-iodoanisole afforded compound 143 in good yield (79%). Compounds 144a (X = O) and 144b (X = S) were prepared in the same tandem desilylation/Sonogashira reaction from [(3,4-dimethoxyphenyl)ethynyl]trimethylsilane (156c) and 3-bromo-2-formylfuran (141a) or 3-bromothiophene-2-carbaldehyde (141b), respectively, and both in good yields (82% and 77%, respectively). Reduction with DIBAL-H, followed by acetylation with acetic anhydride in the presence of pyridine and DMAP afforded compounds 145, which upon complexation with Co₂(CO)₈, afforded the complexed precursors (146).

As was the case with BF₃•OEt₂ initially, gross decomposition was observed with these nominally aromatic systems. Temperatures ranging from -40 °C to 0 °C to room temperature proved futile, as did the addition of Brønsted acid H₂SO₄, as a co-acid. In the case where the nucleophilicity of the benzene ring was increased (X = O, R = OMe), cyclization, however, was actually beginning to be observed (based on TLC analysis). The isolated product yield, unfortunately, was so low, it was barely capable of analysis, nor was it of any synthetic use. These reactions were then attempted again later on with SnCl₄ (Scheme 2.5).
As SnCl₄ proved successful in the previous vinylogous Nicholas reactions with 139, so it did in these cases. While the furan derivative (146b) cyclized quite sluggishly, and still afforded poor yields (147b, 17%), the thiophene derivative (146c) cyclized quite cleanly and in good yield (147c, 73%). The furan derivative bearing the monomethoxyphenyl ring (146a), which is speculated to afford two regioisomers, 147a (para attack) and 147a’ (ortho attack), was not attempted due to time constraints.

2.1.2. CYCLIZATION ATTEMPTS WITH CYCLOALKENE ELECTROPHILIC RING SYSTEMS

With the original ideas not producing useful results initially, it was decided that attention was going to be projected towards targets with a simpler double bond structure, a cycloalkene ring system. With a synthetic route in hand paralleling those outlined earlier (Scheme 2.2 and 2.4), a library of complexed precursors was synthesized (Scheme 2.6).
Scheme 2.6: Synthetic route towards complexed acetate-Co$_2$(CO)$_6$ precursors (152) ($X = \text{Br or I}; R_1-R_4 = H \text{ or OMe}, R_5 = H, \text{Me or Ph}$).

The precursors to the cyclization reactions were envisioned as allylic acetate complexes, with the endocyclic alkene being advantageous in imposing an *anti* geometry on any resulting allyl cation. **Table 1** summarizes the yields of the first Sonogashira reaction of 156 with (trimethylsilyl)acetylene, followed by desilylation with TBAF to afford the terminal acetylene (148).
Table 1: Summary of % Yields for Compounds 156 and 148, respectively.

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<th>Entry 148</th>
<th>R₁</th>
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<th>R₃</th>
<th>R₄</th>
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ᵃYield after chromatographic purification.

Beginning with the simplest case, an unsubstituted benzene ring (R₁ = R₂ = R₃ = R₄ = H), phenylacetylene (148a) was subjected to Sonogashira conditions with a 2-bromocycloalkenecarbaldehyde (149) to afford coupled products 150a (n = 1) and 150b (n = 2). Reduction with DIBAL-H, followed by subsequent acetylation with acetic anhydride in the presence of pyridine and DMAP, gave way to 151a and 151b (both R₅ = H). Complexation with excess Co₂(CO)₈ generated the precursors 152a and 152b, respectively, necessary for the attempted Nicholas cyclization. The yields of this sequence of reactions are summarized in Table 2.
Table 2: Summary of % Yields for Compounds 150, 151, and 152.

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<sup>a</sup>Yield after chromatographic purification.
<sup>b</sup>Yield based on a tandem desilylation/Sonogashira reaction.

Compound 152<sup>a</sup> (n = 1) was tested for its ability to undergo a Lewis acid-mediated Nicholas-type cyclization reaction by being treated with BF₃•OEt₂. The Lewis acid was
added slowly to the reaction flask, which contained 152a dissolved in dry CH₂Cl₂ at a high dilution (7 x 10⁻³ M), at 0 °C, and under an N₂ atmosphere. A high dilution was always used in these Nicholas cyclization reactions due to the fact that in attempting to form medium sized rings based on acyclic closure, entropic factors become a problem, and hence, the use of high dilution techniques helps minimize dimer formation, which occur as a result of competing intermolecular reactions¹⁹³. The reaction, however, did not produce the anticipated 153a (R₅ = H); instead, nothing but gross decomposition was observed. Treatment of 152b (n = 2) also did not give the anticipated cyclized product 153b, however, it did afford elimination product 154a (R₅ = H). Substitution of BF₃•OEt₂ with SnCl₄ did not produce any cyclized product either. Instead, as was observed with BF₃•OEt₂, the same elimination compound, 154a, was isolated (Scheme 2.7). As unfortunate as this was, it ultimately was of no surprise. Benzene itself has been noted to not be nucleophilic enough to react efficiently unless present as solvent⁶⁶, and based on the Mayr scale, the minimum requirement is typically an anisole ring. It became obvious from this set of results that an activating/electron donating group on the benzene may be necessary in order to help facilitate cyclization.
Scheme 2.7: Nicholas reaction chemistry of complexed acetate-Co$_2$(CO)$_6$ precursors (152) to afford cyclized products (153), with the occasional competing elimination product (154).

Commencing with 3-iodoanisole (155a), the sequence of reactions generated complexed precursor 152c ($n = 2$, $R_3 = H$), which bears at least one methoxy group ($R_1 = OMe$, $R_2 = R_3 = R_4 = H$). Exposure of 152c to BF$_3$$^•$OEt$_2$ in dry CH$_2$Cl$_2$ at 0 oC under a N$_2$ atmosphere afforded cyclized products 153c ($R_3 = OMe$, $R_1 = R_2 = R_4 = R_5 = H$) and 153c’ ($R_1 = OMe$, $R_2 = R_3 = R_4 = R_5 = H$) as a pair of separable regioisomers in a 4.9:1 ratio of 153c:153c’ (i.e., para attack:ortho attack) in a combined yield of 82% (refer to Table 3). In attempting to cyclize 152c, the temperature was varied in order to determine whether this variable could affect the ratio, and perhaps minimize the formation of the minor isomer. This was, in fact, the case. At -40 oC, the reaction took 2 h to complete, and afforded a 6.8:1 ratio in favour of the major isomer (153c) with a combined yield of 79%. When the reaction temperature was dropped to -78 oC, the reaction took 3 h to complete (during which time, the reaction was allowed to warm up to 0 oC over the last 45 minutes), and afforded an 8.1:1 ratio in favour of the major isomer (153c), with a combined yield of 81%. This can be rationalized by considering $\Delta G^\ddagger = -RT\ln K_{eq}$, where $\Delta G^\ddagger$ is the change in the Gibbs free energy ($/mol$), $R$ is a constant (8.3145 $/mol*K$), $T$ is the temperature (K), and $K_{eq}$ the equilibrium
constant. Assuming $\Delta G'$ remains fairly constant, as $T$ is lowered, $K$ must increase.

Moving forward to a set of compounds bearing two methoxy groups, an array of compounds was synthesized that showcased different arrangements of the methoxy groups around the benzene ring relative to each other, changing the size of the cycloalkene ring, and allowing for $R_5$ to be something other than an H group. Initiating this group of compounds, 4-iodo-1,2-dimethoxybenzene (155b, $R_1 = R_2 = \text{OMe}$, $R_3 = R_4 = \text{H}$) ultimately afforded complexed precursor 152d ($n = 2$, $R_5 = \text{H}$), which upon exposure to BF$_3$$\cdot$OEt$_2$ under the typical conditions, also afforded a pair of separable regioisomers, 153d ($R_1 = R_4 = \text{H}$, $R_2 = R_3 = \text{OMe}$) and 153d' ($R_1 = R_2 = \text{OMe}$, $R_3 = R_4 = \text{H}$) in an 8.8:1 ratio of 153d:153d' (i.e., para:ortho attack) in a combined yield of 90%. As was the case with 152c, the favoured product stemming from 152d was the one resulting from para attack onto the generated cation. There are two possible reasons governing this: steric and electronic. In terms of steric, it was obvious that cyclization favoured the less sterically hindered side to afford the predominant product. In terms of electronic, methoxy groups are known as ortho/para directing groups as a result of their ability to stabilize a positive charge at both the ortho and para positions through resonance effects that occur by means of the $\pi$-system. Oxygen, however, possesses field/inductive effects due to its greater electronegativity, which occur through the $\sigma$ system, and hence renders the ortho position somewhat electron deficient. This effect is not as dominant at the para position due to its remote location (as compared to the ortho position), and hence the para position experiences such electron deficiency to a (much) less greater extent. In this sense, the steric and inductive effects of the methoxy group(s) combine to actually rather deactivate the ortho position. It is also apparent that the
observed para/ortho product ratios had increased when moving from 152c to 152d. This may be a reflection of the increased steric bulk around the nucleophilic site.

1-Bromo-3,5-dimethoxybenzene (R₁ = R₃ = OMe, R₂ = R₄ = H) (155c) competently produced complexed precursors 152e (n = 1, R₅ = H) and 152f (n = 2, R₅ = H), which cyclized effortlessly into 153e and 153f, respectively, both in good yields (85%, Table 3).

The third set of dimethoxybenzene compounds revolved around a 1,4-arrangement of the methoxy groups around the benzene ring. Beginning with 2-iodo-1,4-dimethoxybenzene (155d, R₁ = R₄ = OMe, R₂ = R₃ = H), the course of reactions outlined in Scheme 2.6 eventually afforded complexed precursors 152g (n = 1, R₅ = H), 152h (n = 2, R₅ = H), 152hh (n = 2, R₅ = Me), and 152i (n = 3, R₅ = H), all of which were subjected to treatment with BF₃•OEt₂ under the typical conditions. Unfortunately, unlike its counterpart 152e, 152g cyclized quite languidly, affording 153g in only 6% yield with the remainder being gross decomposition. Compounds 152h and 152i cyclized in good yields (82% and 85%, respectively, Table 3), however, a little less cleanly than 152f. It is quite possible that the electronics around the ring play an instrumental role in the ease of cyclization. Looking at compounds 152e and 152f, the methoxy groups are both ortho and para to the nucleophilic site on the benzene ring. Compounds 152g-i bear an arrangement of methoxy groups that places the nucleophilic carbon at an ortho position relative to one methoxy group, and meta to the other. Methoxy groups, being ortho/para-directing, typically do not support meta attack, having been established as “meta deactivating” (i.e., the Hammet constant for a meta methoxy group is σ⁺ₘ = 0.047, and most partial rate factors for reactions of anisole at the meta site are less than one178). As mentioned earlier, ortho positions are not the most
favourable either given oxygen’s inductive properties, and hence, make this set of compounds not quite as easily effective in the Nicholas cyclizations as \textbf{152e} and \textbf{152f}. Of interesting note, however, it was observed that as the ring size increased from \( n = 1 \) to \( n = 3 \), the ease of cyclization also increased, with \textbf{152i} cyclizing the most cleanly and in the best yield.

DFT calculations (Scigress Explorer Ultra, V.7.7.0.49., B88-PW91 functional, dzvp basis set) were performed on compounds \textbf{152g}, \textbf{152h}, \textbf{153g}, and \textbf{153h}. Based on the data collected, cyclization of \textbf{152h} is more exothermic than cyclization of \textbf{152g} by 13.6 kJ/mol ($\Delta E_{\text{152g} \rightarrow \text{153g}} = -36.1$ kJ/mol and $\Delta E_{\text{152h} \rightarrow \text{153h}} = -49.7$ kJ/mol), supporting the idea that cyclization of \textbf{152h} is more favourable. Of course, this is the overall energy of the reaction, and does not give much insight into the transition states, however, further calculations regarding bond angles showed that the change in bond angles from the precursor to its cyclized product are more favourable when \( n = 2 \) (i.e., six-membered ring) compared to \( n = 1 \). The sum of the deviations in bond angles from an idealized 120° of the alkene carbons when \( n = 1 \) increases when going from acyclic \textbf{152g} to cyclic \textbf{153g} (i.e., \textbf{153g} deviates greater in those bond angles than does its precursor \textbf{152g}), whereas the deviation in those bond angles from 120° when \( n = 2 \) decreases when going from acyclic \textbf{152h} to cyclic \textbf{153h} (i.e., the overall deviation in bond angles is smaller for \textbf{153h} than it is for \textbf{152h} from an idealized 120°). This suggests that, upon cyclization of \textbf{152g}, an increase in bond angle strain is experienced for the alkene carbons, whereas cyclization of \textbf{152h} results in no such increase in bond angle strain of those same carbons. It is apparent, then, that the structure and properties of the complex, as well as the structure and properties of its respective
product, appear to be important in determining its reactivity.

In attempting to cyclize 152hh, it was observed that elimination was a competing side reaction. A pair of structural isomers, cyclized isomer 153hh and elimination isomer 154b, were isolated as inseparable products. The ratio of 153hh:154b was determined to be 1.0:3.0 by peak analysis of the 1H-NMR spectra (i.e., integration of the methoxy peaks at δ = 3.81 (153hh) and δ = 3.80 (154b)). It became obvious that the substitution of one of the H’s with an alkyl group at the reaction centre was detrimental to the Nicholas reaction, and not very well tolerated.

Moving forward with an additional methoxy group, a trimethoxybenzene ring system was explored in which the first set consisted of complexed precursors 152j (n = 1, R5 = H), 152k (n = 2, R5 = H), and 152kk (n = 2, R5 = Me) being synthesized from starting material, 4-iodo-1,2,3-trimethoxybenzene (155e), according to Scheme 2.6. Treatment of these complexes with BF3•OEt2 led to reactions that afforded their cyclized products, however, contaminated with elimination and decomposition side products. Subjecting them again to Nicholas chemistry with SnCl4 instead of BF3•OEt2 proved more successful, and the reactions proceeded in a much more proficient and clean manner, despite the low yields still (8%, 39%, and 39% respectively). Of interesting note, the reactions appeared to commence with the elimination product being formed or a combination of elimination and cyclized products (based on TLC analysis). Allowing the reactions to continue showed diminished elimination product and increased cyclization product, until eventually, only the cyclized product was seen on the TLC strip. This effect is most likely a result of the liberated acid by-product. While the exact nature of the acid source is unknown, it is obvious that the
reagent combination involving SnCl₄ proves more beneficial in its ability to re-generate the cation from the resulting new alkene function formed in the elimination product (Scheme 2.8). The regenerated cation can then proceed through the cyclization route, and ultimately end up as the sole product.

Scheme 2.8: Regeneration of the vinylogous Nicholas cation from the elimination product due to the presence of H⁺ ions.

Not surprisingly, although to much dismay, the low yields can be attributed to the electronics around the benzene ring. Only one methoxy group is located in a favourable position relative to the nucleophilic site (the middle one, in a para position), whereas the other two are located in unfavourable positions (both meta).

As a result of the above case, an arrangement was then sought that would prove more propitious in this type of chemistry. Originating from 5-iodo-1,2,3-trimethoxybenzene
(155f), synthetic transformations according to Scheme 2.6 led to the set of complexed precursors consisting of 152l \((n = 1, R_5 = H)\), 152m \((n = 2, R_5 = H)\), 152mm \((n = 2, R_5 = \text{Ph})\), and 152n \((n = 3, R_5 = H)\), in which the activating methoxy groups are positioned in such a way that their directive influences, for the most part, reinforce each other. To great satisfaction, these afforded their cyclized products, 153l, 153m, 153mm, and 153n, respectively, cleanly and in quick reaction times. Complexed precursor 152mm, however, afforded a mixture of its cyclized (153mm) and elimination (154c) products in a 1:1.3 ratio favouring the elimination product. Allowing the reaction to proceed for an additional hour after the addition of more BF₃•OEt₂ had no effect in converting the elimination product to the cyclized product, and neither did resubjecting 154c to BF₃•OEt₂ post-purification and separation of the two products. Temperature trials showed that dropping the temperature to -50 °C resulted in the reaction favouring the elimination route, with a ratio of 1:10.4 in favour of 154c, and at -60 °C, that ratio increased to 1:13.8 in favour of the eliminated product 154c, enforcing the fact that elimination is faster than cyclization. Finally, substituting BF₃•OEt₂ for SnCl₄ afforded only the cyclized product 153mm in 79% yield, most likely as a result of the process outlined in Scheme 2.8. It became clear, then, that substitution at the reaction centre is tolerable, and that success of the reaction depends on the Lewis acid instead. Given the quick reaction times, and high yields, it was obvious that this arrangement of methoxy groups would allow for easy cyclization independent of the reagent used (when \(R_5 = H\)). All the products in which the reaction centre bore an alkyl group (153hh, 153kk, and 153mm) are expected to be racemic products, since their starting precursors are racemic, with equal amounts of each enantiomer.
The compounds discussed so far present themselves as attractive synthetic intermediates because they contain the carbocyclic framework of many of the icetexane-diterpene natural compounds isolated to date. It seemed logical then, that this Nicholas-type of chemistry should be tested on a compound resembling such icetexanes as barbatusol, for example. Commencing with 5-iodo-1-isopropyl-2,3-dimethoxybenzene (155g, R₁ = R₂ = OMe, R₃ = 'Pr, R₄ = H), complexed precursor 152o (n = 2, R₅ = H) was synthesized according to Scheme 2.6. Treatment of 152o with BF₃·OEt₂ resulted in two regioisomeric products, 153o (R₁ = 'Pr, R₂ = R₃ = OMe, R₄ = H) and 153o' (R₁ = H, R₂ = R₃ = OMe, R₄ = 'Pr), in a combined yield of 83%. Unfortunately, the intended product, 153o', was the minor product, as determined by NOE experiments (refer to Experimental Chapter for details). A very similar problem was reported by the Majetich group¹¹⁷,¹¹⁹,¹²⁰ in their syntheses of several icetexane-diterpenes. The use of BF₃·OEt₂ in their cyclization step afforded the unwanted isomer as the major product. To circumvent this issue, the group switched their Lewis acid from BF₃·OEt₂ to TiCl₄, and found that, despite still getting both isomers for products, the wanted isomer now became the major product. This strategy was hence employed in the cyclization of 152o. Unsatisfactorily, this did nothing to correct the issue, and 153o still emerged as the major isomer (79% combined yield). The cyclization was also attempted with a lesser amount of Lewis acid. At 1.5 equivalents of TiCl₄ instead of the typical 3 equivalents, the Nicholas cyclization still proceeded efficiently, however, no reverse in which isomer was favoured. SnCl₄ also afforded the same results (79% combined yield). All three Lewis acids afforded a ratio of approximately 14:1 153o:153o'. Perhaps, maybe one day, a diterpene resembling 153o will be isolated from nature.
A summary of the synthesized products is presented in **Table 3**, along with their yields, Lewis acid employed, and product ratios.

**Table 3: Summary of Nicholas Lewis Acid-Promoted Reaction Results**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>% Yield 153(^a)</th>
<th>% Yield 153(^a)</th>
<th>% Yield 154</th>
<th>Ratio 153:153'/154</th>
</tr>
</thead>
<tbody>
<tr>
<td>152(^a)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^b)</td>
<td>–</td>
<td>–</td>
<td>52</td>
<td>–</td>
</tr>
<tr>
<td>152(^c)</td>
<td>68</td>
<td>14</td>
<td>–</td>
<td>4.9:1(^c)</td>
</tr>
<tr>
<td>152(^d)</td>
<td>81</td>
<td>9</td>
<td>–</td>
<td>8.8:1(^c)</td>
</tr>
<tr>
<td>152(^e)</td>
<td>85</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^f)</td>
<td>85</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^g)</td>
<td>6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^h)</td>
<td>82</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^i)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.0:3.0(^f)</td>
</tr>
<tr>
<td>152(^j)</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^k)</td>
<td>39</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^kk)</td>
<td>39</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^l)</td>
<td>85</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^m)</td>
<td>86</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^mm)</td>
<td>34</td>
<td>–</td>
<td>46</td>
<td>1:1.3(^e)</td>
</tr>
<tr>
<td>152(^n)</td>
<td>84</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>152(^o)</td>
<td>74</td>
<td>5</td>
<td>–</td>
<td>13.9:1(^c)</td>
</tr>
</tbody>
</table>

\(^a\)153 refers to the major isomer, 153\(^a\) refers to the minor isomer. Isolated yields after chromatographic purification.

\(^b\)Reacted with BF\(_3\)\(\cdot\)OEt\(_2\) as Lewis acid.

\(^c\)Reacted with SnCl\(_4\) as Lewis acid.

\(^d\)When treated with SnCl\(_4\), the reaction afforded only 153\(^mm\) in 79% yield.

\(^e\)Ratios determined by masses of products.

\(^f\)Ratio determined by \(^1\)H-NMR spectroscopy (combined yield was 80%).
One final series was prepared in which the aromatic ring was a π-excessive heterocycle. 3-Bromothiophene (157) was subjected to chemistry outlined in Scheme 2.9 to afford its complexed precursor (161), which upon treatment with BF₃•OEt₂, afforded 162 in excellent yield (93%). The cyclized product (162) is a result of C-2 substitution, and was observed to be the sole product, with no traces of the C-4 substituted minor product detected.

Scheme 2.9: Synthetic route towards cyclized compound 162.
The initial step in reactions mediated by a Lewis acid is typically complexation of the carbonyl with the Lewis acid\textsuperscript{196}. Subsequently, the activation of the base by coordination leads to an increase in its electrophilicity, and attack by a reactant/nucleophile in the component mixture can occur either inter- or intramolecularly\textsuperscript{22}. It is hypothesized that in treating 152 with the Lewis acid, coordination occurs via the ester carbonyl of the acetate leaving group, forming an adduct as depicted with 163. Sequential loss of this complex generates the allylic cation (164), whose positive charge most likely experiences conjugative stabilization with delocalization onto the alkyne-\(\text{Co}_2(\text{CO})_6\) moiety. Nucleophilic attack by the electron-rich arene onto the remote end of the cation closes the ring, and generates the tricyclic system bearing the central cycloheptyne-\(\text{Co}_2(\text{CO})_6\) ring system (Scheme 2.10).
Scheme 2.10: Proposed mechanism for the generation of the complexed tricyclic products from their respective acetate-Co₂(CO)₆ complexed precursors.

Based on the proposed mechanism, in principle, the Lewis acid should only be required in catalytic amounts. Several groups²⁴,¹²⁹, however, including the Green group³⁶,¹⁸⁰, have reported optimized conditions in their alkyne-Co₂(CO)₆ chemistry that include supra-stoichiometric amounts of Lewis acid in order to obtain the highest yields.

Simple removal of the Co₂(CO)₆ unit from these compounds would give systems whose ring strain would be intolerable at ordinary temperatures. As a result, decomplexation of the alkyne-Co₂(CO)₆ moiety had to be carried out in tandem with another process that transformed the alkyne function into one viable within a seven-membered ring. Previous
success in the group\textsuperscript{35} in removing the Co\textsubscript{2}(CO)\textsubscript{6} moiety, and simultaneously reducing the alkyne to an alkene, involved a modified version of Isobe’s hydrosilylation protocol\textsuperscript{98}, that ultimately afforded the cycloheptene. In attempting to decomplex \textit{153d}, this modified version was the first method pursued. Complex \textit{153d} was treated with triethylsilane in the presence of bis(trimethylsilyl)acetylene (BTMSA) as a trapping reagent for liberated Co\textsubscript{2}(CO)\textsubscript{6}, the latter two forming the corresponding acetylene-cobalt complex. The Isobe group reported that this scavenging alkyne helps minimize side reactions, including olefin isomerization, that would otherwise result from the free Co\textsubscript{2}(CO)\textsubscript{6} unit. The reaction was allowed to go for 6 h at 65 °C, at which point, it was cooled to room temperature, and subsequent \textit{in situ} protodesilylation with trifluoroacetic acid followed. The isolated product (\textit{165}), however, was a result of reductive decomplexation that included further reduction of the alkene functions to afford the benzocycloheptane in 81\% yield (\textbf{A, Scheme 2.11}).

Surprising, although not unheard of, overreduction during decomplexation has been reported by other groups, including \textit{Tanino et. al.}\textsuperscript{184}, who described how their decomplexation protocol with Bu\textsubscript{3}SnH afforded the cycloalkane product. It was reasoned that remaining, excess silane was the culprit in leading to the continued reduction of the alkenes, acting as a hydride source. To test this hypothesis, \textit{153d} was subjected to the same procedure, except that following the hydrosilylation, the product was purified and isolated. This afforded \textit{166} as a regioisomeric mixture of vinylsilanes, with the major one as shown, in a combined yield of 86\% (\textbf{B, Scheme 2.11}). The regiochemistry of the major product was verified via NOE experiments (refer to Experimental Chapter for details). The mixture of both isomers was then subjected to desilylation with TFA, which ultimately afforded \textit{167} in 97\% yield,
supporting the proposed mechanism, in which the excess silane leads to continued reduction.

Decomplexation was also attempted using another method reported by the Isobe group, which employed sodium hypophosphite\textsuperscript{182}. Treatment of 153d in 2-methoxyethanol with excess sodium hypophosphite at 65 °C afforded 167 directly (B, Scheme 2.11), which was isolated in 76% yield following purification.

\begin{center}
\begin{tikzpicture}
\node (a) {153d};
\node (b) [right of=a] {165};
\node (c) [below of=a] {153d};
\node (d) [below right of=a] {166};
\node (e) [below of=d] {167};
\node (f) [above right of=d] {153d};
\node (g) [below right of=f] {166};

\path (a) edge node {1) Et$_3$SiH (5 equiv.)} (b);
\path (a) edge node {2) TFA} (c);
\path (c) edge node {Et$_3$SiH (5 equiv.)} (d);
\path (c) edge node {BTMSA (2 equiv.)} (e);
\path (c) edge node {ClCH$_2$CH$_2$Cl, 65 °C, 6 h, N$_2$} (f);
\path (f) edge node {81\%} (g);
\path (d) edge node {NaH$_2$PO$_2$-H$_2$O (5 equiv.)} (g);
\path (d) edge node {2-methoxyethanol} (e);
\path (e) edge node {86\%*} (b);
\path (g) edge node {TFA} (f);
\path (g) edge node {ClCH$_2$CH$_2$Cl} (e);
\path (g) edge node {RT, N$_2$, 12 h} (f);
\path (g) edge node {97\%} (f);
\end{tikzpicture}
\end{center}

**Scheme 2.11:** Decomplexation of 153d. A) Full reduction observed by \textit{in situ} protodesilylation following hydrosilylation. B) Decomplexation which kept the double bonds intact (* indicates combined yield of regioisomers).
In summary, these preliminary studies have shown that while the size of the cycloalkene ring can be varied, this change was dependent on the electronic nature of the aromatic ring (i.e., the arrangement of the methoxy groups relative to each other around the ring). Para attack was more favourable over ortho attack, with steric effects playing an influential role in these cases alongside the electronics, and while increasing the electron density on the aromatic ring did result in a more rapid reaction time necessary for formation of 153 to complete, there was no quantitative correlation between reaction time and the substitution pattern of the arene behaving as the nucleophile. Finally, as was seen previously, the protons on the carbon bearing the acetate leaving group shifted upfield by 0.2-0.5 ppm in these sets of compounds as well. The majority of these experiments were repeated several times to ensure reproducibility.

2.2. VINYLOGOUS NICHOLAS REACTIONS IN THE SYNTHESIS OF BICYCLIC RING SYSTEMS BEARING A CYCLOHEPTYNE-CO$_2$(CO)$_6$

In expanding the scope of the chemistry developed, a series of bicyclic compounds were targeted. As outlined in Scheme 2.12, starting with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) or 2-bromocyclohept-1-ene-1-carbaldehyde (149c), Sonogashira chemistry afforded 168a ($n = 1$) and 168b ($n = 2$), respectively, in excellent yields (85% and 90%, respectively). Unfortunately, the 2-ethynylcycloalkene-1-carbaldehyde generated from desilylation of 168 was not very stable, started to decompose within an hour of being purified, and afforded poor yields following the second Sonogashira reaction with 171. It was then decided to take a different approach, and 168 was, instead, subjected to reduction.
with DIBAL-H, followed by immediate treatment of the generated alcohol with acetic anhydride in the presence of pyridine and DMAP. This afforded the acetate (169), which upon desilylation with potassium fluoride dihydrate, afforded a much more stable 170. Compound 170 was then subjected to Sonogashira chemistry with 2-bromo-3-(trimethylsilyl)-1-propene (171), which afforded 172a \((n = 1)\) and 172b \((n = 2)\) in much better yields (86\% and 90\%, respectively). Complexation under the standard conditions (\(\text{CH}_2\text{Cl}_2, \text{RT}, \text{N}_2, 2\) h), followed by purification via flash chromatography actually afforded 173 as a pair of isomers, with the second product arising from migration of the double bond from its \textit{exo} position into the chain. On advice from a colleague and some research into troubleshooting this dilemma, complexation was attempted in \(\text{Et}_2\text{O}\) at 0 °C for 1 h. Purification was carried out on neutralized silica, which afforded 173 as the only isomer.
Scheme 2.12: Synthetic route in the generation of bicyclic compounds 174 via vinylogous Nicholas reaction chemistry of 173.

Attempting cyclization was less straightforward than it was for 152. Treatment of 173a (n = 1) with BF₃·OEt₂ in dry CH₂Cl₂ at 0 °C under nitrogen resulted in a mixture of isomers, where the exo double bond migrated into the ring (175, Figure 2.1) (based on ¹H-
NMR analysis). Switching the Lewis acid to TiCl₄ and purifying the cyclized product on neutralized silica still afforded some of 175 (although the reaction did proceed a bit cleaner than it did with BF₃•OEt₂).

![Image](image_url)

**Figure 2.1:** Bicyclic by-product resulting from isomerization of the exo-methylene into the ring during attempted cyclization of 173a.

It was around this time, that, serendipitously, work reported by Mukai et. al.¹³⁶ was reviewed, and it was noticed that there lay potential in the usage of SnCl₄. With this idea in mind, 173a was subjected to vinylogous Nicholas-type chemistry under the typical conditions, however, with SnCl₄ instead of BF₃•OEt₂. To much delight, this was the cleanest reaction by far, and although 175 was still seen in the ¹H- and ¹³C-NMR spectra, it was at its lowest concentration. In trying to troubleshoot this further, work reported by Djurdjevic and Green³⁶ was recalled, in which the authors reported that the addition of 1.5 equivalents of 'Pr₂NEt to their Nicholas cyclization reactions, with the idea in mind to scavenge acid liberated during the reaction, did in fact improve their yields. Cyclization of 173a was then, yet again, attempted with 3 equivalents of SnCl₄ and 1.5 equivalents of Hunig’s base (i.e., 'Pr₂NEt). While the addition of Hunig’s base to the chemistry discussed earlier showed no advantage, it proved quite beneficial here. To great satisfaction, cyclized product 174a (n
Complexed precursor 173b \( (n = 2) \) was then subjected to these same optimized conditions to afford 174b \( (n = 2) \) as the lone product in 83% yield.

