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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

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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

by

Izabela Kolodziej

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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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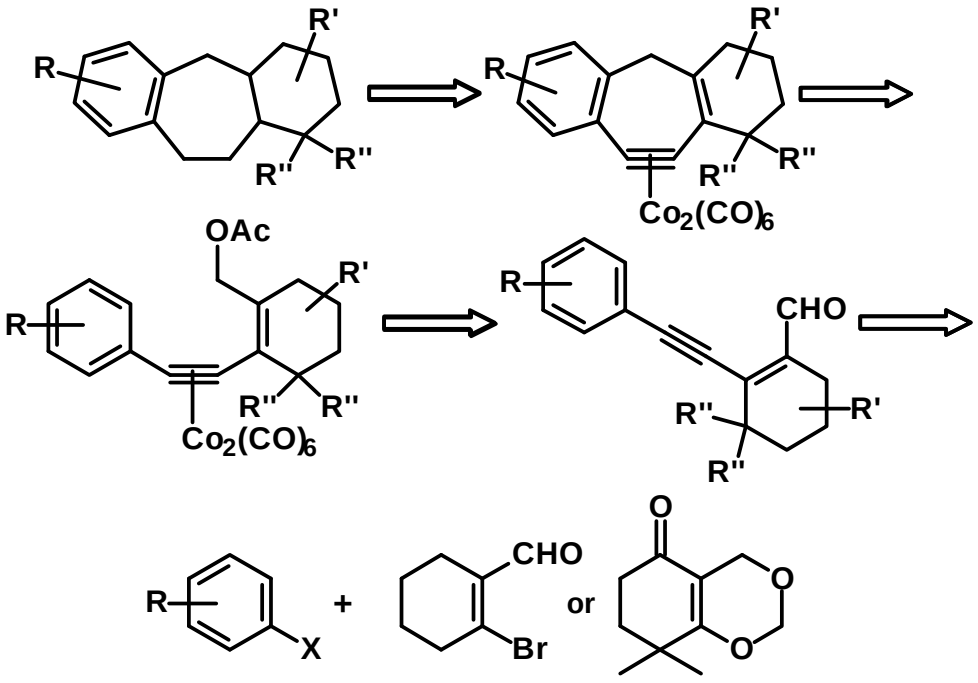
ABSTRACT

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 $[(progargylium)Co_2(CO)_6]^+$ 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/proparyglic 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*

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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.

I would like to extend further thanks to Mike Fuerth and Matt Revington for their assistance with the NMR spectroscopy, to Joe Lichaa for all his technical support, and to all the members in the surrounding labs and department for their interactions, friendship, and for sharing their chemicals. In addition, I would like to thank the administrative staff: Marlene Bezaire, Catherine Wilson, and Elizabeth Kickham for all their assistance during my years at graduate school; to the Janitorial staff for keeping us stocked and clean; to the CCC staff: Jerry, Alina, and Candy; and to Al Ditchburn for his stories and for fixing all our broken glassware.

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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LIST OF ABBREVIATIONS

Ac_2O	Acetic anhydride
$BF_3•OEt_2$	Boron trifluoride etherate
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
Bn	Benzyl
^{n}BuLi	*n*-Butyllithium
^{t}BuOH	*tert*-Butanol
Bu_2BOTf	Dibutyl boron triflate
Bu_3SnH	Tributyltin hydride
BTMSA	Bis(trimethylsilyl)acetylene
$^{n}C_5H_{11}$	*n*-Pentyl
CAN	Ceric ammonium nitrate
cm^{-1}	Wavenumber
m-CPBA	*meta*-Chloroperoxybenzoic acid
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dH_2O	Distilled water
DIB	(Diacetoxyiodo)benzene
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine

DMF	Dimethylformamide
Et	Ethyl
Et_2O	Diethyl ether
EtOH	Ethanol
EtSH	Ethanethiol
Et_3SiH	Triethylsilane
EtSNa	Sodium ethylthiolate
Hz	Hertz
J	J-coupling
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
Me_2AlCl	Dimethylaluminum chloride
MeCN	Acetonitrile
MeI	Iodomethane
MeMgBr	Methyl magnesium bromide
Me_2O	Dimethyl ether
MeOH	Methanol
$Me_2Al(OTf)$	Dimethylaluminum trifluoromethanesulphonate
MeSNa	Sodium methylthiolate
Na/Hg	Sodium amalgam
NaOEt	Sodium ethoxide

NEt_3	Triethylamine
Nu	Nucleophile
OAc	Acetate
OMe	Methoxy
$OSi(^{i}Pr)_3$	Triisopropylsilyl ether
OTBS	*tert*-Butyldimethylsilyl ether (TBDMS)
O/N	Overnight
Pd/C	Palladium on carbon
PDC	Pyridinium dichromate
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphopshine)palladium(II) dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
Ph	Phenyl
Ph_3SiH	Triphenylsilane
Piv	Pivaloyl
PPA	Polyphosphoric acid
ppm	Parts per million
^{i}Pr	Isopropyl
^{n}Pr	Propyl
$^{i}Pr_2NEt$	*N,N*-Diisopropylethylamine
$^{i}PrOH$	Isopropanol
$Pt(PPh_3)_3$	Tris(triphenylphosphino)platinum
Pyr	Pyridine

q	Quartet
R_f	Retention factor
RCM	Ring closing metathesis
ROH	Alcohol
RT	Room temperature
s	Singlet
$SiEt_3$	Triethylsilyl
$SnBu_3H$	Tributyltin hydride
t	Triplet
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
$TsNHNH_2$	*para*-Toluenesulphonyl hydrazide
p-TsOH•H_2O	*para*-Toluenesulphonic acid monohydrate

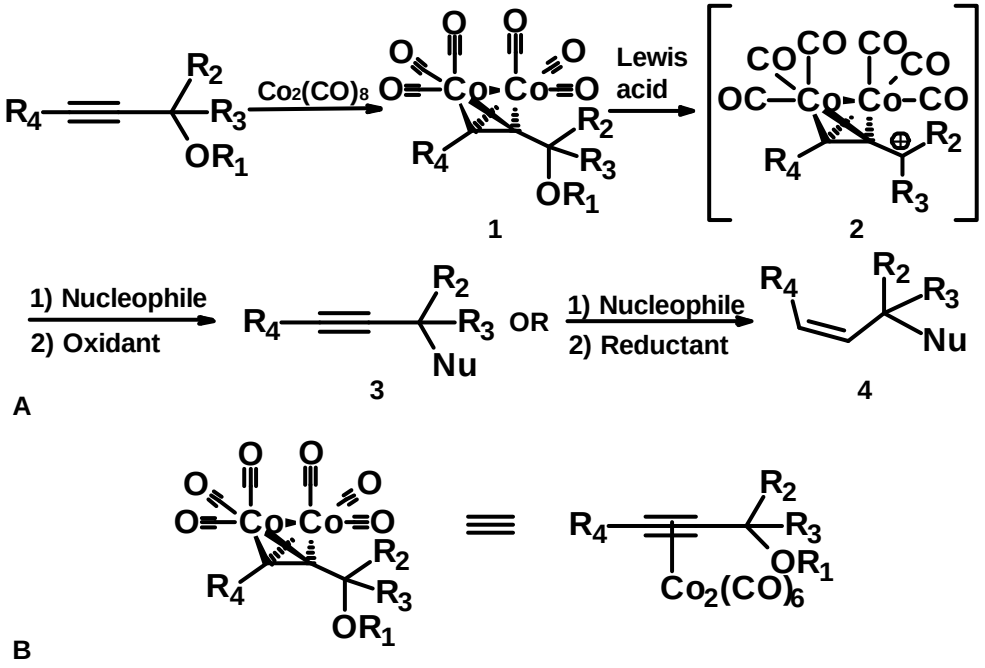
CHAPTER 1: INTRODUCTION

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[3]: the formation of cyclopentenones by the Pauson-Khand reaction[6,38,49,97,133,144], the nucleophilic addition to cobalt-complexed propargylic cations, known as the Nicholas reaction[18,30,51,64,65,66,93,137,139,169,185], and the use of the cobalt moiety as a useful protecting group[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*[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 ^oC) 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-enyne 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_N1 process[169]. Prior to the substitution step, the acetylene unit is treated with dicobalt octacarbonyl to yield the triple bond complexed as its μ-η^2-$Co_2(CO)_6$-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: S_N1' and S_N2' 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-hexafluoro-isopropyl)phosphite[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[66,102,169,185]. Other nucleophiles include hydrides[140], unactivated alkenes[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[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 **Angle Strained Cycloalkynes** section).

Mayr's group[105,125,127] have studied the reaction kinetics of some simple $Co_2(CO)_6$-stabilized propargyl cations with a variety of π-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)[66]. In 2000, the Mayr group[124,126] studied the reactivity of vinyl substituted alkyne-$Co_2(CO)_6$ 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 $[(propargylium)Co_2(CO)_6]^+$

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**).

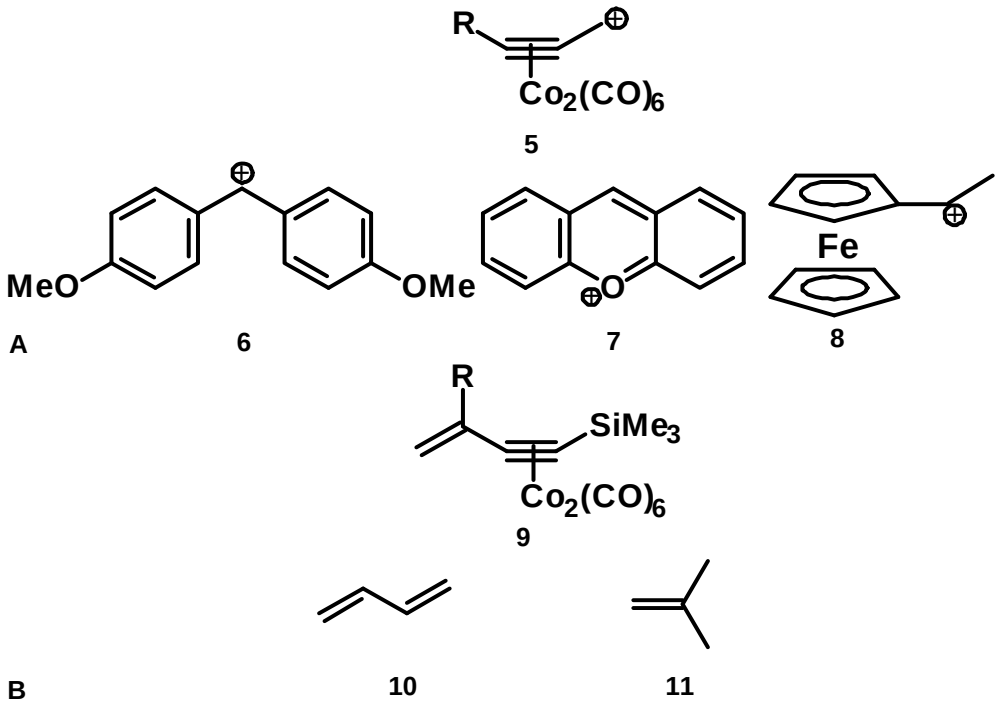


Figure 1.1: A) Relative electrophilicity of the [(propargylium)$Co_2(CO)_6$]$^+$ cation (R = H, *E* = -0.84; R = Ph, *E* = -1.58) (**5**) based on the Mayr scale: dianisylmethylium ion (*E* = 0.00) (**6**), xanthylium ion (*E* = -0.99) (**7**), and ferrocenylmethylium ion (*E* = -2.57) (**8**). B) Relative 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**).

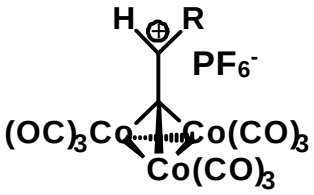
Facile decomplexation of the cobalt moiety has made Nicholas chemistry an even more attractive synthetic tool. After completion of the Nicholas reaction, the cobalt complex

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[185]: $Fe(NO_3)_3$ in alcohol (ROH), ROH/THF, or CH_2Cl_2; CAN in conjunction with a tertiary alcohol in acetone, MeOH, MeOH/H_2O, MeOH/Et_2O, or MeCN; I_2 in C_6H_6 or THF; trimethylamine *N*-oxide in THF, MeOH, or $CHCl_3$; and *N*-methylmorpholine *N*-oxide (in conjunction with 1,4-cyclohexadiene) in THF, CH_2Cl_2, ^{i}PrOH, DMF, or CCl_4/^{t}BuOH. Common reductive methods include: lithium in liquid NH_3; H_2 over Rh/charcoal in EtOH; H_2 over Wilkinson's catalyst in C_6H_6; Bu_3SnH in C_6H_6; $NaH_2PO_2 \bullet H_2O$ in 2-methoxyethanol; and Et_3SiH or Ph_3SiH in C_6H_6, which form their respective vinylsilanes. For other, rarer methods, the reader is directed to the Teobald review[185].

1.1.2. STABILITY OF THE $[(PROPARGYLIUM)Co_2(CO)_6]^+$ CATION

The stability of the propargyl carbocation intermediate arises from the benefit of the β-effect of the cobalt moiety: the complexes are remarkably stable due to significant delocalization of the positive charge onto the $Co_2(CO)_6$ unit. In 1973, *Seyferth et. al.*[168] studied three carbonium salts, $[(CCHR)Co_3(CO)_9]^+PF_6^-$ (**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[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*[29] in 1977 (**13, Figure 1.2**), whose cations provided evidence by an increase in absorption frequencies of the C≡O

ligands, *v*(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) –> π*(CO) donation in the electron deficient cations. ^{1}H-NMR spectra exhibited only small downfield shifts of alkyl groups α- 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[145]; 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.



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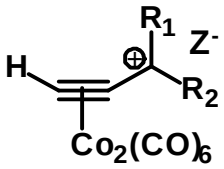

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Figure 1.2: Structures studied by the Seyferth group (R = H, CH_3, or C_6H_5) (**12**), and the Nicholas group ($R_1 = R_2 = CH_3$, Z = SbF_6; $R_1 = R_2 = C_6H_5$, Z = SbF_6; $R_1 = CH_3$, R_2 = H, Z = BF_4; $R_1 = R_2$ = H, Z = BF_4) (**13**).

1.1.3. STRUCTURAL ANALYSIS OF THE [(PROPARGYLIUM)$Co_2(CO)_6$]$^+$ 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, $[(CCH_2)Co_3(CO_9)]^+$ (**14, Figure 1.3**),

as a result of the formation of tilted -CCH_2 structures towards the -Co_3 plane rather than an upright structure above the tricobalt triangle. In 1982, *Edidin et. al.*[43] reported ^{13}C-NMR evidence for $[(CHCHMe_2)Co_3(CO_9)]^+$ (**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-$Co_2(CO)_6$ complexed cations.

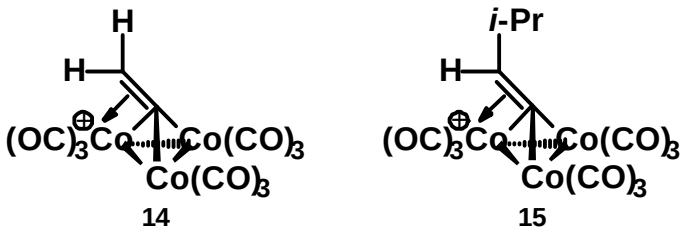

Figure 1.3: Structures studied by *Schilling and Hoffmann* (**14**) and *Edidin et. al* (**15**).

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 $Co_2(CO)_6$ moiety. The model (**Figure 1.4**) features a bending of the propargylic 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[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[70,71], who reported on the X-ray structures and molecular orbital analyses of molybdenum and molybdenum-cobalt clusters.

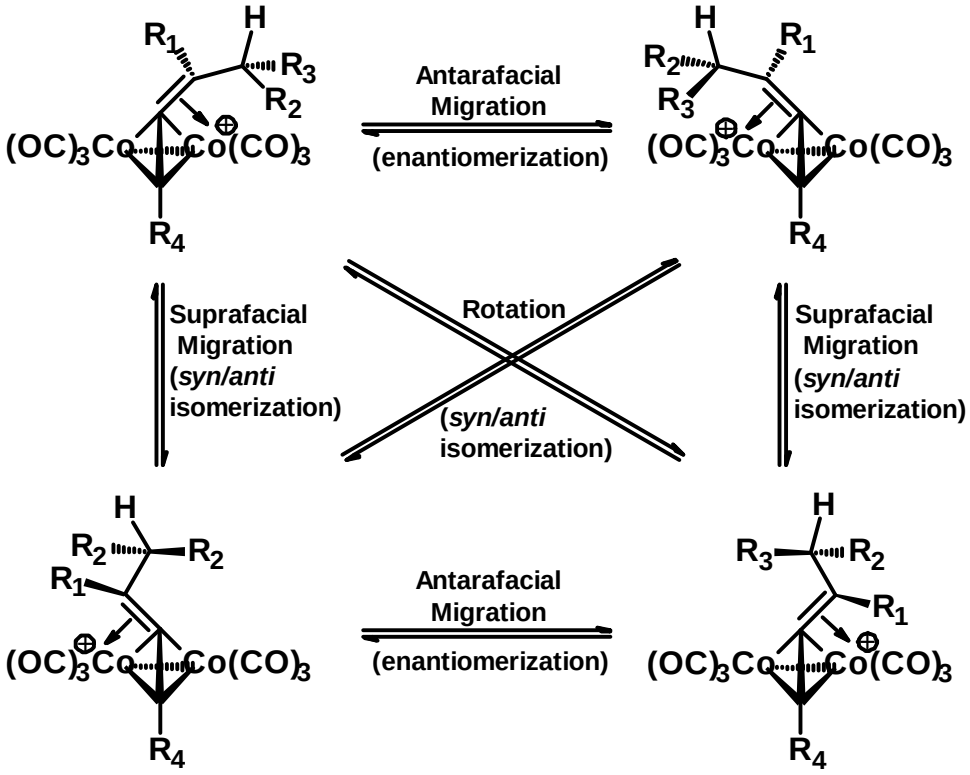

Figure 1.4: Fluxional model of propargyl-$Co_2(CO)_6$ cations as proposed by *Schreiber et. al.* (Reproduced with permission from Reference 840 Copyright 1987 American Chemical Society).

Melikyan et. al.[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.