The cyclization of 173 takes advantage of the cation-stabilizing ability of the alkyne-Co\(_2\)(CO)\(_6\) moiety and the $\beta$-effect of the trimethylsilyl group\(^99\). As depicted in Scheme 2.13, treatment of 173 with the tin Lewis acid leads to coordination through the carbonyl group on the acetate functionality (176). Loss of the leaving group leads to the vinylogous cation (177), which is trapped by the alkene group through nucleophilic attack. The resulting cation (178) is located in a position one removed (\( \beta \)) from the silicon atom, which helps stabilize it through hyperconjugation effects (i.e., the $\beta$-silicon effect, represented by the dashed line). A necessary prerequisite, however, for this stabilization to be effective is that the formally empty p-orbital on the cationic carbon must be co-linear with the adjacent Si-C bond (i.e., the two groups possess an antiperiplanar arrangement\(^192\)). In this way, the filled $\sigma$ molecular orbital of the Si-C bond and the empty p-orbital of the carbocation can engage in a stabilizing overlap interaction. This cation also benefits from stabilization through the alkyne-Co\(_2\)(CO)\(_6\) component. The ensuing elimination of the trimethylsilyl group results in ring closure and generation of the cycloheptyne-Co\(_2\)(CO)\(_6\) unit (174).
Scheme 2.13: Stabilization of the carbocations generated from treatment of 173 with SnCl₄. Cation 178 is doubly stabilized by the alkyne-Co₂(CO)₆ unit and the Si-C σ-bond (i.e., the silicon β-effect). The dashed line is representative of the hyperconjugative stabilization effect.

A third type of vinylogous Nicholas-type reaction was attempted employing these bicyclic compounds (Scheme 2.14). Compound 168b was desilylated to afford 179. This compound, however, had a very limited shelf life, and within the hour, started to decompose at room temperature and in the presence of air. The Sonogashira reaction, hence, had to be carried out quickly and swiftly shortly after purification of 179, however, the yield of 180 was still less than satisfactory (50%). Complexation of 180 afforded a compound (181) that could not be isolated without decomposing within a short amount of time, and hence,
following flash chromatography using a short column of neutralized silica, the complex was promptly dissolved in dichloromethane and treated with the Lewis acid at 0 °C.

Scheme 2.14: Reaction sequence towards the synthesis of complex 181.

The final step in this reaction sequence involves a Hosomi-Sakurai reaction, a Lewis acid-promoted conjugate addition of an allyltrimethylsilane function (typically) to an (α, β-unsaturated) ketone or aldehyde. Use of BF₃•OEt₂ afforded only decomposed material, so SnCl₄ was sought as the alternative. Monitoring the reaction via TLC appeared to show that the reaction was occurring rather cleanly, although with one unfortunate aspect. The product band travelled much quicker up the silica than expected and than the starting material. It was reasoned that the product would travel slower than the starting material (due
to the resulting -OH function), however, this was not observed. It was then hypothesized
that possible elimination of the -OH was occurring due to the presence of liberated acid by-
product, to afford product 183 rather than 182 (Scheme 2.15). This has been observed in
other, very similar work in the group, and hence, did not seem like an unreasonable
inference. Purification of the product, however, proved rather difficult, and made analysis
and a definite resolution to the hypothesis troublesome. Purification on regular and/or
neutralized silica showed immediate decomposition of product as the band travelled down
the column, and only a partial ¹H-NMR [1H as a ‘d’ at δ = 5.88 ppm (J = 1.2 Hz), 1H as a
‘d’ at 5.45 (J = 1.2), 1H as a ‘s’ at 4.65, and 2H as a ‘m’ from 2.32-2.35] and ¹³C-NMR [high
signal to noise made assignment of peaks difficult; ascribed δ = 200 ppm - carbonyl carbons
of the ligands] could be obtained, neither of which were of the best quality to make for
definite determination as to the exact nature of the product. Low resolution mass
spectrometry showed peaks at 371.73 (M-3CO⁺) and 287.44 (M-6CO⁺), and IR showed no
peak indicative of an -OH being present. Use of Hunig’s base might have circumvented this
problem, as might have reduction in the equivalent amount of Lewis acid, however, due to
the trying methodology, mostly because of the limited stability and poor yields of some of
the compounds, and due to time constraints, these alternatives were not attempted.
Scheme 2.15: The Hosomi-Sakurai-Nicholas reaction of 181.

2.3. VINYLLOGOUS NICHOLAS REACTIONS IN THE SYNTHESIS OF FAVELINE- AND ICETEXANE-DITERPENES

Having established the feasibility of the Lewis acid-promoted electrophilic cyclization of vinylogous propargyl-acetate-Co$_2$(CO)$_6$ complexes by way of Nicholas chemistry, the next approach was to demonstrate the practical utilization of this chemistry and apply it to the synthesis of several icetexane-diterpenes. Despite the plethora of methods that have already been developed to construct these systems, it was believed that the methods described thus far in this dissertation employing the Nicholas reaction would provide, not only a novel approach to these natural products, but also offer some exciting new advantages, including the ability to use and manipulate the alkyne-Co$_2$(CO)$_6$ complexes as short-lived intermediates for further functionalizations.

Sight was set on targeting compounds from the pisiferin subclass and the barbatusol subclass of icetexane-diterpenes. Construction of the “C” ring (the aromatic ring) proved
quite manageable and untroublesome. The “C” ring of pisiferin was synthesized starting from 2-isopropylphenol (184), which was treated with iodomethane in the presence of potassium carbonate to afford 2-isopropylanisole (185) in excellent yield (90%). Iodination of 185 afforded 186 as the only isomer, also in excellent yield (91%) (A, Scheme 2.16). The “C” ring of barbatusol was already in hand (155g), however, due to regioselectivity issues upon attempted cyclization of 152o, it was decided that the best way to circumvent this problem was to render that para site (relative to the methoxy; it is ortho relative to the isopropyl group) unreactive with a blocking group. Bromine appeared to be the best choice due to its ease of addition, numerous methods for removal of the atom, and because of the difference in reaction rate of iodides and bromides106, selective Sonogashira coupling with the iodide was expected. Given that cyclization was preferred at that para site (i.e., para relative to the methoxy, and ortho relative to the isopropyl), it was reasoned that bromination should favour that site as well. Treatment of 155g with 1.25 equivalents of Br₂ afforded 187 as a pair of inseparable regioisomers, with bromination occurring at both carbons, although preferentially at that carbon para to the methoxy (as determined by NOE experiments). Reducing the equivalents of Br₂ to 1.0 still afforded some regioisomeric by-product. Finally, it was determined that if the amount of Br₂ was reduced to 0.9 equivalents, 187 was isolated as the sole isomer, along with unreacted 155g.
Scheme 2.16: A) Construction of the “C” ring of the pisiferin family. B) Construction of the “C” ring of the barbatusol family.

Construction of the “A” ring (the cycloalkane ring), on the other hand, proved quite complicated and laborious, a case where the complexity and synthesis of the target appeared not to be necessarily greater than that of the starting material. After extensive experimentation, methods published by Majetich et al. gave way to a synthetic route for the formation of the “A” ring (Scheme 2.17). Dissolving 1,3-cyclohexanedione (188) in ethanol, along with a catalytic amount of p-toluenesulphonic acid, under reflux conditions, led to the generation of the enol ether (189) in excellent yield (96%). Exposing 189 to 1,3,5-trioxane in the presence of BF₃•OEt₂ afforded the dioxinone (190), also in excellent yield (92%). Methylation of 190 twice afforded the gem-dimethyl product (191) in 77% over two steps.
Scheme 2.17: Construction of the “A” ring for use in the synthesis of icetexane-diterpenes.

With the “A” ring and “C” ring building blocks in hand, the complexed precursor necessary for cyclization to form the pisiferin skeleton was synthesized according to Scheme 2.18. Compound 191 was subjected to lithiated (trimethylsilyl)acetylene, which was generated in situ from n-BuLi and (trimethylsilyl)acetylene, and subsequently treated with 3 M HCl to hydrolyze the cyclic acetal. Desilylation of 192 was achieved through KF•2H₂O to afford terminal acetylene 193, which underwent Sonogashira coupling with 186 to afford 194. Treatment of 194 with acetic anhydride in the presence of pyridine and DMAP, followed by complexation with Co₂(CO)₈ ultimately afforded complexed precursor 196 (Scheme 2.18). To much dismay, 196 was only marginally stable at ambient conditions, and started to decompose while still on the rotary evaporator. It was, hence, immediately subjected to cyclization chemistry with BF₃•OEt₂, only to afford decomposed material.
Scheme 2.18: Synthetic route towards complexed precursor 196.

Having come across work reported by the Tyrrell group\textsuperscript{121,187}, in which the group devised a one-pot complexation, Nicholas reaction, decomplexation method, it was decided that this procedure was going to be attempted with 195. Complexation was initiated as per the norm: compound 195 was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (at a dilution factor typical of cyclization, i.e., \(\sim 7.0 \times 10^{-3} \text{ M}\)) along with only a slight excess of Co\textsubscript{2}(CO)\textsubscript{6}, and allowed to stir for 2
hours at room temperature conditions. Following the 2 hours, the reaction flask was submerged into an ice bath to cool it to 0 °C. At this point, SnCl₄ and N,N-diisopropylethylamine were added to the reaction flask as stirring continued. The reaction was monitored via TLC, which showed that, what was speculated to be the cyclized product, was starting to form. The reaction was allowed to warm up to room temperature and progress through 15 hours, at which point TLC analysis showed no more starting material. The solvent was removed under reduced pressure and substituted with 2-methoxyethanol. Decomplexation was commenced with sodium hypophosphite at elevated temperatures over the course of approximately 20 hours. Purification following the reaction isolated compound 197 in 28% yield (Scheme 2.19) as the sole regioisomer. This was confirmed by NOE experiments (refer to Experimental Chapter for details).

Scheme 2.19: One-pot complexation, cyclization, and decomplexation of 195.

The final purification proved rather unpleasant (mostly due to all the cobalt), so in a subsequent round, the residue was passed through a small column of silica to remove any
excess cobalt following the cyclization reaction and prior to decomplexation. This made the final purification much easier and had no dramatic effect on yield, so long as the decomplexation reaction was initiated immediately after the solvent had been removed under reduced pressure following the chromatography. The reaction was also attempted with the omission of \( N,N \)-diisopropylethylamine, as well as using \( \text{Bu}_2\text{BOTf} \) as Lewis acid. In both cases, the yields remained consistent.

The complexed precursor necessary for cyclization to form the barbatusol skeleton was synthesized (Scheme 2.20) in an analogous manner to the pisiferin skeleton. Compound 193 was subjected to Sonogashira chemistry with 187 to afford 198, which was treated with acetic anhydride in the presence of pyridine and DMAP to yield 199. As was the issue with compound 196, the cobalt complex of 199 showed limited stability, and hence complexation and cyclization were carried out as a one-pot reaction. Following 2 hours of exposure of 199 to a slight excess of \( \text{Co}_2(\text{CO})_8 \) at ambient conditions in \( \text{CH}_2\text{Cl}_2 \) (enough to make a solution with concentration \( \sim 7 \times 10^{-3} \text{ M} \)), the reaction flask was submerged into an ice bath to cool to 0 °C, and the stirring solution was then treated with \( \text{SnCl}_4 \). The reaction was allowed to continue stirring for approximately 5 additional hours, at which point TLC analysis showed no more starting material. The reaction was quenched with saturated \( \text{NH}_4\text{Cl}^- \) (aq.), the solvent removed under reduced pressure, and the residue passed through a short column of silica. The collected fragments were dissolved in 2-methoxyethanol and treated with sodium hypophosphite at elevated temperatures over the course of approximately 20 hours. Preparative TLC isolated two cyclized products in a 1:20.2 ratio of intended product:unfavourable regioisomer, in a combined yield of 31%. 

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It was rather surprising and displeasing to observe that the bromine function had not been robust enough to withstand this set of reactions. To help resolve at which point it was that the bromine was being displaced (i.e., perhaps the excess cobalt during the cyclization sequence was posing a problem), this set of reaction was preformed in an isolated manner. Following each reaction, the intermediate product(s) was quickly purified and isolated prior to commencement of the next reaction in the sequence. Both regioisomers were still isolated following the decomplexation, however, in a much less drastic ratio (1:5.9), and with a combined yield of 30%. It was then decided that this would be the preferred experimental route (vs. the one-pot complexation/cyclization) for the synthesis of the barbatusol skeleton. Further attempts included reducing the equivalent amount of SnCl₄ to 1.5 equivalents, and/or the amount of excess Co₂(CO)₈ until a noticeable effect on yield was observed. Neither change helped remedy the situation. This led to the speculation that the bromine atom is being removed during the complexation phase, and hence upon addition of the Lewis acid, both sites are available to take part in the cyclization.
It is clear that a different protecting/blocking group needs to be employed, perhaps a silicon based functionality, although care might need to be applied to avoid anything too bulky. A bulky substituent could lead to complexation starting to pose a new problem (i.e., the proximity of the bulky alkyne-Co$_2$(CO)$_6$ cluster, the isopropyl group, and a bulky protecting group might lead to further instability of the complex). While not the most efficient means of attaining a desired compound, the formation of 200 does still constitute a formal synthesis of (-)-salviasperanol$^{116}$.

In order to achieve a formal synthesis of (±)-pisiferin and isopisiferin, either one of the double bonds (i.e., the one between C6 and C7 - refer to page 37 of this dissertation for
numbering schematic) or both needed to be reduced. Selective hydrogenation was the preferred choice. Given that the double bond between C5 and C10 is nearest the carbonyl, it was presumed that it is a bit more polarized and less easily hydrogenated, and therefore, it was reasoned that the former double bond might be reduced first. This meant that the reaction would need to be monitored to catch over-reduction before it started occurring/proceeded too far. Initial attempts with Wilkinson’s catalyst only gave back starting material. Substituting Wilkinson’s catalyst for the much more reactive Crabtree’s catalyst also only gave back starting material. Using a hydrogenation bomb had no effect either. Finally, it was decided to just use palladium on carbon (Scheme 2.21). Following 48 h of purging H₂ gas through the reaction flask containing excess Pd/C, a set of inseparable diastereomers was isolated. This constituted a formal synthesis of pisiferin¹², as the isomer containing the hydrogens trans to each other was carried forward in the synthetic route towards (±)-pisiferin published by the Matsumoto group. It is worth noting that the NMR spectra obtained in CCl₄ of 202 did not exactly match the chemical shifts published for compound 106 by the group in their report. It is speculated, however, that given the incomplete details of analysis provided by the group in their experimental, and based on further analysis collected on 202, that the compounds isolated are indeed the fully reduced set of diastereomers as outlined in Scheme 2.21.
In a report published by the Sarpong group\textsuperscript{75}, selective hydrogenation of the C6-C7 double bond in a compound similar in nature was obtained via the use of diimide (generated by the triethylamine-induced decomposition of \textit{p}-toluenesulphonyl hydrazide in 1,2-dichloroethane at elevated temperatures). The reduction of carbon-carbon \(\pi\) systems by diimide occurs stereoselectively and stereospecifically\textsuperscript{150}, and hence makes for a favourable alternative. The diimide is also useful for its mild, non-catalytic reaction conditions, and can tolerate the presence of a number of reactive functional groups. Garbisch \textit{et al.}\textsuperscript{56} studied the relative rates of a large number of substituted alkenes toward reduction by diimide generated from triethylamine and \textit{p}-toluenesulphonyl hydrazide in diglyme at 80 °C, and had determined that increasing alkyl substitution on the double bond resulted in decreased activity. With this in hand, the idea was that this would allow for the selective hydrogenation of the C6-C7 double bond in 197. Unfortunately, exposing 197 to excess amount of triethylamine and TsNHNH\textsubscript{2} in 1,2 dichloroethane at 65 °C twice over the course of 48 hours gave back only starting material.

It was decided, then, that an alternative route towards the source of the diimide was going to be explored: dipotassium azodicarboxylate\textsuperscript{74,149}. The dipotassium azodicarboxylate...
was synthesized according to work published by Groves & Ma\textsuperscript{69} from potassium hydroxide and azodicarboxamide. The bright yellow solid was easily isolated and in good yield (86%). The diimide could then be generated through the acid-catalyzed hydrolysis of the salt in a protic solvent: acetic acid and pyridine were dissolved in methanol, along with the salt, at ambient conditions\textsuperscript{2} (Scheme 2.22). The reduction was allowed to stir over the course of several days, however, unfortunately as before, after multiple additions of the reagents over the course of those few days, NMR analysis showed predominately starting material. A limitation to the use of the diimide as a reducing agent appears to be the relative rate at which the diimide reacts with the unsaturated substrate\textsuperscript{150}. If the rate of reduction is sufficiently slower than that of the disproportionation of the diimide, no reduction will be achieved as the latter reaction dominates. Unfortunately, due to time constraints, this reduction could not be optimized further, especially since a number of factors could be explored, including choice of solvent, temperature, and reagents. Upon determining successful reaction conditions, the generation of 203 would constitute a formal synthesis of (±)-pisiferin and isopisiferin\textsuperscript{117}.

\textbf{Scheme 2.22:} Selective hydrogenation of 197 using K\textsuperscript{+}O\textsubscript{2}CN=NCO\textsubscript{2}K\textsuperscript{+} as an diimide source.
One final reaction was envisioned. Demethylation of the methyl ethers in 200 would afford 11,12-dihydroxy-10,6,8,11,13-icetexapentan-1-one\(^{158}\) (204). This would lead to a total synthesis of 204. Reviewing the literature, it was found that the Majetich group\(^{116}\) and the Sarpong group\(^{174}\) had both employed sodium hydride and ethanethiol\(^{48,157}\) in their demethylation reactions towards their synthesis of (+)-demethylsalvicanol and salviasperanol, respectively. Unfortunately, employing their methodology resulted in the demethylation of only one of the methyl ethers. Re-subjecting the mono-demethylated compound to the same reaction conditions only returned the starting mono-demethylated compound. Which methyl ether had been demethylated was not determined, since a SciFinder\(^{8}\) search of both potential products turned up zero hits (i.e., not compounds of interest). Upon reviewing the literature, however, it was found that sodium ethanethiolate is actually sometimes chosen as the reagent of choice for the very reason that it provides a convenient and regioselective method for demethylation of methyl ethers in molecules containing more than one such group\(^{46,47}\), in particular, when other methods prove unsuccessful\(^{37}\) (i.e., unsatisfactory mixtures of demethylated products were obtained). Several groups have studied the demethylation of methyl ethers with EtSNa in order to define the scope and limitations of this regioselective cleavage. Dodge et. al.\(^{37}\) reported selectivity based on electronic factors, where methyl ethers para to electron withdrawing groups reacted preferentially with the thiol anion, and Lal et. al.\(^{107}\) demonstrated selectivity by studying the regiodirecting effects of a remote hydroxyl group using ortho hydroxyalkyl appendages. Wilcox and Seager\(^{194}\) studied the rates of ether cleavage in trisethers and related monoethers by HBr in glacial acetic acid at 76 °C. The authors, in this case, concluded that
the enhanced rate of cleavage of 1,2,3-trimethoxybenzenes could be accounted for as a result of the enhanced basicity (due to partial loss of conjugation) of the central methoxy as it is sterically twisted out of the plane of the benzene ring, and to a (much) lesser extent, electronic substituent effects. Upon re-examination of compound 200, it was hypothesized that it is the central methoxy most likely undergoing demethylation due to electronic effects. That methoxy group (the one residing between the isopropyl group and the other methoxy) is para to the ketone through conjugation, allowing much more significant delocalization of the generated oxygen anion.

Probing further into literature revealed that BBr₃ is a well-known, selective, versatile reagent for aromatic methyl ethers’ demethylation, and would make for a good alternative⁴⁰,¹²⁸,¹⁵⁷ (Scheme 2.23). Unfortunately due to time constraints, this reaction was not attempted.

Scheme 2.23: Possible route towards the deprotection of the methyl ethers in 200.

In summary, while the envisioned methods towards the formal syntheses of the pisiferins or the barbatusols was achieved, much optimization had been achieved in the synthesis of the precursor compounds necessary to finish the formal syntheses. It would be
worthwhile continuing to pursue reaction conditions that would eventually lead to successful selective reduction of the C5-C6 double bond, as well as demethylation of both methyl ethers. Should favourable conditions be found that would selectively hydrogenate 197, it could be further applied to compound 200. Selective hydrogenation of 200 would afford 122 (Figure 2.2), an intermediate in the total synthesis of (±)-barbatusol\textsuperscript{120}, and constitute a formal synthesis. Full hydrogenation of 204 would afford rosmaridiphenol (102, Figure 2.2), and a total synthesis.

\begin{figure}[h]
\centering
\includegraphics[width=0.7\linewidth]{figure22.png}
\caption{Intermediate 122 in Majetich’s total synthesis of (±)-barbatusol; and rosmaridiphenol (102).}
\end{figure}
CHAPTER 3: CONCLUSIONS AND FUTURE WORK

3.1. CONCLUSIONS

One of the foremost goals of this dissertation was to develop a strategy that would provide rapid and efficient access to several differently sized bicyclic and tricyclic ring systems by way of vinylogous propargyl-acetate-Co$_2$(CO)$_6$ complexes. The investigation demonstrated that the strategy developed encompassing aryl-substituted allylic acetoxy-enzyme-Co$_2$(CO)$_6$ complexes, which readily underwent an intramolecular vinylogous Nicholas reaction, indeed, proved to be a powerful method for the assembly of 6,7,\textit{n}-tricyclic-Co$_2$(CO)$_6$ complexed systems. Further extension of this chemistry ultimately afforded \( n,7 \)-bicyclic-Co$_2$(CO)$_6$ complexed systems. These complexed systems proved to be sufficiently versatile to undergo subsequent transformations, such as reductive decomplexation.

Several aspects made this novel synthetic approach towards such ring systems advantageous. Firstly, all starting materials were either commercially available or could be synthesized in a small number of steps from commercially available reagents according to reported methods. Secondly, the majority of the syntheses employ mild conditions and, in most cases, afforded good to excellent yields. Thirdly, a number of reaction parameters including temperature, solvent, choice of reagents, combination of steps into one-pot reactions, and purification techniques could be modified to accommodate different functional groups, and in some cases, improve overall yields further.

The synthesis of the diverse array of complexed ring systems afforded a few key observations. To start, while BF$_3$•OEt$_2$ proved sufficient to promote cyclization of
complexed precursors where the double bond was part of a cycloalkene, SnCl₄ proved to be the far better Lewis acid for promoting cyclization of not only the aforementioned complexed precursors, but also of complexed precursors in which the double bond was part of a nominally aromatic or a conventionally aromatic ring structure. SnCl₄ was also capable of promoting the elimination by-product to undergo cyclization, regardless of whether the reaction centre bore a group other than hydrogen or not, affording only cyclized product by the end of the reaction. Substitution at the reaction centre proved to be detrimental with BF₃•OEt₂, affording both elimination and cyclized products. Finally, SnCl₄ was capable of facilitating cyclization without isomerization of an exo methylene into the ring structure when combined with Hunig’s base.

The reaction employed electron rich aryl groups (and in one case, the π-excessive thiophene), as well as an allyl(trimethyl)silane, as the nucleophile. Increasing the electron density on the aromatic ring through additional methoxy groups in the precursors allowed for a somewhat faster reaction time, although a suitable substitution pattern was necessary for more desirable yields. In cases where regioisomers were possible, the less sterically hindered, para-governed nucleophilic attack afforded the cyclized product as the major product, while the ortho-governed attack product was isolated as the minor product. Reducing the temperature from 0 °C to -78 °C enhanced the amount of the substitution product para to the methoxy function (i.e., increased the ratio of major:minor product in favour of the major product). It was also discovered that the size of the cycloalkene could be varied, for the most part, with no noticeable effect on the cyclization (some exceptions were observed). Finally, sulphur was tolerated in the ring system without complication,
whereas oxygen gave marginal results.

Reductive decomplexation proved quite facile. Subjecting a cyclized-\(\text{Co}_2(\text{CO})_6\) complexed product to hydrosilylation conditions, followed by in situ protodesilylation with TFA afforded an overall reduced tricyclic product. Repeating the same procedure, with the modification that protodesilylation was carried out after purification of the silylated product, afforded both double bonds intact. Reductive decomplexation with sodium hypophosphite monohydrate also afforded the same (i.e., the double bonds were not fully reduced to the alkane).

The dramatic modification in the geometry of the linear acetylenic C-C triple bond unit upon complexation by \(\text{Co}_2(\text{CO})_6\) offered a method for the generation of an assortment of tricyclic systems, which proved to be attractive synthetic building blocks towards the assembly of a variety of faveline- and icetexane-diterpenoid natural products, as they possessed the carbocyclic framework common to that family of compounds. These cycloheptyne-\(\text{Co}_2(\text{CO})_6\) complexes demonstrated a combination of ready preparation and good stability, and can be seen as suitable and highly useful in the synthesis of such seven-membered ring containing natural products. The next goal, hence, was to apply the developed chemistry towards the synthesis of several natural products from the icetexane family. While some of the chemistry needed to be modified in order to successfully build the precursors necessary for the formation of the tricyclic compounds via the Nicholas reaction, formal syntheses of salviasperanol and (±)-pisiferin were ultimately achieved. Optimizing the reaction conditions has the potential for the attainment of formal syntheses of isopisiferin and (±)-barbatusol, and the total synthesis of 11,12-dihydroxy-10,6,8,11,13-
icetexapent-1-one and rosmardiphenol. This unique synthetic strategy ultimately provides a platform for the syntheses of other such related natural products.

3.2. FUTURE WORK

By virtue of being science, in the act of solving questions, it in fact, creates more of them. These questions, however, are what spur the progress of science, and the work outlined in the previous chapters is of no exception. There lay many future possibilities and developments involving vinylogous Nicholas reaction chemistry in the synthesis of cycloheptyne-\(\text{Co}_2\text{(CO)}_6\) ring systems, and given the constant discovery of natural products containing seven-membered rings, coupled with the fact that the modular structure of complexes such as \(\text{152}\) allow for extensive variation of the backbone, this chemistry is bound to prove itself as a rapid, efficient, and valuable method towards the synthesis of many surmountable targets. For example, the 6,7,5-tricyclic systems resulting from cyclization of \(\text{146}\) pave way for the potential synthesis of some pallescensins\(^{25,27}\) (in particular, pallescensin \(\text{E}^{26}\) (\text{205, Figure 3.1})), a class of furanosesquiterpenoids isolated from the marine sponge \textit{Disidea pallescens}. The brown algae of the family \textit{Dictyotaceae} are a prolific source of diterpenes. A specimen of \textit{Dictyota divaricata} contains diterpenes of several structures, including isodolastane diterpene \(\text{206}^{156}\) (\text{Figure 3.1}), which could be obtained from cyclization of \(\text{152} \ (n = 1)\). Finally, \textit{Jiang et. al.}\(^{91}\) recently reported the isolation of a novel C\(_{23}\) terpenoid with a unique 6,7,7-carbon ring skeleton from the shrub \textit{Perovskia atriplicifolia}. Possessing a rearranged 9 (10->20)-abeoabietane, perovskatone A (\(\text{207, Figure 3.1}\)) is the first 6,7,7-tricyclic C\(_{23}\) diterpenoid found in a natural source.
The synthesized cobalt complexed compounds and their precursors are also interesting from a structural and electronic point of view. For structures like 140, in which an arene ring separates the cationic site from the alkyne-Co$_2$(CO)$_6$ unit, the potential for questioning the nature of the cation upon treatment of 139 with Lewis acid arises. How much does the Co$_2$(CO)$_6$ moiety contribute to the stability of the cation? Would the cation, at that point, be better described as more of a benzylic cation vs. a Nicholas cation? DFT calculations (with possible collaborations with a computational chemist such as Dr. James Gauld), in conjunction with kinetic studies of SN1 reactions of structures such as 208 and 209 (Figure 3.2) by trapping methods with a variety of nucleophiles, would make for a project worth pursuing. The addition of electron withdrawing groups to the electrophilic aromatic ring to study their effects on cation stability and reactivity would be another interesting feature to explore.
Further information about structural parameters could be gained from X-ray analyses. This would provide useful information on complexes such as 153g, 153h, and 153i. Comparing experimental data to the theoretical DFT calculations performed would be interesting in determining exactly how much the bond angles and bond lengths actually deviate from the theoretical values, and possibly affect the reactivity of the precursors.

The methodology outlined is a promising method towards seven membered-ring systems, and it would be worthwhile to determine if the conditions described have been truly optimized. It would be interesting to determine if the reaction does indeed proceed best with a transition metal-based Lewis acid or if a stronger boron-based Lewis acid would also improve the cyclization reaction. Hilt et al.\textsuperscript{81}, in their study of Lewis acids, determined that for boron-based Lewis acids, BF$_3$\textbullet$\text{OEt}_2$ surpasses only BH$_3$ in terms of reactivity. Both BCl$_3$ and BBr$_3$ were placed ahead of BF$_3$\textbullet$\text{OEt}_2$ on their reactivity scale (although, caution would need to be kept in mind, as their scale is based on nitrogen as the donor atom. Also, BBr$_3$ might kill the system as it is used to remove methoxy groups). Other groups have reported

\textbf{Figure 3.2:} Model structures for the kinetic study of generated benzylic and Nicholas cations (R = alkyl).
successes with aluminum-based Lewis acids\textsuperscript{129,134} in their work with alkyne-Co\textsubscript{2}(CO)\textsubscript{6} complexes, which might be worth exploring.

One-pot reactions have not been practiced extensively in the Green group. Given the success of the one-pot complexation-cyclization(-decomplexation) reaction discussed (Scheme 2.19), it would be interesting to determine if these reactions could be applied to other systems studied in the laboratory, without the reaction conditions posing any complications in the subsequent reaction in the sequence.

The cyclizations to form bicyclic systems were only minimally examined, hence it would be of interest to expand on that chemistry, given that the most amount of knowledge gained in optimizing the vinylogous Nicholas reaction came from troubleshooting these systems. For example, it would be interesting to determine whether a heteroatom would be tolerated as a substitute for the external -CH\textsubscript{2} group. Subjection of complexed precursor 210, which has substantial enol content, to Nicholas reaction chemistry, should yield the anticipated complexed product 211, which could be further protodecarboxylated\textsuperscript{78} to afford 212 (Scheme 3.1). Given that in keto-enol tautomerism, the ketone is the preferred isomer, this would also remove the issue of isomerization of the double bond into the ring.
Scheme 3.1: Cyclization of complexed $\beta$-keto ester 210 into 211, followed by protodecarboxylation to afford 212.
CHAPTER 4: EXPERIMENTAL

4.1. GENERAL METHODS

All reactions and manipulations outlined in this chapter were conducted in glassware that had been washed with soap and water, rinsed with acetone, oven-dried (110 °C) overnight, and cooled in a dessicator. For reactions kept under a nitrogen atmosphere, the glassware was sealed with a rubber septum throughout the course of the reaction time, unless otherwise noted or unless the addition of further reagents required removal of the septum temporarily. All evacuations of glassware and their reagent contents prior to any reactions were done under a 0.1 Torr vacuum. Solvents (CH₂Cl₂, DMF, Et₂O, THF) used for reactions were obtained from a solvent purification system (Innovative Technologies), and used without further drying. All other solvents were used as purchased, unless otherwise stated. Commercially available chemicals were purchased from Sigma Aldrich, with the exception of: bis(triphenylphosphine)palladium(II) dichloride (Strem Chemicals Inc.), 3-bromoformylfuran (Frontier Scientific Inc.), dicobalt octacarbonyl (Strem Chemicals Inc.), potassium fluoride dihydrate (Fisher Scientific), and trimethylsilylacetylene (GFS Chemicals). Tetrakis(triphenylphosphine) palladium(0) was homemade from palladium dichloride according to methods published by Heck79. The chemicals were used as supplied without further purification unless specifically stated, with the exception of BF₃•OEt₂ and TiCl₄, which were distilled and stored in an inert atmosphere prior to use. Liquid reagents and solvents were transferred via syringe (oven-dried or disposable) or pipette, and under a positive N₂ pressure where necessary. Reactions carried out at -78 °C were performed
using an acetone/dry ice bath, while those carried out at 0 °C used a water/ice bath. Reactions carried out at temperatures in between 0 °C and -78 °C were done using a Thermo NESLAB CC-100 immersion cooler. Reactions done at elevated or reflux temperatures made use of an oil bath.

The course of a reaction was monitored using aluminum-backed TLC strips (thickness: 250 µm, indicator: F-254) purchased from SiliCycle Inc. Flash chromatography purification techniques were carried out on silica gel (SiliaFlash® P60, particle size: 40-63 µm, mesh: 230-400), and preparative TLC purification techniques were carried out on glass-backed TLC plates (thickness: 1000 µm, indicator: F-254), both purchased from SiliCycle Inc. Radial chromatography was carried out on silica gel (thickness: 2000 µm, indicator: F-254) purchased from EM Science. A column of silica gel was neutralized by being washed with hexanes containing 2-3% v/v triethylamine.

Melting points were measured with a Thomas Hoover, Uni-Melt® capillary point apparatus. ¹H-NMR and ¹³C-NMR spectroscopy was carried out in deuterated solvents, and performed on 300 MHz and/or 500 MHz Bruker Avance spectrometers at room temperature, with 7.27 ppm (residual CHCl₃) and 77.0 ppm in CDCl₃, 7.15 ppm (residual C₆H₆) and 128.0 ppm in C₆D₆, and 5.32 (residual CH₂Cl₂) and 54.0 in CD₂Cl₂ as the reference chemical shifts for ¹H-NMR and ¹³C-NMR, respectively. All chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (Me₄Si) as standard, and coupling constants reported in Hertz (Hz). Infrared (IR) spectroscopy was carried out on a Bruker Vector 22 FT-IR spectrometer with a KBr plate or on a Bruker Alpha FT-IR spectrometer containing a platinum/diamond ATR. The peaks are reported in wavenumbers (cm⁻¹). Low
Resolution Mass Spectrometry (LRMS) results were recorded on a Varian 3800/1200L GC/MS by means of a Direct Insertion Probe - Electron Ionization method (20 eV), and used for structural confirmation. High Resolution Mass Spectrometry (HRMS) results were obtained by means of a Direct Insertion Probe - Electron Ionization method (70 eV), on a Waters/Micromass GC-ToF Mass Spectrometer performed at the McMaster Regional Centre for Mass Spectrometry.

Compounds containing a cobalt complex and/or other minimally stable compounds were kept away from hot conditions, prolonged exposure to air, or prolonged standing in solvent, and were stored at -20 °C in order to minimize decomposition.

4.2. EXPERIMENTAL DATA

2-(Trimethylsilyl)ethynyl benzaldehyde (135) (GENERAL PROCEDURE A)

\[
\begin{align*}
\text{CHO} & \quad \text{TMS} \\
\end{align*}
\]

Pd(PPh\textsubscript{3})\textsubscript{4} (0.6143 g, 0.5316 mmol, 3 mol%) and CuI (0.1687 g, 0.8860 mmol, 5 mol%) were added to a round bottom flask and placed under vacuum for 10-15 minutes. The flask was then purged with nitrogen. This was repeated two times more\textsuperscript{44}. A solution of 2-bromobenzaldehyde (3.2595 g, 17.719 mmol) dissolved in dry THF (11.8 mL) was added to the reaction flask, followed by trimethylsilylacetylene (3.4808 g, 35.438 mmol). Triethylamine (118.1 mL), which had been degassed for 1.5 h prior, was then added to the reaction. The reaction was allowed to stir for 15-20 h under a nitrogen atmosphere and at room temperature. The mixture was then filtered through Celite\textsuperscript{5}, the solution dissolved in Et\textsubscript{2}O (75 mL), and then extracted with NH\textsubscript{4}Cl (aq., sat., 2 x 75 mL), followed by brine (1
x 75 mL). The organic layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Kugelrohr distillation, b.p. 125 °C, 0.1 Torr (lit., 98 °C¹ at 0.2 Torr) afforded 135 as a yellow oil (3.2094 g, 15.882 mmol, 90%), which was characterized as spectroscopically identical to reported values¹.

2-Ethynylbenzaldehyde (136) (GENERAL PROCEDURE B)

Desilylation of 135 was carried out under conditions reported by Acheson et. al.¹, with minor modifications. Compound 135 (3.2094 g, 15.882 mmol) was dissolved in dry DMF (10.6 mL). The solution was cooled to 0 °C, at which point, potassium fluoride dihydrate (3.2889 g, 34.940 mmol) was added to the reaction flask, and the stirring mixture was allowed to warm up to room temperature over the course of the reaction under a nitrogen atmosphere. The reaction was done in 3 h, as monitored by TLC. The solution was then filtered to remove the solids, extracted with Et₂O (1 x 75 mL) and dH₂O (2 x 75 mL), the organic layer dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Kugelrohr distillation at 0.1 Torr afforded 136 as a colourless solid (1.7194 g, 13.222 mmol, 83%) with m.p. 59.5-61.5 °C (lit., m.p. 60-60.5 °C¹⁴²). The compound was spectroscopically identical to reported values¹⁴².

2-[(3-Methoxyphenyl)ethynyl] benzaldehyde (137a) (GENERAL PROCEDURE C)

Pd(PPh₃)₄ (0.1508 g, 0.1306 mmol, 3 mol%) and CuI (0.0414 g, 0.218 mmol, 5 mol%) were added to a round bottom flask and placed under vacuum for 10-15 minutes. The flask was then purged with nitrogen. This was
repeated two times more. A solution of 3-iodoanisole (1.5271 g, 6.5275 mmol), dissolved in dry DMF (4.4 mL), was added to the reaction flask, followed by 136 (0.5659 g, 4.352 mmol), also dissolved in DMF (4.4 mL). Triethylamine (29.0 mL), which had been degassed for 1.5 h prior, was then added to the reaction. The reaction was allowed to stir for 15-20 h under a nitrogen atmosphere and at room temperature. The mixture was then filtered through Celite®, the solution dissolved in Et₂O (75 mL), and subsequently extracted with NH₄Cl (aq., sat., 2 x 75 mL), followed by brine (1 x 75 mL). The organic layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Flash chromatography (25:1 hexanes:Et₂O) afforded the product as a yellow oil (0.8583 g, 3.646 mmol, 84%), which was characterized as spectroscopically identical to reported values.

2-[(Methoxyphenyl)ethynyl]benzyl acetate (138a) (GENERAL PROCEDURE D)

In a round bottom flask, compound (0.8583 g, 3.646 mmol) was dissolved in dry THF (42.0 mL), and the solution was cooled to a temperature of -78 °C (acetone/dry ice bath). DIBAL-H (1.0 M in THF, 7.3 mL, 7.3 mmol) was added dropwise, and the reaction was allowed to stir under nitrogen at -78 °C for 1 h. Following the hour, still at -78 °C, pyridine (8.8 mL, 110 mmol) was added to the reaction, followed by acetic anhydride (17.2 mL, 182 mmol) and DMAP (2.2208 g, 18.178 mmol). The reaction was allowed to warm up to room temperature over night (20 h), while still being maintained under a nitrogen atmosphere. The following day, the solution was quenched with NH₄Cl (aq., sat., 75 mL)
and extracted with Et<sub>2</sub>O (3 x 75 mL). The collected organic fractions were extracted further with NH<sub>4</sub><sup>+</sup>Cl<sup>-</sup> (aq., sat., 1 x 75 mL) and brine (1 x 75 mL). The organic fraction was then dried over MgSO<sub>4</sub>, filtered, the solvent removed under pressure, and finally flash chromatography (15:1 hexanes:Et<sub>2</sub>O), afforded compound 138a as a pale yellow oil (0.8677 g, 3.098 mmol, 85%). ¹H-NMR (500 MHz, CDCl<sub>3</sub>): 7.59 (dd, 1H, J = 7.4, J = 1.6), 7.44 (dd, 1H, J = 7.3, J = 1.2), 7.31-7.37 (m, 2H), 7.72 (apparent t, 1H, J = 8.0), 7.18 (d of apparent t, 1H, J = 7.6, J = 1.2), 7.11-7.12 (m, 1H), 6.92 (ddd, 1H, J = 8.3, J = 2.6, J = 1.0), 5.40 (s, 2H), 3.81 (s, 3H), 2.13 (s, 3H); ¹³C-NMR (75 MHz, CDCl<sub>3</sub>): 170.8, 159.5, 137.6, 132.3, 129.6, 128.6, 128.5, 128.2, 124.2, 124.1, 122.7, 116.4, 115.2, 94.4, 86.5, 64.8, 55.3, 21.0; IR (Pt/diamond): 3002, 2938, 1737, 1573, 1492; HRMS: m/e for C<sub>18</sub>H<sub>16</sub>O<sub>3</sub> calculated 280.1099 (M<sup>+</sup>), found 280.1100.

2-[(Methoxyphenyl)ethynyl]benzyl acetate dicobalt hexacarbonyl (139a) (GENERAL PROCEDURE E)

In a round bottom flask, compound 138a (0.8677 g, 3.098 mmol) and dicobalt octacarbonyl (excess) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (35.8 mL). The mixture was allowed to stir at room temperature, under a nitrogen atmosphere, for 2 h. The solvent was then removed under reduced pressure, and the solid loaded onto a column of silica. The column was washed with 100% hexanes to remove excess, uncomplexed dicobalt octacarbonyl. Following that, the column was loaded with a 15:1 hexanes:Et<sub>2</sub>O mixture, which eluted compound 139a as a dark brown solid (1.6404 g, 2.8985 mmol, 94%). ¹H-NMR (500 MHz, CDCl<sub>3</sub>): 7.67 (dd, 1H, J = 7.8, J = 1.4), 7.43 (dd, 1H, J = 7.4, J = 1.4),
7.34-7.40 (m, 2H), 7.30 (apparent t, 1H, J = 8.0), 7.07 (ddd, 1H, J = 7.6, J = 1.6, J = 0.9),
7.01-7.02 (m, 1H), 6.91 (ddd, 1H, J = 8.2, J = 2.5, J = 0.9), 5.13 (s, 2H), 3.83 (s, 3H), 2.04
(s, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): 199.1, 170.5, 159.8, 140.0, 136.1, 134.5, 132.4, 129.9,
129.6, 128.8, 128.4, 121.8, 115.0, 113.4, 95.0, 88.9, 63.6, 55.2, 20.8; IR (Pt/diamond): 3019,
2905, 2087, 2048, 2010, 1993, 1748, 1584, 1231; HRMS: m/e for C$_{24}$H$_{16}$Co$_2$O$_9$ calculated
509.9560 (M-2CO$^+$), found 509.9543.

**Compound 140a and 140a' (GENERAL PROCEDURE F)**

Compound 140a and 140a' (GENERAL PROCEDURE F) were prepared as follows:

Compound 139a (0.2279 g, 0.4027 mmol) was dissolved in dry CH$_2$Cl$_2$ to a concentration of 7x10$^{-3}$ M (57.5 mL) under a nitrogen atmosphere, and cooled down to 0 °C. SnCl$_4$ (141 µL, 1.21 mmol) was added dropwise. The reaction was allowed to warm to room temperature over the course of 15 h, at which point the reaction was done (as determined by TLC). The reaction was then quenched with saturated NH$_4$Cl (50 mL), and subsequently extracted with dH$_2$O (2 x 75mL). The organic fraction was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Flash chromatography (15:1 hexanes:Et$_2$O) on neutralized silica afforded compound 140a as the major product (and the second band on the column) as a dark maroon solid (0.1060 g, 0.2095 mmol, 52%). $^1$H-NMR (500 MHz, CDCl$_3$): 7.69-7.71 (m, 1H), 7.32-7.36 (m, 2H), 7.27-7.31 (m, 1H), 7.26 (d,
1H, J = 2.8), 7.22 (d, 1H, J = 8.6), 6.89 (dd, 1H, J = 8.5, J = 2.8), 3.87 (s, 2H), 3.86 (s, 3H);
$^{13}$C-NMR (75 MHz, CDCl$_3$): 199.4, 159.3, 138.4, 137.8, 137.1, 132.2, 130.4, 129.7, 129.4,
128.7, 127.7, 117.5, 113.9, 90.9, 55.4, 42.2; IR (Pt/diamond): 2942, 2843, 2087, 2048, 2034,
2019, 1995, 1270; HRMS: m/e for C$_{22}$H$_{12}$Co$_2$O$_7$ calculated 449.9349 (M-2CO$^+$), found
Compound 140a' was isolated as the minor product (and the first band off the column) as a dark maroon solid (0.0286 g, 0.0565 mmol, 14%). The combined yield was 66%, with a 3.7:1 para:ortho attack (i.e., major:minor products). ¹H-NMR (500 MHz, CDCl₃): 7.68-7.70 (m, 1H), 7.36-7.38 (m, 1H), 7.32-7.34 (m, 3H), 7.29 (apparent t, 1H, J = 8.0), 6.94 (d, 1H, J = 8.3), 4.01 (s, 2H), 3.92 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 199.6, 156.3, 138.8, 137.7, 137.6, 131.9, 129.9, 128.6, 127.9, 127.6, 125.7, 124.6, 111.1, 91.2, 90.8, 56.1, 32.2; IR (Pt/diamond): 2920, 2839, 2091, 2047, 2018, 2002, 1568, 1254; HRMS: m/e for C₂₂H₁₂Co₂O₇ calculated 477.9298 (M-CO⁺), found 477.9301.

2-[(3,5-Dimethoxyphenyl)ethynyl]benzaldehyde (137b)

Compound 136 (0.6020 g, 4.629 mmol) was subjected to General Procedure C along with 1-bromo-3,5-dimethoxybenzene (1.4997 g, 6.9439 mmol), with the modification that Pd(PPh₃)₂Cl₂ (0.0975 g, 0.139 mmol, 3 mol%) was used as catalyst instead of Pd(PPh₃)₄, and the reaction flask was placed in an oil bath set to a temperature of 60 °C instead of room temperature for overnight (20 h). The product 137b was isolated using flash chromatography (10:1 hexanes:Et₂O) as a yellow solid (0.9732 g, 3.657 mmol, 79%), with a m.p. 75-77 °C (lit., m.p. 76-77 °C¹¹⁶), and which was characterized as spectroscopically identical to reported values¹¹⁶.
2-[(3.5-Dimethoxyphenyl)ethynyl]benzyl acetate (138b)

Compound 138b was synthesized according to General Procedure D from 137b (0.9732 g, 3.657 mmol). The product was isolated as a pale yellow oil (0.9656 g, 3.114 mmol, 85%) via flash chromatography (7:1 hexanes:Et₂O). ¹H-NMR (300 MHz, CDCl₃): 7.55-7.58 (m, 1H), 7.40-7.43 (m, 1H), 7.28-7.37 (m, 2H), 6.71 (dd, 2H, J = 2.4, J = 0.5), 6.48 (t, 1H, J = 2.3), 5.36 (s, 2H), 3.79 (s, 6H), 2.12 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 170.8, 160.7, 137.6, 132.3, 128.6, 128.5, 128.2, 124.3, 122.6, 109.4, 102.1, 94.5, 86.2, 64.8, 55.4, 21.0; IR (Pt/Diamond): 2953, 2836, 1742, 1585, 1355, 1233; HRMS: m/e for C₁₉H₁₈O₄ calculated 310.1205 (M⁺), found 310.1205.

2-[(3.5-Dimethoxyphenyl)ethynyl]benzyl acetate dicobalt hexacarbonyl (139b)

Compound 138b (0.9656 g, 3.114 mmol) was complexed using General Procedure E to afford product 139b (1.7463 g, 2.9302 mmol, 94%) as a dark brown solid. The product was eluted from a column of silica using 7:1 hexanes:Et₂O. ¹H-NMR (500 MHz, CDCl₃): 7.67 (dd, 1H, J = 7.3, J = 1.85), 7.42 (dd, 1H, J = 7.6, J = 1.7), 7.33-7.40 (m, 2H), 6.63 (d, 2H, J = 2.2), 6.47 (t, 1H, J = 2.3), 5.16 (s, 2H), 3.80 (s, 6H), 2.05 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 1992.1, 170.5, 160.9, 140.7, 136.0, 134.6, 132.4, 129.6, 128.8, 128.4, 107.6, 100.0, 95.3, 89.0, 63.6, 55.4, 20.8; IR (Pt/diamond): 2940, 2839, 2085, 2032, 2000, 1737, 1586, 1421, 1241; HRMS: m/e for C₂₅H₁₈Co₂O₁₀ calculated 483.9767 (M-4CO⁻), found 483.9752.
Compound 140b

Compound 140b was synthesized according to General Procedure F from starting material 139b (0.2052 g, 0.3443 mmol). The reaction was complete in 15 h, as monitored by TLC. The product was recovered as a dark maroon solid (0.0938 g, 0.175 mmol, 51%) using flash chromatography (10:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.68-7.71 (m, 1H), 7.31-7.38 (m, 3H), 6.87 (d, 1H, J = 2.5), 6.54 (d, 1H, J = 2.5), 3.94 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 199.6, 159.6, 157.2, 139.4, 138.1, 137.6, 132.0, 129.8, 128.6, 127.5, 118.4, 108.3, 99.1, 91.6, 90.9, 56.1, 55.4, 31.8; IR (Pt/diamond): 2938, 2840, 2090, 2052, 1996, 1572, 139.4, 138.1, 137.6, 132.0, 129.8, 128.6, 127.5, 118.4, 108.3, 99.1, 91.6, 90.9, 56.1, 55.4, 31.8; HRMS: m/e for C₂₃H₁₄Co₂O₈ calculated 479.9454 (M-2CO⁺), found 479.9455.

3-[(Trimethylsilyl)ethynyl]furan-2-carbaldehyde (142)

Compound 142 was synthesized according to General Procedure A from 3-bromo-2-formylfuran (3.0857 g, 17.741 mmol). The product was isolated as a colourless solid (3.1350 g, 16.323 mmol, 92%) using flash chromatography (15:1 hexanes:Et₂O), with a m.p. of 49-50 °C (lit., m.p. 50 °C⁴²), and characterized as spectroscopically identical to reported values⁴².

3-[(3-Methoxyphenyl)ethynyl]furan-2-carbaldehyde (143) (GENERAL PROCEDURE G)

Compound 143 was synthesized using a tandem desilylation/Sonogashira reaction. Pd(PPh₃)₄ (0.2208 g, 0.1911 mmol, 3 mol%) and CuI (0.0607 g, 0.318 mmol, 5 mol%) were placed in a round bottom flask, and put under vacuum for 10 minutes. The flask was then
purged with nitrogen. This was repeated two times more\textsuperscript{44}. 3-
Iodoanisole (2.6084 g, 11.149 mmol), dissolved in THF (10.6 mL) was added to the reaction flask, followed by 142 (1.2236 g, 6.3709 mmol), also dissolved in THF (10.6 mL). NE\textsubscript{3} (42.5 mL) (which had been bubbled through with N\textsubscript{2} for 1.5 h prior) was added, and the mixture was cooled to 0 °C. TBAF (1.0 M in THF, 12.7 mL, 12.7 mmol) was added dropwise to the reaction flask. The reaction was allowed to proceed for 10 minutes at 0 °C under nitrogen before being brought to room temperature and allowed to go overnight (20 h) while still under a nitrogen atmosphere. The next day, the reaction was filtered through Celite\textsuperscript{®}, dissolved in Et\textsubscript{2}O (75 mL), and extracted with NH\textsubscript{4}\textsubscript{+}Cl\textsuperscript{−} (aq., sat., 2 x 75 mL), followed by brine (1 x 75 mL). The organic fraction was dried over MgSO\textsubscript{4}, filtered, and the solvent removed under reduced pressure. Flash chromatography (10:1 hexanes:Et\textsubscript{2}O) eluted the product (143) as a pale yellow oil (1.1380 g, 5.0340 mmol, 79%).

\textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): 9.84 (s, 1H), 7.62-7.63 (m, 1H), 7.26 (apparent t, 1H, J = 7.9), 7.12 (dd, 1H, J = 7.6, J = 1.0), 7.04-7.05 (m, 1H), 6.96 (dd, 1H, J = 8.4, J = 2.6), 6.65-6.66 (m, 1H), 3.80 (s, 3H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): 176.1, 159.4, 152.7, 147.6, 129.6, 124.3, 122.8, 119.5, 116.5, 116.0, 115.2, 97.3, 78.1, 55.3; IR (Pt/diamond): 2834, 2213, 1671, 1572, 1476, 1238; HRMS: m/e for C\textsubscript{14}H\textsubscript{10}O\textsubscript{3} calculated 226.0630 (M\textsuperscript{+}), found 226.0626.

**[3-((3-Methoxyphenyl)ethynyl)furan-2-yl]methyl acetate (145a)**

Compound 145a was synthesized according to General Procedure D from 143 (1.1380 g, 5.0340 mmol). The product (145a) was isolated as a yellow oil (1.3001 g, 4.8136 mmol,
96%) via flash chromatography (7:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.40 (d, 1H, J = 1.3), 7.25 (apparent t, 1H, J = 8.0), 7.11 (apparent d of t, 1H, J = 7.6, J = 1.2), 7.04-7.05 (m, 1H), 6.90 (ddd, 1H, J = 8.3, J = 2.6, J = 0.9), 6.51 (d, 1H, J = 1.9), 5.22 (s, 2H), 3.82 (s, 3H), 2.12 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): 170.6, 159.4, 152.1, 143.1, 129.5, 124.1, 123.9, 116.2, 115.1, 113.1, 108.1, 93.3, 79.5, 56.6, 55.3, 20.8; IR (Pt/diamond): 2951, 2830, 2217, 1733, 1591, 1227; HRMS: m/e for C₁₆H₁₄O₄ calculated 270.0892 (M⁺), found 270.0885.

[3-((3-Methoxyphenyl)ethynyl)furan-2-yl]methyl acetate dicobalt hexacarbonyl (146a)

Compound 146a (2.2480 g, 4.0437 mmol, 84%) was isolated as a dark brown solid from 145a (1.3001 g, 4.8136 mmol) being treated according to General Procedure E. Flash chromatography (7:1 Hexanes:Et₂O) eluted the complexed product. ¹H-NMR (500 MHz, CDCl₃): 7.46 (d, 1H, J = 1.8), 7.29 (apparent t, 1H, J = 8.0), 7.13 (apparent ddd, 1H, J = 7.6, J = 1.6, J = 0.9), 7.07-7.08 (m, 1H), 6.90 (ddd, 1H, J = 8.3, J = 2.6, J = 0.9), 6.56 (d, 1H, J = 2.0), 5.08 (s, 2H), 3.82 (s, 3H), 2.03 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): 198.9, 170.5, 159.8, 146.8, 143.4, 139.4, 129.9, 122.7, 121.6, 114.8, 113.4, 113.0, 92.7, 79.4, 56.6, 55.2, 20.5; IR (Pt/diamond): 2943, 2087, 2046, 2003, 1988, 1744, 1226; HRMS: m/e for C₂₂H₁₄Co₂O₁₀ calculated 471.9403 (M-3CO⁺), found 471.9389.

3-[(3,5-Dimethoxyphenyl)ethynyl]furan-2-carbaldehyde (144a)

[(3,5-Dimethoxyphenyl)ethynyl]trimethylsilane (156c) (0.9212 g, 3.935 mmol) was subjected to tandem desilylation/Sonogashira chemistry according to General Procedure G
with 3-bromo-2-formylfuran (1.1977 g, 6.8861 mmol) and 
Pd(PPh₃)₂Cl₂ (0.0828 g, 0.118 mmol, 3 mol%) as the catalyst.

The product (144a) was isolated with flash chromatography 
(7:1 hexanes:Et₂O) as a light yellow solid (0.8263 g, 3.227 
mmol, 82%) with a m.p. of 88-88.5 °C. ¹H-NMR (500 MHz, 
CDCl₃): 9.85 (d, 1H, J = 0.8), 7.64 (dd, 1H, J = 1.8, J = 0.8), 
6.68 (d, 2H, J = 2.3), 6.66 (d, 1H, J = 1.8), 6.50 (t, 1H, J = 2.3), 3.79 (s, 6H); ¹³C-NMR (125 
MHz, CDCl₃): 176.1, 160.6, 152.8, 147.6, 123.1, 119.4, 115.2, 109.5, 102.7, 97.4, 77.8, 55.5;
IR (Pt/diamond): 2940, 2832, 2219, 1669, 1586, 1424, 1208; HRMS: m/e for C₁₅H₁₂O₄ 
calculated 256.0736 (M⁺), found 256.0731.

[3-((3,5-Dimethoxyphenyl)ethynyl)furan-2-yl]methyl acetate (145b)

Compound 144a (0.8263 g, 3.227 mmol) was treated according 
to General Procedure D.  The product (145b) was isolated 
using flash chromatography (5:1 hexanes:Et₂O) as a colourless 
solid (0.8552 g, 2.850 mmol, 88%) with m.p. 58.5-60 °C. ¹H-
NMR (500 MHz, CDCl₃): 7.39 (d, 1H, J = 1.9), 6.66 (d, 2H, J 
= 2.3), 6.50 (d, 1H, J = 1.8), 6.46 (t, 1H, J = 2.2), 5.20 (s, 2H), 
3.78 (s, 6H), 2.10 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): 170.5, 160.6, 152.2, 143.1, 124.1, 
113.1, 109.2, 108.0, 101.9, 93.4, 79.3, 56.6, 55.4, 20.8; IR (KBr): 3125, 2941, 2840, 2218, 
1745, 1590, 1156; HRMS: m/e for C₁₇H₁₆O₅ calculated 300.0998 (M⁺), found 300.0998.
**[3-((3,5-Dimethoxyphenyl)ethynyl)furan-2-yl]methyl acetate dicobalt hexacarbonyl (146b)**

Compound **145b** (0.8552 g, 2.850 mmol) was complexed according to General Procedure E. The complexed product **146b** was isolated using flash chromatography (5:1 Hexanes:Et₂O) after washing the column with 100% hexanes to remove any excess, uncomplexed Co₂(CO)₈. The product (1.5958 g, 2.7235 mmol, 96%) was a dark brown solid in appearance. ¹H-NMR (500 MHz, CDCl₃): 7.46 (d, 1H, J = 2.0), 6.68 (d, 2H, J = 2.2), 6.56 (d, 1H, J = 1.9), 6.46 (t, 1H, J = 2.3), 5.08 (s, 2H), 3.81 (s, 6H), 2.04 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): 198.9, 170.5, 160.9, 146.8, 143.4, 140.0, 122.7, 112.9, 107.4, 99.9, 92.9, 79.3, 56.6, 55.4, 55.3, 20.5; IR (KBr): 2972, 2941, 2089, 2049, 2028, 2008, 1994, 1743, 1587, 1225; HRMS: m/e for C₂₃H₁₆Co₂O₁₁ calculated 529.9458 (M⁺), found 529.9470.

**Compound 147b**

Compound **146b** (0.1582 g, 0.2700 mmol) was treated according to General Procedure F. The product **147b** was isolated using flash chromatography (neutralized silica, 15:1 hexanes:Et₂O) as a maroon solid (0.0232 g, 0.0441 mmol, 17%). ¹H-NMR (500 MHz, CDCl₃): 7.38 (d, 1H, J = 1.4), 6.86 (d, 1H, J = 2.2), 6.60 (d, 1H, J = 1.4), 6.50 (d, 1H, J = 2.2), 4.14 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): 199.3, 159.5, 157.3, 150.1, 142.5, 139.3, 118.0, 114.5, 111.9, 109.9, 98.9, 91.6, 81.5, 55.9, 55.3, 25.4; IR (Pt/diamond): 2928, 2836,
2086, 2016, 1995, 1561, 1318, 1141; HRMS: m/e for C\textsubscript{27}H\textsubscript{22}Co\textsubscript{2}O\textsubscript{9} calculated 469.9247 (M-2CO\textsuperscript{+}), found 469.9245.

3-Bromothiophene-2-carbaldehyde (141b)

\text{CHO} \quad \text{CHO} \\
\text{Br} \quad \text{S} \\

Compound 141b was synthesized (with slight modifications) according to reported procedures by Fuller et al.\textsuperscript{52}. 3-Bromothiophene (2.5412 g, 15.695 mmol) was added dropwise to a stirred solution of LDA [prepared by addition of \textit{n}-butyllithium (2.5 M in hexanes, 6.3 mL, 16 mmol) to diisopropylamine (2.2 mL, 16 mmol) at 0 °C] in THF (28.6 mL) at 0 °C, and the resulting mixture was stirred for a further 30 minutes at this temperature. DMF (3.6 mL, 47 mmol) was then added, and the mixture was stirred further for overnight (20 h), allowing the reaction to come to room temperature. The next day, the reaction was quenched with NH\textsubscript{4}\textsuperscript{+}Cl\textsuperscript{-} (aq., sat., 30 mL), extracted with Et\textsubscript{2}O (2 x 50 mL), dried over MgSO\textsubscript{4}, and filtered. The organic solvent was removed under reduced pressure, and Kugelrohr distillation with b.p. 95 °C at 0.1 Torr (lit., b.p. 75 °C at 0.2 Torr\textsuperscript{52}) afforded the product as a yellow oil (2.2360 g, 11.774 mmol, 75%), which was spectroscopically identical to reported values\textsuperscript{52}.

3-[(3,5-Dimethoxyphenyl)ethynyl]thiophene-2-carbaldehyde (144b)

\text{CHO} \quad \text{CHO} \\
\text{Br} \quad \text{S} \\

[(3,5-Dimethoxyphenyl)ethynyl]trimethylsilane 156c (0.7501 g, 3.204 mmol) was subjected to tandem desilylation/Sonogashira chemistry according to General Procedure G with 3-bromothiophene-2-carbaldehyde 141b (1.0648 g, 5.6071 mmol). The product 144b was isolated via flash chromatography (7:1 hexanes:Et\textsubscript{2}O) as a colourless solid
(0.6715 g, 2.468 mmol, 77%) with m.p. 94.5-95 °C. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): 10.21 (d, 1H, J = 0.7), 7.67 (dd, 1H, J = 0.7, J = 5.0), 7.23 (d, 1H, J = 5.0), 6.68 (d, 2H, J = 2.3), 6.50 (t, 1H, J = 2.2), 3.79 (s, 6H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}): 183.0, 160.7, 143.7, 134.0, 131.6, 130.8, 123.2, 109.6, 102.7, 96.2, 81.1, 55.5; IR (Pt/diamond): 3008, 2964, 2835, 2209, 1659, 1585, 1203; HRMS: m/e for C\textsubscript{15}H\textsubscript{12}O\textsubscript{3}S calculated 272.0507 (M\textsuperscript{+}), found 272.0512.

\textbf{[3-((3,5-Dimethoxyphenyl)ethynyl)thiophen-2-yl]methyl acetate (145c)}

![Chemical structure of 145c]

Compound 144b (0.6715 g, 2.468 mmol) was reduced and acetylated according to General Procedure D. The product 145c was isolated as a yellow oil (0.7250 g, 2.294 mmol, 93%) using flash chromatography (5:1 hexanes:Et\textsubscript{2}O). \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): 7.29 (d, 1H, J = 5.0), 7.12 (d, 1H, J = 5.0), 6.69 (m, 2H), 6.48 (m, 1H), 5.42 (s, 2H), 3.81 (s, 6H), 2.12 (s, 3H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): 170.7, 160.6, 140.5, 129.7, 125.8, 124.2, 122.4, 109.3, 101.9, 92.9, 82.3, 59.4, 55.4, 20.9; IR (Pt/diamond): 3000, 2838, 1736, 1586, 1419, 1155; HRMS: m/e for C\textsubscript{17}H\textsubscript{16}O\textsubscript{4}S calculated 316.0769 (M\textsuperscript{+}), found 316.0756.