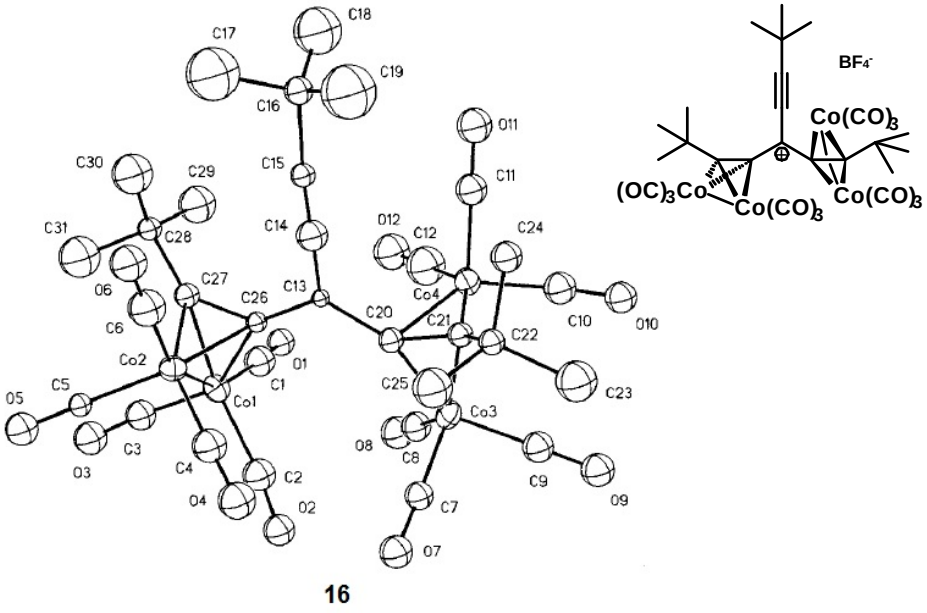

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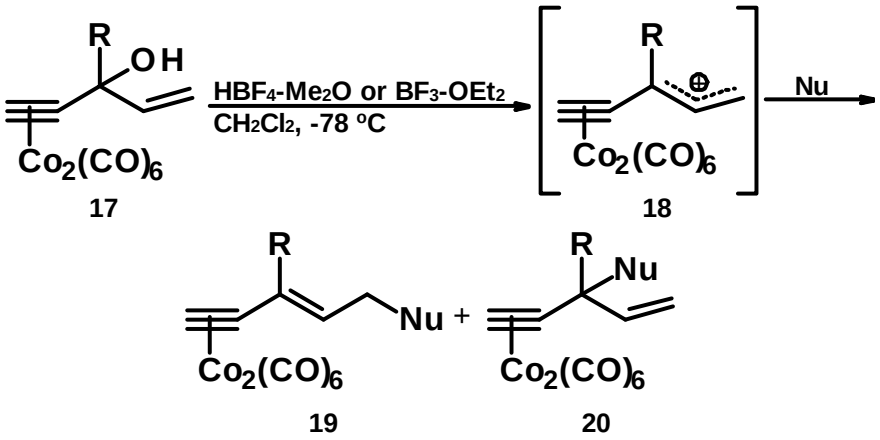
Figure 1.5: X-ray crystal structure analysis of the [(propargylium)$Co_2(CO)_6$]$^+$ cation (**16**). (Reproduced with permission from Reference 814 Copyright 1998 Wiley-VCH).

1.1.4. VINYLOGOUS NICHOLAS REACTIONS

To probe further the steric and electronic properties of the carbonium ion-stabilizing

alkynyl-$Co_2(CO)_6$ 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 Nicholas*[146] 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 $Co_2(CO)_6$). 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 α-vinylpropargylic cations, exposed such cations to three electron rich heterocycles to examine their coupling reactions[179]. The alkylation reactions were carried out by adding a furan derivative to a generated vinylogous cationic species at -78 °C in CH_2Cl_2, with the reaction taking place at the remote terminus of the α-vinyl cation. Interestingly, they noticed that if alkylation was performed at temperatures above -45 °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[113] (probability of the chain ends meeting), and enthalpic factors[85] (increasing strain in the transition state, transannular interactions). One of the most important influences on isolability of carbocycles is ring size[103].

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[130]. The smallest isolable, unsubstituted cycloalkyne that can be isolated in its free state is cyclooctyne[103] (**24**), first synthesized and purified in 1953 by *Blomquist & Liu*[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.*[195] seven years later in 1960.

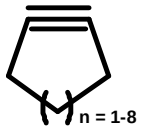
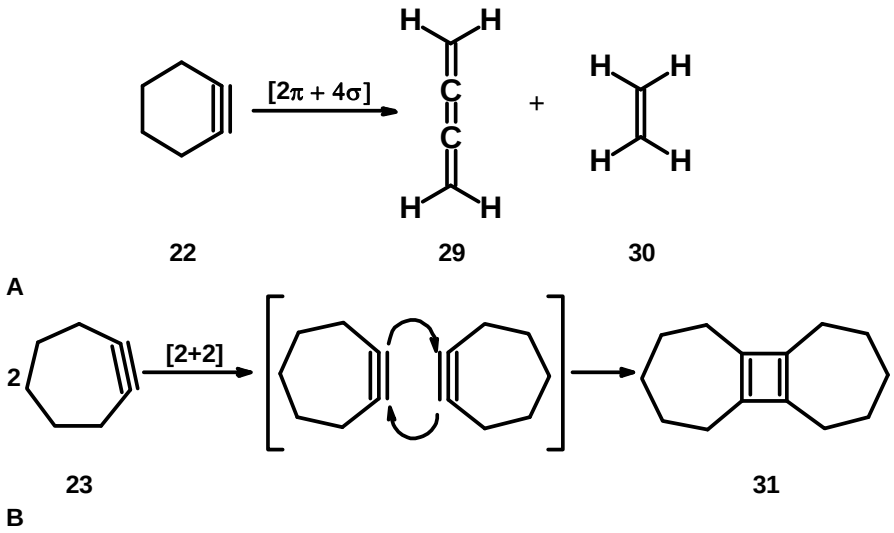


Figure 1.6: Small- and medium-sized carbocycles (*n* = 1, cyclopentyne (**21**); *n* = 2, cyclohexyne (**22**); *n* = 3, cycloheptyne (**23**); *n* = 4, cyclooctyne (**24**); *n* = 5, cyclononyne (**25**); *n* = 6, cyclodecyne (**26**); *n* = 7, cycloundecyne (**27**); *n* = 8, cyclododecyne (**28**)).

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[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[61], and in dilute CH_2Cl_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[195].

Experimental evidence for cyclobutyne and cylopropyne has not yet been established[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[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**) (**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 cyclobutadicycloheptene compound (**31**) (**B, Scheme 1.3**).



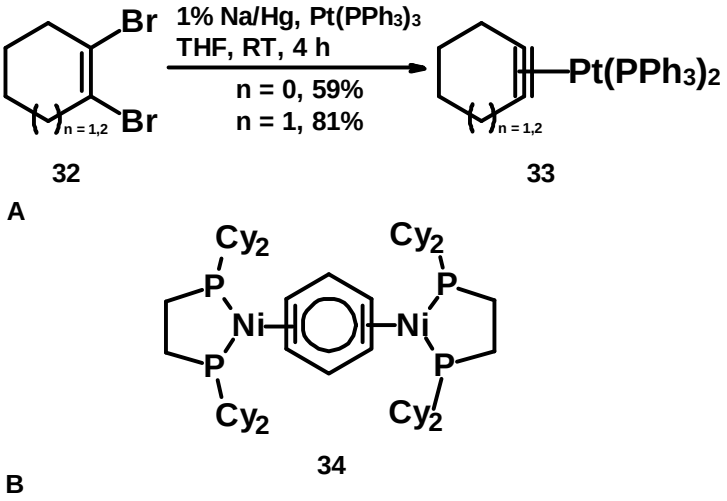
Scheme 1.3: A) Retro-Diels-Alder of cyclohexyne. B) Dimerization of cycloheptyne.

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[200].

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*[8] reported on the *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 $Pt(PPh_3)_3$, the cyclohexyne complex, $Pt(C_6H_8)(PPh_3)_2$ (**33a**), and the cycloheptyne complex, $Pt(C_7H_{10})(PPh_3)_2$ (**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, $Pt(PPh_3)_2(C_5H_6)$, a colourless, very reactive solid[7]. As was expected, the cycloalkyne-$Pt(PPh_3)_2$ 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[17], the zirconocene complexes of benzyne[16], and the dizirconium complexes of benzdiyne[15].

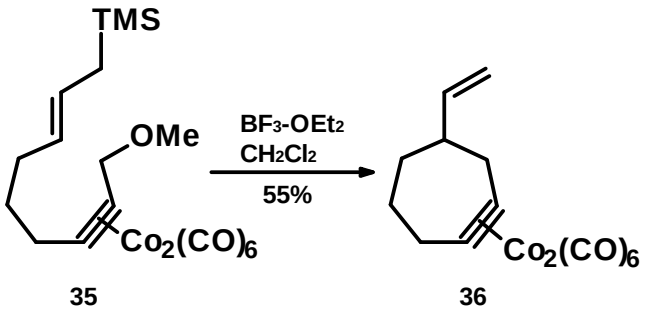


Scheme 1.4: A) Bennett's cyclohexyne-platinum (*n* = 1) (**33a**) and cycloheptyne-platinum (*n* = 2) (**33b**) complexes. B) Bennett's dinickel complex of 1,4-benzdiyne (**34**) (Cy = cyclohexyl).

1.2.3. STABILIZATION OF CYCLOALKYNES WITH COBALT

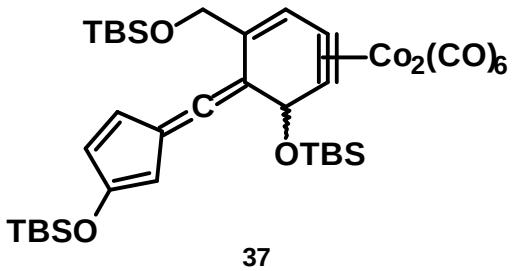
Dicobalt hexacarbonyl fragments have been used commonly as protecting groups to allow geometrically disfavoured cyclization reactions by bending and stabilizing the alkyne moiety[159]. *Sly*[175] reported, in as early as 1959, the dramatic modification in the geometry of the linear acetylenic -C≡C- upon complexation by an M_2L_6 unit. Complexation of diphenylacetylene by $Co_2(CO)_6$ reduced the alkynyl angles of Ph-C≡C-Ph from 180° to 137° and 138°. In 1986, *Schreiber et. al.*[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 cyclopentadienylallenecyclohexenyne-$Co_2(CO)_6$ (**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 napthalene 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).



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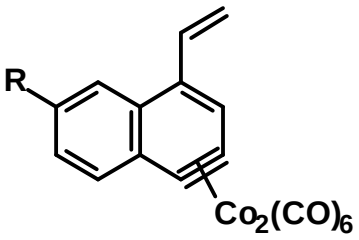

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Figure 1.7: Cyclopentadienylallenecyclohexenyne-$Co_2(CO)_6$ (**37**) synthesized by *Magnus et. al.*, and the naphthalyne-$Co_2(CO)_6$ complex (R = H, OMe, or Br) (**38**) isolated by *Iwasawa et. al.*

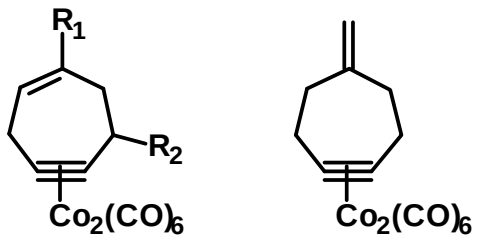
1.3. APPLICATIONS OF THE NICHOLAS REACTION IN SYNTHESIS

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-

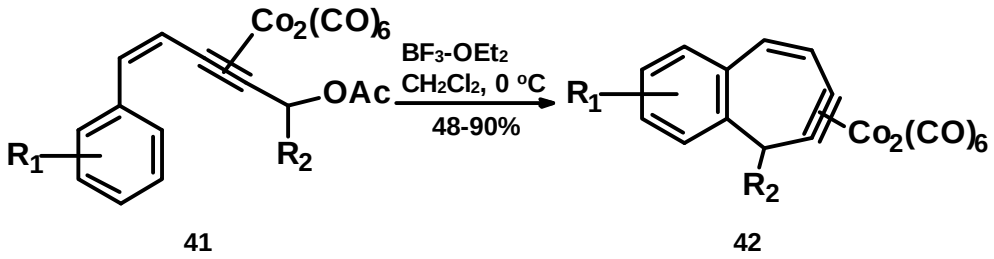
mediated 7-*endo trig* cyclization of suitably constructed allylsilanes onto the generated [(propargyl)$Co_2(CO)_6$]$^+$ cation. Allylsilane cyclizations on the formed cations could also be made to result in the formation of *exo*-methylene systems (**40**) by choosing the appropriate allylsilane (**Figure 1.8**) .



39 **40**

Figure 1.8: Cycloheptyne-$Co_2(CO)_6$ complexes generated by intramolecular Nicholas reactions of allylsilanes with Nicholas cations ($R_1 = R_2 = H$; $R_1 = Ph$, $R_2 = H$; $R_1 = Me$, $R_2 = H$; $R_1 = H$, $R_2 = Me$).

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 analogues[34] (**Scheme 1.6**). Treatment of aryl (*Z*)-enyne propargyl acetate-$Co_2(CO)_6$ complexes (**41**) (prepared from their corresponding benzaldehydes) with BF_3•OEt_2 mediated an intramolecular nucleophilic attack by the arene to afford the benzo-fused cycloheptenyne-$Co_2(CO)_6$ complexes (**42**).

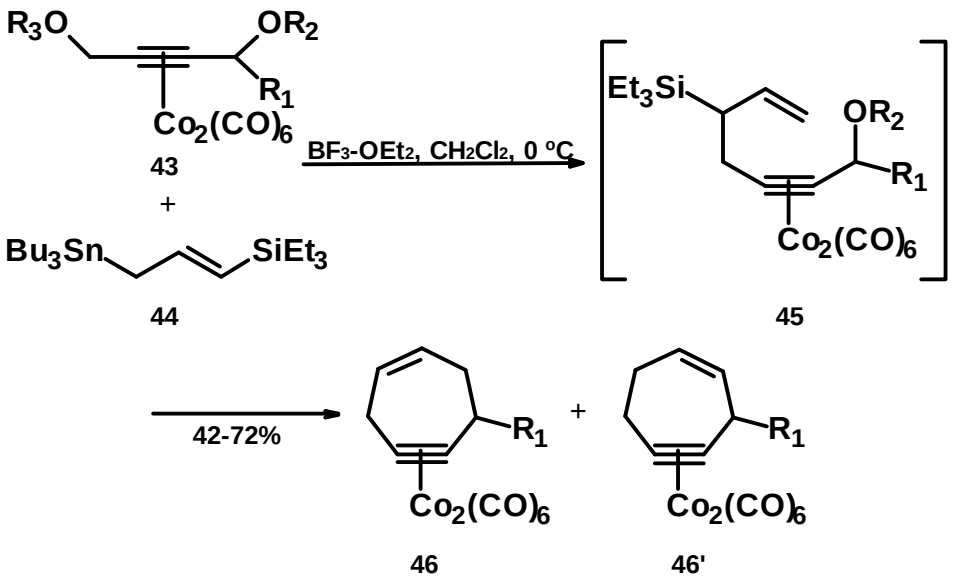


41 42

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).

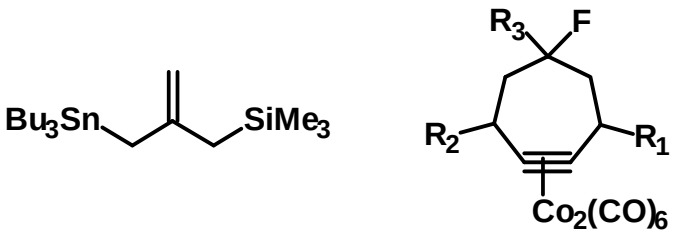
1.3.2. CYCLOHEPTYNE-$Co_2(CO)_6$ SYNTHESIS VIA CYCLOADDITION AND RING CLOSING METATHESIS METHODS

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 ^{i}Pr; 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**).



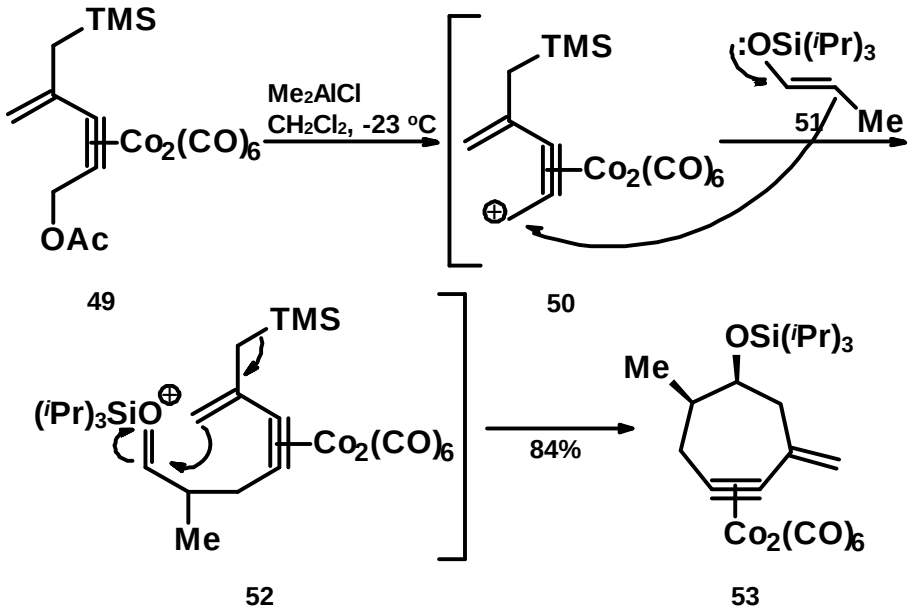
47 48

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[110].

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

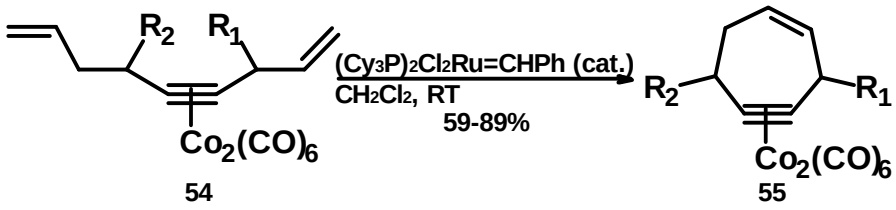
reaction proceeded step-wise, involving a silyloxonium ion intermediate (**52**) arising from nucleophilic attack of the silyl enol ether (**51**) onto the Nicholas cation (**50**). Ring closure afforded the cycloheptyne-$Co_2(CO)_6$ product (**53**) in good yield, with the stereochemistry arising during 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.