\textbf{[3-((3,5-Dimethoxyphenyl)ethynyl)thiophen-2-yl]methyl acetate dicobalt hexacarbonyl (146c)}

![Chemical structure of 146c]

Compound 145c (0.7250 g, 2.294 mmol) was subjected to complexation according to General Procedure E. The product 146c was isolated as a dark brown solid (1.1616 g, 1.9298 mmol, 84%) using flash chromatography (5:1
hexanes:Et₂O), after removing excess, uncomplexed Co₂(CO)₈ with 100% hexanes. ¹H-NMR (500 MHz, CDCl₃): 7.31 (d, 1H, J = 5.2), 7.15 (d, 1H, J = 5.2), 6.67 (d, 2H, J = 2.3), 6.46 (t, 1H, J = 2.2), 5.23 (s, 2H), 3.80 (s, 6H), 2.03 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): 199.0, 170.5, 160.9, 140.3, 136.5, 134.9, 130.5, 126.1, 107.5, 99.9, 93.3, 82.4, 58.6, 55.3, 20.6; IR (Pt/diamond): 2966, 2840, 2086, 2044, 1990, 1741, 1579, 1227; HRMS: m/e for C₂₃H₁₆Co₂O₁₀S calculated 517.9281 (M-3CO⁺), found 517.9290.

**Compound 147c**

Compound 146c (0.1291 g, 0.2145 mmol) was subjected to Nicholas reaction chemistry according to General Procedure F. The reaction was complete after 10 minutes, as determined by TLC, and the product (147c) was isolated as a dark maroon solid (0.0851 g, 0.157 mmol, 73%) using flash chromatography (15:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.24 (½ ABq, 1H, J = 13.7), 7.18 (½ ABq, 1H, J = 5.4), 6.86 (d, 1H, J = 2.6), 6.53 (d, 1H, J = 2.6), 4.11 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 199.5, 159.7, 157.1, 134.0, 137.4, 135.8, 129.4, 123.8, 116.0, 109.4, 99.1, 91.2, 84.6, 56.1, 55.4, 25.0; IR (Pt/diamond): 2963, 2832, 2086, 2035, 2004, 1567, 1210; HRMS: m/e for C₂₁H₁₂Co₂O₈S calculated 513.8968 (M-CO⁺), found 513.8949.

**2-(Phenylethynyl)cyclo-pent-1-enecarbaldehyde (150a)**

Compound 150a was synthesized from phenylacetylene (0.5000 g, 4.900 mmol) and 2-bromocyclopent-1-ene-1-carbaldehyde (149a) (1.2860 g, 7.3496 mmol) according to General Procedure C at a
temperature of 75 °C. It was isolated by preparative TLC (25:1 hexanes:Et₂O) as a yellow oil (0.6907 g, 3.522 mmol, 72%). ¹H-NMR (500 MHz, CDCl₃): 10.16 (s, 1H), 7.49 (apparent dd, 2H, J = 7.6, J = 1.8), 7.33-7.38 (m, 3H), 2.79 (t, 2H, J = 7.9), 2.64 (t, 2H, J = 7.9), 1.98 (apparent pentet, 2H, J = 7.9); ¹³C-NMR (75 MHz, CDCl₃): 188.9, 148.1, 143.2, 132.0, 129.5, 128.7, 122.2, 100.8, 83.4, 39.1, 29.8, 22.3; IR (KBr): 3312, 3081, 2969, 2850, 2811, 2722, 2199, 1676, 1353; HRMS: m/e for C₁₄H₁₂O calculated 196.0888 (M⁺), found 196.0883.

[2-(Phenylethynyl)cyclopent-1-enyl]methyl acetate (151a)

Compound 150a (0.5077 g, 2.589 mmol) was subjected to reduction and acetylation according to General Procedure D. Product 151a was isolated by preparative TLC (15:1 hexanes:Et₂O) as a yellow oil (0.5531 g, 2.303 mmol, 89%). ¹H-NMR (500 MHz, CDCl₃): 7.45 (apparent dd, 2H, J = 6.5, J = 3.1), 7.31-7.33 (m, 3H), 4.89 (s, 2H), 2.63 (t, 2H, J = 7.7), 2.52 (t, 2H, J = 7.9), 2.10 (s, 3H), 1.97 (apparent pentet, 2H, J = 7.7); ¹³C-NMR (75 MHz, CDCl₃): 171.2, 144.8, 131.6, 128.4, 128.3, 123.4, 123.1, 95.0, 84.7, 62.1, 37.1, 34.2, 22.5, 21.0; IR (KBr): 2960, 2852, 1743, 1225; HRMS: m/e for C₁₆H₁₆O₂ calculated 240.1150 (M⁺), found 240.1145.

[2-(Phenylethynyl)cyclopent-1-enyl]methyl acetate dicobalt hexacarbonyl (152a)

Compound 151a (0.5067 g, 2.110 mmol) was subjected to complexation procedures according to General Procedure E. Product 152a was isolated as a dark brown solid (1.002 g, 1.9051 mmol, 90%) following flash chromatography (15:1
hexanes:Et₂O).  ¹H-NMR (500 MHz, CDCl₃): 7.44-7.47 (m, 2H), 7.30-7.37 (m, 3H), 4.63 (s, 2H), 2.79 (t, 2H, J = 7.8), 2.56 (t, 2H, J = 7.9), 2.03 (apparent pentet, 2H, J = 7.9), 2.00 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 199.4, 170.8, 138.5, 137.6, 137.2, 129.3, 128.9, 127.9, 93.1, 84.7, 61.2, 39.9, 36.3, 21.9, 20.9; IR (KBr): 3077, 2957, 2848, 2089, 2050, 2021, 1745, 1231; HRMS: m/e for C₂₂H₁₆Co₂O₈ calculated 497.9560 (M-CO⁺), found 497.9552.

2-(Phenylethynyl)cyclohex-1-enecarbaldehyde (150b)

Compound 150b was synthesized from phenylacetylene (0.2773 g, 2.717 mmol) and 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (0.7134 g, 4.076 mmol) according to General Procedure C at a reaction temperature of 80 °C using an oil bath. The product was isolated using preparative TLC (25:1 hexanes:Et₂O) as a yellow oil (0.4687 g, 2.231 mmol, 82%). ¹H-NMR (500 MHz, CDCl₃): 10.32 (s, 1H), 7.47-7.49 (m, 2H), 7.35-7.37 (m, 3H), 2.52 (t, 2H, J = 6.1), 2.31 (t, 2H, J = 6.2), 1.66-1.75 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 193.0, 142.7, 140.1, 131.8, 129.2, 128.6, 122.4, 98.7, 86.4, 32.5, 22.2, 22.0, 21.2; IR (KBr): 2934, 2835, 2199, 1673, 1604, 1223; HRMS: m/e for C₁₅H₁₄O calculated 210.1045 (M⁺), found 210.1045.

[2-(Phenylethynyl)cyclohex-1-enyl]methyl acetate (151b)

Compound 150b (0.4687 g, 2.231 mmol) was subjected to reduction and acetylation according to General Procedure D. Product 151b was isolated via preparative TLC (15:1 hexanes:Et₂O) as a yellow oil (0.4889 g, 1.924 mmol, 86%). ¹H-NMR (500 MHz, CDCl₃): 7.43-7.45 (m, 2H), 7.29-7.33 (m, 3H),
4.90 (s, 2H), 2.31 (m, 2H), 2.18 (m, 2H), 2.10 (s, 3H), 1.66-1.71 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 171.3, 139.1, 131.6, 128.4, 128.2, 123.5, 120.1, 93.2, 88.2, 66.7, 30.3, 27.2, 22.3, 22.1, 21.1; IR (KBr): 3058, 2934, 2861, 1740, 1228; HRMS: m/e for C$_{17}$H$_{18}$O$_2$ calculated 254.1307 (M$^+$), found 254.1302.

**[2-(Phenylethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152b)**

Compound 151b (0.4889 g, 1.924 mmol) was subjected to complexation procedures according to General Procedure E. Product 152b was isolated as a dark brown solid (0.9272 g, 1.717 mmol, 89%) following flash chromatography (15:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 7.41 (apparent d, 2H, J = 7.1), 7.30-7.36 (m, 3H), 4.53 (s, 2H), 2.40 (t, 2H, J = 6.1), 2.14 (t, 2H, J = 6.2), 1.95 (s, 3H), 1.72-1.80 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.6, 170.8, 138.7, 133.4, 132.1, 129.3, 128.8, 127.8, 93.7, 91.7, 65.3, 33.3, 28.5, 23.4, 22.2, 20.9; IR (KBr): 2935, 2861, 2088, 2047, 2016, 1743, 1233; HRMS: m/e for C$_{23}$H$_{18}$Co$_2$O$_8$ calculated 483.9767 (M-2CO$^+$), found 483.9759.

**[(6-Methylenecyclohex-1-enyl)ethynyl]benzene dicobalt hexacarbonyl (154a)**

Compound 152b (0.1068 g, 0.1978 mmol) was subjected to General Procedure F using BF$_3$·OEt$_2$ (75 µL, 0.59 mmol). The reaction was done within 2 h, as determined by TLC analysis. The product was isolated as a dark brown-green solid (0.0494 g, 0.103 mmol, 52%) following flash chromatography with 100% hexanes. $^1$H-NMR (500 MHz, CDCl$_3$): 7.48 (apparent d, 2H, J = 7.1), 7.28-7.36 (m, 3H), 6.51 (t, 1H, J = 4.2), 4.85
(s, 1H), 4.73 (s, 1H), 2.48 (t, 2H, J = 6.4), 2.35 (apparent q, 2H, J = 5.7), 1.83 (apparent pentet, 2H, J = 6.3); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.9, 140.5, 138.5, 136.8, 135.2, 130.2, 128.7, 127.8, 112.9, 94.9, 93.6, 32.9, 29.8, 27.7, 22.9; IR (KBr): 2940, 2828, 2087, 2047, 2015, 1633; HRMS: m/e for C$_{21}$H$_{14}$Co$_2$O$_6$ calculated 479.9454 (M$^+$), found 479.9465.

[(3-Methoxyphenyl)ethynyl]trimethylsilane (156a)

Compound 156a was synthesized according to General Procedure A from 3-iodoanisole 155a (1.0028 g, 4.2863 mmol). The product was isolated as a yellow oil (0.8470 g, 4.150 mmol, 97%), and was characterized as spectroscopically identical to reported values$^{45}$.

Ethynyl-3-methoxybenzene (148b) (GENERAL PROCEDURE H)

Desilylation of 156a was achieved according to methods adapted from Anderson & Gothelf$^5$. Compound 156a (0.8470 g, 4.150 mmol) was dissolved in CH$_2$Cl$_2$ (48.0 mL), and the reaction flask was cooled to 0 °C. TBAF (1.0 M in THF, 8.3 mL, 8.3 mmol) was added dropwise to the reaction, which was then allowed to stir for 1 h at that temperature. Upon completion (as monitored by TLC), the solvent was removed under reduced pressure, and extraction was carried out using Et$_2$O (1 x 75 mL) and brine (3 x 75 mL). The organic fraction was dried over MgSO$_4$, filtered, and removed under reduced pressure. Kugelrohr distillation at 0.1 Torr afforded the product 148b as a yellow oil (0.4596 g, 3.480 mmol, 84%), which was characterized as spectroscopically identical to reported values$^{58}$.

2-[(3-Methoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150c)

Compound 150c was synthesized according to General Procedure C from 148b (0.4596 g
3.480 mmol) and 2-bromocyclohex-1-ene-1-carbaldehyde 149b (0.9918 g, 5.220 mmol). The product was isolated as a yellow oil (0.6204 g, 2.584 mmol, 74%) via preparative TLC (20:1 hexanes:Et<sub>2</sub>O). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 10.32 (s, 1H), 7.26 (apparent t, 1H, J = 8.0), 7.07 (d of t, 1H, J = 7.6, J = 1.2), 6.99 (dd, 1H, J = 2.5, J = 1.4), 6.93 (ddd, 1H, J = 8.3, J = 2.6, J = 0.9), 3.82 (s, 3H), 2.50-2.53 (m, 2H), 2.30-2.33 (m, 2H), 1.66-1.75 (m, 4H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 193.0, 159.5, 142.8, 140.0, 129.7, 124.3, 123.4, 116.4, 115.9, 98.6, 86.2, 55.4, 32.4, 22.2, 22.0, 21.2; IR (KBr): 2937, 2835, 2194, 1673, 1212; HRMS: m/e for C<sub>16</sub>H<sub>16</sub>O<sub>2</sub> calculated 240.1150 (M<sup>+</sup>), found 240.1158.

**[2-((3-Methoxyphenyl)ethynyl)cyclohex-1-enyl)methyl acetate (151c)**

Compound 150c (0.6204 g, 2.584 mmol) was subjected to General Procedure D. The product 151c was isolated as a pale yellow oil (0.6542 g, 2.302 mmol, 89%) via preparative TLC (10:1 hexanes:Et<sub>2</sub>O). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 7.22 (apparent t, 1H, J = 8.0), 7.03 (d of t, 1H, J = 7.6, J = 1.0), 6.96 (dd, 1H, J = 2.4, J = 1.4), 6.86 (ddd, 1H, J = 8.4, J = 2.6, J = 0.7), 4.90 (s, 2H), 3.81 (s, 3H), 2.31 (m, 2H), 2.17 (m, 2H), 2.10 (s, 3H), 1.65-1.71 (m, 4H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 171.3, 159.4, 139.3, 129.4, 124.5, 124.1, 120.0, 116.2, 114.9, 93.1, 88.0, 66.6, 55.4, 30.3, 27.2, 22.2, 22.1, 21.1; IR (KBr): 3022, 2935, 2861, 2198, 1738, 1596, 1230; HRMS: m/e for C<sub>18</sub>H<sub>20</sub>O<sub>3</sub> calculated 284.1412 (M<sup>+</sup>), found 284.1415.
[2-((3-Methoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl

(152c)

Compound 151c (0.6542 g, 2.302 mmol) was subjected to complexation as outlined in General Procedure E. The complexed product 152c was isolated as a dark brown solid (1.2123 g, 2.1269 mmol, 92%) by flash chromatography (10:1 hexanes:Et$_2$O), after washing through excess, uncomplexed Co$_2$(CO)$_6$ with 100% hexanes. $^1$H-NMR (500 MHz, CDCl$_3$): 7.26 (t, 1H, $J = 7.9$), 7.01 (apparent ddd, 1H, $J = 7.6, J = 1.6, J = 0.9$), 6.95 (dd, 1H, $J = 2.4, J = 1.7$), 6.85 (ddd, 1H, $J = 8.3, J = 2.6, J = 0.9$), 4.55 (s, 2H), 3.83 (s, 3H), 2.38 (t, 2H, $J = 6.0$), 2.13 (t, 2H, $J = 6.1$), 1.97 (s, 3H), 1.72-1.79 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.6, 170.9, 159.6, 140.2, 133.5, 132.0, 129.8, 122.0, 115.2, 113.0, 93.5, 91.7, 65.3, 55.3, 33.3, 28.5, 23.4, 22.2, 20.8; IR (KBr): 2088, 2049, 2019, 1742, 1230; HRMS: m/e for C$_{24}$H$_{20}$Co$_2$O$_9$ calculated 430.0026 (M-5CO$^+$), found 430.0021.

Dicobalt hexacarbonyl[µ-((10,11-η:10,11-η)-2,3,4,5-tetrahydro-8-methoxy-1H-dibenzo[a,d]cycloheptene)] (153c) and Dicobalt hexacarbonyl[µ-((10,11-η:10,11-η)-2,3,4,5-tetrahydro-6-methoxy-1H-dibenzo[a,d]cycloheptene)] (153c')

Complexed compound 152c (0.0322 g, 0.0565 mmol) was subjected to General Procedure F, with the use of BF$_3$•OEt$_2$ (21 µL, 0.17 mmol) as Lewis acid. The reaction was complete in 1.5 h, as monitored by TLC. The regioisomers were separable by flash chromatography using 100% hexanes. The major product 153c (0.0195 g, 0.0382 mmol, 68%) eluted as the second band, and as a dark maroon solid. $^1$H-NMR (500
MHz, CDCl₃): 7.20 (d, 1H, J = 2.7), 7.04 (d, 1H, J = 8.3), 6.84 (dd, 1H, J = 8.4, J = 2.7), 3.58 (s, 3H), 3.20 (s, 2H), 2.36 (t, 2H, J = 5.8), 2.28 (t, 2H, J = 6.0), 1.67-1.78 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 200.0, 159.0, 139.0, 137.2, 130.1, 129.9, 129.3, 117.4, 113.6, 94.9, 89.5, 55.3, 42.1, 33.7, 30.5, 23.0, 22.7; IR (KBr): 2930, 2086, 2046, 2017, 1270; HRMS: m/e for C₂₂H₁₆Co₂O₇ calculated 481.9625 (M-CO⁺), found 481.9634.

Compound 153c' eluted as the first band, as a dark maroon solid, and as the minor product (0.0040 g, 0.0078 mmol, 14%). The product ratio of major:minor 153c:153c' (i.e., para attack:ortho attack) was 4.9:1, with a combined yield of 82%. ¹H-NMR (500 MHz, CDCl₃): 7.28 (dd, 1H, J = 7.9, J = 1.2), 7.23 (apparent t, 1H, J = 7.8), 6.90 (dd, 1H, J = 8.0, J = 1.1), 3.87 (s, 3H), 3.33 (s, 2H), 2.31-2.35 (m, 4H), 1.67-1.77 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 200.2, 155.9, 139.6, 137.7, 130.9, 127.6, 125.4, 124.8, 110.7, 95.2, 90.0, 56.0, 33.8, 32.3, 30.5, 23.1, 22.8; IR (KBr): 2933, 2086, 2046, 2017, 1570, 1262; HRMS: m/e for C₂₂H₁₆Co₂O₇ calculated 481.9611 (M-CO⁺), found 481.9624.

4-Iodo-1,2-dimethoxybenzene (155b) (GENERAL PROCEDURE I)

Compound 155b was synthesized according methods reported by Karade et al. The reaction mixture was washed with Na₂S₂O₃ (aq., sat., 75 mL), and extracted with CH₂Cl₂ (2 x 75 mL). The organic fractions were combined and dried using MgSO₄.
Filtration, followed by removal of the solvent under reduced pressure, and finally Kugelrohr distillation at 0.1 Torr afforded compound 155b (4.4454 g, 16.841 mmol, 93%) as a yellow oil, which was characterized as spectroscopically identical to reported values\(^9^4\).

**(3,4-Dimethoxyphenyl)ethynyl]trimethylsilane (156b)**

Compound 156b was synthesized from 4-iodo-1,2-dimethoxybenzene (155b) (1.7822 g, 6.7516 mmol) according to General Procedure A. Compound 156b was isolated as a yellow oil (1.5212 g, 6.4979 mmol, 96%) using flash chromatography (10:1 hexanes:Et\(_2\)O) for the final purification step, and was characterized as spectroscopically identical to reported values\(^1^3^5\).

**4-Ethynyl-1,2-dimethoxybenzene (148c)**

Compound 156b (1.5212 g, 6.4979 mmol) was subjected to desilylation according to General Procedure H. The product was isolated as a colourless solid (0.8136 g, 5.020 mmol, 87%) using flash chromatography (10:1 hexanes:Et\(_2\)O), with a m.p. of 72-73 °C (lit., 70-71 °C\(^1^3^5\)), and was characterized as spectroscopically identical to reported values\(^1^3^5\).

**2-[(3,4-Dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150d)**

Compound 148c (0.8136 g, 5.020 mmol) was subjected to Sonogashira conditions according to General Procedure C with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (1.4306 g, 7.5302 mmol). Compound 150d was isolated as a yellow oil (1.0838 g, 4.0122 mmol, 80%) via flash chromatography (10:1 hexanes:Et\(_2\)O), and was characterized as
spectroscopically identical to reported values\textsuperscript{84}.

**[2-((3,4-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151d)**

Compound 150d (1.0838 g, 4.0122 mmol) was subjected to General Procedure D. The product was isolated via flash chromatography (5:1 hexanes:Et\textsubscript{2}O), as a pale yellow oil (1.1207 g, 3.5674 mmol, 89%). \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): 7.03 (dd, 1H, J = 8.2, J = 1.9), 6.93 (d, 1H, J = 1.9), 6.79 (d, 1H, J = 8.3), 4.89 (s, 2H), 3.88 (s, 6H), 2.29 (m, 2H), 2.16 (m, 2H), 2.08 (s, 3H), 1.63-1.70 (m, 4H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): 171.2, 149.3, 148.6, 138.4, 124.7, 120.1, 115.7, 114.1, 111.0, 93.2, 86.7, 66.6, 56.0, 55.9, 30.3, 27.0, 22.2, 22.0, 21.0; IR (KBr): 2934, 2837, 1737, 1514, 1247; HRMS: m/e for C\textsubscript{19}H\textsubscript{22}O\textsubscript{4} calculated 314.1518 (M\textsuperscript{+}), found 314.1513.

**[2-((3,4-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152d)**

Compound 151d (1.1207 g, 3.5674 mmol) was complexed according to General Procedure E. After washing the column of silica with 100% hexanes to remove excess, uncomplexed Co\textsubscript{2}(CO)\textsubscript{8}, the product 152d was eluted using 5:1 hexanes:Et\textsubscript{2}O, and isolated as a dark brown solid (2.0001 g, 3.3336 mmol, 93%). \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): 7.04 (dd, 1H, J = 8.3, J = 2.0), 6.92 (d, 1H, J = 2.0), 6.84 (d, 1H, J = 8.4), 4.61 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 2.40 (t, 2H, J = 6.2), 2.14 (t, 2H, J = 6.0), 1.98 (s, 3H), 1.72-1.81 (m, 4H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}): 199.6, 170.8, 149.0, 148.9, 133.4, 132.0, 130.7, 122.1, 112.5, 111.4, 94.0,
Compound 152d (1.0023 g, 1.6705 mmol) was reacted according to General Procedure F, using BF$_3$•OEt$_2$ (635 μL, 5.01 mmol) as Lewis acid. The product was obtained as a pair of regioisomers, 153d (0.7280 g, 1.348 mmol, 81%) as the major product, and 153d' (0.0823 g, 0.152 mmol, 9%) as the minor product. Both were isolated as maroon solids. The major product, 153d, eluted as the first band upon purification via flash chromatography (10:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 7.14 (s, 1H), 6.64 (s, 1H), 3.92 (s, 6H), 3.20 (s, 2H), 2.37 (t, 2H, J = 6.2), 2.29 (t, 2H, J = 6.0), 1.68-1.79 (m, 4H); $^{13}$C-NMR (125 MHz, CDCl$_3$): 200.1, 149.2, 148.4, 136.3, 130.5, 129.7, 114.6, 112.3, 95.1, 90.5, 56.0, 42.6, 33.8, 30.5, 23.1, 22.7; IR (KBr): 2935, 2084, 2043, 2012, 1505, 1265; HRMS: m/e for C$_{25}$H$_{22}$Co$_2$O$_{10}$ calculated 571.9928 (M-CO$^+$), found 571.9925.

Dicobalt hexacarbonyl[μ-(10,11-η:10,11-η)-2,3,4,5-tetrahydro-7,8-dimethoxy-1H-dibenzo[a,d]cycloheptene] (153d) and Dicobalt hexacarbonyl[μ-(10,11-η:10,11-η)-2,3,4,5-tetrahydro-6,7-dimethoxy-1H-dibenzo[a,d]cycloheptene] (153d')

Compound 153d' eluted as the second band in the chromatography purification sequence. The two products had a combined yield of 90%, and a ratio of 8.8:1 para attack:ortho attack (i.e., major:minor (153d:153d')). $^1$H-
NMR (500 MHz, CDCl₃): 7.39 (d, 1H, J = 8.6), 6.87 (d, 1H, J = 8.7), 3.90 (s, 3H), 3.84 (s, 3H), 3.34 (s, 2H), 2.31-2.36 (m, 4H), 1.67-1.79 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 200.2, 153.4, 145.7, 136.3, 131.2, 131.1, 130.9, 128.2, 110.9, 95.2, 90.4, 61.4, 55.9, 33.8, 33.2, 30.6, 23.1, 22.8; IR (KBr): 2962, 2917, 2849, 2085, 2048, 2017, 1463, 1283; HRMS: m/e for C₂₃H₁₈Co₂O₈ calculated 539.9666 (M⁺), found 539.9672.

[(3,5-Dimethoxyphenyl)ethynyl]trimethylsilane (156c)

Compound 156c was synthesized from 1-bromo-3,5-dimethoxybenzene (3.8393 g, 17.684 mmol) according to General Procedure A. It was isolated as a colourless solid (3.6129 g, 15.433 mmol, 87%), with a m.p. of 62-63 °C (lit., 61-65 °C²¹), and which was characterized as spectroscopically identical to reported values²¹.

2-[(3,5-Dimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150e)

Compound 156c (1.0490 g, 4.4808 mmol) was subjected to a tandem desilylation/Sonogashira reaction according to General Procedure G with 2-bromocyclopent-1-ene-1-carbaldehyde (149a) (1.1764 g, 6.7213 mmol). The reaction was heated to 75 °C overnight (20 h) using an oil bath instead of leaving it at room temperature. The product 150e was isolated as a pale yellow solid (1.0474 g, 4.0896 mmol, 91%) following flash chromatography (10:1 hexanes:Et₂O), with a m.p. of 120-122 °C. ¹H-NMR (300 MHz, CDCl₃): 10.16 (s, 1H), 6.64 (d, 2H, J = 2.3), 6.50 (apparent t, 1H, J = 2.3), 3.79 (s, 6H), 2.80 (t, 2H, J = 7.6), 2.65 (t, 2H, J = 7.6), 2.00
(apparent pentet, 2H, J = 7.6); $^{13}$C-NMR (75 MHz, CDCl$_3$): 188.9, 160.7, 148.2, 143.0, 123.3, 109.6, 102.9, 100.9, 82.8, 55.5, 38.9, 29.7, 22.2; IR (KBr): 3080, 2995, 2936, 2838, 2190, 1669, 1587, 1156; HRMS: m/e for C$_{16}$H$_{16}$O$_3$ calculated 256.1099 (M$^+$), found 256.1096.

[2-((3,5-Dimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate (151e)

Compound 150e (1.0474 g, 4.0896 mmol) was subjected to reduction and acetylation according to General Procedure D. Product 151e was isolated as a yellow oil (1.0852 g, 3.6157 mmol, 88%) following flash chromatography (5:1 hexanes:Et$_2$O). $^1$H-NMR (300 MHz, CDCl$_3$): 6.58 (d, 2H, J = 2.3), 6.41 (t, 1H, J = 2.3), 4.86 (s, 2H), 3.76 (s, 6H), 2.60 (t, 2H, J = 7.5), 2.49 (t, 2H, J = 7.5), 2.07 (s, 3H), 1.93 (apparent pentet, 2H, J = 7.57); $^{13}$C-NMR (75 MHz, CDCl$_3$): 170.9, 160.6, 145.0, 124.6, 122.7, 109.2, 101.8, 94.9, 84.2, 61.9, 55.4, 37.0, 34.2, 22.4, 20.8; IR (KBr): 3002, 2842, 2202, 1741, 1595, 1420, 1231; HRMS: m/e for C$_{18}$H$_{20}$O$_4$ calculated 300.1362 (M$^+$), found 300.1357.

[2-((3,5-Dimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate dicobalt hexacarbonyl (152e)

Compound 151e (1.0852 g, 3.6157 mmol) was subjected to complexation according to General Procedure E. The complexed compound 152e was isolated via flash chromatography (5:1 hexanes:Et$_2$O) following removal of excess, uncomplexed Co$_2$(CO)$_8$ with 100% hexanes. The product was isolated as a dark
brown solid (1.8212 g, 3.1080 mmol, 86%). $^1$H-NMR (500 MHz, CDCl$_3$): 6.62 (d, 2H, J = 2.2), 6.42 (t, 1H, J = 2.1), 4.67 (s, 2H), 3.81 (s, 6H), 2.79 (t, 2H, J = 7.8), 2.55 (t, 2H, J = 7.9), 2.02 (apparent pentet, 2H, J = 7.9), 2.02 (s, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.9, 170.8, 160.8, 140.5, 137.7, 137.1, 107.6, 99.9, 93.1, 84.6, 61.1, 55.4, 39.8, 36.3, 21.9, 20.7; IR (Pt/diamond): 3020, 2977, 2838, 2087, 2046, 2005, 1989, 1734, 1586, 1205; HRMS: m/e for C$_{24}$H$_{20}$Co$_2$O$_{10}$ calculated 473.9925 (M-4CO$^+$), found 473.9930.

**Compound 153e**

Compound 152e (0.1874 g, 0.3198 mmol) was reacted according to General Procedure F using BF$_3$•OEt$_2$ (121 μL, 0.959 mmol). The reaction was complete within 45 minutes, as assessed by TLC analysis. The cyclized product (153e) was isolated by flash chromatography (15:1 hexanes:Et$_2$O) as a maroon solid (0.1433 g, 0.2724 mmol, 85%). $^1$H-NMR (500 MHz, CDCl$_3$): 6.82 (d, 1H, J = 2.2), 6.48 (d, 1H, J = 2.4), 3.85 (s, 3H), 3.83 (s, 3H), 3.50 (s, 2H), 2.71 (t, 2H, J = 7.6), 2.54 (t, 2H, J = 7.7), 2.05 (apparent pentet, 2H, J = 7.6); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.8, 159.3, 157.3, 142.4, 139.6, 134.6, 116.3, 109.3, 99.0, 91.0, 87.8, 55.9, 55.4, 39.4, 35.4, 27.1, 22.6; IR (KBr): 3004, 2956, 2838, 2087, 2047, 2016, 1600, 1458, 1141; HRMS: m/e for C$_{25}$H$_{16}$Co$_2$O$_8$ calculated 525.9509 (M$^+$), found 525.9510.

2-[(3,5-Dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150f)

Compound 156c (0.8926 g, 3.813 mmol) was subjected to a tandem desilylation/Sonogashira reaction according to General Procedure G with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (1.0866 g, 5.7192 mmol). The reaction was heated to 75 °C overnight (20 h) using
an oil bath instead of leaving it at room temperature. The coupled product (150f) was isolated as a yellow oil (0.9252 g, 3.425 mmol, 90%) following flash chromatography (10:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 10.30 (s, 1H), 6.60 (d, 2H, $J = 2.2$), 6.47 (t, 1H, $J = 2.1$), 3.78 (s, 6H), 2.50 (t, 2H, $J = 6.1$), 2.29 (t, 2H, $J = 6.1$), 1.64-1.73 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 192.9, 160.7, 142.9, 139.9, 123.6, 109.5, 102.6, 98.6, 85.8, 55.6, 32.4, 22.2, 22.0, 21.1; IR (KBr): 3001, 2936, 2830, 2201, 1739, 1590, 1420, 1233; HRMS: m/e for C$_{17}$H$_{18}$O$_3$ calculated 270.1256 (M$^+$), found 270.1251.

**[2-((3,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151f)**

Compound 150f (0.9252 g, 3.425 mmol) was subjected to reduction and acetylation according to General Procedure D. Product 151f was isolated as a yellow oil (0.9761 g, 3.107 mmol, 91%) following flash chromatography (5:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 6.58 (d, 2H, $J = 2.3$), 6.42 (t, 1H, $J = 2.3$), 4.88 (s, 2H), 3.78 (s, 6H), 2.30 (m, 2H), 2.16 (m, 2H), 2.09 (s, 3H), 1.64-1.70 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 171.2, 160.6, 139.4, 124.8, 119.9, 109.2, 101.7, 93.2, 87.8, 66.6, 55.5, 30.2, 27.1, 22.2, 22.0, 21.0; IR (KBr): 3001, 2936, 2840, 2201, 1739, 1590, 1420, 1233; HRMS: m/e for C$_{19}$H$_{22}$O$_4$ calculated 314.1518 (M$^+$), found 314.1519.
[2-((3,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152f)

Compound 151f (0.9761 g, 3.107 mmol) was subjected to complexation according to General Procedure E. The complexed compound (152f) was isolated via flash chromatography (5:1 hexanes:Et₂O) following removal of excess, uncomplexed Co₂(CO)₈ with 100% hexanes. The product was isolated as a dark brown solid (1.7135 g, 2.8559 mmol, 92%). ¹H-NMR (500 MHz, CDCl₃): 6.57 (d, 2H, J = 2.2), 6.41 (t, 1H, J = 2.2), 4.58 (s, 2H), 3.81 (s, 6H), 2.39 (t, 2H, J = 5.9), 2.13 (t, 2H, J = 5.9), 1.98 (s, 3H), 1.70-1.80 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 199.7, 170.8, 160.8, 140.8, 133.6, 131.9, 107.8, 99.6, 93.8, 91.6, 65.2, 55.4, 33.3, 28.5, 23.4, 22.2, 20.7; IR (KBr): 2937, 2836, 2089, 2012, 1740, 1590, 1421, 1234; HRMS: m/e for C₂₅H₂₂Co₂O₁₀ calculated 543.9979 (M-2CO⁺), found 543.9975.

Compound 153f

Compound 152f (0.0783 g, 0.130 mmol) was reacted according to General Procedure F using BF₃•OEt₂ (50 µL, 0.39 mmol). The reaction was complete within 45 minutes, as assessed by TLC analysis. The cyclized product (153f) was isolated by flash chromatography (15:1 hexanes:Et₂O) as a maroon solid (0.0601 g, 0.111 mmol, 85%). ¹H-NMR (500 MHz, CDCl₃): 6.80 (d, 1H, J = 2.2), 6.49 (d, 1H, J = 2.1), 3.84 (s, 3H), 3.83 (s, 3H), 3.25 (s, 2H), 2.30-2.34 (m, 4H), 1.66-1.78 (m, 4H); ¹³C-NMR (125 MHz, CDCl₃): 200.0, 159.2, 156.7, 140.1, 138.2, 130.5, 140.1
118.2, 108.0, 98.8, 95.2, 90.4, 55.9, 55.4, 33.7, 31.8, 30.4, 23.0, 22.8; IR (KBr): 3020, 2086, 2046, 2015, 1600, 1279; HRMS: m/e for C_{23}H_{18}Co_{2}O_{8} calculated 539.9666 (M⁺), found 539.9669.

2-Iodo-1,4-dimethoxybenzene (155d)

1,4-Dimethoxybenzene (2.0000 g, 14.486 mmol) was subjected to General Procedure I. Compound 155d was isolated as a yellow oil (3.4415 g, 13.038 mmol, 90%), and was characterized as spectroscopically identical to reported values.94

[(2,5-Dimethoxyphenyl)ethynyl]trimethylsilane (156d)

Compound 156d was synthesized from 2-iodo-1,4-dimethoxybenzene (155d) (3.4084 g, 12.912 mmol) according to General Procedure A. It was isolated as a cream-coloured solid (2.9066 g, 12.416 mmol, 96%), with a m.p. of 55-57 °C, and spectroscopically identical to reported values.198

2-Ethynyl-1,4-dimethoxybenzene (148d)

Compound 156d (2.9066 g, 12.416 mmol) was desilylated according to General Procedure H. The terminal acetylene product (148d) was isolated as a colourless solid (1.7486 g, 10.789 mmol, 87%), with m.p. 42-44 °C, and spectroscopically identical to reported values.198

2-[(2,5-Dimethoxyphenyl)ethynyl]cyclopent-1-ene-carbaldehyde (150g)

Compound 148d (0.6523 g, 4.025 mmol) was subjected to Sonogashira chemistry according to General Procedure C with 2-bromocyclopent-1-ene-1-carbaldehyde (149a) (1.0567 g,
6.0373 mmol). Product **150g** was isolated as a cream-coloured solid (0.8184 g, 3.196 mmol, 79%) following flash chromatography (10:1 hexanes:Et₂O), with a m.p. of 109-110 °C. ¹H-NMR (500 MHz, CDCl₃): 10.21 (s, 1H), 6.97 (d, 1H, J = 3.0), 6.92 (dd, 1H, J = 9.0, J = 3.1), 6.83 (d, 1H, J = 9.1), 3.85 (s, 3H), 3.78 (s, 3H), 2.82 (t, 2H, J = 7.8), 2.66 (t, 2H, J = 7.8), 2.01 (apparent pentet, 2H, J = 7.8); ¹³C-NMR (75 MHz, CDCl₃): 189.6, 155.1, 153.3, 148.1, 143.5, 117.9, 117.3, 112.1, 111.8, 97.4, 87.5, 56.5, 56.0, 38.9, 29.7, 22.4; IR (KBr): 2960, 2834, 2193, 1667, 1500, 1238; HRMS: m/e for C₁₆H₁₆O₃ calculated 256.256.1099 (M⁺), found 256.1087.

**[2-((2,5-Dimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate (151g)**

Compound **150g** (0.8184 g, 3.196 mmol) was subjected to reduction and acetylation according to General Procedure D. Product **151g** was isolated as a colourless solid (0.8595 g, 2.864 mmol, 90%) following flash chromatography (7:1 hexanes:Et₂O), with m.p. 63-65 °C. ¹H-NMR (500 MHz, CDCl₃): 6.95 (d, 1H, J = 2.7), 6.84 (dd, 1H, J = 8.9, J = 2.8), 6.80 (d, 1H, J = 9.0), 4.92 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 2.64 (t, 2H, J = 7.8), 2.51 (t, 2H, J = 7.8), 2.09 (s, 3H), 1.96 (apparent pentet, 2H, J = 7.8); ¹³C-NMR (75 MHz, CDCl₃): 171.3, 154.5, 153.3, 145.0, 123.2, 117.8, 115.8, 113.1, 112.1, 91.2, 88.9, 62.2, 56.5, 55.9, 37.0, 34.2, 22.6, 21.0; IR (KBr): 3002, 2960, 2834, 1746, 1504, 1228; HRMS: m/e for C₁₈H₂₀O₄ calculated 300.1362 (M⁺), found 300.1340.
**[2-((2,5-Dimethoxyphenyl)ethynyl)cyclopent-1-enyl)methyl acetate dicobalt hexacarbonyl (152g)]**

Compound **151g** (0.8595 g, 2.864 mmol) was subjected to complexation according to General Procedure E. The complexed compound **152g** was isolated using flash chromatography (7:1 hexanes:Et₂O) following removal of excess, uncomplexed \( \text{Co}_2(\text{CO})_8 \) with 100% hexanes. The product was isolated as a dark brown solid (1.5256 g, 2.6035 mmol, 91%). \(^1\)H-NMR (500 MHz, CDCl₃): 7.05 (d, 1H, \( J = 3.0 \)), 6.87 (dd, 1H, \( J = 8.8, J = 3.1 \)), 6.77 (d, 1H, \( J = 9.0 \)), 4.59 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.76 (t, 2H, \( J = 7.8 \)), 2.54 (t, 2H, \( J = 7.8 \)), 2.0 (apparent pentet, 2H, \( J = 7.9 \)), 1.98 (s, 3H); \(^1^3\)C-NMR (75 MHz, CDCl₃): 199.8, 170.9, 153.6, 150.6, 137.0, 137.0, 127.3, 117.3, 113.7, 110.5, 89.0, 88.0, 61.2, 55.8, 54.6, 39.8, 36.2, 22.1, 20.8; IR (KBr): 2959, 2835, 2087, 2047, 2014, 1746, 1494, 1223; HRMS: m/e for \( \text{C}_{24}\text{H}_{20}\text{Co}_2\text{O}_{10} \) calculated 529.9822 (M-2CO\(^+\)), found 529.9818.

**Compound 153g**

Compound **152g** (0.0502 g, 0.0857 mmol) was reacted according to General Procedure F using BF₃•OEt₂ (32 μL, 0.26 mmol) and at -40 °C. The reaction was stopped after 2 h, as assessed by TLC analysis. The cyclized product **153g** was isolated by flash chromatography (15:1 hexanes:Et₂O) as a maroon solid (0.0028 g, 0.0053 mmol, 6%). \(^1\)H-NMR (500 MHz, CDCl₃): 6.90 (½ABq, 1H, \( J = 9.0 \)), 6.74 (½ABq, 1H, \( J = 9.0 \)), 3.86 (s, 3H), 3.80 (s, 3H), 3.58 (s, 2H), 2.71 (t, 2H, \( J = 7.5 \)), 2.52 (t, 2H, \( J = 7.7 \)), 2.04 (apparent pentet, 2H, \( J = 7.6 \)); \(^1^3\)C-NMR (125 MHz, CDCl₃, partial): 200.3, 135.5,
112.3, 108.5, 56.6, 54.6, 39.1, 35.3, 28.1, 22.7; IR (KBr): 2919, 2850, 2086, 2048, 2024, 1650, 1464, 1263; HRMS: m/e for C_{22}H_{16}Co_{2}O_{8} calculated 469.9611 (M-2CO\(^{+}\)), found 469.9628.

2-[(2,5-Dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150h)

Compound 148d (0.7563 g, 4.666 mmol) was subjected to Sonogashira chemistry according to General Procedure C with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (1.3299 g, 6.9998 mmol). Product 150h was isolated as a pale yellow solid (1.0691 g, 3.9578 mmol, 85%) following flash chromatography (10:1 hexanes:Et\(_2\)O), and with a m.p. of 75-76 °C. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): 10.38 (s, 1H), 6.96 (d, 1H, J = 3.0), 6.90 (dd, 1H, J = 9.0, J = 3.0), 6.83 (d, 1H, J = 9.0), 3.85 (s, 3H), 3.78 (s, 3H), 2.54 (t, 2H, J = 5.8), 2.31 (t, 2H, J = 5.9), 1.66-1.75 (m, 4H); \(^13\)C-NMR (75 MHz, CDCl\(_3\)): 193.7, 155.0, 153.3, 142.6, 140.2, 117.8, 116.8, 112.1, 95.1, 90.6, 56.5, 55.9, 32.3, 22.2, 22.0, 21.2; IR (KBr): 2999, 2937, 2834, 2195, 1670, 1499, 1226, 1214; HRMS: m/e for C\(_{17}\)H\(_{18}\)O\(_3\) calculated 270.1256 (M), found 270.1250.

[2-(2,5-Dimethoxyphenyl)ethynyl]cyclohex-1-enyl]methyl acetate (151h)

Compound 150h (0.6059 g, 2.243 mmol) was subjected to reduction and acetylation according to General Procedure D. Product 151h was isolated as a yellow solid (0.6362 g, 2.025 mmol, 90%) following preparative TLC (7:1 hexanes:Et\(_2\)O), and with m.p. 54-56 °C. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): 6.94 (d, 1H, J
= 2.9), 6.82 (dd, 1H, J = 9.0, J = 2.9), 6.79 (d, 1H, J = 9.0), 4.95 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 2.33 (m, 2H), 2.17 (m, 2H), 2.09 (s, 3H), 1.64-1.70 (m, 4H); \(^{13}\text{C}-\text{NMR}\) (125 MHz, CDCl\(_3\)): 171.2, 154.2, 153.2, 139.1, 120.1, 117.6, 115.5, 113.2, 112.0, 92.4, 89.2, 66.8, 56.4, 55.8, 30.0, 27.0, 22.2, 22.0, 21.0; IR (KBr): 2935, 2835, 1737, 1500, 1234; HRMS: m/e for C\(_{19}\)H\(_{22}\)O\(_4\) calculated 314.1518 (M\(^+\)), found 314.1526.

\[2-(2,5-\text{Dimethoxyphenyl})\text{ethynyl}]\text{cyclohex-1-enyl}]* \text{methyl acetate dicobalt hexacarbonyl} (152h)

Compound 151h (0.6362 g, 2.025 mmol) was subjected to complexation according to General Procedure E. The complexed compound (152h) was eluted via flash chromatography (7:1 hexanes:Et\(_2\)O) following removal of excess, uncomplexed Co\(_2\)(CO\(_8\)) with 100% hexanes. The product was isolated as a dark brown solid (1.0050 g, 1.6750 mmol, 83%). \(^{1}\text{H}-\text{NMR}\) (500 MHz, CDCl\(_3\)): 7.03 (d, 1H, J = 2.9), 6.85 (dd, 1H, J = 8.8, J = 3.0), 6.74 (d, 1H, J = 8.9), 4.50 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 2.37 (m, 2H), 2.11 (m, 2H), 1.95 (s, 3H), 1.70-1.75 (m, 4H); \(^{13}\text{C}-\text{NMR}\) (75 MHz, CDCl\(_3\)): 199.9, 171.0, 153.6, 150.3, 133.2, 132.5, 127.7, 117.4, 113.6, 110.4, 95.0, 89.9, 65.1, 55.8, 54.6, 33.1, 28.3, 23.5, 22.4, 20.9; IR (KBr): 2938, 2834, 2086, 2049, 2016, 1740, 1490, 1228; HR-MS: m/e for C\(_{25}\)H\(_{22}\)Co\(_2\)O\(_{10}\) calculated 543.9979 (M-2CO\(^+\)), found 543.9979.

\text{Dicobalt hexacarbonyl[μ-((10.11-η:10.11-η)-10,11-didehydro-2,3,4,5-tetrahydro-6,9-dimethoxy-1H-dibenzo[a,d]cycloheptene)]} (153h)

Compound 152h (0.3248 g, 0.5413 mmol) was reacted according to General Procedure F using BF\(_3\)•OEt\(_2\) (206 µL, 1.62 mmol). The reaction was complete after 1 h, as assessed by
TLC analysis. The cyclized product (153h) was isolated by flash chromatography (15:1 hexanes:Et₂O) as a maroon solid (0.2405 g, 0.4454 mmol, 82%). ¹H-NMR (500 MHz, CDCl₃): 6.92 (d, 1H, J = 9.0), 6.74 (d, 1H, J = 9.0), 3.87 (s, 3H), 3.82 (s, 3H), 3.34 (s, 2H), 2.30-2.36 (m, 4H), 1.73-1.78 (m, 2H), 1.66-1.71 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃): 200.4, 154.0, 150.3, 136.3, 131.5, 127.4, 126.6, 112.2, 108.7, 96.0, 84.8, 56.7, 54.7, 33.6, 32.8, 30.5, 23.1, 22.9; IR (KBr): 2924, 2850, 2085, 2046, 2026, 1739, 1463, 1261; HRMS: m/e for C₂₃H₁₈Co₂O₈ calculated 539.9666 (M⁺), found 539.9669.

1-[2-((2,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]ethyl acetate (151hh)

Compound 150h (0.4632 g, 1.715 mmol) was subjected to General Procedure D, where DIBAL-H was substituted with MeLi (1.6 M in Et₂O, 2.1 mL, 3.4 mmol). The product (151hh) was isolated as a yellow oil (0.4671 g, 1.423 mmol, 83%) following preparative TLC (7:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 6.97 (d, 1H, J = 2.8), 6.78-6.83 (m, 2H), 6.17 (q, 1H, J = 6.5), 3.86 (s, 3H), 3.77 (s, 3H), 2.30 (m, 2H), 2.17 (m, 2H), 2.05 (s, 3H), 1.61-1.70 (m, 4H), 1.38 (d, 3H, J = 6.58); ¹³C-NMR (75 MHz, CDCl₃): 170.2, 154.6, 153.3, 144.1, 117.7, 116.8, 115.4, 113.7, 112.2, 92.6, 89.9, 72.8, 56.6, 55.9, 30.0, 23.6, 22.4, 22.1, 21.4, 18.7; IR (KBr): 2934, 2835, 2199, 1737, 1499, 1243; HRMS: m/e for C₂₀H₂₄O₄ calculated 328.1675 (M⁺), found 328.1672.
**1-(2-((2,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl)ethyl acetate dicobalt hexacarbonyl (152hh)**

Compound **151hh** (0.4671 g, 1.423 mmol) was subjected to complexation according to General Procedure E. The complexed compound **(152hh)** was isolated via flash chromatography (7:1 hexanes:Et₂O) following removal of excess, uncomplexed Co₂(CO)₈ with 100% hexanes. The product was isolated as a dark brown solid (0.8023 g, 1.307 mmol, 92%). ¹H-NMR (500 MHz, CDCl₃): 7.01 (d, 1H, J = 3.0), 6.86 (dd, 1H, J = 8.9, J = 3.1), 6.74 (d, 1H, J = 8.9), 6.07 (q, 1H, J = 6.5), 3.81 (s, 3H), 3.72 (s, 3H), 2.13-2.32 (m, 4H), 1.93 (s, 3H), 1.62-1.72 (m, 4H), 1.19 (d, 3H, J = 6.5); ¹³C-NMR (75 MHz, CDCl₃): 200.0, 169.9, 153.5, 149.8, 137.6, 130.1, 128.2, 117.6, 113.4, 110.4, 94.0, 92.1, 70.6, 55.8, 54.5, 32.7, 24.5, 23.5, 22.5, 21.3, 18.2; HRMS: m/e for C₂₆H₂₄Co₂O₁₀ calculated 474.0288 (M-5CO⁺), found 474.0270.

**Compounds 154b and 153hh**

Compound **152hh** (0.7070 g, 1.151 mmol) was reacted according to General Procedure F using BF₃•OEt₂ (438 µL, 3.45 mmol). The reaction was complete after 1 h, as assessed by TLC analysis. The cyclized product **(153hh)** and its elimination isomer **(154b)** were inseparable by flash chromatography, and hence, eluted as one band using a 25:1 hexanes:Et₂O solvent mixture. The products were isolated as a green-maroon solid (0.5102 g, 0.9210 mmol, 80%). ¹H-NMR (500 MHz, CDCl₃): 7.06 (d, 1H, J = 3.1), 6.87 (dd, 1H, J = 8.9, J = 3.1), 6.76 (d, 1H, J = 8.9), 6.38 (t,
1H, J = 4.4), 5.19 (q, 1H, J = 7.1), 3.80 (s, 3H), 3.70 (s, 3H), 2.42 (t, 2H, J = 6.0), 2.32 (apparent q, 2H, J = 5.6), 1.78 (apparent pentet, 2H, J = 6.2), 1.52 (d, 3H, J = 7.0); 13C-NMR (CDCl3, 75 MHz): 200.2, 153.3, 151.5, 136.9, 133.2, 127.6, 121.4, 117.1, 114.0, 112.7, 110.9, 97.8, 91.1, 55.8, 54.8, 27.4, 25.8, 22.6, 12.8.

The ratio of the two products was determined by peak analysis of the 1H-NMR spectra, and calculated to be 1.0:3.0 in favour of the elimination product (i.e., cyclized 153hh:elimination 154b). 1H-NMR (500 MHz, CDCl3): 6.92 (d, 1H, J = 9.0), 6.72 (d, 1H, J = 9.0), 4.18 (q, 1H, J = 7.3), 3.86 (s, 3H), 3.81 (s, 3H), 2.13-2.17 (m, 2H), 1.63-1.74 (m, 4H), 1.12 (d, 3H, J = 7.3); 13C-NMR (75 MHz, CDCl3): 200.2, 154.5, 149.8, 139.9, 133.1, 131.4, 128.4, 112.7, 107.8, 93.4, 83.4, 56.6, 54.2, 39.4, 33.5, 30.7, 23.4, 22.8, 21.0; IR (KBr, sample containing both isomers): 3000, 2936, 2833, 2085, 2046, 2017, 1493, 1277, 1225; HRMS: m/e for C24H20Co2O8 (sample containing both isomers) calculated 525.9873 (M-CO⁺), found 525.9872.

2-[(2,5-Dimethoxyphenyl)ethynyl]cyclohept-1-enecarbaldehyde (150i)

Compound 148d (0.3400 g, 2.098 mmol) was subjected to Sonogashira chemistry according to General Procedure C with 2-bromocyclohept-1-ene-1-carbaldehyde (149c) (0.6390 g, 3.147 mmol). Product 150i was isolated as a yellow oil (0.4406 g, 1.551 mmol, 74%) following preparative TLC (10:1 hexanes:Et₂O). 1H-NMR (500 MHz, CDCl3): 10.34 (s, 1H), 6.94 (d, 1H, J = 3.0), 6.88 (dd, 1H, J = 8.9, J = 3.1), 6.80 (d, 1H, J = 9.1), 3.83 (s, 3H), 3.76 (s, 3H), 2.69-2.72 (m, 2H),...
2.52-2.54 (m, 2H), 1.81 (apparent pentet, 2H, J = 5.9), 1.68 (apparent pentet, 2H, J = 5.7), 1.46 (apparent pentet, 2H, J = 6.0); $^{13}$C-NMR (125 MHz, CDCl$_3$): 193.0, 154.9, 153.2, 148.2, 145.9, 117.6, 116.9, 112.0, 111.9, 96.8, 92.0, 56.4, 55.8, 37.4, 32.3, 25.8, 24.3; IR (KBr): 2999, 2922, 2852, 2188, 1667, 1499, 1221; HRMS: m/e for C$_{18}$H$_{20}$O$_3$ calculated 284.1412 (M$^+$), found 284.1412.

**[2-((2,5-Dimethoxyphenyl)ethynyl)cyclohept-1-enyl]methyl acetate (151i)**

![Chemical Structure](image)

Compound 150i (0.4406 g, 1.551 mmol) was subjected to reduction and acetylation according to General Procedure D. Product 151i was isolated as a pale yellow oil (0.4327 g, 1.318 mmol, 85%) following preparative TLC (7:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 6.92 (d, 1H, J = 2.7), 6.80 (dd, 1H, J = 8.5, J = 2.5), 6.77 (d, 1H, J = 9.0), 4.96 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 2.49-2.51 (m, 2H), 2.30-2.32 (m, 2H), 2.08 (s, 3H), 1.78 (apparent pentet, 2H, J = 5.8), 1.61 (apparent pentet, 2H, J = 5.4), 1.52 (apparent pentet, 2H, J = 5.5); $^{13}$C-NMR (125 MHz, CDCl$_3$): 171.2, 154.1, 153.2, 145.2, 126.0, 117.4, 115.4, 113.3, 111.8, 94.0, 90.0, 68.1, 56.3, 55.8, 34.7, 31.3, 26.2, 26.1, 21.1; IR (KBr): 2919, 2850, 1739, 1498, 1228; HRMS: m/e for C$_{20}$H$_{24}$O$_4$ calculated 328.1675 (M$^+$), found 328.1683.

**[2-((2,5-Dimethoxyphenyl)ethynyl)cyclohept-1-enyl]methyl acetate dicobalt hexacarbonyl (152i)**

![Chemical Structure](image)

Compound 151i (0.4327 g, 1.318 mmol) was subjected to complexation according to General Procedure E. The complexed compound (152i) was isolated via flash chromatography (5:1...
hexanes:Et$_2$O) following removal of excess, uncomplexed Co$_2$(CO)$_8$ with 100% hexanes. The product was isolated as a dark brown-green solid (0.6867 g, 1.118 mmol, 85%). $^1$H-NMR (500 MHz, CDCl$_3$): 7.01 (d, 1H, J = 3.0), 6.86 (dd, 1H, J = 8.9, J = 3.1), 6.75 (d, 1H, J = 8.9), 4.52 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.60-2.62 (m, 2H), 2.30-2.32 (m, 2H), 1.95 (s, 3H), 1.82 (apparent pentet, 2H, J = 5.8), 1.54-1.63 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.9, 171.0, 153.6, 150.2, 139.2, 138.8, 127.8, 117.3, 113.6, 110.3, 96.0, 91.1, 65.7, 55.8, 54.6, 37.6, 32.7, 32.5, 26.7, 26.4, 21.0; IR (KBr): 2926, 2852, 2085, 2058, 2013, 1742, 1486, 1222; HRMS: m/e for C$_{26}$H$_{24}$Co$_2$O$_{10}$ calculated 558.0106 (M-2CO$^+$), found 558.0117.

**Dicobalt hexacarbonyl [μ-(11,12-η:11,12-η)-11,12-didehydro-5,6,7,8,9,10-hexahydro-1,4-dimethoxybenzo[b]heptalene)] (153i)**

Compound 152i (0.2234 g, 0.3638 mmol) was reacted according to General Procedure F using BF$_3$·OEt$_2$ (138 μL, 1.09 mmol). The reaction was complete after 1 h, as assessed by TLC analysis. The cyclized product (153i) was isolated by flash chromatography (15:1 hexanes:Et$_2$O) as a maroon solid (0.1687 g, 0.3045 mmol, 85%). $^1$H-NMR (500 MHz, CDCl$_3$): 6.92 (d, 1H, J = 9.0), 6.74 (d, 1H, J = 9.0), 3.86 (s, 3H), 3.82 (s, 3H), 3.40 (s, 2H), 2.52-2.56 (m, 4H), 1.78 (apparent pentet, 2H, J = 6.0), 1.56-1.67 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 200.6, 153.8, 150.2, 141.7, 136.8, 127.1, 126.7, 112.3, 108.5, 97.7, 85.5, 56.8, 54.6, 38.6, 35.6, 34.7, 31.4, 26.2; IR (KBr): 2965, 2919, 2849, 2085, 2051, 2029, 1466, 1261; HRMS: m/e for C$_{24}$H$_{20}$Co$_2$O$_8$ calculated 553.9822 (M$^+$), found 553.9802.
1-Iodo-2,3,4-trimethoxybenzene (155e)

Compound 155e was synthesized according to General Procedure I from 1,2,3-trimethoxybenzene (5.0000 g, 29.748 mmol). The product was isolated as a yellow oil (8.1235 g, 27.633 mmol, 93%), and was characterized as spectroscopically identical to reported values153.

[(2,3,4-Trimethoxyphenyl)ethynyl]trimethylsilane (156e)

1-Iodo-2,3,4-trimethoxybenzene (155e) (4.0256 g, 13.694 mmol) was subjected to Sonogashira chemistry according to General Procedure A. The product (156e) was isolated as a yellow oil (3.4107 g, 12.914 mmol, 94%), and was characterized as spectroscopically identical to reported values55.

1-Ethynyl-2,3,4-trimethoxybenzene (148e)

Compound 156e (3.4107 g, 12.914 mmol) was desilylated according to General Procedure H. The product (148e) was isolated as a yellow oil (2.1870 g, 11.386 mmol, 88%) following flash chromatography (2:1 hexanes:Et2O). 1H-NMR (500 MHz, CDCl3): 7.17 (d, 1H, J = 8.6), 6.61 (d, 1H, J = 8.6), 3.98 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.20 (s, 1H); 13C-NMR (75 MHz, CDCl3): 155.5, 154.9, 142.2, 128.8, 109.3, 107.4, 79.9, 61.4, 61.2, 56.2; IR (KBr): 3283, 2999, 2941, 2840, 2105, 1594, 1492, 1295; HRMS: m/e for C11H12O3 calculated 192.0786 (M+), found 192.0781.

2-[(2,3,4-Trimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150j)

Compound 148e (0.9223 g, 4.802 mmol) was subjected to Sonogashira coupling with 2-
bromocyclopent-1-ene-1-carbaldehyde (149a) (1.2606 g, 7.2025 mmol) according to General Procedure C. Flash chromatography (2:1 hexanes:Et₂O) afforded the product (150j) as a pale yellow solid (1.1881 g, 4.1524 mmol, 86%) with m.p. of 74-76 °C. ¹H-NMR (500 MHz, CDCl₃): 10.19 (s, 1H), 7.17 (d, 1H, J = 9.0), 6.66 (d, 1H, J = 9.0), 3.98 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.81 (t, 2H, J = 7.9), 2.66 (t, 2H, J = 7.9), 2.01 (apparent pentet, 2H, J = 7.9); ¹³C-NMR (75 MHz, CDCl₃): 189.2, 155.6, 155.3, 147.3, 143.8, 142.4, 128.5, 109.4, 107.6, 97.6, 86.4, 61.5, 61.2, 56.2, 39.0, 29.7, 22.3; IR (KBr): 2942, 2841, 2191, 1668, 1496, 1295; HRMS: m/e for C₁₇H₁₈O₄ calculated 286.1205 (M⁺), found 286.1214.

[2-((2,3,4-Trimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate (151j)

Compound 150j (1.1881 g, 4.1524 mmol) was treated according to General Procedure D. Flash chromatography (2:1 hexanes:Et₂O) afforded 151j as a pale yellow oil (1.2573 g, 3.8083 mmol, 92%). ¹H-NMR (500 MHz, CDCl₃): 7.10 (d, 1H, J = 8.9), 6.60 (d, 1H, J = 8.9), 4.88 (s, 2H), 3.95 (s, 3H), 3.85 (s, 6H), 2.60 (t, 2H, J = 7.8), 2.49 (t, 2H, J = 7.9), 2.07 (s, 3H), 1.94 (apparent pentet, 2H, J = 7.8); ¹³C-NMR (75 MHz, CDCl₃): 171.1, 154.7, 154.4, 144.1, 143.0, 128.0, 123.5, 110.6, 107.4, 91.0, 87.4, 62.1, 61.3, 61.2, 56.2, 37.0, 34.1, 22.5, 21.0; IR (KBr): 2940, 2841, 2199, 1739, 1490, 1226; HRMS: m/e for C₁₉H₂₂O₅ calculated 330.1467 (M⁺), found 330.1468.
[2-((2,3,4-Trimethoxyphenyl)ethynyl)cyclopent-1-enyl)methyl acetate dicobalt hexacarbonyl (152j)]

Compound 151j (1.0012 g, 3.0326 mmol) was subjected to complexation according to General Procedure E. After washing excess, uncomplexed Co$_2$(CO)$_8$ off a column of silica, the product (152j) was eluted using 2:1 hexanes:Et$_2$O as a dark brown solid (1.6176 g, 2.6260 mmol, 87%). $^1$H-NMR (500 MHz, CDCl$_3$): 7.16 (d, 1H, $J = 8.8$), 6.64 (d, 1H, $J = 8.9$), 4.65 (s, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 2.76 (t, 2H, $J = 7.8$), 2.56 (t, 2H, $J = 7.8$), 2.00 (apparent pentet, 2H, $J = 7.8$), 1.99 (s, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.9, 171.0, 154.4, 151.0, 141.1, 138.0, 136.5, 126.6, 122.9, 106.6, 89.7, 87.5, 61.3, 60.9, 60.2, 56.1, 40.2, 36.2, 22.1, 20.8; IR (KBr): 2944, 2844, 2086, 2045, 2014, 1742, 1486, 1231; HRMS: m/e for C$_{25}$H$_{22}$Co$_2$O$_{11}$ calculated 448.0131 (M-6CO$^+$), found 448.0139.

**Compound 153j**

Compound 152j (1.2170 g, 1.9757 mmol) was subjected to General Procedure F. The reaction appeared to be complete in 1 h, as monitored by TLC. Flash chromatography on neutralized silica (20:1 hexanes:Et$_2$O) afforded the product as a maroon solid (0.0903 g, 0.162 mmol, 8%). $^1$H-NMR (500 MHz, CDCl$_3$): 6.42 (s, 1H), 4.05 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.41 (s, 2H), 2.71 (t, 2H, $J = 7.8$), 2.54 (t, 2H, $J = 7.8$), 2.05 (apparent pentet, 2H, $J = 7.7$); $^{13}$C-NMR (75 MHz, CDCl$_3$): 200.3, 154.7, 153.9, 141.1, 139.8, 136.2, 131.3, 123.3, 108.6, 89.6, 84.5, 60.8, 60.2, 56.0,
38.8, 38.0, 35.5, 22.6; IR (Pt/diamond): 2931, 2850, 2083, 2025, 2009, 1993, 1588, 1487, 1319, 1120; HRMS: m/e for C_{23}H_{18}CoO_9 calculated 499.9716 (M-2CO’), found 499.9699.