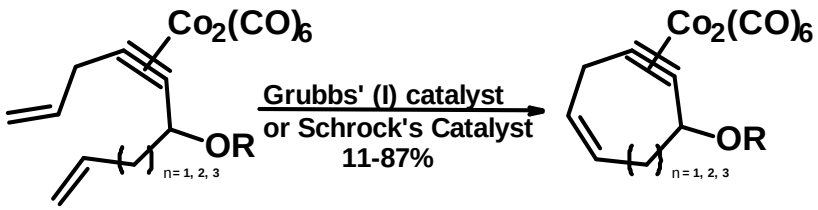
The Green group[67] found that the alkyne-$Co_2(CO)_6$ unit is not affected by most metathesis pre-catalysts, and hence these pre-catalysts could be used in the synthesis of cycloheptyne-$Co_2(CO)_6$ compounds via ring closing metathesis (**Scheme 1.9**). Acyclic 1,8-nonadiene-4-yne-$Co_2(CO)_6$ complexes (**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: Ring closing metathesis in the synthesis of cycloheptyne-$Co_2(CO)_6$ substrates (**55**) (R_1 = OAc or H; R_2 = H, *n*-Pr, *n*-C_5H_{11}, or OAc; $(Cy_3P)_2Cl_2Ru$=CHPh = 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.

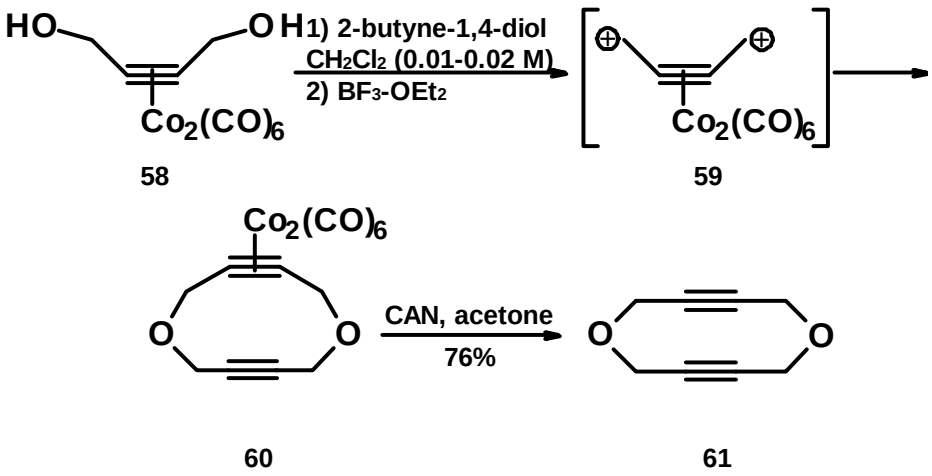


56 **57**

Scheme 1.10: *Young et. al*'s RCM using $Co_2(CO)_6$ complex linked alkenes (R = H, Ac, TBS, =O; Grubbs' (I) catalyst: $(PCy_3)_2Cl_2Ru$=CHPh; Schrock's catalyst: 2,6-diisopropylphenyl-imidoneophylidene-molybdenum (VI) bis(hexafluoro-*tert*-butoxide).

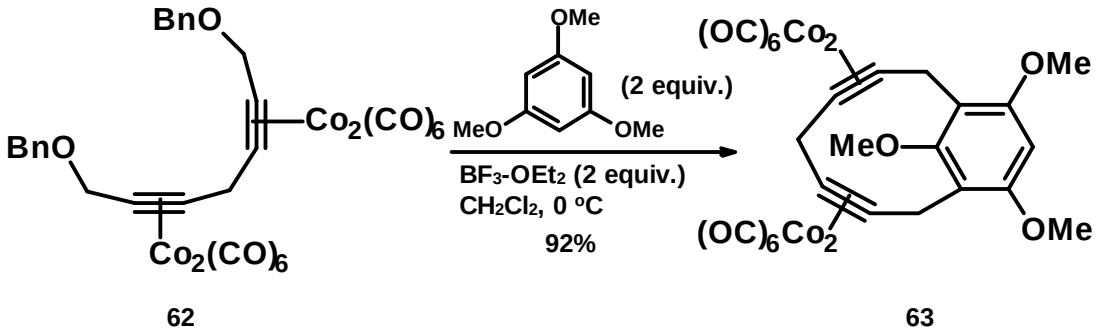
1.3.3. MACROCYCLIC CYCLOALKYNE SYNTHESIS

Diaz et. al.[31], in their study of formal propargylic dications, generated from treatment of alkyne-$Co_2(CO)_6$ diols with BF_3•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 BF_3•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-diyne-$Co_2(CO)_6$ 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 π-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].



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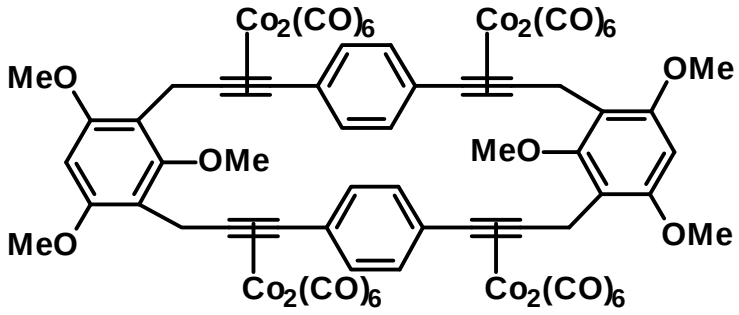
A



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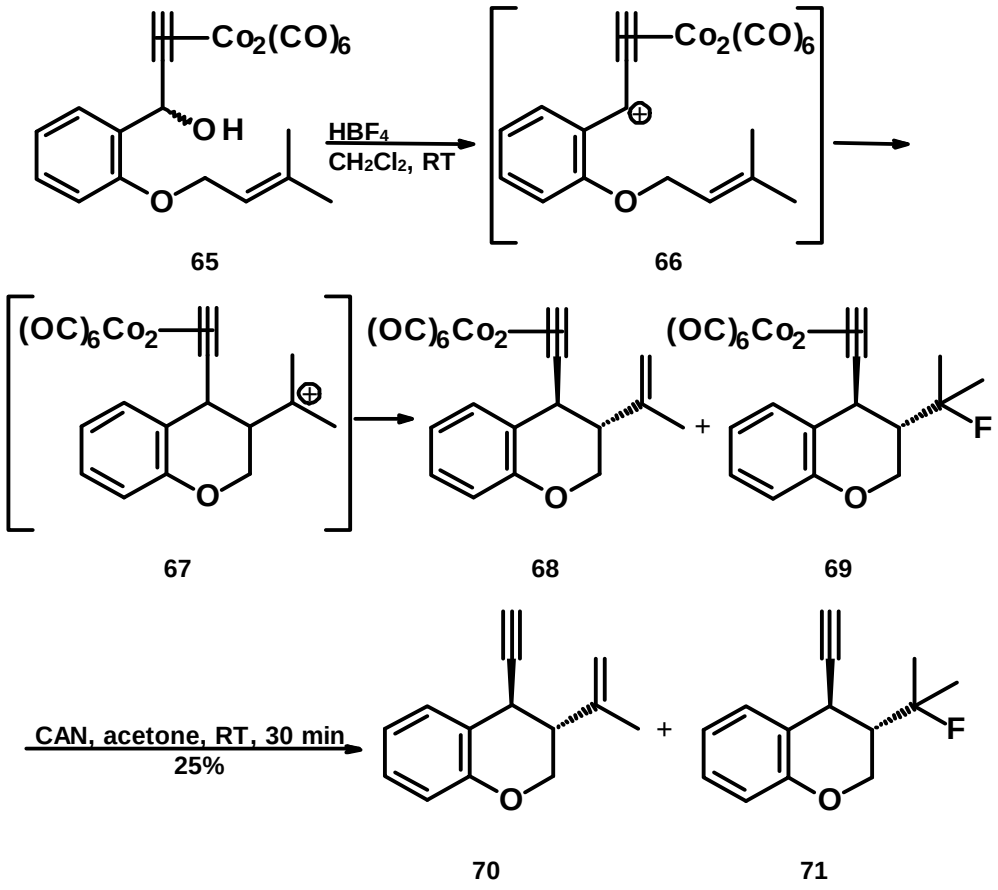
B

Scheme 1.12: A) *Guo and Green's* synthesis of [7]metacyclophanediyne(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

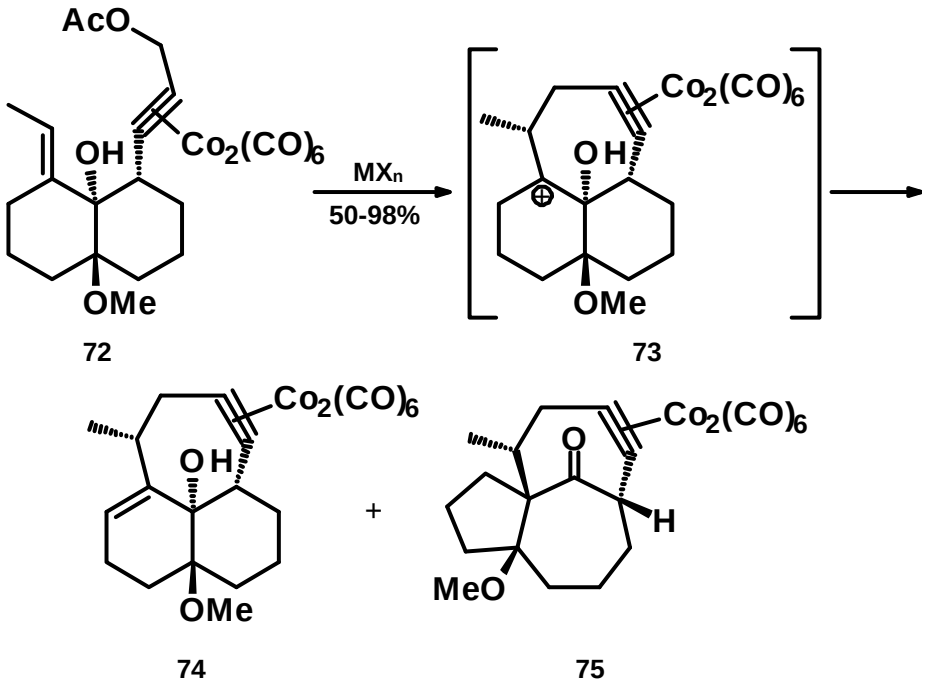
second product (**69**) was reasoned to occur by the generation of the second cation (**67**), a consequence of the intramolecular Nicholas reaction, which was then quenched by a fluoride ion. Subsequent decomplexation using CAN afforded an equimolar mixture of the benzopyrans (**70**) and (**71**), separable by chromatography, in a 25% overall yield over the three steps. Extensive ^{1}H-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**).

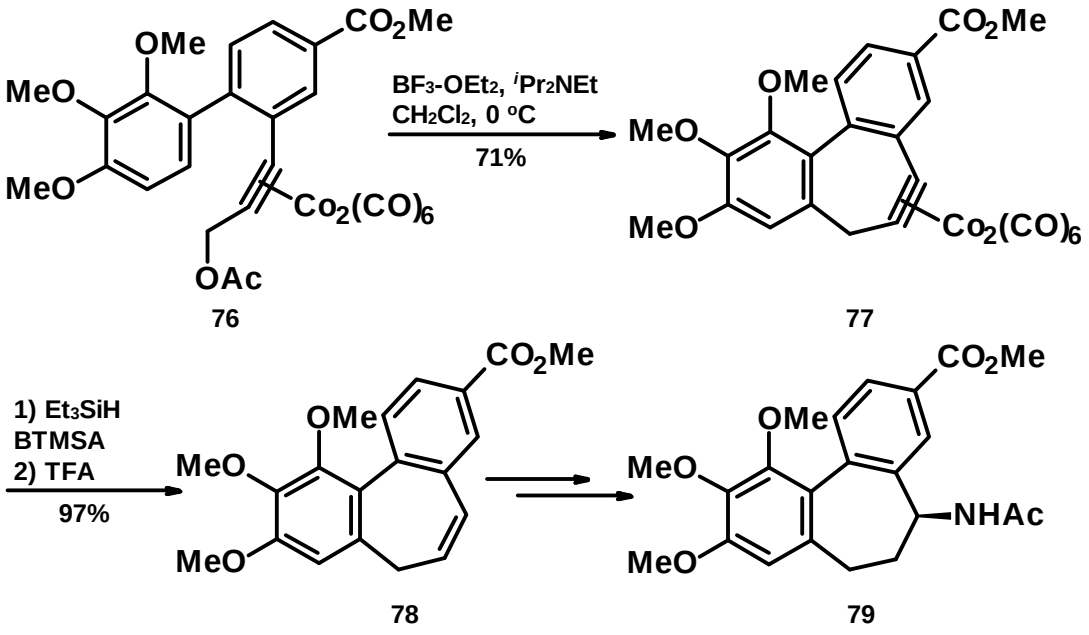


Scheme 1.14: Intramolecular cyclization of the *trans*-decalin system possessing an exocyclic alkylidene and a propargyl acetate-$Co_2(CO)_6$ (**72**) to afford either a 7,6,6-ring system (**74**) or a 7,5,5-ring system (**75**). Lewis acid, MX_n = Me_2AlCl, $Me_2Al(OTf)$, $MeAl(OTf)_2$, $MeAl(OCOCF_3)_2$, or $MeAl(OCOCF_3)(OAr)$; Ar = 2,6-$(CH_3)_2$-4-$(NO_2)C_6H_2$ or 4-$NO_2C_6H_4$.

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

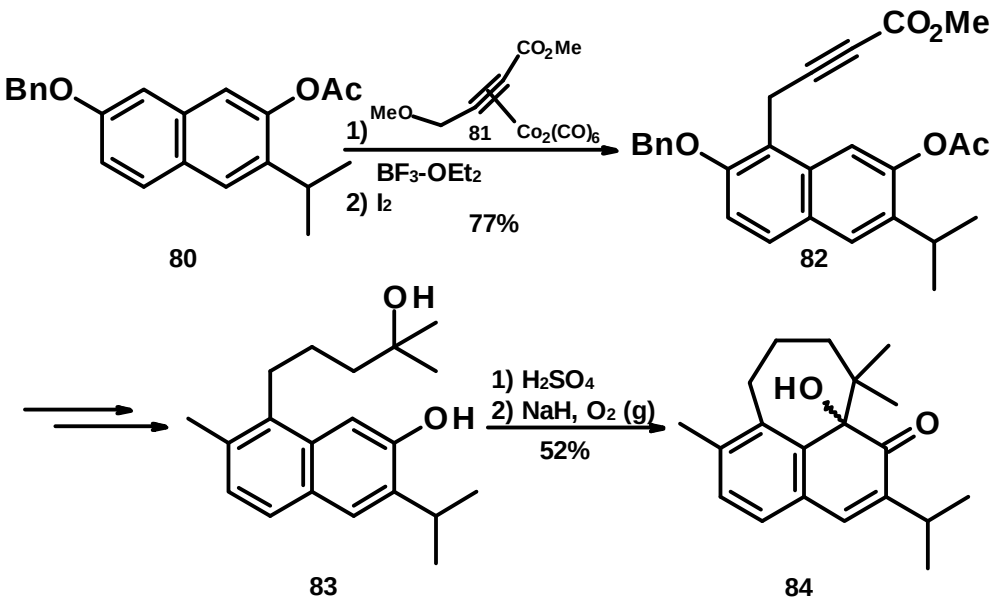
nucleophilic attack of the electron rich aromatic ring onto the propargylic cation formed to yield the dibenzocycloheptyne-$Co_2(CO)_6$ complex (**77**). Reductive decomplexation was achieved by use of triethylsilane in the presence of bis(trimethylsilyl)acetylene (BTMSA, a trapping reagent used to minimize 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

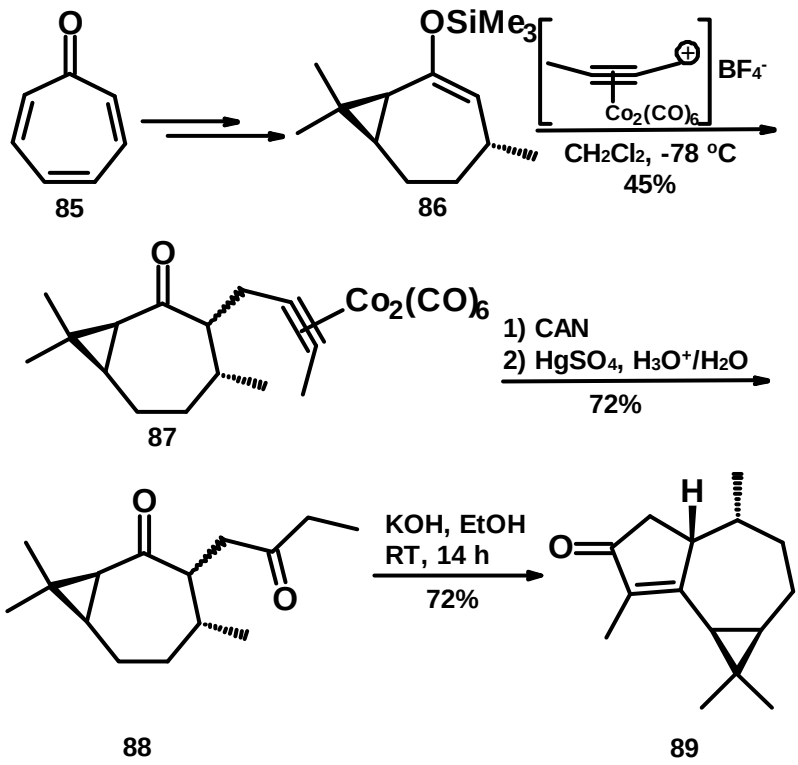
cation chemistry in the assembly of cyclohepta[*de*]naphthalene rings, and in the construction of the rearranged abietane framework of microstegiol[181], the authors arrived at the racemic product a year later. The reaction of protected 3-isopropyl-2,7-naphthalenediol (**80**) with the alkyne-$Co_2(CO)_6$ complex (**81**) under acidic conditions afforded the monosubstitution product (**82**) following decomplexation with iodine. Upon arriving at alcohol (**83**), cyclization was initiated with H_2SO_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.*[160], who reported a total synthesis of the guiane, (±)-

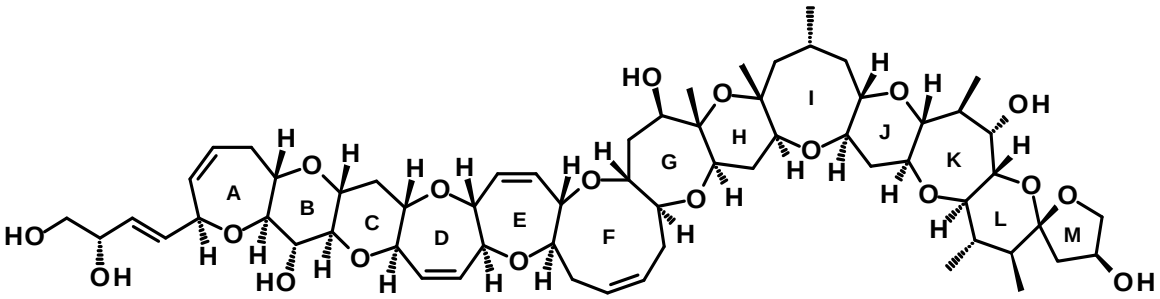
cyclocolorenone (**Scheme 1.17**).



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 $Fe_2(CO)_9$ 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.

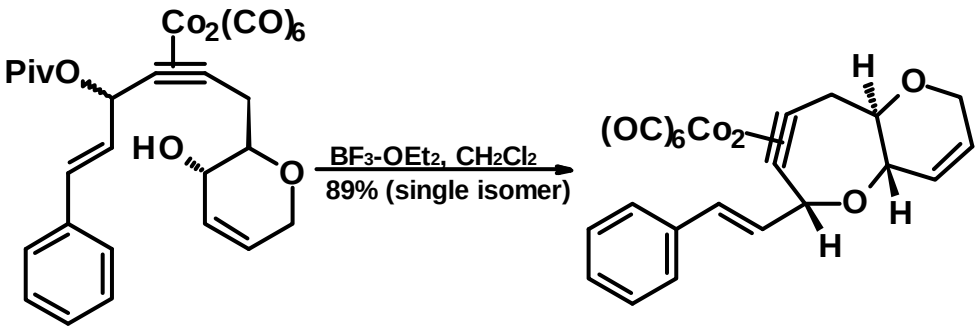
Isobe and co-workers have spent more than 25 years pursuing the total synthesis of ciguatoxin (**90, Figure 1.10**), and in 2009, reported the final total synthesis of the marine toxin. Their numerous processes relied heavily on the Nicholas reaction for ring construction, with one of the key reactions being a cyclization to form the F ring in the final total synthesis[73].



90

Figure 1.10: Structure of ciguatoxin (**90**).

One example[86] 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 $BF_3 \bullet OEt_2$ 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.

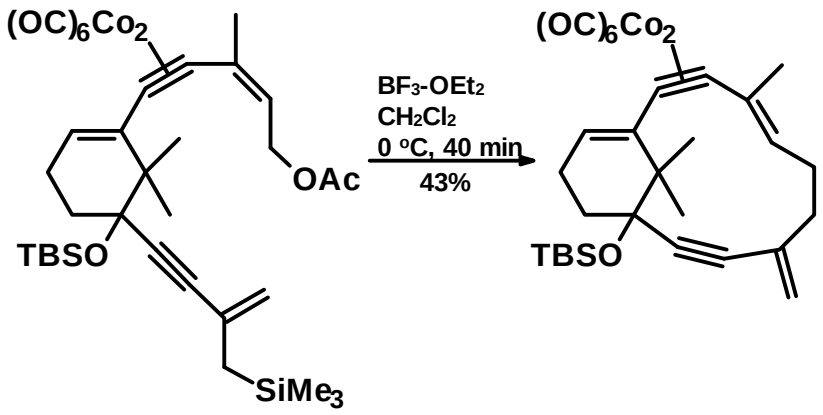


91 **92**

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

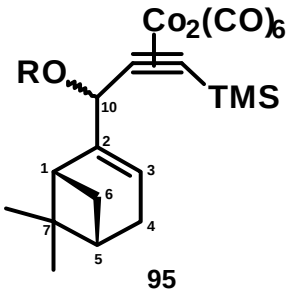
Shibuya and Isobe[170,171] reported on the synthesis of the bicyclo[9.3.1]pentadecatriene skeleton seen in taxachitiene natural products. Their application of the vinylogous Nicholas reaction featured a Hosomi-Sakurai type reaction as the key step in the Lewis acid-mediated intramolecular cyclization between the enyne-$Co_2(CO)_6$ complex electrophile and allytrimethylsilane nucleophile (**93**) to generate the twelve-membered ring (**94**) (**Scheme 1.19**).



93 94

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.

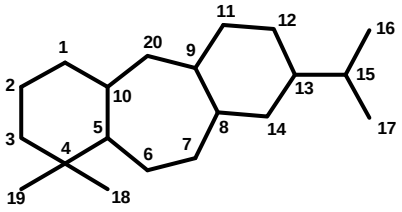


95

Figure 1.11: Alvaro's complexed precursor (**95**) for vinylogous Nicholas chemistry.

1.4. FAVELINE- AND ICETEXANE-DITERPENE NATURAL PRODUCTS

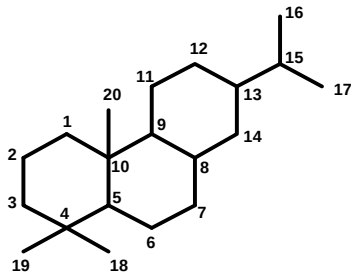
The icetexanes are a family of diterpenoid natural products which have been isolated from a variety of terrestrial plant sources[172]. They encompass a variety of structurally unique and interesting features, and exhibit a broad spectrum of attractive bioactive properties (i.e., anti-cancer, anti-bacterial, anti-fungal, anti-Chagasic activities)[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).



96

Figure 1.12: 6,7,6-tricyclic skeleton of an icetexane diterpenoid (**96**).

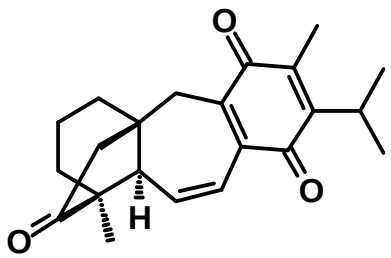
Biosynthetically, the architecture of the icetexane is hypothesized to arise from a ring-expanding rearrangement of the more common abietane (**97, Figure 1.13**), giving rise to the 6,7,6-tricyclic skeleton that bears the systematic name 9(10–>20)-*abeo*-abietane. In accordance with this hypothesis, 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[172].



97

Figure 1.13: Structural skeleton of an abietane (**97**).

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[172]. The icetexanes that have been discovered so far vary widely in the degree of oxygenation and oxidation in each ring.

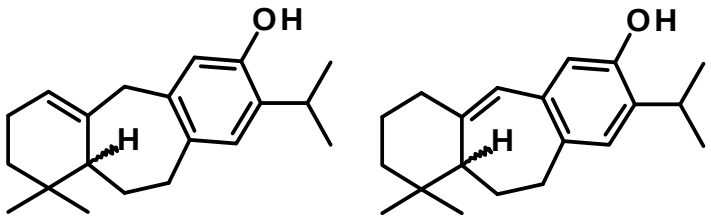


98

Figure 1.14: Structure of icetexone (**98**).

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 *Chamaeyparis pisifera* in 1980[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**

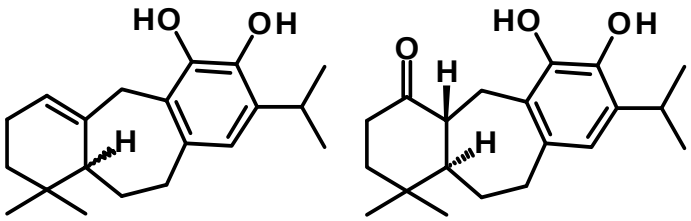
1.15) from the same plant species, its structure was revised to its current structure[76]. Other members of this subclass include pisiferanol, 12-deoxypisiferanol, 1β-hydroxyisopisiferin, and pisiferdiol, among others[172]. The biological activities of the pisiferins are less well explored.



99 **100**

Figure 1.15: Structures of (±)-pisiferin (**99**) and (±)-isopisiferin (**100**).

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[96]. 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[83]. 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].



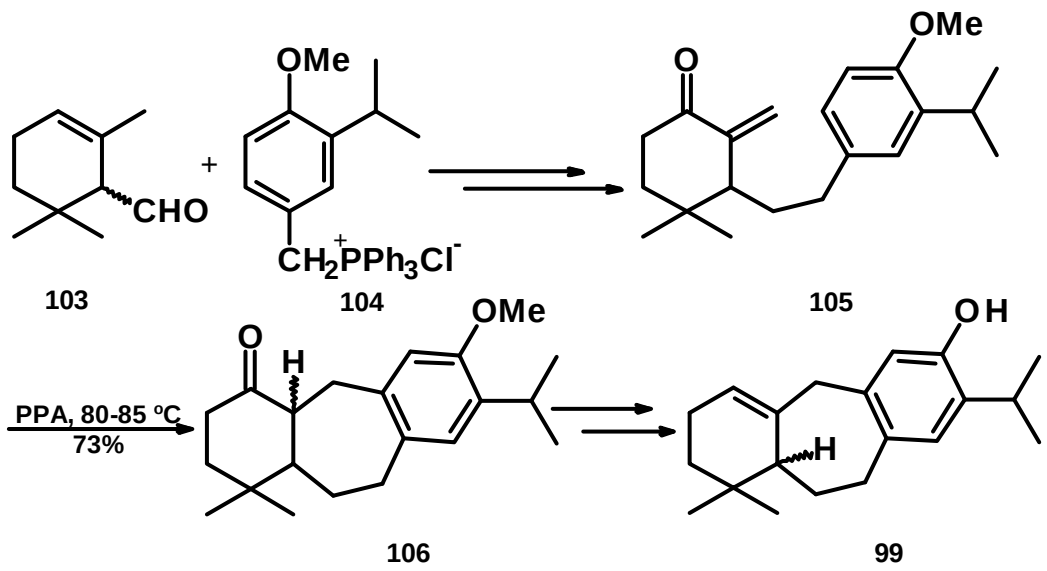
101 **102**

Figure 1.16: Structure of (±)-barbatusol (**101**) and rosmaridiphenol (**102**).

1.4.1. EXAMPLES OF TOTAL SYNTHESES 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[123] (**Scheme 1.20**). Starting with racemic α-cyclocitral (**103**) and a benzylic Wittig reagent (**104**), a series of reactions were preformed which ultimately afforded the α,β-unsaturated ketone (**105**). Next, an intramolecular cyclization was achieved by heating with polyphosphoric acid (PPA) at 80-85 ^{o}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%.

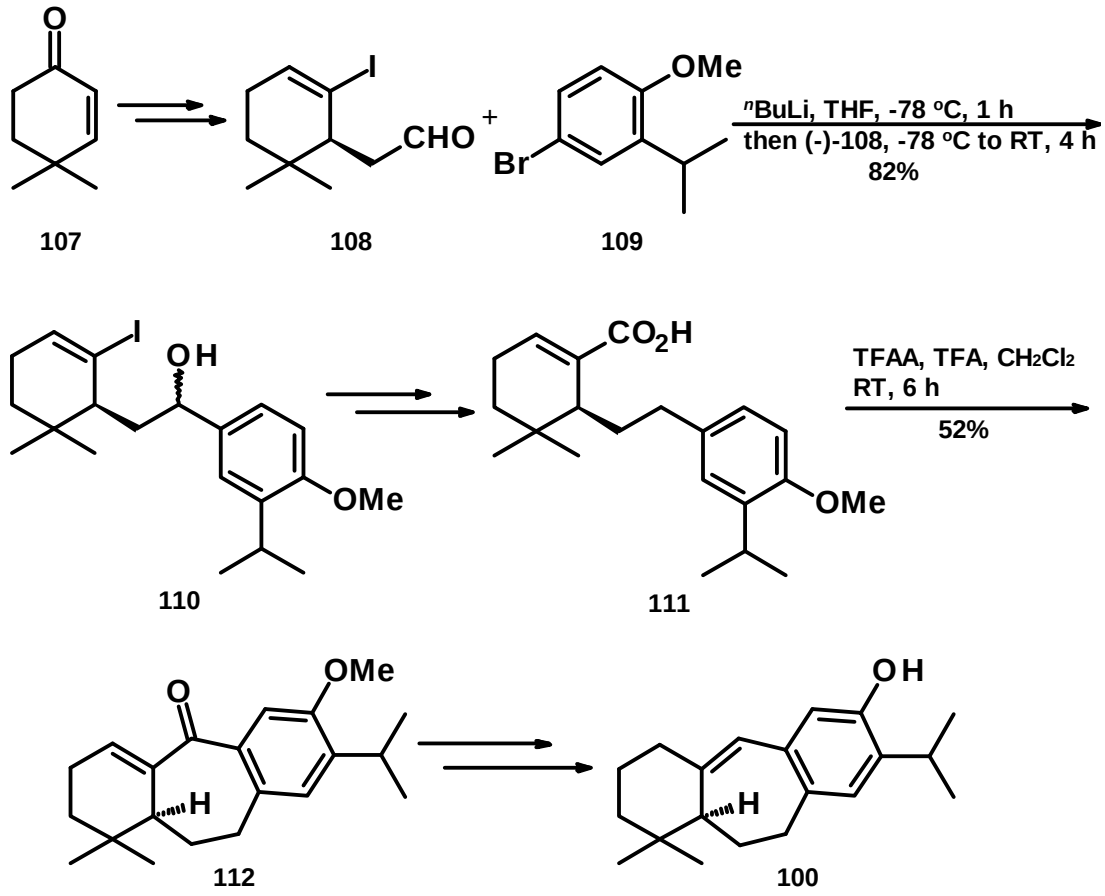


Scheme 1.20: First total synthesis of (±)-pisiferin (**99**) reported by *Matsumoto et. al.*

The second total synthesis of (±)-pisiferin and the first total synthesis of (±)-isopisiferin was reported by *Kametani et. al.* in 1990[92].

In 2010, *Jan et. al.* reported the first enantioselective synthesis of (-)-isopisiferin[90] (**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 ^{n}BuLi 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 $NaBH_4$, followed by mesylation in the presence of NEt_3, and

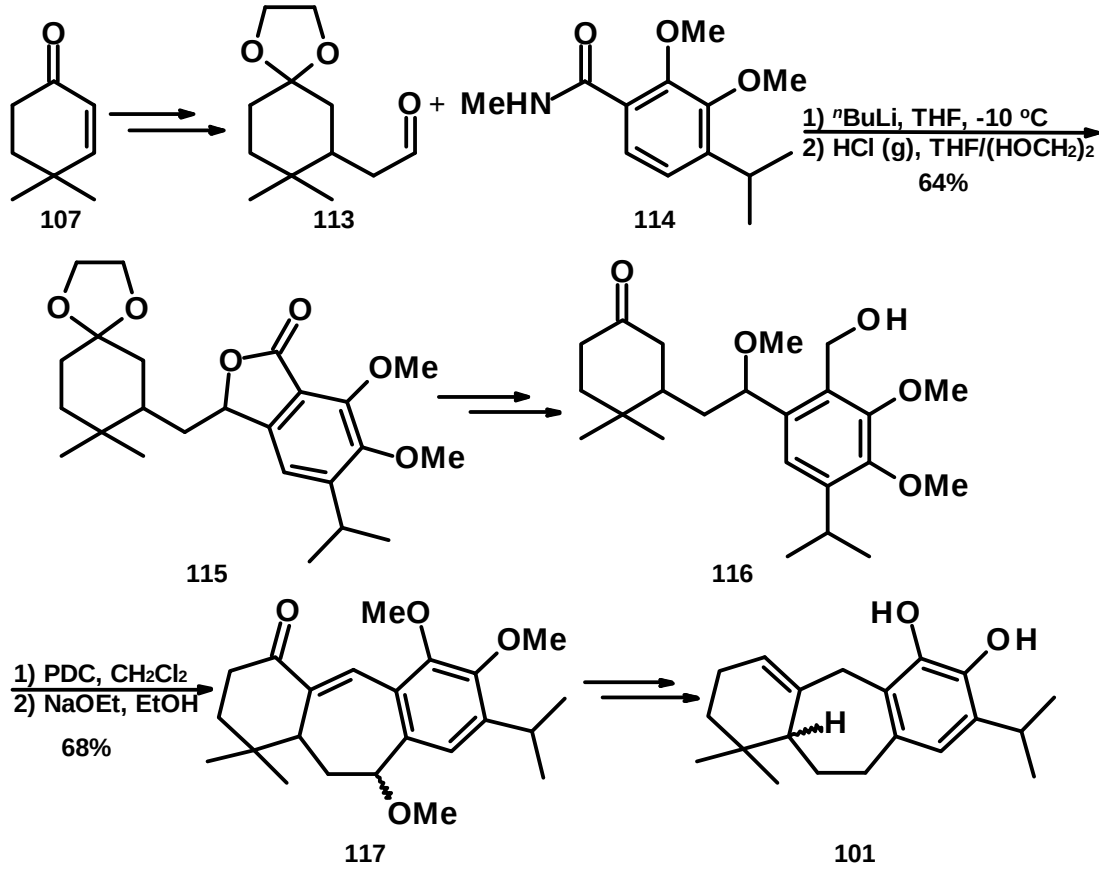
finally, deprotection with EtSNa, which converted **112** to the target compound, (-)-isopisiferin, in 15 steps with an overall yield of 11.4%.