2-[(2,3,4-Trimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150k)

Compound 148e (1.2647 g, 6.5843 mmol) was subjected to Sonogashira conditions with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (1.8764 g, 9.8764 mmol) according to General Procedure C. Coupled product 150k was isolated via flash chromatography (2:1 hexanes:Et₂O) for the last purification step. The product was obtained as a yellow solid (1.6237 g, 5.4099 mmol, 82%) with a m.p. of 119-120 °C. ³¹H-NMR (300 MHz, CDCl₃): 10.32 (s, 1H), 7.12 (d, 1H, J = 8.7), 6.63 (d, 1H, J = 8.7), 3.95 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.51 (m, 2H), 2.28 (m, 2H), 1.62-1.74 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 193.3, 155.2, 155.1, 142.3, 142.0, 140.5, 128.2, 109.6, 107.6, 95.3, 89.3, 61.5, 61.2, 56.2, 32.4, 22.2, 22.0, 21.2; IR (KBr): 2937, 2190, 1668, 1494, 1276; HRMS: m/e for C_{18}H_{20}O₄ calculated 300.1362 (M⁺), found 300.1355.

[2-((2,3,4-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151k)

Compound 150k (0.8787 g, 2.928 mmol) was reacted according to General Procedure D. Product 151k was isolated as a yellow oil (0.8956 g, 2.600 mmol, 89%) via flash chromatography (2:1 hexanes:Et₂O). ¹¹H-NMR (500 MHz, CDCl₃): 7.10 (d, 1H, J = 8.8), 6.61 (d, 1H, J = 8.9), 4.93 (s, 2H), 3.96 (s, 3H), 3.87 (s, 6H), 2.32 (m, 2H), 2.17 (m, 2H), 2.09 (s, 3H), 1.65-1.70
(m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 171.3, 154.7, 154.3, 142.3, 138.4, 127.9, 120.4, 110.8, 107.4, 91.0, 89.2, 66.8, 61.3, 61.2, 56.2, 30.3, 27.1, 22.3, 22.1, 21.1; IR (KBr): 2940, 2839, 2196, 1746, 1494, 1234; HRMS: m/e for C$_{20}$H$_{24}$O$_5$ calculated 344.0624 (M$^+$), found 344.0627.

**[2-((2,3,4-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152k)**

Compound 151k (0.8956 g, 2.600 mmol) was subjected to complexation according to General Procedure E. The complexed product (152k) was isolated as a dark green solid (1.5445 g, 2.4516 mmol, 94%) following flash chromatography (2:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 7.14 (d, 1H, J = 9.0), 6.64 (d, 1H, J = 9.0), 4.53 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 2.39 (t, 2H, J = 6.0), 2.13 (t, 2H, J = 6.1), 1.94 (s, 3H), 1.71-1.77 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 200.1, 170.9, 154.4, 150.5, 140.8, 132.8, 132.4, 126.6, 123.0, 106.4, 94.4, 90.3, 65.3, 60.9, 60.0, 56.0, 33.3, 28.3, 23.5, 22.4, 20.8; IR (KBr): 2940, 2838, 2084, 2044, 2012, 1742, 1486, 1229; HRMS: m/e for C$_{26}$H$_{24}$Co$_2$O$_{11}$ calculated 462.0288 (M-6CO$^+$), found 462.0298.

**Compound 153k**

Compound 152k (0.8100 g, 1.286 mmol) was subjected to General Procedure F. The reaction was complete in 1 h, as assessed by TLC analysis. The cyclized product 153k (0.2865 g, 0.5026 mmol, 39%) was isolated as a maroon
solid following flash chromatography using neutralized silica (20:1 hexanes:Et₂O). ¹H-NMR
(500 MHz, CDCl₃): 6.48 (s, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.18 (s, 2H), 2.35
(t, 2H, J = 6.3), 2.28 (t, 2H, J = 6.2), 1.67-1.78 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 200.5,
154.3, 153.9, 141.2, 135.3, 133.1, 131.3, 123.2, 108.1, 96.7, 84.8, 60.8, 60.2, 56.0, 43.4,
33.6, 30.6, 23.1, 22.8; IR (Pt/diamond): 2932, 2855, 2086, 2044, 1992, 1586, 1484, 1326;
HRMS: m/e for C₂₄H₂₀Co₂O₉ calculated 513.9873 (M-2CO⁺), found 513.9852.

1-[2-((2,3,4-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl]ethyl acetate (151kk)

Compound 150k (0.7450 g, 2.482 mmol) was subjected to General Procedure D, where DIBAL-H was substituted with MeLi (1.6 M in Et₂O, 3.1 mL, 5.0 mmol). The product (151kk) was isolated as a yellow/orange oil (0.7888 g, 2.202 mmol, 89%) following flash chromatography (2:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.12 (d, 1H, J = 8.6), 6.60 (d, 1H, J = 8.7), 6.13 (q, 1H, J = 6.5), 3.98 (s, 3H),
3.86 (s, 3H), 3.85 (s, 3H), 2.27 (m, 2H), 2.15 (m, 2H), 2.04 (s, 3H), 1.62-1.69 (m, 4H), 1.36 (d, 3H, J = 6.6); ¹³C-NMR (75 MHz, CDCl₃): 170.2, 154.6, 154.2, 143.2, 142.3, 128.0, 117.0,
111.0, 107.4, 91.0, 89.7, 72.7, 61.4, 61.2, 56.2, 30.1, 23.4, 22.4, 22.1, 21.4, 18.8; IR (KBr):
2935, 2839, 2194, 1737, 1593, 1494, 1243; HRMS: m/e for C₂₁H₂₆O₃ calculated 358.1780
(M⁺), found 358.1777.
**1-(2-(2,3,4-Trimethoxyphenyl)ethyl)cyclohex-1-enyl)ethyl acetate dicobalt hexacarbonyl (152kk)**

Compound 151kk (0.7888 g, 2.202 mmol) was subjected to complexation according to General Procedure E. Compound 152kk (1.2896 g, 2.0024 mmol, 91%) was isolated as a dark green solid following flash chromatography (2:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.11 (d, 1H, J = 8.7), 6.64 (d, 1H, J = 8.7), 6.14 (q, 1H, J = 6.3), 3.96 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 2.15-2.33 (m, 4H), 1.93 (s, 3H), 1.60-1.75 (m, 4H), 1.26 (d, 3H, J = 6.3); ¹³C-NMR (75 MHz, CDCl₃): 200.1, 170.0, 154.2, 150.2, 140.9, 137.4, 130.2, 126.6, 123.6, 106.3, 93.2, 92.8, 70.6, 60.9, 60.0, 56.0, 33.0, 24.5, 23.6, 22.4, 21.3, 18.3; IR (KBr): 2938, 2839, 2084, 2046, 2016, 1737, 1485, 1241; HRMS: m/e for C₇₇H₆₆Co₂O₁₁ calculated 588.0241 (M-2CO⁺), found 588.0226.

**Compound 153kk**

Compound 152kk (0.8530 g, 1.324 mmol) was subjected to General Procedure F. The cyclized product (153kk) was isolated as a maroon solid (0.3018 g, 0.5168 mmol, 39%) following flash chromatography (20:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 6.44 (s, 1H), 4.07 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.25 (q, 1H, J = 7.7), 2.16-2.46 (m, 4H), 1.75 (m, 4H), 1.26-1.3 (m, 3H); ¹³C-NMR (75 MHz, CDCl₃): 200.6, 154.5, 154.3, 140.7, 139.1, 137.7, 129.3, 121.9, 106.5, 95.3, 83.8, 60.8, 60.1, 56.0, 47.4, 31.0, 23.2, 22.8, 19.5; IR (Pt/diamond): 2930, 2859, 2081, 2038, 1993, 1586, 1486,
1319, 1259; HRMS: m/e for C_{25}H_{22}Co_{2}O_{9} calculated 555.9979 (M-CO'), found 555.9996.

**(3,4,5-Trimethoxyphenyl)ethynyltrimethylsilane (156f)**

Compound **156f** was synthesized according to General Procedure A from 5-ido-1,2,3-trimethoxybenzene (**155f**) (1.5110 g, 5.1399 mmol). The product was isolated as a cream-coloured solid (1.3208 g, 5.0008 mmol, 97%), with a m.p. of 55-56 °C, and spectroscopically identical to reported values^41.

**(5-Ethynyl-1,2,3-trimethoxybenzene (148f)**

Compound **156f** (1.3208 g, 5.0008 mmol) was subjected to General Procedure H. The desilylated product was isolated as a colourless solid (0.8322 g, 4.333 mmol, 87%), with a m.p. of 71-73 °C (lit., 68-68.5 °C^95), and spectroscopically identical to reported values^95.

**(2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150l)**

Compound **148f** (0.2514 g, 1.309 mmol) was subjected to General Procedure C with 2-bromocyclopent-1-ene-carbaldehyde (**149a**) (0.3436 g, 1.963 mmol). Preparative TLC (2:1 hexanes:Et₂O) afforded the product as a yellow solid (0.3109 g, 1.087 mmol, 83%) with a m.p. of 131-133 °C. ¹H-NMR (500 MHz, CDCl₃): 10.15 (s, 1H), 6.71 (s, 2H), 3.85 (s, 9H), 2.79 (t, 2H, J = 7.8), 2.64 (t, 2H, J = 7.8), 1.99 (apparent pentet, 2H, J = 7.9); ¹³C-NMR (125 MHz, CDCl₃): 189.0, 153.3, 148.0, 143.3, 139.9, 117.0, 109.2, 101.0, 82.6, 61.1, 56.3, 39.0, 29.7, 22.3; IR (KBr): 2941, 2834, 2192, 1661, 1239; HRMS: m/e for C₁₇H₁₈O₄
calculated 286.1205 (M’), found 286.1206.

**[2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate (151l)**

Compound 150l (0.3099 g, 1.083 mmol) was subjected to General Procedure D. The product compound (151l) was isolated as a yellow oil (0.3093 g, 0.9368 mmol, 89%) via preparative TLC (2:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 6.64 (s, 2H), 4.84 (s, 2H), 3.82 (s, 6H), 3.81 (s, 3H), 2.58 (t, 2H, J = 7.7), 2.47 (t, 2H, J = 7.8), 2.05 (s, 3H), 1.92 (apparent pentet, 2H, J = 7.7); ¹³C-NMR (75 MHz, CDCl₃): 171.0, 153.1, 144.7, 138.8, 122.8, 118.8, 108.0, 95.0, 83.8, 62.0, 61.0, 56.2, 37.1, 34.2, 22.4, 20.9; IR (KBr): 2940, 1741, 1503, 1234; HRMS: m/e for C₁₉H₂₂O₅ calculated 330.1467 (M+), found 330.1464.

**[2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate dicobalt hexacarbonyl (152l)**

Compound 151l (0.3093 g, 0.9368 mmol) was complexed using General Procedure E to afford product 152l (0.5156 g, 0.8370 mmol, 89%) as a dark brown solid following flash chromatography (1:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 6.71 (s, 2H), 4.72 (s, 2H), 3.90 (s, 3H), 3.88 (s, 6H), 2.81 (t, 2H, J = 7.8), 2.56 (t, 2H, J = 7.9), 2.04 (apparent pentet, 2H, J = 7.8), 2.02 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃): 199.5, 170.7, 153.3, 138.0, 137.7, 136.9, 133.7, 106.5, 93.4, 84.4, 61.2, 61.0, 56.2, 39.9, 36.2, 21.8, 20.7; IR (KBr): 2940, 2088, 2050, 2020, 1743, 1576, 1230; HRMS: m/e for C₂₅H₂₂Co₂O₁₁ calculated 559.9928 (M-2CO⁻), found 559.9924.
Dicobalt hexacarbonyl[μ-((9,10-η:9,10-η)-9,10-didehydro-1,2,3,4-tetrahydro-5,6,7-trimethoxybenz[f]azulene)] (153l)

Compound 152l (0.4123 g, 0.6693 mmol) was cyclized according to General Procedure F with BF₃•OEt₂ (254 µL, 2.01 mmol) as Lewis acid. The reaction was complete within 30 minutes, as assessed by TLC analysis. The cyclized product 153l (0.3159 g, 0.5682 mmol, 85%) was isolated via flash chromatography (5:1 hexanes:Et₂O) as a dark maroon solid. ¹H-NMR (500 MHz, CDCl₃): 6.99 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.48 (s, 2H), 2.71 (t, 2H, J = 7.5), 2.56 (t, 2H, J = 7.4), 2.06 (apparent pentet, 2H, J = 7.6); ¹³C-NMR (75 MHz, CDCl₃): 199.9, 152.4, 150.9, 143.0, 141.6, 135.3, 133.5, 121.6, 122.3, 91.0, 88.0, 61.3, 60.9, 56.0, 39.3, 35.5, 27.5, 22.7; IR (KBr): 2938, 2086, 2048, 2018, 1118; HRMS: m/e for C₂₃H₁₈Co₂O₉ calculated 527.9666 (M-Co⁺), found 527.9654.

2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150m)

Compound 148f (0.3386 g, 1.763 mmol) was subjected to General Procedure C with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (0.5024 g, 2.644 mmol). Preparative TLC (2:1 hexanes:Et₂O) was used to isolate 150m as a cream-coloured solid (0.4510 g, 1.503 mmol, 85%), with a m.p. of 121-123 °C. ¹H-NMR (500 MHz, CDCl₃): 10.31 (s, 1H), 6.70 (s, 2H), 3.87 (s, 9H), 2.52 (t, 2H, J = 5.9), 2.31 (t, 2H, J = 5.9), 1.67-1.74 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 193.0, 153.3, 142.6, 140.2, 139.6, 117.4, 109.0, 98.8, 85.6, 61.1, 56.3, 32.5, 22.2,
22.0, 21.2; IR (KBr): 2933, 2195, 1664, 1238; HRMS: m/e for C_{18}H_{20}O_{4} calculated 300.1362 (M^+), found 300.1361.

**2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl)methyl acetate (151m)**

Compound 150m (0.1994 g, 0.6644 mmol) was subjected to General Procedure D. The product compound (151m) was isolated as a yellow oil (0.2003 g, 0.5820 mmol, 88%) using preparative TLC (2:1 hexanes:EtO).  ^1^H-NMR (500 MHz, CDCl₃): 6.66 (s, 2H), 4.89 (s, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 2.30 (m, 2H), 2.17 (m, 2H), 2.09 (s, 3H), 1.64-1.70 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 171.2, 153.2, 139.2, 138.8, 120.0, 118.6, 108.8, 93.3, 87.3, 66.7, 61.1, 56.3, 30.3, 27.2, 22.3, 22.1, 21.1; IR (KBr): 2938, 1737, 1576, 1504, 1237; HRMS: m/e for C_{20}H_{24}O_{5} calculated 344.1624 (M^+), found 344.1631.

**2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl)methyl acetate dicobalt hexacarbonyl (152m)**

Compound 151m (0.2003 g, 0.5820 mmol) was complexed using General Procedure E to afford product 152m (0.3162 g, 0.5019 mmol, 86%) as a dark brown solid following flash chromatography (1:1 hexanes:EtO). ¹H-NMR (500 MHz, CDCl₃): 6.65 (s, 2H), 4.62 (s, 2H), 3.89 (s, 3H), 3.87 (s, 6H), 2.39 (t, 2H, J = 6.1), 2.13 (t, 2H, J = 6.1), 1.98 (s, 3H), 1.72-1.81 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 199.4, 170.8, 153.2, 137.9, 134.0, 133.6, 131.8, 106.7, 94.1, 91.5, 65.3, 61.0, 56.2, 33.4, 28.3, 23.4, 22.2, 20.8; IR (KBr): 2938, 2087, 2048, 2020,
Dicobalt hexacarbonyl[μ-((10.11-η:10.11-η)-10.11-didehydro-2,3,4,5-tetrahydro-6,7,8-trimethoxy-1H-dibenzo[a,d]cycloheptene)] (153m)

Compound 152m (0.3033 g, 0.4814 mmol) was cyclized according to General Procedure F with BF₃•OEt₂ (183 µL, 1.44 mmol) as Lewis acid. The reaction was complete within 30 minutes, as assessed by TLC analysis. The cyclized product (153m) (0.2368 g, 0.4154 mmol, 86%) was isolated via flash chromatography (5:1 hexanes:Et₂O) as a dark maroon solid. ¹H-NMR (500 MHz, CDCl₃): 6.98 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.25 (s, 2H), 2.32-2.36 (m, 4H), 1.69-1.78 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 200.1, 152.5, 150.5, 143.0, 137.1, 133.8, 130.9, 123.4, 111.1, 95.3, 90.5, 61.7, 60.9, 56.1, 33.8, 32.9, 30.5, 23.1, 22.8; IR (KBr): 2936, 2085, 2045, 2016, 1591, 1127; HRMS: m/e for C₂₄H₂₀Co₂O₉ calculated 541.9822 (M-CO⁺), found 541.9821.

Phenyl[2-((3,4,5-trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151mm)

Compound 150m (0.2516 g, 0.8383 mmol) was subjected to General Procedure D, where DIBAL-H was substituted with PhMgBr (1.0 M in THF, 1.7mL, 1.7 mmol). The product 151mm was isolated as a yellow oil (0.2826 g, 0.6725 mmol, 80%) following preparative TLC (2:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.43 (apparent d, 2H, J = 7.2), 7.37 (apparent t, 2H, J = 7.6), 7.29-7.32 (m, 1H), 7.27 (s, 1H), 6.77
(s, 2H), 3.90 (s, 6H), 3.89 (s, 3H), 2.33-2.41 (m, 2H), 2.22 (s, 3H), 1.92-1.98 (m, 2H), 1.55-1.73 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 169.8, 153.2, 142.6, 139.5, 138.8, 128.4, 127.5, 125.7, 119.1, 118.7, 108.8, 93.5, 88.2, 76.3, 61.1, 56.3, 30.2, 23.8, 22.2, 22.0, 21.3; IR (KBr): 3062, 3004, 2939, 2839, 2197, 1731, 1574, 1505, 1411, 1234; HRMS: m/e for C$_{26}$H$_{28}$O$_5$ calculated 420.1937 (M$^+$), found 420.1950.

**Phenyl[2-((3,4,5-trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152mm)**

Compound 151mm (0.2826 g, 0.6725 mmol) was complexed using General Procedure E to afford product 152mm (0.4118 g, 0.5833 mmol, 87%) as a dark brown solid following flash chromatography (1:1 hexanes:Et$_2$O).

$^1$H-NMR (500 MHz, CDCl$_3$): 7.18-7.20 (m, 3H), 6.94 (s, 1H), 6.87-6.89 (m, 2H), 6.36 (s, 2H), 3.85 (s, 3H), 3.70 (s, 6H), 2.48-2.50 (m, 2H), 2.09 (s, 3H), 2.00-2.05 (m, 2H), 1.60-1.88 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 199.7, 169.8, 152.4, 137.9, 137.0, 136.3, 135.0, 131.3, 128.2, 127.6, 126.7, 107.2, 98.0, 92.1, 75.2, 60.9, 55.8, 33.0, 26.1, 23.4, 22.4, 21.1; IR (KBr): 3001, 2938, 2860, 2835, 2091, 2047, 2034, 1738, 1578, 1407, 1235; HRMS: m/e for C$_{32}$H$_{28}$Co$_2$O$_{11}$ calculated 538.0601 (M-6CO$^+$), found 538.0601.
Dicobalt hexacarbonyl[µ-(1,2,3-trimethoxy-5-((1,2-η;1,2-η)-2-(6-(phenylmethylene)-1-cyclohexen-1-yl)ethynyl)benzene)] (154c) and Dicobalt hexacarbonyl[µ-((10,11-η;10,11-η)-10,11,-didehydro-2,3,4,5-tetrahydro-6,7,8-trimethoxy-5-phenyl-1H-dibenzo[a,d]cycloheptene)] (153mm)

Compound 152mm (0.1300 g, 0.1841 mmol) was reacted according to General Procedure F using BF₃•OEt₂ (70 µL, 0.55 mmol). The reaction was complete after 1 h, as assessed by TLC analysis. The cyclized product (153mm) was separated from its elimination isomer (154c) by flash chromatography (10:1 hexanes:Et₂O). The elimination product came off the column as the second band, and was isolated as a green solid (0.0546 g, 0.0845 mmol, 46%).

¹H-NMR (500 MHz, CDCl₃): 7.26 (apparent t, 2H, J = 7.7), 7.16 (apparent t, 1H, J = 7.3), 7.03 (d, 2H, J = 7.9), 6.82 (s, 2H), 6.67 (t, 1H, J = 4.6), 6.49 (s, 1H), 3.91 (s, 3H), 3.81 (s, 6H), 2.77 (t, 2H, J = 6.4), 2.42 (apparent q, 2H, J = 5.7), 1.81 (apparent pentet, 2H, J = 6.3);

¹³C-NMR (75 MHz, CDCl₃): 199.9, 153.2, 137.9, 137.7, 137.3, 136.2, 134.0, 133.8, 129.2, 128.2, 127.9, 126.6, 107.6, 95.8, 93.8, 61.0, 56.1, 27.6, 27.4, 22.7; IR (KBr): 3000, 2937, 2835, 2083, 2046, 2032, 1574, 1498, 1409, 1322, 1232; HRMS: m/e for C₃₀H₂₄Co₂O₉ calculated 562.0237 (M-3CO⁺), found 562.0231.

The cyclized product came off the column first, and was isolated as a maroon solid (0.0406 g, 0.0628 mmol, 34%).

The combined yield was 80%, and a ratio of cyclized:elimination of 1:1.3 was determined. ¹H-NMR
(500 MHz, CDCl₃): 7.05-7.15 (m, 4H), 6.90 (apparent d, 2H, J = 7.6), 5.32 (s, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 2.37-2.68 (m, 4H), 1.71-1.94 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 199.8, 152.8, 151.6, 142.9, 141.0, 138.4, 132.8, 131.5, 128.5, 126.9, 126.4, 125.1, 112.3, 91.7, 87.7, 61.8, 60.9, 55.8, 47.6, 35.9, 31.5, 23.5, 22.9; IR (KBr): 2928, 2858, 2084, 2027, 2015, 1638, 1448, 1242; HRMS: m/e for C₃₀H₂₄Co₂O₉ calculated 562.0237 (M-3CO⁺), found 562.0240.

2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclohept-1-enecarbaldehyde (150n)

Compound 148f (0.2422 g, 1.261 mmol) was subjected to General Procedure C with 2-bromocyclohept-1-ene-1-carbaldehyde (149c) (0.3841 g, 1.891 mmol). Preparative TLC (2:1 hexanes:Et₂O) isolated the product as a cream-coloured solid (0.3408 g, 1.085 mmol, 86%), with a m.p. of 115-116 °C. ¹H-NMR (500 MHz, CDCl₃): 10.29 (s, 1H), 6.70 (s, 2H), 3.87 (s, 9H), 2.69-2.71 (m, 2H), 2.53-2.55 (m, 2H), 1.83 (apparent pentet, 2H, J = 5.2), 1.68 (apparent pentet, 2H, J = 5.3), 1.47 (apparent pentet, 2H, J = 5.3); ¹³C-NMR (75 MHz, CDCl₃): 192.4, 153.3, 148.3, 145.9, 139.8, 117.4, 109.0, 100.6, 87.0, 68.1, 61.1, 56.3, 37.6, 32.3, 25.9, 24.4; IR (KBr): 2924, 2850, 2185, 1668, 1575, 1503, 1238; HRMS: m/e for C₁₉H₂₂O₄ calculated 314.1518 (M⁺), found 314.1526.

[2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclohept-1-enyl]methyl acetate (151n)

Compound 150n (0.3408 g, 1.085 mmol) was subjected to General Procedure D. The product compound (151n) was isolated as a yellow oil (0.3498 g, 0.9766 mmol, 90%) via preparative TLC (2:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 6.66 (s, 2H), 4.90 (s,
2H), 3.86 (s, 6H), 3.85 (s, 3H), 2.48-2.50 (m, 2H), 2.31-2.33 (m, 2H), 2.10 (s, 3H), 1.79 (apparent pentet, 2H, J = 5.8), 1.61 (apparent pentet, 2H, J = 5.4), 1.53 (apparent pentet, 2H, J = 5.5); 13C-NMR (75 MHz, CDCl3): 171.3, 153.4, 145.1, 138.8, 125.9, 118.7, 108.7, 94.0, 88.8, 68.0, 61.1, 56.3, 34.9, 32.4, 31.4, 26.3, 26.1, 21.1; IR (KBr): 2959, 2929, 2858, 1730, 1576, 1464, 1275; HRMS: m/e for C21H26O5 calculated 358.1780 (M+), found 358.1776.

[2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclohept-1-enyl]methyl acetate dicobalt hexacarbonyl (152n)

Compound 151n (0.3498 g, 0.9766 mmol) was complexed using General Procedure E to afford product 152n (0.5788 g, 0.8987 mmol, 92%) as a dark green solid following flash chromatography (1:1 hexanes:Et2O). 1H-NMR (500 MHz, CDCl3): 6.64 (s, 2H), 4.69 (s, 2H), 3.89 (s, 3H), 3.86 (s, 6H), 2.62-2.64 (m, 2H), 2.33-2.35 (m, 2H), 1.99 (s, 3H), 1.83 (apparent pentet, 2H, J = 6.0), 1.62 (apparent pentet, 2H, J = 5.4), 1.55 (apparent pentet, 2H, J = 5.42); 13C-NMR (75 MHz, CDCl3): 199.4, 170.9, 153.2, 139.5, 138.9, 137.9, 134.2, 106.6, 95.8, 91.8, 65.7, 61.0, 56.2, 37.5, 32.9, 32.3, 27.1, 26.2, 20.7; IR (KBr): 2928, 2853, 2087, 2049, 1742, 1577, 1501, 1408, 1231; HRMS: m/e for C27H26Co2O11 calculated 588.0241 (M-2CO+), found 588.0234.
Dicobalt hexacarbonyl[μ-((11,12-η:11,12-η)-11,12-didehydro-5,6,7,8,9,10-hexahydro-2,3,4-trimethoxybenzo[b]heptalene)] (153n)

Compound 152n (0.4989 g, 0.7747 mmol) was cyclized according to General Procedure F with BF$_3$•OEt$_2$ (294 μL, 2.32 mmol) as Lewis acid. The reaction was complete within 30 minutes, as assessed by TLC analysis. The cyclized product (153n) (0.3804 g, 0.6514 mmol, 84%) was isolated via flash chromatography (5:1 hexanes:Et$_2$O) as a maroon solid. $^1$H-NMR (500 MHz, CDCl$_3$): 6.97 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.32 (s, 2H), 2.54-2.58 (m, 4H), 1.78 (apparent pentet, 2H, J = 5.8), 1.59-1.67 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 200.2, 152.5, 150.3, 142.9, 136.4, 133.6, 123.4, 110.8, 97.2, 91.0, 61.8, 61.0, 56.1, 39.1, 35.5, 35.0, 31.7, 26.3; IR (KBr): 2918, 2850, 2085, 2046, 2016, 1590, 1480, 1328; HRMS: m/e for C$_{25}$H$_{22}$Co$_2$O$_9$ calculated 528.0029 (M-2CO$^+$), found 528.0030.

5-Iodo-1-isopropyl-2,3-dimethoxybenzene (155g)

Compound 155g was synthesized through a series of reactions adapted from Cong et. al.$^{28}$, Chin et. al.$^{23}$, and Karade et. al.$^{94}$. 2,3-Dimethoxybenzaldehyde (5.0000 g, 30.109 mmol) was dissolved in methanol (50.0 mL) along with a 50% aqueous solution of KOH (9.0 mL, 120 mmol). The solution was placed in an oil bath set to 65 °C, and aqueous H$_2$O$_2$ (30%, 24.0 mL, 240 mmol) was added dropwise over 20 minutes. The mixture was then stirred at that same temperature for 10 minutes, cooled to 0 °C, and acidified with concentrated HCl. The crystals were collected via filtration. The carboxylic acid product,
2,3-dimethoxybenzoic acid, was subsequently subjected to esterification by being dissolved in methanol (200 mL) along with a catalytic amount of \( pTosOH \) (0.5727 g, 3.011 mmol), and reflux over 72 h. The solvent was then removed under reduced pressure, and Kugelrohr distillation at 0.1 Torr afforded the ester product, methyl 2,3-dimethoxybenzoate, as an ivory solid (5.7363 g, 29.256 mmol, 97% over 2 steps). This ester product was verified by \(^1\)H- and \(^{13}\)C-NMR spectroscopy, and found to be identical to reported values\(^{23}\).

The ester was then dissolved in THF (45.0 mL), and the solution cooled to 0 °C. MeMgBr (3.0 M in Et\(_2\)O, 97.4 mL, 292 mmol) was added slowly to the reaction flask, which was then stirred at that temperature for 30 minutes before it was allowed to warm up to room temperature. Once at room temperature, the reaction flask was placed in an oil bath set at 60 °C for overnight (20 h). The next day, the reaction was slowly quenched with \( NH_4^+Cl^- \) (aq., sat.), and the aqueous fraction was extracted with Et\(_2\)O (3 x 150 mL). The collected organic fractions were then further extracted with \( NH_4^+Cl^- \) (1 x 150 mL) and brine (1 x 150 mL). The solvent was removed under reduced pressure, and the alcohol, 2-(2,3-dimethoxyphenyl)propan-2-ol, was isolated quite cleanly as a yellow oil (5.5598 g, 28.332 mmol, 97%). It was verified by \(^1\)H- and \(^{13}\)C-NMR spectroscopy, and found to be identical to reported values\(^{23}\).

This alcohol was then subjected to General Procedure I. The reaction was left over 72 h, with a stir bar to agitate the reaction once the solids had liquified. Following the allotted time, the product was eventually isolated, following Kugelrohr distillation at 0.1 Torr, as the iodinated product with the alcohol dehydrated, 5-iodo-1,2-dimethoxy-3-(prop-1-en-2-yl)benzene (8.0002 g, 26.317 mmol, 93%). This product was verified by \(^1\)H- and \(^{13}\)C-
NMR spectroscopy, and immediately subjected to its next and final synthetic transformation.

As the last step, this compound was dissolved in methanol (150 mL) along with Wilkinson’s catalyst (0.5700 g, 0.6161 mmol). H₂ was bubbled through the solution, which was stirring at room temperature. The reaction was done after 1.5 days, as assessed by ¹H-NMR. The solvent was removed under reduced pressure, and Kugelrohr distillation at 0.1 Torr afforded the final product (155g) as a pale yellow oil (7.4897 g, 24.475 mmol, 93%). ¹H-NMR (500 MHz, CDCl₃): 7.16 (d, 1H, J = 1.8), 7.04 (d, 1H, J = 1.8), 3.84 (s, 3H), 3.80 (s, 3H), 3.29 (septet, 1H, J = 7.1), 1.20 (d, 6H, J = 7.1); ¹³C-NMR (125 MHz, CDCl₃): 153.4, 146.4, 144.7, 127.8, 119.1, 87.3, 61.0, 56.0, 26.7, 23.4; IR (KBr): 2962, 2870, 2004, 1568, 1479, 1291, 1218; HRMS: m/e for C₁₁H₁₅lO₂ calculated 306.0117 (M⁺), found 306.0122.