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*[104] (**Scheme 1.22**). Enone (**107**) underwent Hosomi-Sakurai addition of allyltrimethylsilane in the presence of titanium tetrachloride ($TiCl_4$), with the resulting ketone being protected as the ketal. Ozonolysis yielded the aldehyde (**113**). Metallation of the amide (**114**) (prepared separately) with ^{n}BuLi, followed by treatment with the aldehyde (**113**), and the subsequent

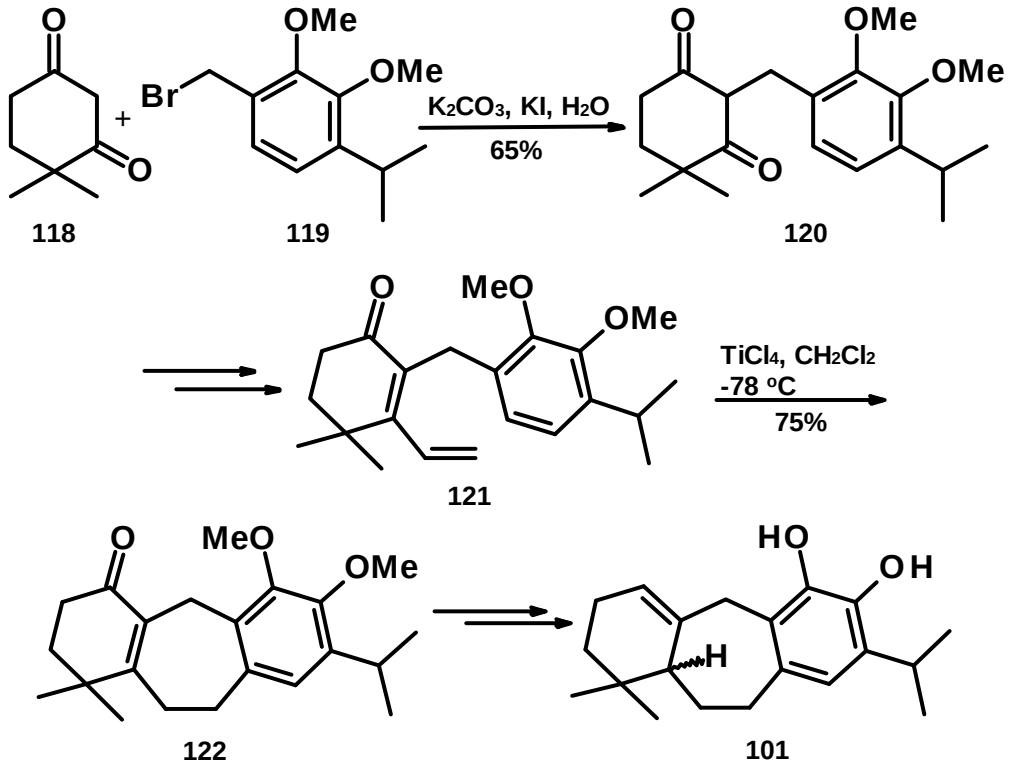
treatment of the resulting adduct with anhydrous acid, provided the lactone (**115**) as an inseparable mixture of diastereomers. The alcohol (**116**) was then generated via saponification of (**115**) with NaOH, methylation with MeI, and treatment with $LiAlH_4$. Oxidation of (**116**) with PDC provided 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 $Et_3SiH/BF_3{\bullet}OEt_2$, followed by reductive transposition of the enone with $TsNHNH_2$ and $NaBH_3CN$. 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 *Kroft*.

The second total synthesis of (±)-barbatusol was reported by *Majetich et. al.* in 1993[120] (**Scheme 1.23**), which featured a $TiCl_4$ 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[117]; (-)-barbatusol, (+)-demethylsalvicanol, (-)-brussonol, and (+)-grandione[116]; as well as related natural products, including diterpene (±)-nimbidiol[118], and triterpene (±)-perovskone and (+)-perovskone[115]. In their 1993 synthesis of (±)-

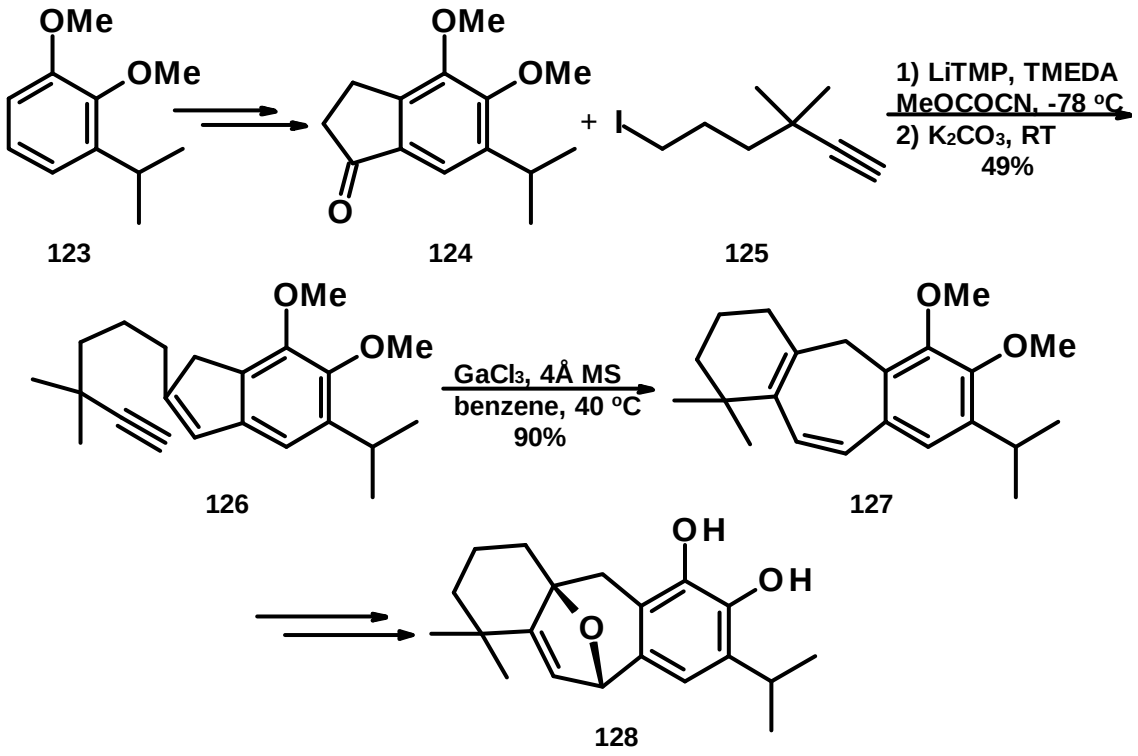
barbatusol, 4,4-diemthylcyclohexane-1,3-dione (**118**) was alkylated with benzyl bromide (**119**) (synthesized from 3-isopropylveratrole) to generate product (**120**). Once converted to the dienone (**121**), treatment with $TiCl_4$ in CH_2Cl_2 at -78 °C effected a cycloalkylation reaction to generate tricycle (**122**). Reductive transposition of the generated enone moiety (**122**) with $TsNHNH_2$ and $NaBH_3CN$, 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 ($GaCl_3$)[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 $GaCl_3$ at 40 ^oC 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 synthesis[173].



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

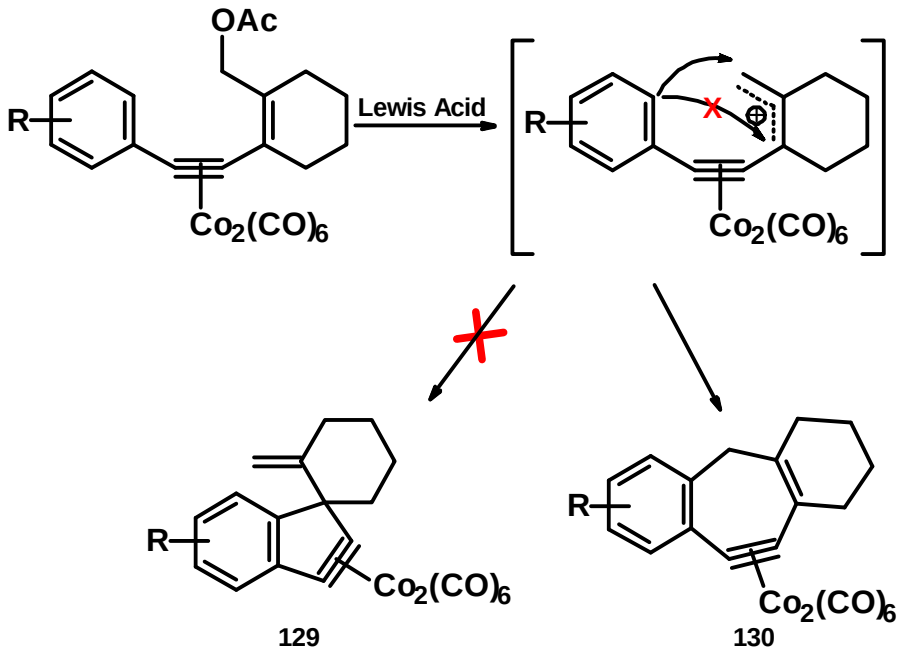
The Green group's ongoing interest in the synthesis of seven-membered rings has led to the expansion of the scope of reaction methods for ring construction in conjunction with Nicholas chemistry: cycloadditions, ring closing metathesis reactions, and Umpolung

chemistry[188], 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.



Scheme 1.25: Anticipated mode of cyclization by intramolecular Nicholas reaction.

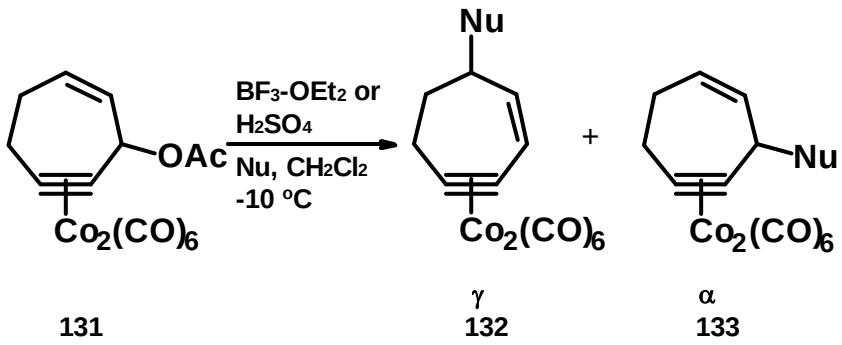
ii) As the idea was to formulate a general and modular entry into this class of compounds, the reaction was then expanded to include the synthesis of a few bicyclic *n*,7-ring systems under similar reaction conditions.

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.

CHAPTER 2: DISCUSSION

2.1. VINYLOGOUS 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 (γ) (**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 α-site (**133**) was preferred by nucleophiles with the greatest nucleophilicity, based on the Mayr scale[105,125,127].



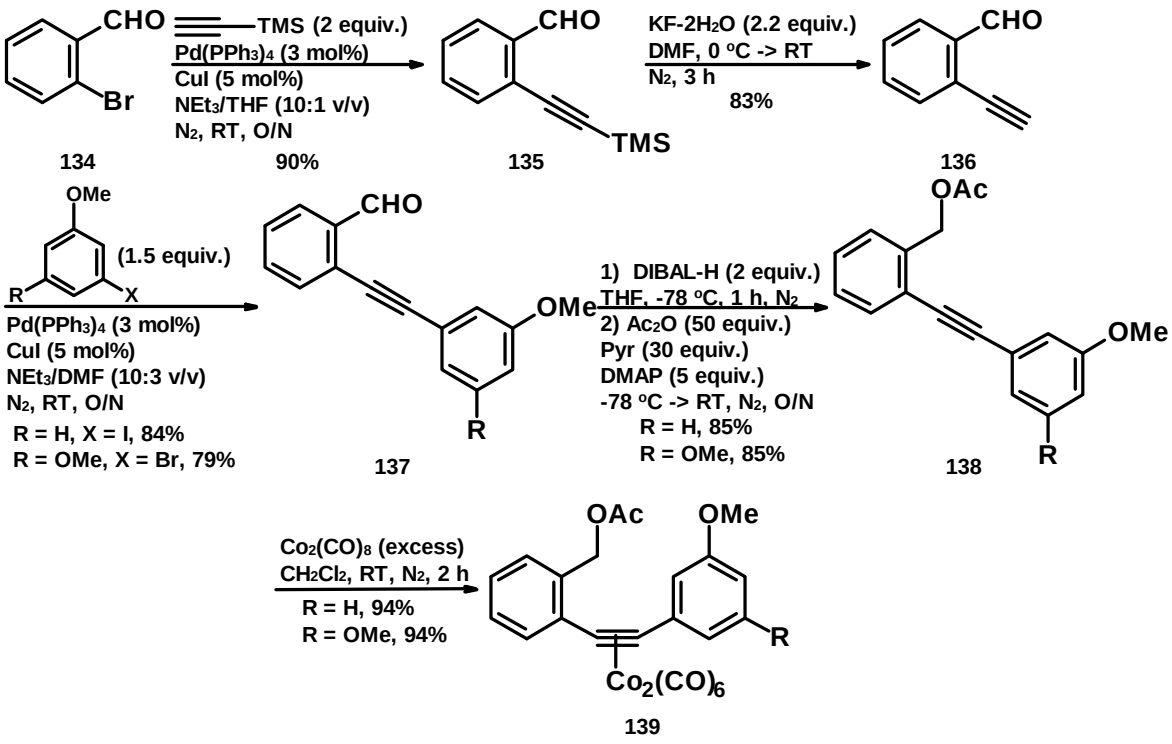
Scheme 2.1: Nucleophilic regioselectivity as reported by *DiMartino and Green*.

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 cyclopentyne-$Co_2(CO)_6$ 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•$2H_2O$ 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.



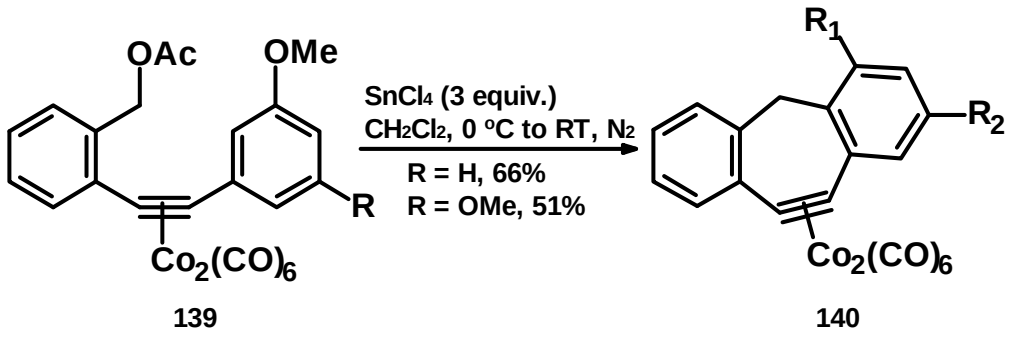
Scheme 2.2: Synthetic route towards complexed acetate-$Co_2(CO)_6$ precursors (**139**).

Early attempts to cyclize compounds **139** proved unsuccessful. Treatment of **139** with three equivalents of $BF_3 \bullet OEt_2$ in CH_2Cl_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_2SO_4, also

did not afford any product. In 2004, the Mayr group[82] reported a scale comparing the nucleophilicity parameter, N_1, of solvents with the N parameter of typical π systems. They predicted that solvolytically generated cations should be trapped by π nucleophiles if the N parameter of the corresponding π nucleophile is greater than the N_1 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_1 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 BF_3•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 CH_2Cl_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 $SnCl_4$ as a Lewis acid in place of BF_3•OEt_2, and hence this set of reactions was returned to in order to decipher whether

such successes would be observed with $SnCl_4$ in cyclizing (**139**). Sure enough, treatment of **139a** (R = H) with three equivalents of $SnCl_4$ under the same reaction conditions as initially attempted (dry CH_2Cl_2, 0 °C, N_2) gave products **140a** (R_1 = H, R_2 = OMe) and **140a'** (R_1 = OMe, R_2 = 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** (R_1 = R_2 = 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.



139 **140**

Scheme 2.3: Cyclization of benzyl acetate-$Co_2(CO)_6$ complexes (**139**) using $SnCl_4$ (when R = H, R_1 = H, R_2 = OMe or R_1 = OMe, R_2 = H; when R = OMe, R_1 = R_2 = OMe).

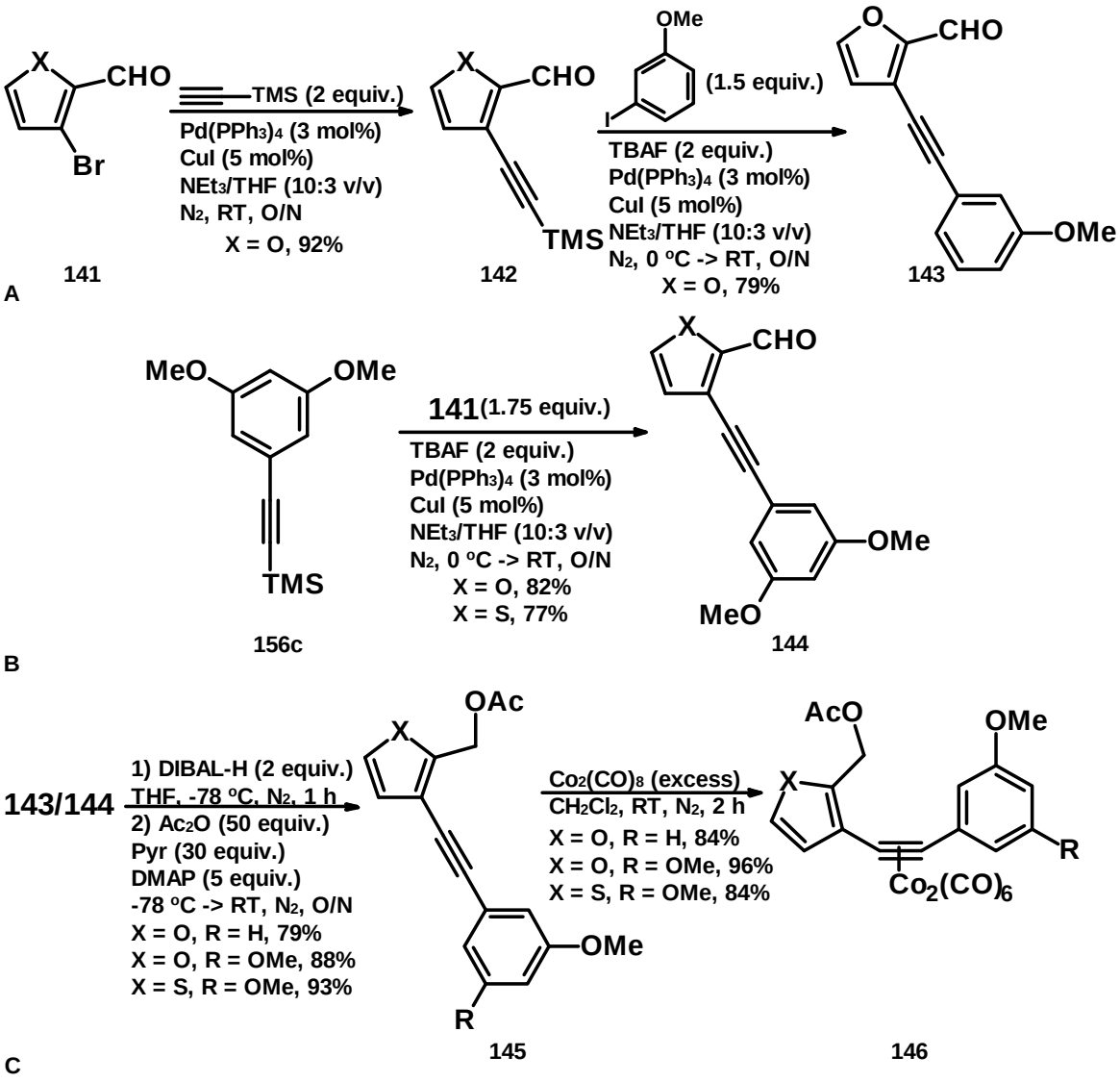
One advantage of working with cobalt complexes is the case of visualizing the characteristic colour of the cobalt components in the reaction mixture by TLC. Both the starting complexed precursors (**139**) and their cyclized products (**140**), dark brown and maroon in colour, respectively, coupled with their significant R_f 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•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 $SnCl_4$[50,62,136], $TiCl_4$[119], HBF_4[121], or $B(C_6F_5)_3$[110]. It may be possible that the molecule of Et_2O has an influential role in the diminished reactive ability of the boron trifluoride Lewis acid under these conditions.

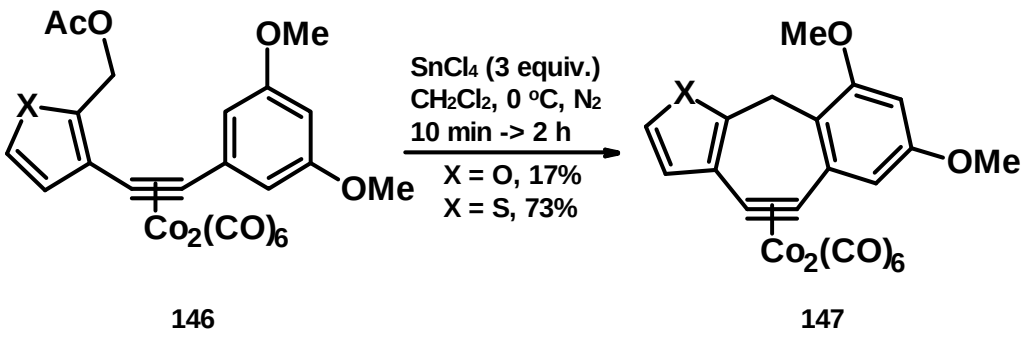
When the cyclizations of (**139**) did not initially work with BF_3•OEt_2, it was reasoned that perhaps the generated benzyl cation gained no additional stabilization from the $Co_2(CO)_6$ moiety, or perhaps that the rate of decomposition was faster than the rate of cyclization under the reaction conditions. 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 $Co_2(CO)_8$, afforded the complexed precursors (**146**).

As was the case with BF_3•OEt_2 initially, gross decomposition was observed with these nominally aromatic systems. Temperatures ranging from -40 ^oC to 0 ^oC to room temperature proved futile, as did the addition of Brønsted acid H_2SO_4, 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 $SnCl_4$ (**Scheme 2.5**).



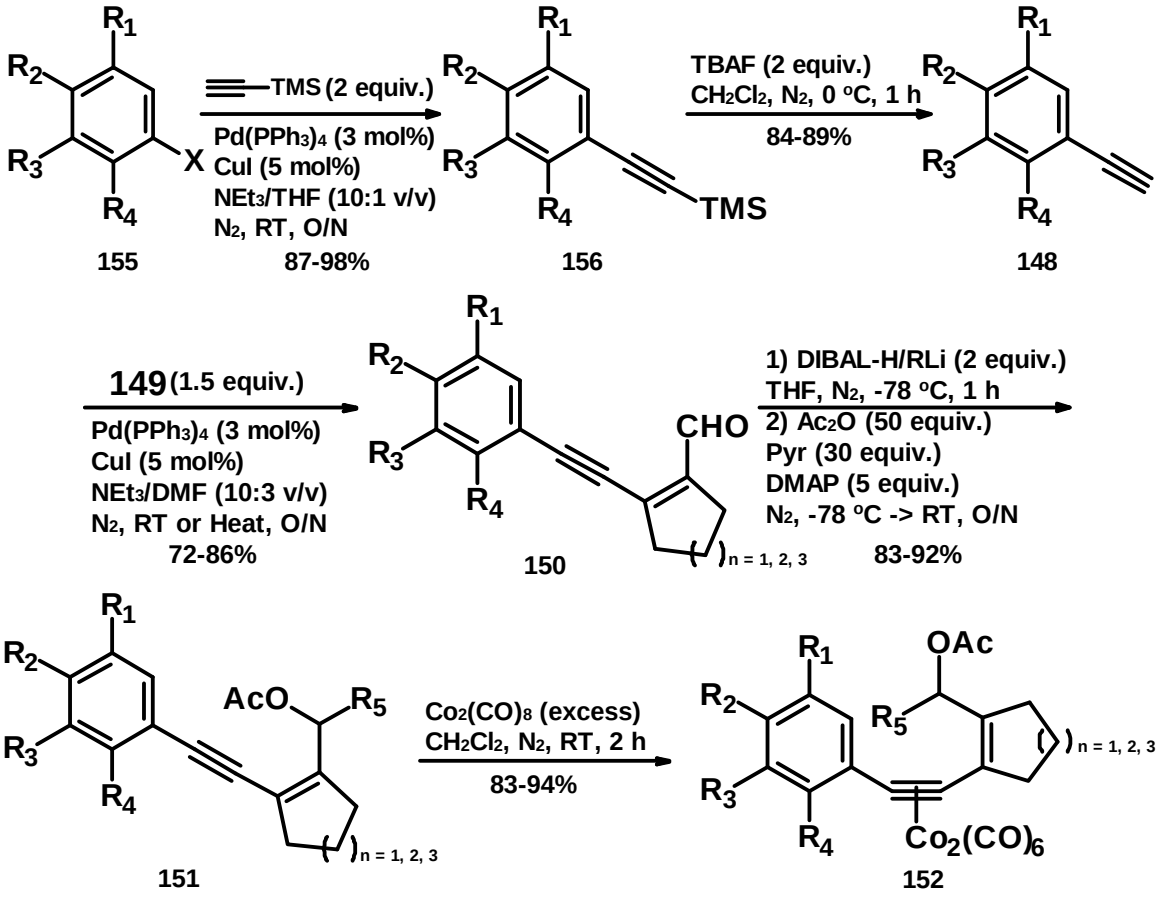
146 **147**

Scheme 2.5: Cyclization of nominally aromatic precursors (**146**).

As $SnCl_4$ 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

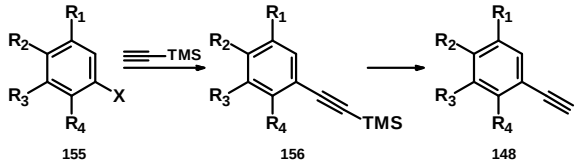
With the original ideas not producing useful results initially, it was decided that attention was going to be projected towards targets with a simpler double bond structure, a cycloalkene ring system[101]. With a synthetic route in hand parallelling those outlined earlier (**Scheme 2.2** and **2.4**), 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 = Br or I; R_1-R_4 = H or OMe, R_5 = H, Me or Ph).

The precursors to the cyclization reactions were envisioned as allylic acetate complexes, with the endocylic 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.



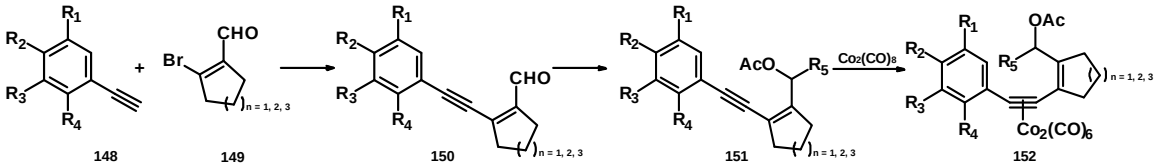
155 156 148

Entry 156	Entry 148	R_1	R_2	R_3	R_4	% Yield 156[a]	%Yield 148[a]
a	**b**	OMe	H	H	H	97	84
b	**c**	OMe	OMe	H	H	96	87
c	**n/a**	OMe	H	OMe	H	87	–
d	**d**	OMe	H	H	OMe	96	87
e	**e**	H	OMe	OMe	OMe	94	88
f	**f**	OMe	OMe	OMe	H	97	87
g	**g**	OMe	OMe	^{i}Pr	H	98	89

[a]Yield after chromatographic purification.

Beginning with the simplest case, an unsubstituted benzene ring ($R_1 = R_2 = R_3 = R_4$ = 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 R_5 = H). Complexation with excess $Co_2(CO)_8$ 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**.

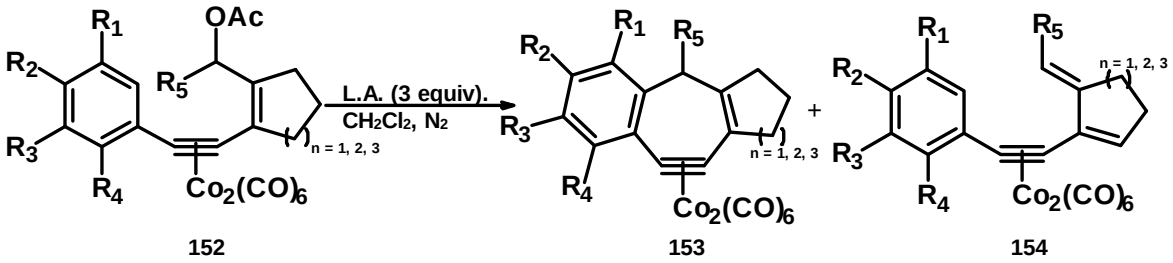


Entry	R_1	R_2	R_3	R_4	R_5	n	% Yield 150[a]	% Yield 151[a]	% Yield 152[a]
a	H	H	H	H	H	1	72	89	90
b						2	82	86	89
c	OMe	H	H	H	H	2	74	89	92
d	OMe	OMe	H	H	H	2	80	89	93
e	OMe	H	OMe	H	H	1	91[b]	88	86
f						2	90[b]	91	92
g	OMe	H	H	OMe	H	1	79	90	91
h						2	85	90	83
i						3	74	85	85
hh	OMe	H	H	OMe	Me	2	–	83	92
j	H	OMe	OMe	OMe	H	1	86	92	87
k						2	82	89	94
kk	H	OMe	OMe	OMe	Me	2	–	89	91
l	OMe	OMe	OMe	H	H	1	83	89	89
m						2	85	88	86
n						3	86	90	92
mm	OMe	OMe	OMe	H	Ph	2	–	80	87
o	OMe	OMe	^{i}Pr	H	H	2	86	90	89

[a]Yield after chromatographic purification.
[b]Yield based on a tandem desilylation/Sonogashira reaction.

Compound **152a** (n = 1) was tested for its ability to undergo a Lewis acid-mediated Nicholas-type cyclization reaction by being treated with BF_3•OEt_2. The Lewis acid was

added slowly to the reaction flask, which contained **152a** dissolved in dry CH_2Cl_2 at a high dilution (7×10^{-3} M), at 0 °C, and under an N_2 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 reactions[193]. The reaction, however, did not produce the anticipated **153a** (R_5 = 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** (R_5 = H). Substitution of BF_3•OEt_2 with $SnCl_4$ did not produce any cyclized product either. Instead, as was observed with BF_3•OEt_2, 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 solvent[66], 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.



152 **153** **154**

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_5 = 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_2Cl_2 at 0 °C 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 °C, 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 °C, the reaction took 3 h to complete (during which time, the reaction was allowed to warm up to 0 °C 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 $\Delta G^{\ddagger} = -RTlnK_{eq}$, where $\Delta G^{\ddagger}$ is the change in the Gibbs free energy ($^{J}/_{mol}$), R is a constant (8.3145 $^{J}/_{mol \bullet K}$), T is the temperature (K), and K_{eq} the equilibrium

constant. Assuming $\Delta G^{\ddagger}$ 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**, $R_1 = R_2 = OMe$, $R_3 = R_4 = H$) ultimately afforded complexed precursor **152d** ($n = 2$, $R_5 = H$), which upon exposure to $BF_3 \bullet OEt_2$ under the typical conditions, also afforded a pair of separable regioisomers, **153d** ($R_1 = R_4 = H$, $R_2 = R_3 = OMe$) and **153d'** ($R_1 = R_2 = OMe$, $R_3 = R_4 = H$) 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: sterics and electronics. In terms of sterics, it was obvious that cyclization favoured the less sterically hindered side to afford the predominant product. In terms of electronics, 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 π-system. Oxygen, however, possesses field/inductive effects due to its greater electronegativity, which occur through the σ 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 ($R_1 = R_3 = OMe$, $R_2 = R_4 = H$) (**155c**) competently produced complexed precursors **152e** (n = 1, R_5 = H) and **152f** (n = 2, R_5 = 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**, $R_1 = R_4 = OMe$, $R_2 = R_3 = H$), the course of reactions outlined in **Scheme 2.6** eventually afforded complexed precursors **152g** (n = 1, R_5 = H), **152h** (n = 2, R_5 = H), **152hh** (n = 2, R_5 = Me), and **152i** (n = 3, R_5 = H), all of which were subjected to treatment with BF_3•OEt_2 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 $\sigma^+_m = 0.047$, and most partial rate factors for reactions of anisole at the meta site are less than one[178]). 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 **152e** and **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 **152i** cyclizing the most cleanly and in the best yield.

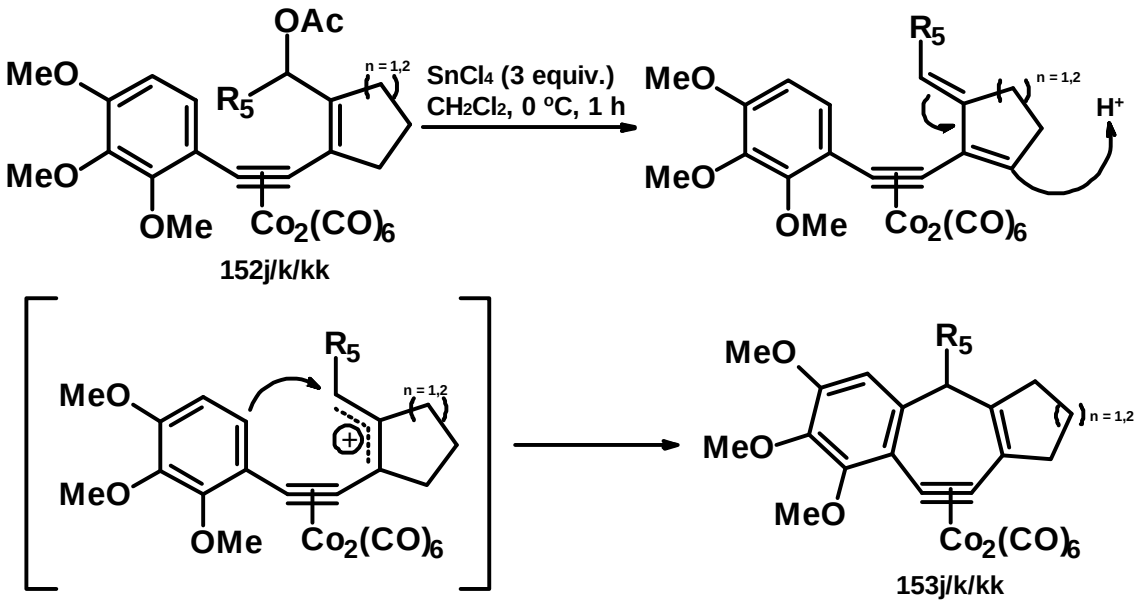
DFT calculations (Scigress Explorer Ultra, V.7.7.0.49., B88-PW91 functional, dzvp basis set) were performed on compounds **152g**, **152h**, **153g**, and **153h**. Based on the data collected, cyclization of **152h** is more exothermic than cyclization of **152g** by 13.6 kJ/mol ($\Delta E_{152g->153g}$ = -36.1 kJ/mol and $\Delta E_{152h->153h}$ = -49.7 kJ/mol), supporting the idea that cyclization of **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^o of the alkene carbons when n = 1 increases when going from acyclic **152g** to cyclic **153g** (i.e., **153g** deviates greater in those bond angles than does its precursor **152g**), whereas the deviation in those bond angles from 120^o when n = 2 decreases when going from acyclic **152h** to cyclic **153h** (i.e., the overall deviation in bond angles is smaller for **153h** than it is for **152h** from an idealized 120^o). This suggests that, upon cyclization of **152g**, an increase in bond angle strain is experienced for the alkene carbons, whereas cyclization of **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 ^{1}H-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, R_5 = H), **152k** (*n* = 2, R_5 = H), and **152kk** (*n* = 2, R_5 = Me) being synthesized from starting material, 4-iodo-1,2,3-trimethoxybenzene (**155e**), according to **Scheme 2.6**. Treatment of these complexes with BF_3•OEt_2 led to reactions that afforded their cyclized products, however, contaminated with elimination and decomposition side products. Subjecting them again to Nicholas chemistry with $SnCl_4$ instead of BF_3•OEt_2 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 $SnCl_4$ 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).