[(3-Isopropyl-4,5-dimethoxyphenyl)ethynyl]trimethylsilane (156g)

Compound 156g was synthesized from 5-iodo-1-isopropyl-2,3-dimethoxybenzene (155g) (2.2563 g, 7.3732 mmol) according to General Procedure A. Compound 156g was isolated by flash chromatography (10:1 hexanes:Et₂O) for the final purification step as a pale yellow oil (2.0005 g, 7.2441 mmol, 98%). ¹H-NMR (500 MHz, CDCl₃): 7.00 (d, 1H, J = 1.8), 6.87 (d, 1H, J = 1.8), 3.86 (s, 3H), 3.82 (s, 3H), 3.32 (septet, 1H, J = 6.9), 1.21 (d, 6H, J = 6.94), 0.27 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃): 152.2, 147.2, 142.5, 122.8, 118.9, 113.2, 105.5, 92.6, 61.0, 55.8, 26.8, 23.3, 0.08; IR (KBr): 2962, 2152, 1573, 1484, 1317, 1250; HRMS: m/e for C₁₆H₂₄O₂Si calculated 276.1546 (M⁺), found 276.1542.
5-Ethynyl-1-isopropyl-2,3-dimethoxybenzene (148g)

Compound 156g (2.0005 g, 7.2441 mmol) was subjected to desilylation according to General Procedure H. The product was isolated via flash chromatography (10:1 hexanes:Et₂O) as a pale yellow oil (1.3196 g, 6.4650 mmol, 89%). ¹H-NMR (500 MHz, CDCl₃): 7.03 (d, 1H, J = 1.8), 6.89 (d, 1H, J = 1.9), 3.85 (s, 3H), 3.83 (s, 3H), 3.33 (septet, 1H, J = 6.9), 3.03 (s, 1H), 1.21 (d, 6H, J = 6.9); ¹³C-NMR (125 MHz, CDCl₃): 152.3, 147.4, 142.6, 123.0, 117.4, 113.4, 84.1, 75.9, 61.0, 55.8, 26.7, 23.3; IR (KBr): 3286, 2962, 2830, 2107, 1577, 1316, 1224; HRMS: m/e for C₁₃H₁₆O₂ calculated 204.1150 (M⁺), found 204.1145.

2-[(3-Isopropyl-4,5-dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150o)

Compound 148g (1.3196 g, 6.4650 mmol) was subjected to Sonogashira conditions according to General Procedure C with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (1.8424 g, 9.6975 mmol). Compound 150o was isolated via flash chromatography (10:1 hexanes:Et₂O) as a yellow oil (1.7456 g, 5.5918 mmol, 86%). ¹H-NMR (500 MHz, CDCl₃): 10.31 (s, 1H), 6.97 (d, 1H, J = 1.7), 6.83 (d, 1H, J = 1.7), 3.84 (s, 3H), 3.82 (s, 3H), 3.31 (septet, 1H, J = 7.0), 2.50 (t, 2H, J = 6.1), 2.28 (t, 2H, J = 6.1), 1.63-1.72 (m, 4H), 1.19 (d, 6H, J = 7.1); ¹³C-NMR (125 MHz, CDCl₃): 193.0, 152.4, 147.7, 142.8, 142.2, 140.3, 122.6, 117.6, 112.8, 99.2, 85.2, 61.0, 55.8, 32.4, 26.8, 23.3, 22.1, 21.9, 21.1; IR (KBr): 2936, 2868, 2192, 1673, 1484, 1323, 1226; HRMS: m/e for C₂₀H₂₄O₃ calculated 312.1725 (M⁺), found
[2-((3-Isopropyl-4,5-dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151o)

Compound 150o (1.7456 g, 5.5918 mmol) was subjected to General Procedure D. The product was purified via flash chromatography (5:1 hexanes:Et₂O) as a pale yellow oil (1.7960 g, 5.0421 mmol, 90%). ¹H-NMR (500 MHz, CDCl₃): 6.93 (d, 1H, J = 1.5), 6.82 (d, 1H, J = 1.5), 4.89 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.30 (septet, 1H, J = 7.0), 2.30 (m, 2H), 2.16 (s, 3H), 2.08 (m, 2H), 1.64-1.70 (m, 4H), 1.20 (d, 6H, J = 7.0); ¹³C-NMR (125 MHz, CDCl₃): 171.2, 152.3, 146.8, 142.5, 138.6, 122.1, 120.0, 118.8, 112.7, 93.4, 86.9, 66.6, 61.0, 55.8, 30.3, 27.0, 26.8, 23.4, 22.2, 22.0, 21.0; IR (KBr): 2935, 2869, 2836, 2198, 1739, 1573, 1484, 1341, 1273; HR m/e for C₂₂H₂₈O₄ calculated 356.1988 (M⁺), found 356.1990.

[2-((3-Isopropyl-4,5-dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152o)

Compound 151o (1.7960 g, 5.0421 mmol) was complexed according to General Procedure E. After washing the column of silica with 100% hexanes to remove excess, uncomplexed Co₂(CO)₈, the product (152o) was eluted using 5:1 hexanes:Et₂O, and isolated as a dark brown solid (2.8905 g, 4.5021 mmol, 89%). ¹H-NMR (500 MHz, CDCl₃): 6.92 (d, 1H, J = 1.8), 6.80 (d, 1H, J = 1.8), 4.66 (s, 2H), 3.86 (s, 3H), 3.86 (s, 3H), 3.34 (septet, 1H, J = 7.1), 2.40 (t, 2H, J = 6.0), 2.13 (t, 2H, J = 6.2), 1.98 (s, 3H), 1.70-1.80 (m, 4H), 1.22 (d,
Compounds 153o and 153o’

Compound 152o (0.2042 g, 0.3180 mmol) was reacted according to General Procedure F. The product was obtained as a pair of regioisomers, 153o (0.1361 g, 0.2338 mmol, 74%) and 153o’ (0.0098 g, 0.0168 mmol, 5%). The two regioisomers were separable by flash chromatography on neutralized silica (25:1 hexanes:Et₂O). The major product, 153o, eluted as the first band, and was isolated as a maroon solid. ¹H-NMR (500 MHz, CDCl₃): 7.09 (s, 1H), 3.88 (s, 6H), 3.47-3.53 (m, 1H), 3.15 (s, 2H), 2.33-2.37 (m, 4H), 1.69-1.80 (m, 4H), 1.40 (d, 6H, J = 7.2); NOE (500 MHz, CDCl₃): Irradiation at δ7.08 resonance gave enhancement of the δ3.88 resonance; ¹³C-NMR (75 MHz, CDCl₃): 200.3, 151.9, 149.0, 138.8, 138.0, 133.7, 131.2, 128.1, 113.9, 95.7, 92.1, 60.8, 55.7, 36.7, 33.0, 30.2, 29.0, 23.1, 22.8, 20.3; IR (Pt/diamond): 2955, 2931, 2871, 2083, 2042, 2006, 1586, 1459, 1307, 1241; HRMS: m/e for C₂₆H₂₄Co₂O₈ calculated 526.0237 (M-2CO⁺), found 526.0241.

Product compound 153o’ came off the column as the second band, and was isolated as a maroon solid. The combined yield was 79%, with a ratio of 13.9:1 major:minor (153o:153o’). ¹H-NMR (500 MHz, CDCl₃): 7.28 (s, 1H),
3.90 (s, 3H), 3.85 (s, 3H), 3.30 (septet, 1H, J = 7.2), 3.28 (s, 2H), 2.30-2.36 (m, 4H), 1.67-1.79 (m, 4H), 1.24 (d, 6H, J = 7.0); $^{13}$C-NMR (125 MHz, CDCl$_3$): 200.1, 151.0, 149.5, 141.5, 136.6, 133.8, 131.0, 128.3, 125.2, 95.0, 90.6, 61.0, 60.6, 33.7, 33.0, 30.5, 26.9, 23.4, 23.0, 22.7; IR (Pt/diamond): 2961, 2920, 2849, 2084, 2043, 2010, 1407, 1306, 1226; HRMS: m/e for C$_{26}$H$_{24}$Co$_2$O$_8$ calculated 554.0186 (M-CO$^+$), found 554.0197.

3-(Trimethylsilyl)ethynyl)thiophene (158)

Compound 158 was prepared according to General Procedure A from 3-bromothiophene (3.2657 g, 20.169 mmol). The reaction was placed in an oil bath set at 75 °C over the course of 20 h. The product was isolated as a yellow oil (2.2692 g, 12.604 mmol, 63%) via flash chromatography (100% hexanes), and was characterized as spectroscopically identical to reported values$^{45}$.

2-(Thiophen-3-ylethynyl)cyclohex-1-enecarbaldehyde (159)

3-(Trimethylsilyl)ethynyl)thiophene (158) (0.3651 g, 2.028 mmol) was subjected to General Procedure G with 2-bromocyclohex-1-ene-1-carbaldehyde (149b) (0.5779 g, 3.042 mmol). The reaction flask was placed in an oil bath set to 75 °C for the overnight (20 h) portion of the reaction. The product (159) (0.3511 g, 1.625 mmol, 80%) was isolated via preparative TLC (15:1 hexanes:Et$_2$O) as a yellow oil. $^1$H-NMR (500 MHz, CDCl$_3$): 10.29 (s, 1H), 7.53 (d, 1H, J = 2.1), 7.32 (dd, 1H, J = 5.0, J = 3.1), 7.15 (d, 1H, J = 5.4), 2.51 (t, 2H, J = 6.1), 2.31 (t, 2H, J = 6.2), 1.66-1.75 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): 193.0, 142.6, 140.1, 129.8, 129.7, 125.9, 121.5, 93.8,
86.1, 32.4, 22.2, 22.0, 21.2; IR (KBr): 3320, 3106, 2936, 2861, 2834, 2201, 1668, 1596; HRMS: m/e for C_{13}H_{12}OS calculated 216.0609 (M^+), found 216.0616.

**[2-(Thiophen-3-ylethynyl)cyclohex-1-enyl]methyl acetate (160)**

Compound 159 (0.3511 g, 1.625 mmol) was subjected to reduction and acetylation according to General Procedure D. The product (160) was isolated as a yellow oil (0.3957 g, 1.521 mmol, 94%) via preparative TLC (10:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.42 (d, 1H, J = 2.2), 7.27 (dd, 1H, J = 4.8, J = 2.9), 7.11 (d, 1H, J = 5.0), 4.88 (s, 2H), 2.30 (m, 2H), 2.17 (m, 2H), 2.10 (s, 3H), 1.65-1.68 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 171.3, 139.0, 129.9, 128.3, 125.4, 122.5, 120.0, 88.2, 87.7, 66.7, 30.2, 27.1, 22.2, 22.1, 21.1; IR (KBr): 3108, 2934, 2860, 2205, 1738, 1233; HR-MS: m/e for C_{15}H_{16}O₂S calculated 260.0871 (M^+), found 260.0876.

**[2-(Thiophen-3-ylethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (161)**

Compound 160 (0.3957 g, 1.521 mmol) was subjected to complexation procedures according to General Procedure E. The product (161) was isolated as a dark brown solid (0.7527 g, 1.379 mmol, 91%) via flash chromatography (10:1 hexanes:Et₂O). ¹H-NMR (500 MHz, CDCl₃): 7.32-7.34 (m, 2H), 7.06 (dd, 1H, J = 4.6, J = 1.7), 4.57 (s, 2H), 2.38 (t, 2H, J = 6.0), 2.14 (t, 2H, J = 6.1), 1.99 (s, 3H), 1.69-1.80 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 199.5, 170.8, 139.1, 133.6, 132.0, 128.5, 126.4, 123.7, 91.2, 87.3, 65.3, 33.2, 28.6, 23.3, 22.2, 20.9; IR (KBr): 2936, 2862, 2088, 2049, 2020, 1742, 1231; HRMS: m/e for C_{21}H_{16}Co₂O₈S calculated 461.9382 (M-3CO⁻), found 461.9398.
**Compound 162**

Compound 161 (0.1230 g, 0.2253 mmol) was treated with BF₃•OEt₂ (86 µL, 0.68 mmol) according to General Procedure F. The reaction was complete within 40 minutes, as assessed by TLC. The cyclized product was isolated as a maroon solid (0.1013 g, 0.2085 mmol, 93%) via flash chromatography (100% hexanes). ³H-NMR (500 MHz, CDCl₃): 7.20 (½ABq, 1H, J = 5.2), 7.15 (½ABq, 1H, J = 5.2), 3.43 (s, 2H), 2.40 (t, 2H, J = 6.0), 2.20 (t, 2H, J = 6.2), 1.70-1.79 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 199.9, 136.0, 135.9, 133.2, 131.1, 129.8, 123.7, 93.8, 83.2, 36.3, 34.0, 31.4, 23.1, 22.7; IR (KBr): 2934, 2864, 2091, 2045, 2016, 1424; HRMS: m/e for C₁₉H₁₂Co₂O₆S calculated 457.9069 (M-CO⁺), found 457.9088.

2,3,4,4a,5,10,11,11a-Octahydro-7,8-dimethoxy-1H-dibenzo[a,d]cycloheptene (165)

To a stirred solution of compound 153d (0.5101 g, 0.9446 mmol), dissolved in degassed 1,2-dichloroethane (14.4 mL), was added bis(trimethylsilyl)acetylene (429 µL, 1.89 mmol) and triethylsilane (754 µL, 4.72 mmol). The reaction was placed in an oil bath set at 65 °C, and allowed to stir for 6 h under a nitrogen atmosphere. Following the allotted time, the oil bath was removed, and the solution allowed to cool to room temperature, at which point, trifluoroacetic acid (3.6 mL) was added. After stirring for an additional 12 h, the mixture was dissolved in Et₂O (75 mL) and extracted with dH₂O (3 x 75 mL). The organic fraction was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Preparative TLC (15:1 hexanes:Et₂O) afforded compound 165 as a colourless solid of inseparable diastereomers (0.1980 g, 0.7610 mmol, 81%). ³H-NMR (500 MHz, CDCl₃):
6.66 (s, 1H), 6.65 (s, 1H), 6.64 (s, 1H), 6.60 (s, 1H), 3.86 (s, 9H), 3.85 (s, 3H), 2.86 (apparent t, 1H, J = 13.1), 2.76 (dd, 1H, J = 10.4, J = 14.0), 2.69 (m, 1H), 2.61 (dd, 1H, J = 14.0, J = 6.7), 2.32 (d, 1H, J = 14.0), 0.89-1.96 (m, 27H); ¹³C-NMR (125 MHz, CDCl₃):

146.6, 146.5, 146.5, 146.4, 135.4, 135.1, 134.3, 113.9, 113.1, 112.6, 112.5, 56.1, 56.0, 55.9, 48.5, 44.0, 43.8, 38.1, 36.4, 35.9, 35.4, 35.0, 26.8, 26.4; IR (KBr): 2919, 2851, 1516, 1449, 1271; HRMS: m/e for C₁₇H₂₄O₂ calculated 260.1776 (M⁺), found 260.1775.

**Compound 166**

To a stirred solution of compound 153d (0.1437 g, 0.2661 mmol) dissolved in degassed 1,2-dichloroethane (4.1 mL) was added bis(trimethylsilyl)acetylene (121 L, 0.532 mmol) and triethylsilane (213 L, 1.33 mmol). The reaction was placed in an oil bath set at 65 °C, and allowed to stir for 6 h under a nitrogen atmosphere. Following the 6h, the reaction was cooled, dissolved in Et₂O (75 mL) and extracted with dH₂O (3 x 75 mL). The organic fraction was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Preparative chromatography (15:1 hexanes:Et₂O) afforded compound 166 as the major isomer, and as a colourless solid (0.0862 g, 0.233 mmol, 86% combined yield) with a m.p. of 95-97 °C. ¹H-NMR (500 MHz, CDCl₃): 6.88 (s, 1H), 6.62 (s, 1H), 6.52 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.76 (s, 2H), 2.33 (m, 2H), 2.08 (m, 2H), 1.60 (m, 4H), 0.96 (t, 9H, J = 7.8), 0.78 (q, 6H, J = 7.8); NOE (500 MHz, CDCl₃): Pulsed SiEt₃ protons, saw aromatic; pulsed aromatic H, saw SiEt₃ protons; ¹³C-NMR (125 MHz, CDCl₃): 148.2, 146.1, 142.4, 138.4, 135.5, 131.8, 131.6, 128.4, 110.5, 110.4, 55.9, 55.8, 40.4, 30.9, 28.8, 22.9, 22.8, 7.6, 4.5; IR (KBr): 2950, 2932, 2873, 1604, 1508, 1463, 1262;
Compound 167

**METHOD A:** To a stirred solution of 166 (0.0849 g, 0.229 mmol) in degassed 1,2-dichloroethane (3.5 mL) was added trifluoroacetic acid (88 µL, 1.2 mmol), and the reaction was allowed to stir for 3 h at room temperature under a nitrogen atmosphere. Following the allotted time, the mixture was dissolved in Et₂O (75 mL) and extracted with dH₂O (3 x 75 mL). The organic fraction was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Preparative TLC (15:1 hexanes:Et₂O) afforded compound 167 as a colourless solid (0.0570 g, 0.222 mmol, 97%), with a m.p. of 88-90 °C.

**METHOD B:** Compound 153d was decomplexed according to methods adapted from Takai *et. al.* To a stirred solution of 153d (0.3209 g, 0.5943 mmol) in degassed 2-methoxyethanol (9.1 mL) was added sodium hypophosphite monohydrate (0.3149 g, 2.972 mmol). The solution was placed in an oil bath set at 65 °C, and allowed to stir for overnight (18 h) under a nitrogen atmosphere. The next day, the reaction mixture was filtered through Celite® and extracted with ethyl acetate (3 x 75 mL). The pooled organic fraction were dried over MgSO₄, filtered, and the organic solvent removed under reduced pressure. Preparative TLC afforded compound 167 as colourless crystals (0.1164 g, 0.4544 mmol, 76%). ¹H-NMR (300 MHz, CDCl₃): 6.84 (d, 1H, J = 11.6), 6.81 (s, 1H), 6.65 (s, 1H), 6.24 (d, 1H, J = 11.5), 3.91 (s, 3H), 3.88 (s, 3H), 2.89 (s, 2H), 2.35 (m, 2H), 2.12 (m, 2H), 1.56-1.66 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): 149.7, 146.9, 132.2, 129.8, 129.5, 128.8, 128.1, 110.4, 110.1, 56.1, 40.5, 31.6, 29.4, 23.1, 23.0; IR (KBr): 2998, 2930, 2833, 1605, 1510, 1353, 1263; HRMS:
m/e for \(\text{C}_{17}\text{H}_{20}\text{O}_{2}\) calculated 256.1463 \((\text{M}^+)\), found 256.1457.

2-Bromocyclopent-1-ene-1-carbaldehyde (149a) (GENERAL PROCEDURE J)

A stirred solution of \(\text{CH}_2\text{Cl}_2\) (56.6 mL) and DMF (13.8 mL, 178 mmol) under a nitrogen atmosphere was cooled to 0 °C. PBr\(_3\) (15.1 mL, 160 mmol) was added dropwise, and the slurry allowed to stir for 1 h at that temperature. After the hour, cyclopentanone (5.0000 g, 59.440 mmol) was added to the solution, and the reaction was allowed to warm up to room temperature and proceed overnight (20 h). The following day, the solution was poured over ice and neutralized with NaHCO\(_3\) (s) to a pH of 7-8. The mixture was then extracted with Et\(_2\)O (3 x 150 mL), and the combined organic fractions further extracted with brine (3 x 150 mL). The organic fraction was then dried over MgSO\(_4\), filtered, and the solvent removed under reduced pressure. Flash chromatography (15:1 hexanes:Et\(_2\)O) afforded compound 149a as a yellow oil (3.9653 g, 22.656 mmol, 38%). The compound was spectroscopically identical to reported values\(^{161}\).

2-Bromocyclohex-1-ene-1-carbaldehyde (149b)

Cyclohexanone (10.0000 g, 101.895 mmol) was treated according to General Procedure J. Compound 149b was isolated using flash chromatography (15:1 hexanes:Et\(_2\)O) as a yellow oil (14.2846 g, 75.5599 mmol, 74%), that was characterized with spectroscopically identical values to those reported\(^{161}\).

2-Bromocyclohept-1-ene-1-carbaldehyde (149c)

Cycloheptanone (5.0000 g, 44.574 mmol) was treated according to General Procedure J.
Compound 149c was isolated using flash chromatography (15:1 hexanes:Et₂O) as a yellow oil (7.1250 g, 35.085 mmol, 79%), that was characterized with spectroscopically identical values to those reported.\textsuperscript{161}

**2-Bromo-3-(trimethylsilyl)-1-propene (171)**

2,3-Dibromopropene was treated according to methods adapted from Trost \textit{et. al.}\textsuperscript{186}. Prior to use, 2,3-dibromopropene was distilled via Kugelrohr distillation at 120 °C using a 200 Torr vacuum line. A mixture of 2,3-dibromopropene (10.0000 g, 50.5388 mmol) and trichlorosilane (7.7354 g, 57.109 mmol) was added dropwise to a stirred solution of copper (I) chloride (0.2501 g, 2.527 mmol) in Et₂O (24.5 mL) containing NEt₃ (7.0 mL, 50 mmol), at a rate to maintain a gentle reflux. A voluminous white precipitate formed, and when addition was complete, the slurry was stirred an additional 6 h. After the mixture was cooled to 0 °C, MeMgBr (3.0 M in Et₂O, 75.8 mL, 227 mmol) was added dropwise, and stirring was continued over a 12 h period. The reaction was quenched carefully with 1 L of NH₄Cl (aq., sat.), the mixture was poured into a mixture of 500 mL of Et₂O and 500 mL of water, and the layers were separated. The organic layer was washed with two 200 mL portions of water, and the combined aqueous layers were extracted with two 200 mL portions of Et₂O. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. Kugelrohr distillation at 200 Torr and 120 °C afforded compound 171 (8.0839 g, 42.104 mmol, 83%) as a pale yellow oil, which was characterized as spectroscopically identical to reported values.\textsuperscript{186}

**2-[(Trimethylsilyl)ethynyl]cyclohex-1-enecarbaldehyde (168a)**

2-Bromocyclohex-1-ene-1-carbaldehyde (149b) (2.5314 g, 13.466 mmol) was subjected to
General Procedure C with trimethylsilylacetylene (2.6453 g, 26.932 mmol), and with THF in place of DMF. Compound 168a was isolated as a yellow oil (2.3527 g, 11.415 mmol, 85%) via flash chromatography (20:1 hexanes:Et$_2$O). The material was spectroscopically identical to reported values.$^{190}$

**[2-((Trimethylsilyl)ethynyl)cyclohex-1-enyl]methyl acetate (169a)**

Compound 168a (1.4485 g, 7.0277 mmol) was subjected to General Procedure D. The product was isolated as a pale yellow oil (1.6033 g, 6.4096 mmol, 91%) via flash chromatography (10:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, C$_6$D$_6$): 4.94 (s, 2H), 2.08 (t, 2H, J = 6.1), 1.91 (t, 2H, J = 6.1), 1.66 (s, 3H), 1.26-1.33 (m, 4H), -0.15 (s, 9H); $^{13}$C-NMR (75 MHz, C$_6$D$_6$): 169.6, 140.5, 119.7, 104.5, 97.7, 66.0, 29.9, 26.7, 21.9, 21.8, 20.1, -0.2; IR (Pt/diamond): 2933, 2861, 2140, 1741, 1366, 1227; HRMS: m/e for C$_{14}$H$_{22}$O$_2$Si calculated 250.1389 (M$^+$), found 250.1386.

**(2-Ethynylcyclohex-1-enyl)methyl acetate (170a)**

Compound 169a (1.6033 g, 6.4096 mmol) was desilylated according to General Procedure B (with the modification that 1.3 equivalents of KF•2H$_2$O were used instead of 2.2 equivalents). The reaction was allowed to warm to room temperature over the course of 2 h, at which point, TLC analysis showed the desilylation to be complete. Compound 170a was isolated as a yellow oil (1.0047 g, 5.6412 mmol, 88%) following flash chromatography (10:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, C$_6$D$_6$): 4.84 (s, 2H), 2.98 (s, 1H), 2.03 (t, 2H, J = 6.0), 1.89 (t, 2H, J = 6.0),
1.70 (s, 3H), 1.26-1.33 (m, 4H); $^{13}$C-NMR (75 MHz, $\text{C}_6\text{D}_6$): 169.8, 140.7, 118.7, 82.4, 81.4, 65.9, 29.9, 26.6, 21.8, 21.7, 20.1; IR (Pt/diamond): 3286, 2932, 2861, 1736, 1366, 1227; HRMS: m/e for $\text{C}_{11}\text{H}_{14}\text{O}_2$ calculated 178.0994 (M$^+$), found 178.0998.

[2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohex-1-enyl)methyl acetate (170a)]

Compound 170a (1.0047 g, 5.6412 mmol) was subjected to Sonogashira conditions according to General Procedure C with 2-bromo-3-(trimethylsilyl)-1-propene (171) (1.8413 g, 9.5901 mmol). The coupled compound 172a was isolated as a yellow oil (1.4095 g, 4.8575 mmol, 86%) using flash chromatography (10:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 5.15 (d, 1H, J = 2.0), 4.98 (m, 1H), 4.77 (s, 2H), 2.18 (m, 2H), 2.10 (m, 2H), 2.05 (s, 3H), 1.66 (s, 2H), 1.58-1.65 (m, 4H), 0.04 (s, 9H); $^{13}$C-NMR (125 MHz, CDCl$_3$): 171.0, 138.3, 128.8, 120.1, 118.6, 95.3, 87.0, 66.5, 30.1, 28.3, 26.9, 22.1, 22.0, 20.9, -1.6; IR (KBr): 2934, 2894, 2862, 2195, 1743, 1594, 1376, 1232; HRMS: m/e for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Si}$ calculated 290.1702 (M$^+$), found 290.1708.

[2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohex-1-enyl)methyl acetate dicobalt hexacarbonyl (173a) (GENERAL PROCEDURE K)]

Compound 172a (1.4095 g, 4.8575 mmol) was dissolved in Et$_2$O (dry) (56.2 mL) along with excess Co$_2$(CO)$_8$. The solution was cooled to 0°C, and allowed to stir for 1 h at that temperature under a nitrogen atmosphere. Following the hour, the solvent was removed under reduced pressure, and the residue was loaded onto a flash chromatographic column containing neutralized silica. The complexed compound (173a)
was isolated by first washing the column with 100% hexanes to remove any excess, uncomplexed Co$_2$(CO)$_8$, followed by 10:1 hexanes:Et$_2$O to elute the product as a maroon solid (2.5800 g, 4.4791 mmol, 92%). $^1$H-NMR (500 MHz, C$_6$D$_6$): 5.41 (s, 1H), 5.17 (s, 1H), 4.92 (s, 2H), 2.35 (t, 2H, J = 5.9), 1.98 (t, 2H, J = 6.1), 1.85 (s, 2H), 1.70 (s, 3H), 1.44-1.49 (m, 2H), 1.34-1.39 (m, 2H), 0.07 (s, 9H); $^{13}$C-NMR (75 MHz, C$_6$D$_6$): 200.0, 169.8, 144.1, 133.8, 131.4, 116.0, 100.0, 93.9, 65.0, 33.4, 28.1, 26.8, 23.2, 22.0, 20.1, -1.1; IR (KBr): 2938, 2863, 2087, 2048, 2020, 1744, 1607, 1377, 1231; HRMS: m/e for C$_{23}$H$_{26}$Co$_2$O$_8$Si calculated 408.0366 (M+-6CO), found 408.0363.

**Compound 174a (GENERAL PROCEDURE L)**

Complexed compound 173a (0.1836 g, 0.3187 mmol) was placed in a round bottom flask, and put under vacuum for 5 minutes. The flask was then purged with nitrogen. This was repeated two times more. Dry CH$_2$Cl$_2$ (45.5 mL) was added to the reaction flask, and the solution was cooled to 0°C. N,N-Diisopropylethylamine (83 μL, 0.48 mmol) was added to the solution, followed by the dropwise addition of SnCl$_4$ (112 μL, 0.956 mmol). The reaction was allowed to stir for 20 minutes under nitrogen, at which point TLC analysis showed the reaction to be complete. The solution was then quenched with NH$_4^+$Cl$^{-}$ (aq., sat.), and extracted with NH$_4^+$Cl$^{-}$ (aq., sat., 2 x 75 mL) and brine (1 x 75 mL). The organic fraction was then dried over MgSO$_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography on neutralized silica using 100% hexanes eluted compound 174a (0.1115 g, 0.2512 mmol, 79%) as a maroon solid. $^1$H-NMR (300 MHz, C$_6$D$_6$): 5.63-5.64 (m, 1H), 5.24 (apparent q, 1H, J = 1.3), 2.34-2.38 (m, 2H), 2.27-2.30 (m, 2H), 1.99-2.02
(m, 2H), 1.68-1.72 (m, 2H), 1.42-1.50 (m, 2H), 1.30-1.39 (m, 2H); \textsuperscript{13}C-NMR (75 MHz, C\textsubscript{6}D\textsubscript{6}): 200.3, 147.7, 140.5, 128.4, 118.9, 94.2, 89.1, 35.9, 33.7, 33.2, 30.2, 22.9, 22.6; IR (KBr): 2933, 2863, 2087, 2053, 1612, 1432, 1237; HRMS: m/e for C\textsubscript{18}H\textsubscript{14}Co\textsubscript{2}O\textsubscript{6} calculated 415.9505 (M-CO\textsuperscript{+}), found 415.9513.

2-[(Trimethylsilyl)ethynyl]cyclohept-1-enecarbaldehyde (168b)

![Chemical structure]

2-Bromocyclohept-1-ene-1-carbaldehyde (149c) (0.5512 g, 2.729 mmol) was subjected to General Procedure C with trimethylsilylacetylene (0.5360 g, 5.457 mmol), and with THF in place of DMF. Compound 168b was isolated as a yellow oil (0.5393 g, 2.450 mmol, 90%) via preparative TLC (20:1 hexanes:Et\textsubscript{2}O). \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): 10.13 (s, 1H), 2.53-2.55 (m, 2H), 2.42-2.44 (m, 2H), 1.74 (apparent pentet, 2H, J = 5.8), 1.58 (apparent pentet, 2H, J = 5.6), 1.38 (apparent pentent, 2H, J = 5.6), 0.17 (s, 9H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): 192.4, 148.3, 145.4, 106.3, 102.7, 37.2, 32.2, 25.6, 25.5, 24.1, -0.27; IR (KBr): 2958, 2925, 2853, 2133, 1675, 1449, 1251; HRMS: m/e for C\textsubscript{13}H\textsubscript{20}OSi calculated 220.1283 (M\textsuperscript{+}), found 220.1274.

[2-((Trimethylsilyl)ethynyl)cyclohept-1-enyl]methyl acetate (169b)

Compound 168b (0.5340 g, 2.426 mmol) was subjected to General Procedure D. The product was isolated as a yellow oil (0.6001 g, 2.272 mmol, 94%) via radial chromatography (10:1 hexanes:Et\textsubscript{2}O). \textsuperscript{1}H-NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): 4.99 (s, 2H), 2.28-2.30 (m, 2H), 2.06-2.09 (m, 2H), 1.65 (s, 3H), 1.45 (apparent pentet, 2H, J = 5.9), 1.26-1.35 (m, 4H), 0.16 (s, 9H); \textsuperscript{13}C-NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): 169.6, 146.5, 125.6, 105.7, 98.3, 67.3,
34.4, 32.1, 30.9, 25.9, 25.8, 20.0, -0.27; IR (Pt/diamond): 2922, 2851, 2136, 1740, 1375, 1226; HRMS: m/e for C_{15}H_{24}O_{2}Si calculated 264.1546 (M⁺), found 264.1547.

**2-Ethynylcyclohept-1-enyl)methyl acetate (170b)**

Compound 169b (0.6001 g, 2.272 mmol) was desilylated according to General Procedure B (with the modification that 1.3 equivalents of KF•2H_{2}O were used instead of 2.2 equivalents). The reaction was kept at 0 °C over 1.5 h, at which point, TLC analysis showed the desilylation to be complete. Compound 170b was isolated as a yellow oil (0.3601 g, 1.874 mmol, 82%) following radial chromatography (10:1 hexanes:Et_{2}O). ^1H-NMR (500 MHz, C₆D₆): 4.95 (s, 2H), 2.94 (s, 1H), 2.23-2.26 (m, 2H), 2.04-2.06 (m, 2H), 1.66 (s, 3H), 1.44 (apparent pentet, 2H, J = 5.8), 1.25-1.34 (m, 4H); ^13C-NMR (125 MHz, C₆D₆): 169.8, 146.7, 124.7, 83.7, 82.0, 67.2, 34.4, 32.0, 30.8, 25.8, 25.7, 20.0; IR (Pt/diamond): 3282, 2922, 2850, 1736, 1376, 1227; HRMS: m/e for C_{12}H_{16}O_{2} calculated 192.1150 (M⁺), found 192.1142.