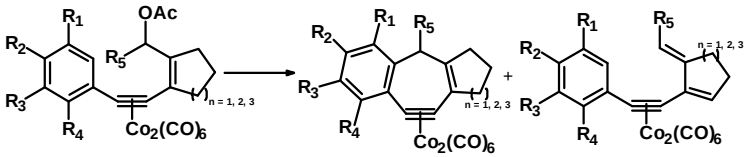
As a result of the above case, an arrangement was then sought that would prove more propitious in this type of chemistry. Originating from 5-iodo-1,2,3-trimethoxybenzene

(**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 = 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 BF_3•OEt_2 had no effect in converting the elimination product to the cyclized product, and neither did resubjecting **154c** to BF_3•OEt_2 post-purification and separation of the two products. Temperature trials showed that dropping the temperature to -50 ^oC resulted in the reaction favouring the elimination route, with a ratio of 1:10.4 in favour of **154c**, and at -60 ^oC, 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 BF_3•OEt_2 for $SnCl_4$ 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**, $R_1 = R_2 =$ OMe, $R_3 = {}^{i}$Pr, $R_4 =$ H), complexed precursor **152o** ($n = 2$, $R_5 =$ H) was synthesized according to **Scheme 2.6**. Treatment of **152o** with $BF_3{\bullet}OEt_2$ resulted in two regioisomeric products, **153o** ($R_1 = {}^{i}$Pr, $R_2 = R_3 =$ OMe, $R_4 =$ H) and **153o'** ($R_1 =$ H, $R_2 = R_3 =$ OMe, $R_4 = {}^{i}$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 group[117,119,120] in their syntheses of several icetexane-diterpenes. The use of $BF_3{\bullet}OEt_2$ in their cyclization step afforded the unwanted isomer as the major product. To circumvent this issue, the group switched their Lewis acid from $BF_3{\bullet}OEt_2$ to $TiCl_4$, 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 $TiCl_4$ instead of the typical 3 equivalents, the Nicholas cyclization still proceeded efficiently, however, no reverse in which isomer was favoured. $SnCl_4$ 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.

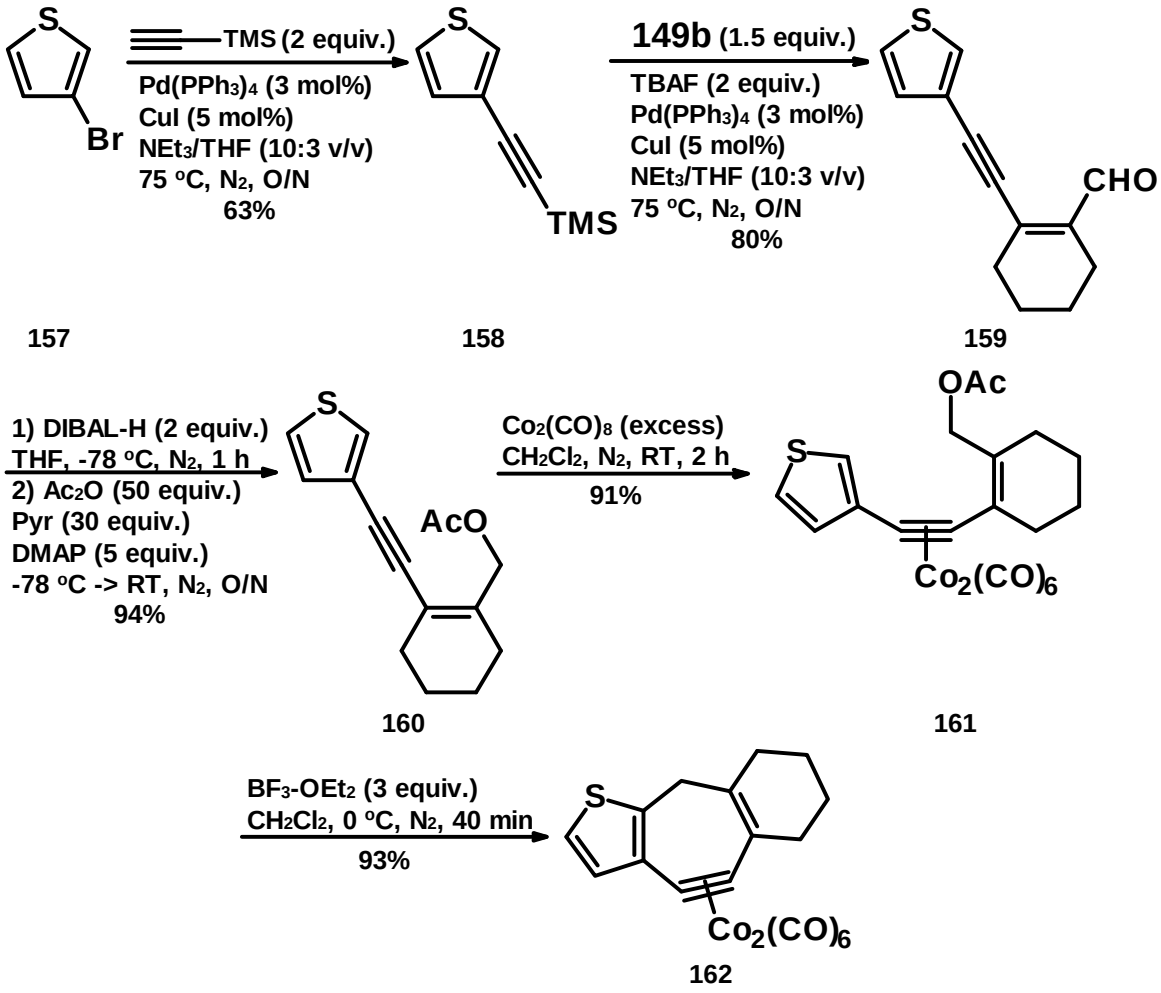
Table 3: Summary of Nicholas Lewis Acid-Promoted Reaction Results



Starting Material	% Yield 153[a]	% Yield 153'[a]	% Yield 154	Ratio 153:153'/154
152a[b]	–	–	–	–
152b[b]	–	–	52	–
152c[b]	68	14	–	4.9:1[e]
152d[b]	81	9	–	8.8:1[e]
152e[b]	85	–	–	–
152f[b]	85	–	–	–
152g[b]	6	–	–	–
152h[b]	82	–	–	–
152hh[b]	–	–	–	1.0:3.0[f]
152i[b]	85	–	–	–
152j[c]	8	–	–	–
152k[c]	39	–	–	–
152kk[c]	39	–	–	–
152l[b]	85	–	–	–
152m[b]	86	–	–	–
152mm[b,d]	34	–	46	1:1.3[e]
152n[b]	84	–	–	–
152o[c]	74	5	–	13.9:1[e]

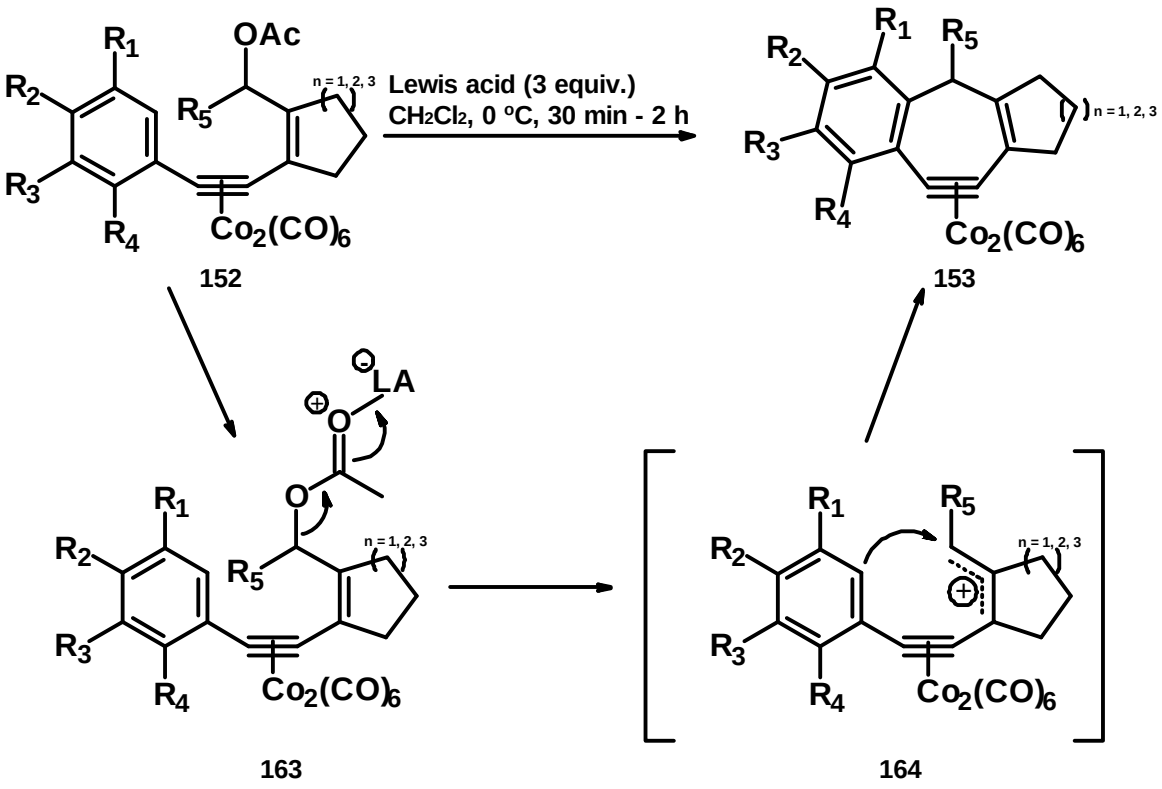
[a]**153** refers to the major isomer, **153'** refers to the minor isomer. Isolated yields after chromatographic purification.
[b]Reacted with $BF_3 \bullet OEt_2$ as Lewis acid.
[c]Reacted with $SnCl_4$ as Lewis acid.
[d]When treated with $SnCl_4$, the reaction afforded only **153mm** in 79% yield.
[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 BF_3•OEt_2, 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[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[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-$Co_2(CO)_6$ 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-$Co_2(CO)_6$ ring system (**Scheme 2.10**).



Scheme 2.10: Proposed mechanism for the generation of the complexed tricyclic products from their respective acetate-$Co_2(CO)_6$ complexed precursors.

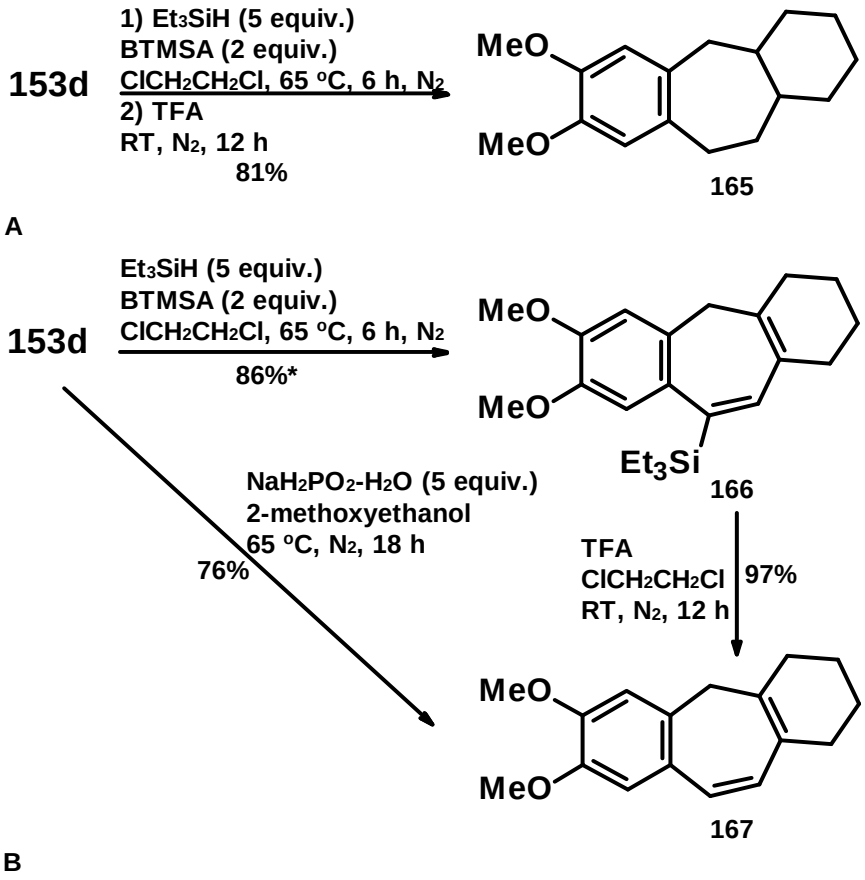
Based on the proposed mechanism, in principle, the Lewis acid should only be required in catalytic amounts. Several groups[24,129], however, including the Green group[36,180], have reported optimized conditions in their alkyne-$Co_2(CO)_6$ chemistry that include supra-stoichiometric amounts of Lewis acid in order to obtain the highest yields.

Simple removal of the $Co_2(CO)_6$ unit from these compounds would give systems whose ring strain would be intolerable at ordinary temperatures. As a result, decomplexation of the alkyne-$Co_2(CO)_6$ 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[35] in removing the $Co_2(CO)_6$ moiety, and simultaneously reducing the alkyne to an alkene, involved a modified version of Isobe's hydrosilylation protocol[98], that ultimately afforded the cycloheptene. In attempting to decomplex **153d**, this modified version was the first method pursued. Complex **153d** was treated with triethylsilane in the presence of bis(trimethylsilyl)acetylene (BTMSA) as a trapping reagent for liberated $Co_2(CO)_6$, 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 $Co_2(CO)_6$ unit. The reaction was allowed to go for 6 h at 65 ^oC, at which point, it was cooled to room temperature, and subsequent *in situ* protodesilylation with trifluoroacetic acid followed. The isolated product (**165**), however, was a result of reductive decomplexation that included further reduction of the alkene functions to afford the benzocylcoheptane in 81% yield (**A, Scheme 2.11**). Surprising, although not unheard of, overreduction during decomplexation has been reported by other groups, including *Tanino et. al.*[184], who described how their decomplexation protocol with Bu_3SnH 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, **153d** was subjected to the same procedure, except that following the hydrosilylation, the product was purified and isolated. This afforded **166** as a regioisomeric mixture of vinylsilanes, with the major one as shown, in a combined yield of 86% (**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 **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[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.



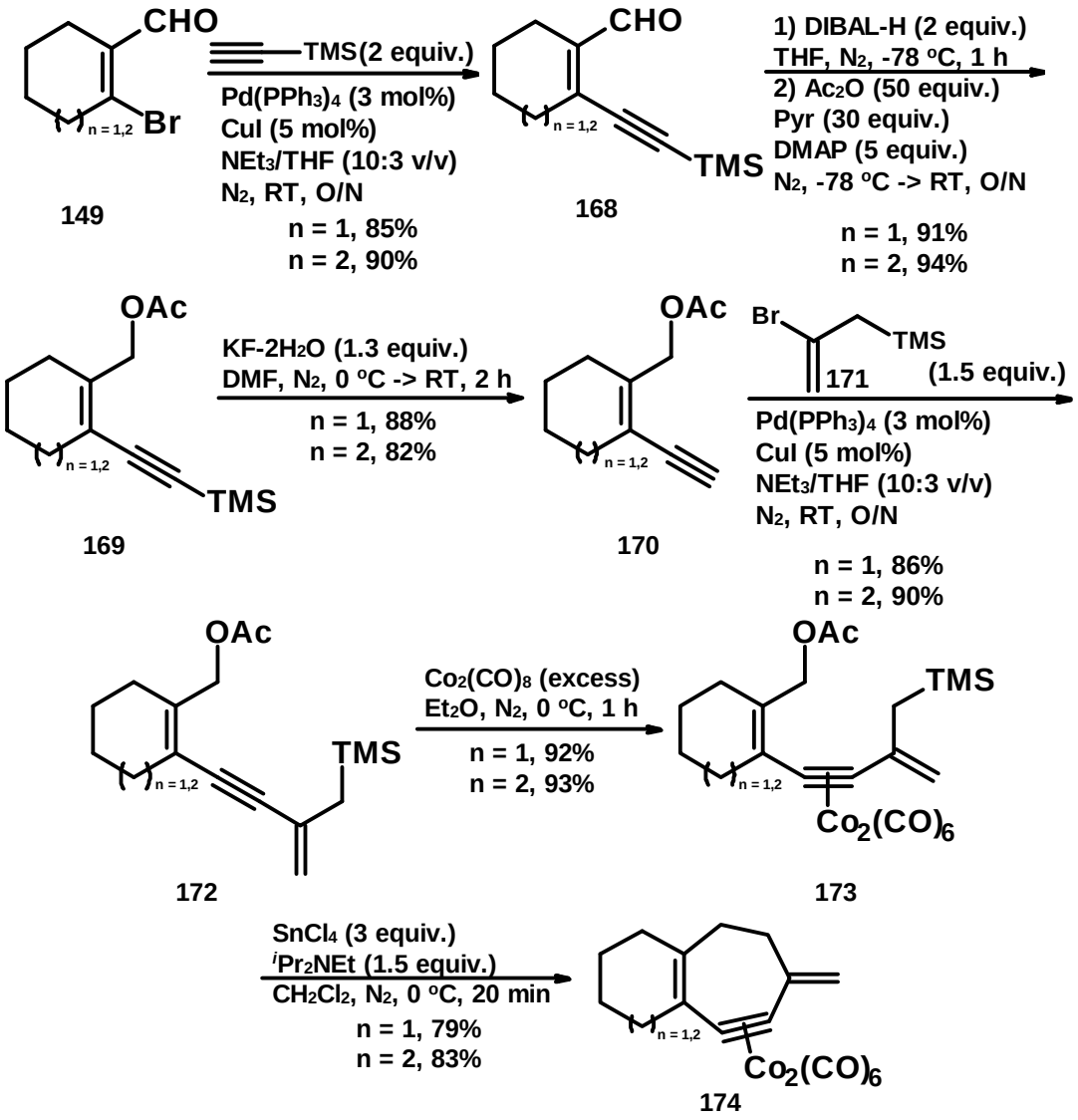
Scheme 2.11: Decomplexation of **153d**. A) Full reduction observed by *in situ* protodesilylation following hydrosilylation. B) Decomplexation which kept the double bonds intact (* indicates combined yield of regioisomers).

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 sterics 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-carbaldehye (**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

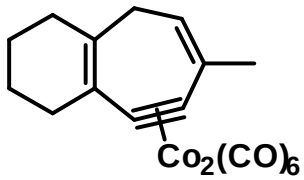
with DIBAL-H, followed by immediate treatment of the generated alcohol with acetic anhydride in the presence of pyridine and DMAP. This afforded the acetate (**169**), which upon desilylation with potassium fluoride dihydrate, afforded a much more stable **170**. Compound **170** was then subjected to 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 (CH_2Cl_2, RT, 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 *exo* position into the chain. On advice from a colleague and some research into troubleshooting this dilemma, complexation was attempted in Et_2O at 0 ^oC 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 BF_3•OEt_2 in dry CH_2Cl_2 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 ^{1}H-

NMR analysis). Switching the Lewis acid to $TiCl_4$ 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 $BF_3 \bullet OEt_2$).