**2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohept-1-enyl)methyl acetate (172b)**

Compound 170b (0.3601 g, 1.874 mmol) was subjected to Sonogashira conditions according to General Procedure C with 2-bromo-3-(trimethylsilyl)-1-propene (171) (0.6118 g, 3.186 mmol). The coupled compound (172b) was isolated as a yellow oil (0.5127 g, 1.685 mmol, 90%) via preparative TLC (10:1 hexanes:Et₂O). ^1H-NMR (500 MHz, C₆D₆): 5.28 (d, 1H, J = 2.2), 4.96 (s, 2H), 4.92-4.93 (m, 1H), 2.31-2.33 (m, 2H), 2.10-2.12 (m, 2H), 1.68 (s, 3H), 1.66 (d, 2H, J = 1.0), 1.50 (apparent pentet, 2H, J = 5.8), 1.38 (apparent pentet, 2H, J = 5.6), 1.32 (apparent pentet, 2H, J = 5.7), 0.08 (s, 9H); ^13C-NMR (75
Compound 173b (0.5127 g, 1.685 mmol) was complexed using General Procedure K to afford complexed product 173b (0.9250 g, 1.568 mmol, 93%) as a dark green solid, which eluted off a flash chromatographic column of neutralized silica using 10:1 hexanes:Et₂O after all the excess, uncomplexed Co₂(CO)₆ had been washed off with 100% hexanes. ¹H-NMR (500 MHz, C₆D₆): 5.40 (s, 1H), 5.15 (s, 1H), 4.94 (s, 2H), 2.50-2.52 (m, 2H), 2.14-2.16 (m, 2H), 1.84 (s, 2H), 1.71 (s, 3H), 1.49-1.55 (m, 4H), 1.36 (apparent pentet, 2H, J = 5.4), 0.09 (s, 9H); ¹³C-NMR (75 MHz, C₆D₆): 200.0, 169.8, 144.3, 139.3, 138.5, 115.9, 101.6, 94.4, 65.5, 37.5, 32.6, 32.1, 27.0, 26.9, 25.9, 20.1, -1.1; IR (KBr): 2926, 2854, 2087, 2049, 2020, 1743, 1229; HRMS: m/e for C₁₈H₂₈O₂Si calculated 304.1859 (M⁺), found 304.1872.

Compound 174b

Compound 173b (0.6755 g, 1.145 mmol) was treated according to General Procedure L. The reaction was complete within 20 minutes, as assessed by TLC. The cyclized product (174b) was isolated as a maroon solid (0.4346 g, 0.9490 mmol, 83%), using 100% hexanes for flash chromatography on neutralized silica. ¹H-NMR (500 MHz, C₆D₆):
5.60 (s, 1H), 5.21 (s, 1H), 2.45-2.47 (m, 2H), 2.30-2.32 (m, 2H), 2.15-2.18 (m, 2H), 1.99-2.01 (m, 2H), 1.45-1.58 (m, 4H), 1.28 (apparent pentet, 2H, J = 5.7); $^{13}$C-NMR (75 MHz, C$_6$D$_6$): 200.3, 147.6, 147.0, 133.9, 118.4, 95.4, 90.0, 39.2, 38.4, 34.7, 33.8, 32.2, 26.5, 26.1; IR (KBr): 2924, 2851, 2086, 2046, 2016, 1598, 1432, 1213; HRMS: m/e for C$_{19}$H$_{16}$Co$_2$O$_6$ calculated 457.9611 (M$^+$), found 457.9631.

2-Ethynylcyclohept-1-enecarbaldehyde (179)

Compound 168b (2.2063 g, 10.023 mmol) was desilylated according to General Procedure B (with the modification that 1.3 equivalents of KF•2H$_2$O were used instead of 2.2 equivalents). The reaction was kept at 0 °C over 0.5 h, at which point, TLC analysis showed the desilylation to be complete. Compound 179 was isolated as a yellow oil (1.1224 g, 7.579 mmol, 76%) following radial chromatography (10:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 10.13 (s, 1H), 3.60 (s, 1H), 2.58-2.6.0 (m, 2H), 2.46-2.48 (m, 2H), 1.77 (apparent p, 2H, J = 6.0), 1.60 (apparent p, 2H, J = 5.6), 1.41 (apparent p, 2H, J = 5.9); $^{13}$C-NMR (75 MHz, CDCl$_3$): 192.1, 150.3, 144.4, 88.1, 81.8, 37.2, 32.2, 25.6, 25.4, 24.2; IR (KBr): 3259, 2925, 2852, 2086, 1673, 1449, 1254; HRMS: m/e for C$_{10}$H$_{12}$O calculated 148.0888 (M$^+$), found 148.0888.

2-[3-((Trimethylsilyl)methyl)but-3-en-1-ynyl]cyclohept-1-enecarbaldehyde (180)

Compound 179 (0.4557 g, 3.077 mmol) was subjected to Sonogashira conditions according to General Procedure C with 2-bromo-3-(trimethylsilyl)-1-propene (171) (1.0044 g, 5.2312 mmol). Triethylamine was substituted with diisopropylamine (20.5 mL), which had also been degassed for 1.5 h prior to use. The
coupled compound (180) was isolated as a yellow oil (0.4022 g, 1.546 mmol, 50%) via preparative TLC (10:1 hexanes:Et₂O). ¹H-NMR (300 MHz, C₆D₆): 10.52 (s, 1H), 5.25 (d, 1H, J = 1.8), 4.94 (apparent q, 1H, J = 1.3), 2.43-2.47 (m, 2H), 2.29-2.33 (m, 2H), 1.58 (s, 2H), 1.24-1.57 (m, 4H), 1.16 (apparent p, 2H, J = 5.6), 0.03 (s, 9H); ¹³C-NMR (75 MHz, C₆D₆): 190.7, 148.6, 144.1, 128.6, 120.5, 102.1, 87.1, 37.1, 32.0, 27.8, 25.6, 25.5, 24.2, -1.8; IR (Pt/diamond): 2923, 2851, 1670, 1598, 1248; HRMS: m/e for C₁₆H₂₄OSi calculated 260.1596 (M⁺), found 260.1590.

4-Iodo-2-isopropyl-1-methoxybenzene (186)

2-Isopropylanisole was synthesized using conditions reported by Hassan et al. 2-Isopropylanisole (0.6793 g, 4.992 mmol), K₂CO₃ (1.3798 g, 9.9832 mmol), and iodomethane (1.4170 g, 9.9832 mmol) were all dissolved in DMF (2.5 mL) in a round bottom flask. The solution was stirred overnight (20 h) at 40 °C. The reaction mixture was then diluted with Et₂O (100 mL) and washed with brine (3 x 100 mL). The organic portion was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Flash chromatography (15:1 hexanes:Et₂O) afforded 2-isopropylanisole as a yellow oil (0.6744 g, 4.493 mmol, 90%), which was characterized as spectroscopically identical to reported values. This product was then subjected to General Procedure I. The iodinated product (186) was recovered as a yellow oil (1.1301 g, 4.0945 mmol, 91%) as the sole regioisomer, and was characterized as spectroscopically identical to reported values.

2-Bromo-1-iodo-3-isopropyl-4,5-dimethoxybenzene (187)

5-Iodo-1-isopropyl-2,3-dimethoxybenzene (155g) was brominated using conditions reported
by Fürstner and Kennedy. To a stirred solution of compound 155g (0.8493 g, 2.775 mmol) dissolved in glacial acetic acid (4.2 mL), Br₂ (127 µL, 2.50 mmol) was added dropwise, and the resulting orange mixture was allowed to stir at room temperature under a nitrogen atmosphere for 26 h. Following this time, the solution was diluted with water (100 mL) and extracted with hexanes (3 x 75 mL). The combined orange extracts were washed with Na₂S₂O₃ (aq., sat, 3 x 75 mL) and brine (1 x 75 mL), dried over MgSO₄, filtered, and the organic solvent removed under reduced pressure. Flash chromatography (10:1 hexanes:Et₂O) resulted in the isolation of compound 187 as a yellow oil (0.6468 g, 1.685 mmol, 61%, 75% based on recovered starting material), and the first band eluted. The starting material eluted off the column as the second band and was recovered as its yellow oil (0.1630 g, 0.5326 mmol, 19%). ¹H-NMR (500 MHz, CDCl₃): 7.30 (s, 1H), 3.82 (s, 6H), 3.69 (m, 1H), 1.32 (d, 6H, J = 7.1); NOE (500 MHz, CDCl₃): Irradiation at δ7.30 resonance gave enhancement of the δ3.82 resonance; ¹³C-NMR (75 MHz, CDCl₃): 152.4, 142.3, 121.9, 61.0, 56.1, 37.8, 21.1; IR (Pt/diamond): 2958, 2932, 2871, 1562, 1420, 1225; HRMS: m/e for C₁₁H₁₄BrI₂O₂ calculated 383.9222 (M⁺), found 383.9218.

6,6-Dimethyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (191)

Compound 191 was synthesized according to methods adapted from Majetich and Grove and Smith et. al. 1,3-Cyclohexanedione (10.0000 g, 89.2439 mmol) and pTsOH•H₂O (0.5000 g, 2.628 mmol) were dissolved in ethanol (200 mL), and refluxed for 72 h under a nitrogen atmosphere. The solvent was then evaporated, and Kugelrohr distillation at 0.1
Torr afforded 3-ethoxycyclohex-2-enone (12.0515 g, 86.0307 mmol, 96%) as a colourless solid. This compound was verified by $^1$H- and $^{13}$C-NMR spectroscopy, and found to be identical to reported values\textsuperscript{114}.

This compound was then dissolved in CH$_2$Cl$_2$ (118 mL), along with 1,3,5-trioxane (16.6528 g, 184.966 mmol) under a nitrogen atmosphere. The reaction flask was cooled to 0 °C, at which point BF$_3$$\cdot$OEt$_2$ (20.8 mL, 164 mmol) was added dropwise over 5 minutes. The reaction was allowed to warm up to room temperature, and continue for another 16 h. Following this time, the mixture was filtered through Celite®, and subsequently rinsed twice with CH$_2$Cl$_2$. The solution was then cooled to 0 °C, and slowly quenched with NaHCO$_3$ (aq., sat.). The organic layer was then extracted with brine (2 x 150 mL), dried over MgSO$_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography (1:1 hexanes:Et$_2$O) led to the isolation of the dioxinone as a yellow oil (12.2595 g, 79.5746 mmol, 92%). This compound was verified by $^1$H- and $^{13}$C-NMR spectroscopy, and found to be identical to reported values\textsuperscript{114}.

A fraction of this dioxinone (2.0906 g, 13.570 mmol) was then subjected to monomethylation. A stirred solution of diisopropylamine (2.7 mL, 19 mmol) in THF (27.1 mL) was cooled to -78 °C. $^n$BuLi (2.5 M in hexanes, 6.8 mL 17 mmol) was added dropwise, and the solution allowed to stir for 30 minutes to generate LDA. Following the 0.5 h, the dioxinone, dissolved in THF (13.6 mL), was added to the reaction flask dropwise over 5 minutes. This solution was allowed to stir for 1 h at -78 °C. MeI (3.8522 g, 27.140 mmol), dissolved in THF (7.7 mL), was added to the reaction following the hour, and stirring continued at -78 °C for another hour. The reaction was warmed to -30 °C over 30 minutes,
and stirred at this temperature for a further hour. It was then warmed to 0 °C and stirred for an additional three hours. At this point, the reaction was quenched with NH$_4$Cl (aq., sat.), and then the aqueous layer was extracted with Et$_2$O (3 x 75 mL). The collected organic fractions were then extracted with NH$_4$Cl (aq., sat., 1 x 150 mL) and brine (1 x 150 mL). Drying over MgSO$_4$, filtration, and removal of solvent under reduced pressure provided the monomethylated product in a sufficiently pure state for further use as a yellow oil (1.8475 g, 10.992 mmol, 81%). This product was verified by $^1$H- and $^{13}$C-NMR spectroscopy, and found to be identical to reported values.

The monomethylated compound, without further purification, was then subjected to the same procedure to generate the gem-dimethyl product (191) (1.9012 g, 10.441 mmol, 95%), which was isolated as a viscous pale yellow oil following flash chromatography (2:1 hexanes:Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$): 5.11 (s, 2H), 4.39 (t, 2H, J = 1.9), 2.40-2.44 (m, 2H), 1.81 (t, 2H, J = 6.4), 1.10 (s, 6H); $^{13}$C-NMR (125 MHz, CDCl$_3$): 201.2, 168.2, 109.7, 91.3, 63.2, 40.1, 34.3, 24.8, 24.4; IR (Pt/diamond): 2961, 2928, 2865, 1630, 1392, 1236; HRMS: m/e for C$_{10}$H$_{14}$O$_3$ calculated 182.0943 (M$^+$), found 182.0944.

2-(Hydroxymethyl)-4,4-dimethyl-3-[(trimethylsilyl)ethynyl]cyclohex-2-enone (192)

Compound 192 was synthesized according to methods adapted from Majetich and Grove, and Brummond and Gao. In a round bottom flask, (trimethylsilyl)acetylene (1.7652 g, 17.972 mmol) was dissolved in THF (30.0 mL). The reaction flask was cooled to -78 °C, at which point, n-BuLi (2.5 M in hexanes, 5.4 mL, 13 mmol) was added dropwise into the stirred solution, and allowed to stir for 30 minutes. After the 30 minutes,
the reaction mixture was allowed to warm to 0 °C, at which point 191 (1.6363 g, 8.9860 mmol), dissolved in THF (9.0 mL), was added dropwise into the reaction flask, and the solution allowed to stir for 1 h. After the hour, the reaction was allowed to warm up to room temperature and proceed for another 6 h. The reaction was then quenched with NH₄⁺Cl⁻ (aq, sat.), and extraction of the aqueous layer with Et₂O (3 x 100 mL) was performed. The organic fractions were combined and extracted with NH₄⁺Cl⁻ (aq., sat., 1 x 100 mL) and brine (1 x 100 mL). The organic layer was then dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The viscous yellow oil was then dissolved in THF (38.0 mL), and 3 M HCl (1.3 mL) was added dropwise into the flask. This reaction was allowed to stir for 1 h at room temperature, after which it was quenched with NaHCO₃ (aq., sat.), and extracted with Et₂O (1 x 100 mL). The organic layer was then extracted with brine (2 x 100 mL), dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and flash chromatography (1:1 hexanes:Et₂O) afforded 192 (1.8928 g, 7.5670 mmol, 84%) as a pale yellow oil. ¹H-NMR (500 MHz, CDCl₃): 4.44 (d, 2H, J = 6.7), 3.04 (t, 1H, J = 6.8), 2.44 (t, 2H, J = 6.9), 1.82 (t, 2H, J = 6.9), 1.21 (s, 6H), 0.18 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃): 199.7, 148.1, 139.2, 113.0, 99.8, 60.6, 35.8, 35.4, 34.2, 27.4, -0.41; IR (KBr): 3474, 2963, 2930, 2902, 2869, 2137, 1664, 1581, 1356, 1251; HRMS: m/e for C₁₄H₂₂O₂Si calculated 250.1389 (M⁺), found 250.1387.

3-Ethynyl-2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (193)

Compound 192 (1.8928 g, 7.5670 mmol) was desilylated according to General Procedure B (with the modification that 1.3 equivalents of KF·2H₂O were used instead of 2.2 equivalents). The reaction was
complete within 30 minutes as assessed by TLC, and still while at 0 °C. The desilylated product (193) was isolated as a colourless solid (1.1875 g, 6.67 mmol, 88%) following flash chromatography (1:1 hexanes:Et₂O), with a m.p. of 83-84.5 °C. ¹H-NMR (500 MHz, CDCl₃): 4.39 (s, 2H), 3.82 (s, 1H), 3.04 (s, 1H), 2.43 (t, 2H, J = 6.9), 1.81 (t, 2H, J = 6.9), 1.19 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃): 199.9, 147.4, 140.4, 93.6, 73.9, 60.0, 35.9, 35.4, 34.2, 27.3; IR (Pt/diamond): 3395, 3201, 2956, 2930, 2895, 2867, 2080, 1644, 1574, 1360, 1196; HRMS: m/e for C₁₁H₁₄O₂ calculated 178.0994 (M⁺), found 178.0994.

2-(Hydroxymethyl)-3-[(3-isopropyl-4-methoxyphenyl)ethynyl]-4,4-dimethylcyclohex-2-enone (194) (GENERAL PROCEDURE M)

\[
\begin{align*}
\text{Pd(PPh₃)₄} & (0.1008 \text{ g, 0.08723 mmol, 5 mol\%}) \text{ and CuI} & (0.0266 \text{ g, 0.140 mmol, 8 mol\%}) \text{ were added to a round bottom flask and placed under vacuum for 10-15 minutes. The flask was then purged with nitrogen. This was repeated two times more}^{44}. \text{ A solution of 186 (0.7225 \text{ g, 2.618 mmol}) dissolved in dry DMF (2.9 mL) was added to the reaction flask, followed by a solution of 193 (0.3108 \text{ g, 1.745 mmol}) in dry DMF (2.9 mL). Diisopropylamine (11.6 mL), which had been degassed for 1.5 h prior, was then added to the reaction. The reaction was allowed to stir for 48 h under a nitrogen atmosphere and at room temperature. The mixture was then filtered through Celite®, the solution dissolved in Et₂O (75 mL), and then extracted with NH₄Cl (aq., sat., 2 x 75 mL), followed by brine (1 x 75 mL). The organic layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Preparative TLC (1:1 hexanes:Et₂O) afforded 194 as a thick yellow oil (0.3983 g, 1.221 mmol, 70%). ¹H-
\end{align*}
\]
NMR (500 MHz, CDCl₃): 7.30-7.34 (m, 2H), 6.80 (d, 1H, J = 8.4), 4.61 (d, 2H, J = 6.7), 3.84 (s, 3H), 3.28 (septet, 1H, J = 6.9), 3.16 (t, 1H, J = 6.8), 2.52 (t, 2H, J = 6.8), 1.91 (t, 2H, J = 6.8), 1.34 (s, 6H), 1.20 (d, 6H, J = 6.9); ¹³C-NMR (125 MHz, CDCl₃): 199.7, 158.2, 149.3, 137.6, 131.1, 129.8, 113.9, 110.4, 107.8, 84.1, 60.9, 55.4, 36.0, 35.8, 34.3, 27.7, 26.7, 22.4; IR (Pt/diamond): 3453, 2961, 2929, 2869, 2839, 2183, 1648, 1493, 1245; HR-MS: m/e for C₂₁H₂₆O₃ calculated 326.1882 (M⁺), found 326.1882.

[2-((3-Isopropyl-4-methoxyphenyl)ethynyl)-3,3-dimethyl-6-oxocyclohex-1-enyl]methyl acetate (195) (GENERAL PROCEDURE N)

In a round bottom flask, compound 194 (0.3983 g, 1.221 mmol) was dissolved in dry THF (14.1 mL), and the solution was cooled to a temperature of -78 °C (acetone/dry ice bath). Pyridine (3.0 mL, 37 mmol) was added to the reaction, followed by acetic anhydride (5.8 mL, 61 mmol) and DMAP¹⁶⁵,¹⁹⁷ (0.7459 g, 6.105 mmol). The reaction was allowed to warm up to room temperature under a nitrogen atmosphere over the course of 4 h, at which point TLC analysis showed the reaction to be done. The solution was then quenched with NH₄⁺Cl⁻ (aq., sat., 75 mL) and extracted with Et₂O (3 x 75 mL). The collected organic fractions were extracted further with NH₄⁺Cl⁻ (aq., sat., 1 x 75 mL) and brine (1 x 75 mL). The organic fraction was then dried over MgSO₄, filtered, the solvent removed under pressure, and finally preparative TLC (1:1 hexanes:Et₂O) afforded compound 195 as an off-white solid (0.4240 g, 1.152 mmol, 94%) with a m.p. of 123.5-124.5 °C. ¹H-NMR (500 MHz, CDCl₃): 7.30-7.32 (m, 2H), 6.78 (d, 1H, J = 8.3), 5.00 (s, 2H), 3.80 (s, 3H), 3.25 (septet, 1H, J = 6.9), 2.51 (t,
Compound 197

Compound 195 (0.2507 g, 0.6809 mmol) was dissolved in dry CH₂Cl₂ (97.2 mL) along with a slight excess of Co₂(CO)₈. The reaction was allowed to stir at room temperature under a nitrogen atmosphere for 2 h. Following the allotted time, the reaction flask was submerged into an ice bath to cool the reaction to 0 °C. At this point, SnCl₄ (238 μL, 2.04 mmol) was added dropwise into the reaction, followed by N,N-diisopropylethylamine (optional) (178 μL, 1.02 mmol). The reaction was then allowed to stir under a nitrogen atmosphere for another 15 h, while warming up to room temperature. Following the 15 h, the reaction was quenched with NH₄⁺Cl⁻ (aq., sat., 75 mL), as TLC analysis had shown the reaction to be complete. The organic portion was rinsed once more with NH₄⁺Cl⁻ (aq., sat., 75 mL) in a separatory funnel, and then with brine (75 mL). The organic fraction was then dried over MgSO₄, filtered, removed under reduced pressure, and the remaining residue quickly passed through a short column of silica to remove any excess impurities (100% hexanes, then 3:1 hexanes:Et₂O). The collected fraction (~0.16 g, ~0.27 mmol) was dissolved in degassed 2-methoxyethanol (4.1 mL) along with 5 equivalents of NaH₂PO₂•H₂O (0.1185 g, 1.347 mmol). The solution
was allowed to stir at 65 °C for 20 h under a nitrogen atmosphere. Following the allotted time, the reaction was passed through Celite®, and the collected fraction extracted in a separatory funnel with ethyl acetate (3 x 75 mL) and dH₂O (1 x 75 mL). The collected organic fractions were dried over MgSO₄, filtered, and the organic solvent removed under reduced pressure. Preparative chromatography (2:1 hexanes:Et₂O) isolated the product as a yellow oil (0.0592 g, 0.191 mmol, 28%). ¹H-NMR (500 MHz, CD₂Cl₂): 7.30 (d, 1H, J = 12.0), 7.15 (s, 1H), 6.77 (s, 1H), 6.67 (d, 1H, J = 11.9), 3.85 (s, 3H), 3.22-3.30 (m, 3H), 2.42 (t, 2H, J = 6.8), 1.82 (t, 2H, J = 6.8), 1.20 (s, 9H), 1.18 (s, 3H); NOE (500 MHz, CDCl₃): Irradiation at δ7.14 resonance gave enhancement of doublet further downfield and isopropyl protons at δ1.21. Irradiation at δ6.79 resonance gave enhancement of methoxy protons at 3.87; ¹³C-NMR (75 MHz, CD₂Cl₂): 196.3, 158.8, 155.9, 138.4, 137.1, 134.6, 128.3, 126.0, 125.8, 109.3, 55.5, 37.2, 34.8, 34.4, 30.5, 27.6, 26.6, 22.4; IR (Pt/diamond): 2957, 2923, 2866, 1657, 1496, 1255; HR-MS: m/e for C₂₁H₂₆O₂ calculated 310.1933 (M⁺), found 310.1932.

3-[(2-Bromo-3-isopropyl-4,5-dimethoxy phenyl)ethynyl]-2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (198)

Compound 198 was synthesized according to General Procedure M from 193 (0.3101 g, 1.741 mmol) and 187 (1.0027 g, 2.6117 mmol). Diisopropylamine was replaced with triethylamine. Preparative TLC (1:1 hexanes:Et₂O) afforded 198 as a thick yellow oil (0.4777 g, 1.100 mmol, 63%). ¹H-NMR (500 MHz, CDCl₃): 6.92 (s, 1H), 4.63 (d, 2H, J =
6.6), 3.85-3.87 (m, 6H), 3.65 (m, 1H), 3.12 (t, 1H, J = 7.2), 2.54 (t, 2H, J = 7.0), 1.93 (t, 2H, J = 7.0), 1.38 (s, 6H), 1.32 (d, 6H, J = 7.4); $^{13}$C-NMR (125 MHz, CDCl$_3$): 199.7, 152.2, 148.5, 141.4, 138.7, 115.0, 105.8, 88.2, 61.2, 60.9, 56.0, 36.1, 36.0, 34.3, 27.8, 20.8; IR (Pt/diamond): 3428, 2960, 2930, 2188, 1652, 1424, 1334; HR-MS: m/e for C$_{22}$H$_{27}$BrO$_4$ calculated 434.1093 (M$^+$), found 434.1075.

[2-((2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)ethynyl)-3,3-dimethyl-6-oxocyclohex-1-enyl]methyl acetate (199)

Compound 199 was synthesized according to General Procedure N from 198 (0.4777 g, 1.100 mmol). The product was isolated following preparative TLC (1:1 hexanes:Et$_2$O) as a colourless solid (0.4732 g, 0.9939 mmol, 90%) with m.p. 110-112 °C. $^1$H-NMR (500 MHz, CDCl$_3$): 7.04 (s, 1H), 5.05 (s, 2H), 3.88 (s, 6H), 3.64 (m, 1H), 2.57 (t, 2H, J = 7.0), 2.03 (s, 3H), 1.96 (t, 2H, J = 7.0), 1.41 (s, 6H), 1.32 (d, 6H, J = 7.4); $^{13}$C-NMR (75 MHz, CDCl$_3$): 196.4, 170.9, 152.5, 152.2, 141.3, 135.0, 119.8, 119.4, 115.5, 106.7, 88.3, 61.2, 59.6, 56.0, 36.5, 32.1, 34.1, 27.9, 21.1, 20.8; IR (Pt/diamond): 2936, 2869, 2185, 1725, 1669, 1569, 1425, 1213; HR-MS: m/e for C$_{24}$H$_{29}$BrO$_5$ calculated 476.1198 (M$^+$), found 476.1204.

Compound 200 and 201

Compound 199 (0.1123 g, 0.6809 mmol) was dissolved in dry CH$_2$Cl$_2$ (33.7 mL) along with a slight excess of Co$_2$(CO)$_8$. The reaction was allowed to stir at room temperature under a
nitrogen atmosphere for 2 h. Following the allotted time, the solvent was removed under reduced pressure and the residue passed through a short column of silica. The excess Co$_2$(CO)$_8$ was eluted first with 100% hexanes, followed by the complexed product with a 1:1 hexanes:Et$_2$O mix. The product was concentrated on a rotary evaporator, and immediately dissolved in dry CH$_2$Cl$_2$ (33.7 mL). The reaction flask was then submerged into an ice bath to cool the reaction to 0 °C. At this point, SnCl$_4$ (184 µL, 0.708 mmol) was added dropwise into the reaction, which was then allowed to continue stirring under a nitrogen atmosphere for another 5 h, while warming up to room temperature. Following the 5 h, the reaction was quenched with NH$_4^+$Cl$^-$ (aq., sat., 75 mL), as TLC analysis had shown the reaction to be complete. The organic portion was extracted with NH$_4^+$Cl$^-$ (aq., sat., 75 mL) in a separatory funnel, and then with brine (75 mL). The organic fraction was then dried over MgSO$_4$, filtered, removed under reduced pressure, and the remaining residue passed through a column of silica quickly to remove any excess impurities (1:1 hexanes:Et$_2$O). The collected fractions were dissolved in degassed 2-methoxyethanol (3.6 mL) along with 5 equivalents of NaH$_2$PO$_2$•H$_2$O (0.1038 g, 1.179 mmol). The solution was allowed to stir at 65 °C for 20 h under a nitrogen atmosphere. Following the allotted time, the reaction was passed through Celite®, and the collected fraction extracted in a separatory funnel with ethyl acetate (3 x 75 mL) and H$_2$O (1 x 75 mL). The collected organic fractions were dried over MgSO$_4$, filtered, and the organic solvent removed under reduced pressure. Preparative chromatography (2:1 hexanes:Et$_2$O) isolated the products as colourless solids with 201 (0.0207 g, 0.0608 mmol) as the major isomer (top band), m.p. 103-105 °C, and 200 (0.0035 g, 0.010 mmol) as the minor isomer (bottom band), m.p. 151-152 °C (ratio of 1:5.9 200:201). Compound 200 is
spectroscopically identical to reported values\textsuperscript{10}.

\textbf{201}: $^1$H-NMR (300 MHz, CD$_2$Cl$_2$): 7.29 (d, 1H, J = 11.9), 6.71-6.75 (m, 2H), 4.39 (m, 2H), 3.93 (septet, 1H, J = 7.0), 3.83 (s, 3H), 3.82 (s, 3H), 2.44 (t, 2H, J = 6.7), 1.82 (t, 2H, J = 6.6), 1.21-1.33 (m, 12H); NOE (500 MHz, CDCl$_3$): Irradiation at $\delta$6.73 resonance gave enhancement of doublet at $\delta$7.28 and methoxy protons at $\delta$3.86; $^{13}$C-NMR (75 MHz, CD$_2$Cl$_2$): 196.2, 155.8, 150.8, 138.9, 138.4, 131.6, 130.2, 129.5, 127.4, 109.5, 60.4, 55.5, 37.2, 34.6, 34.5, 28.5, 27.6, 26.2, 21.8; IR (Pt/diamond): 2956, 2930, 1655, 1461, 1328; HR-MS: m/e for C$_{22}$H$_{28}$O$_3$ calculated 340.2038 (M$^+$), found 340.2035.

\textbf{Compound 202}

Compound 197 (0.0152 g, 0.0490 mmol) was dissolved in dry, anhydrous CH$_2$Cl$_2$ (20.0 mL) along with excess Pd/C. The reaction was then allowed to stir at room temperature conditions while H$_2$ was purged through the solution. This was allowed to continue over 48 h. Following the allotted time, the mixture was filtered through Celite\textsuperscript{®}, the solvent removed under reduced pressure, and preparative chromatography (2:1 hexanes:Et$_2$O) isolated the products (0.0136 g, 0.0433 mmol, 88\%) as a colourless solid (the diastereomers were inseparable). $^1$H-NMR (500 MHz, CDCl$_3$): 6.91 (s, 1H), 6.68 (s, 1H), 3.80 (s, 3H), 3.38 (dd, 1H, J = 14.7, J = 1.1), 3.26 (septet, 1H, J = 6.9), 2.72-2.74 (m, 2H), 2.60-2.65 (m, 1H), 2.53 (triplet of doublets, 1H, J = 13.7, J = 6.9), 2.35 (doublet of triplets, 1H, J = 13.6, J = 3.2), 2.25 (t, 1H, J = 10.9), 2.13-2.18 (m, 1H), 1.67-1.77
(m, 2H), 1.61 (triplet of doublets, 1H, J = 11.5, J = 2.8), 1.18-1.22 (two sets of doublets, 6H, J = 6.9), 1.00-1.04 (two sets of singlets, 6H); $^{13}$C-NMR (125 MHz, CDCl$_3$): 212.6, 154.9, 138.2, 135.4, 134.4, 125.9, 112.0, 57.5, 55.6, 51.1, 42.2, 38.6, 34.2, 33.9, 33.8, 29.7, 29.6, 29.5, 26.4, 23.0, 22.6, 20.1; IR (Pt/diamond): 2948, 2859, 1707, 1503, 1261.
REFERENCES


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“The scientist is not a person who gives the right answers, but one who asks the right questions.” - *Claude Lévi-Strauss*