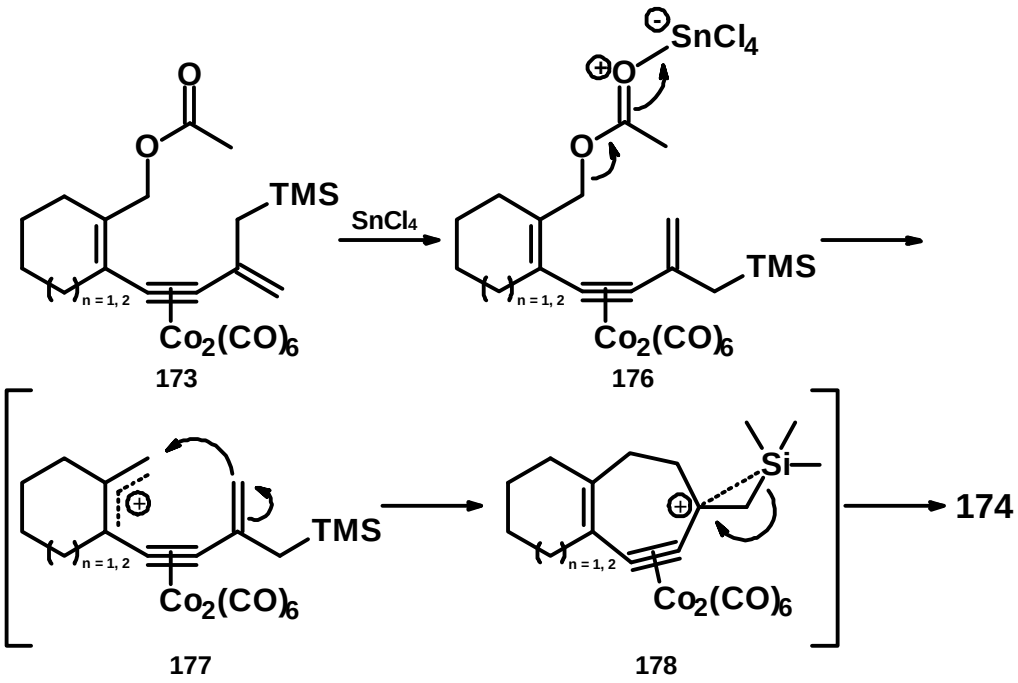
175

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 $SnCl_4$. With this idea in mind, **173a** was subjected to vinylogous Nicholas-type chemistry under the typical conditions, however, with $SnCl_4$ instead of $BF_3 \bullet OEt_2$. To much delight, this was the cleanest reaction by far, and although **175** was still seen in the ^{1}H- and ^{13}C-NMR spectra, it was at its lowest concentration. In trying to troubleshoot this further, work reported by *Djurdjevic and Green*[36] was recalled, in which the authors reported that the addition of 1.5 equivalents of $^i Pr_2NEt$ 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 $SnCl_4$ and 1.5 equivalents of Hunig's base (i.e., $^i Pr_2NEt$). 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*

= 1) was isolated (on neutralized silica) as the sole isomer in 79% yield (**Scheme 2.12**). 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.

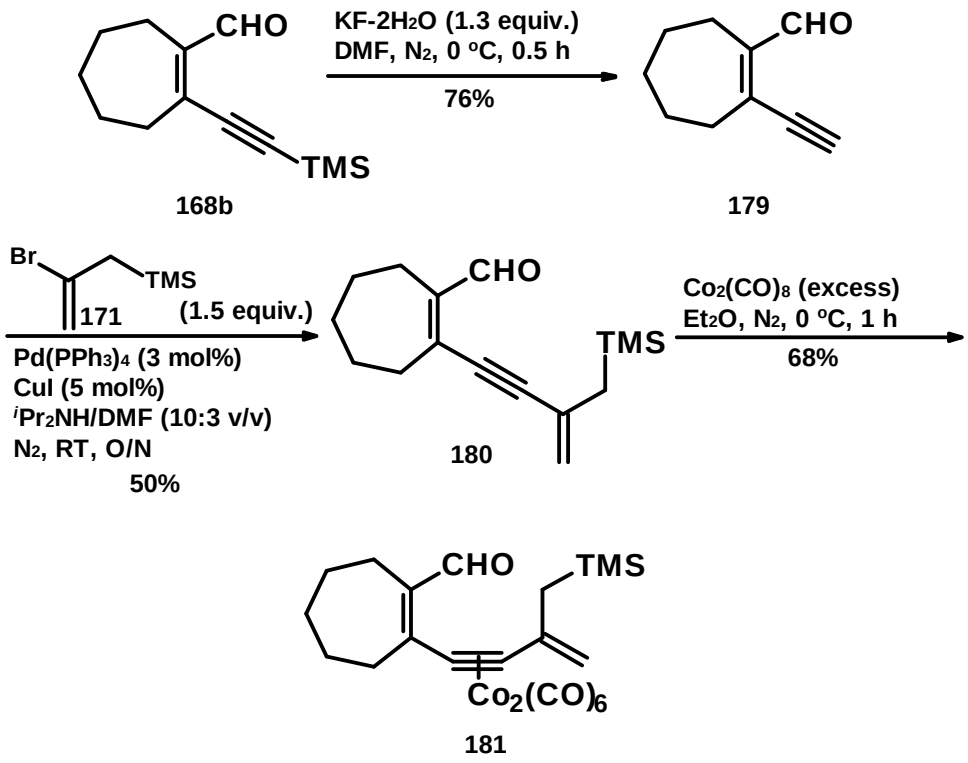
The cyclization of **173** takes advantage of the cation-stabilizing ability of the alkyne-$Co_2(CO)_6$ moiety and the β-effect of the trimethylsilyl group[99]. As depicted in **Scheme 2.13**, treatment of **173** with the tin Lewis acid leads to coordination through the carbonyl group on the acetate 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 (β) from the silicon atom, which helps stabilize it through hyperconjugation effects (i.e., the β-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 σ 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 $SnCl_4$. Cation **178** is doubly stabilized by the alkyne-$Co_2(CO)_6$ 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,

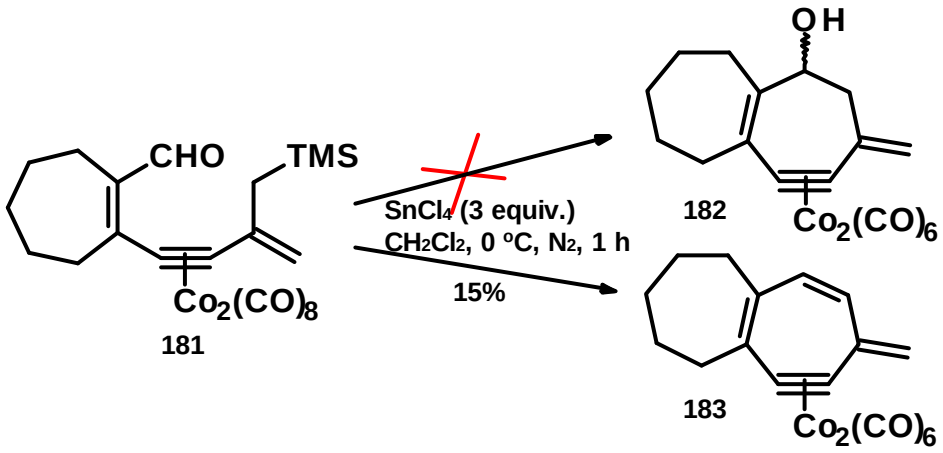
following flash chromatography using a short column of neutralized silica, the complex was promptly dissolved in dichloromethane and treated with the Lewis acid at 0 °C.



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[106]. Use of BF_3•OEt_2 afforded only decomposed material, so $SnCl_4$ 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 ^{1}H-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 ^{13}C-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.



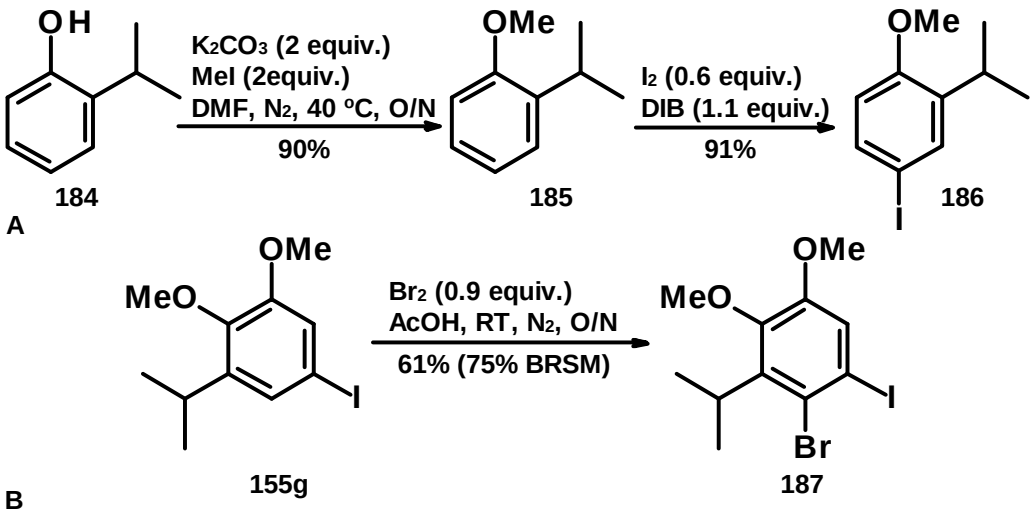
Scheme 2.15: The Hosomi-Sakurai-Nicholas reaction of **181**.

2.3. VINYLOGOUS 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.

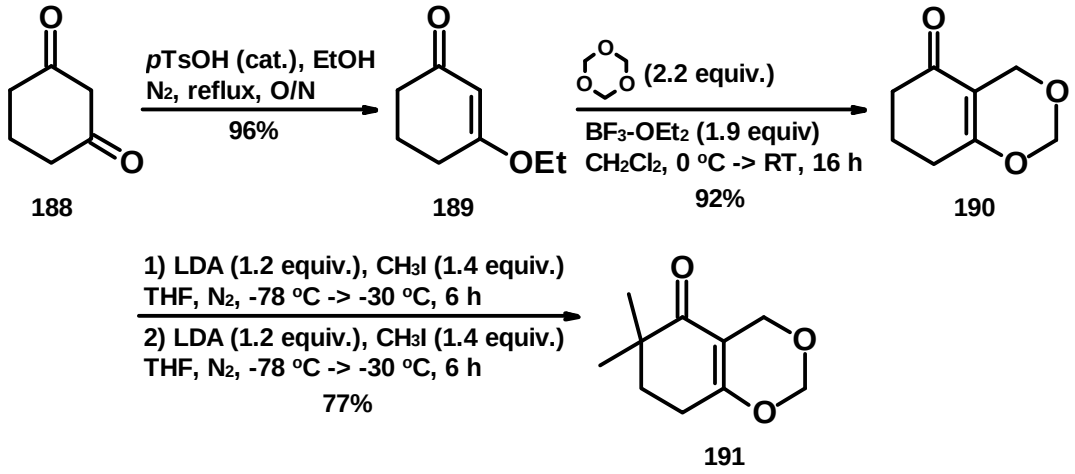
Sight was set on targeting compounds from the pisiferin subclass and the barbatusol subclass of icetexane-diterpenes. Construction of the "C" ring (the aromatic ring) proved

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 bromides[106], 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 Br_2 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 Br_2 to 1.0 still afforded some regioisomeric by-product. Finally, it was determined that if the amount of Br_2 was reduced to 0.9 equivalents, **187** was isolated as the sole isomer, along with unreacted **155g**.



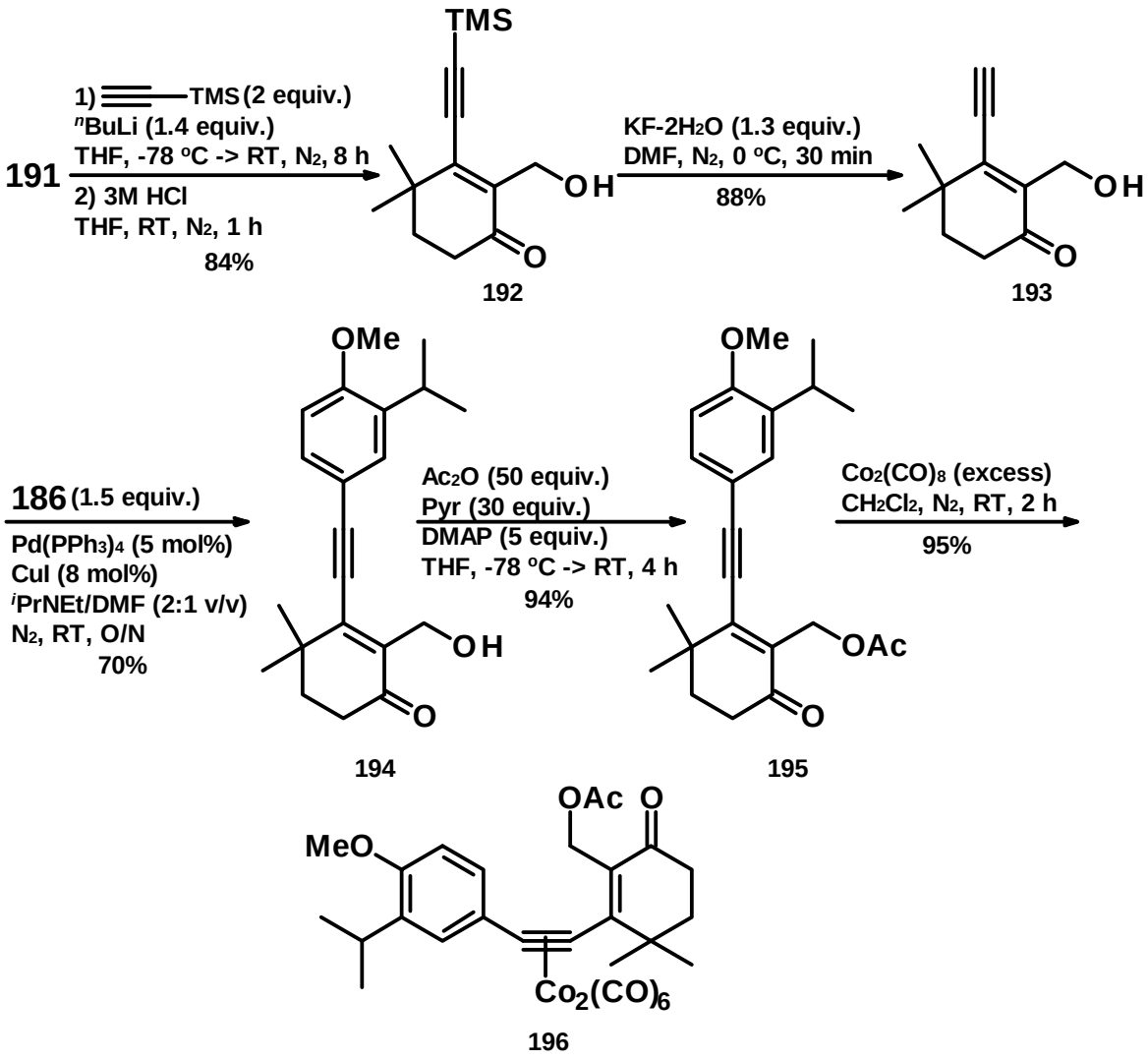
Scheme 2.16: A) Construction of the "C" ring of the pisiferin family. B) Construction of the "C" ring of the barbatusol family.

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.*[114] 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 $BF_3 \bullet OEt_2$ 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.

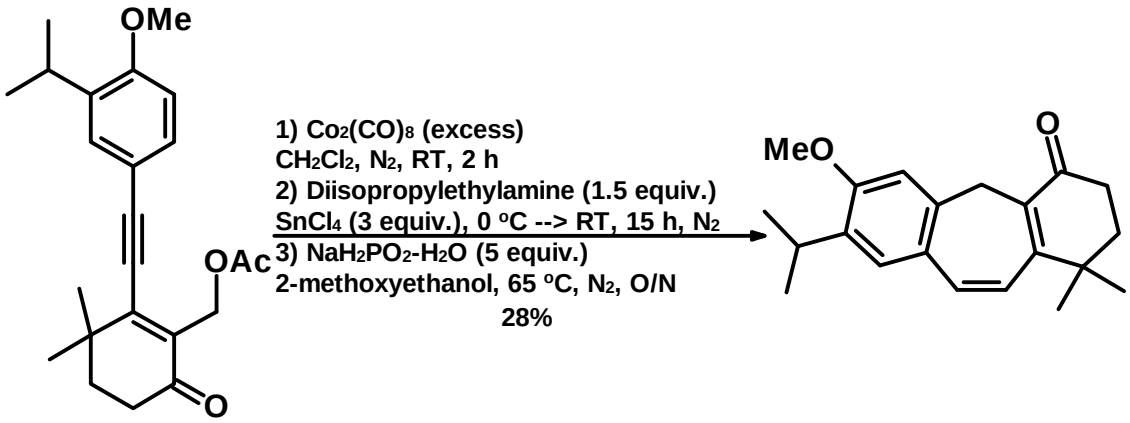
With the "A" ring and "C" ring building blocks in hand, the complexed precursor necessary for cyclization to form the pisiferin skeleton was synthesized according to **Scheme 2.18**. Compound **191** was subjected to lithiated (trimethylsilyl)acetylene, which was generated *in situ* from ^{n}BuLi and (trimethylsilyl)acetylene, and subsequently treated with 3 M HCl to hydrolyze the cyclic acetal. Desilylation of **192** was achieved through KF•$2H_2O$ 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 $Co_2(CO)_8$ 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 BF_3•OEt_2, only to afford decomposed material.



Scheme 2.18: Synthetic route towards complexed precursor **196**.

Having come across work reported by the Tyrrell group[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_2Cl_2 (at a dilution factor typical of cyclization, i.e., ~ 7.0 x 10^{-3} M) along with only a slight excess of $Co_2(CO)_8$, 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, $SnCl_4$ 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).



195 **197**

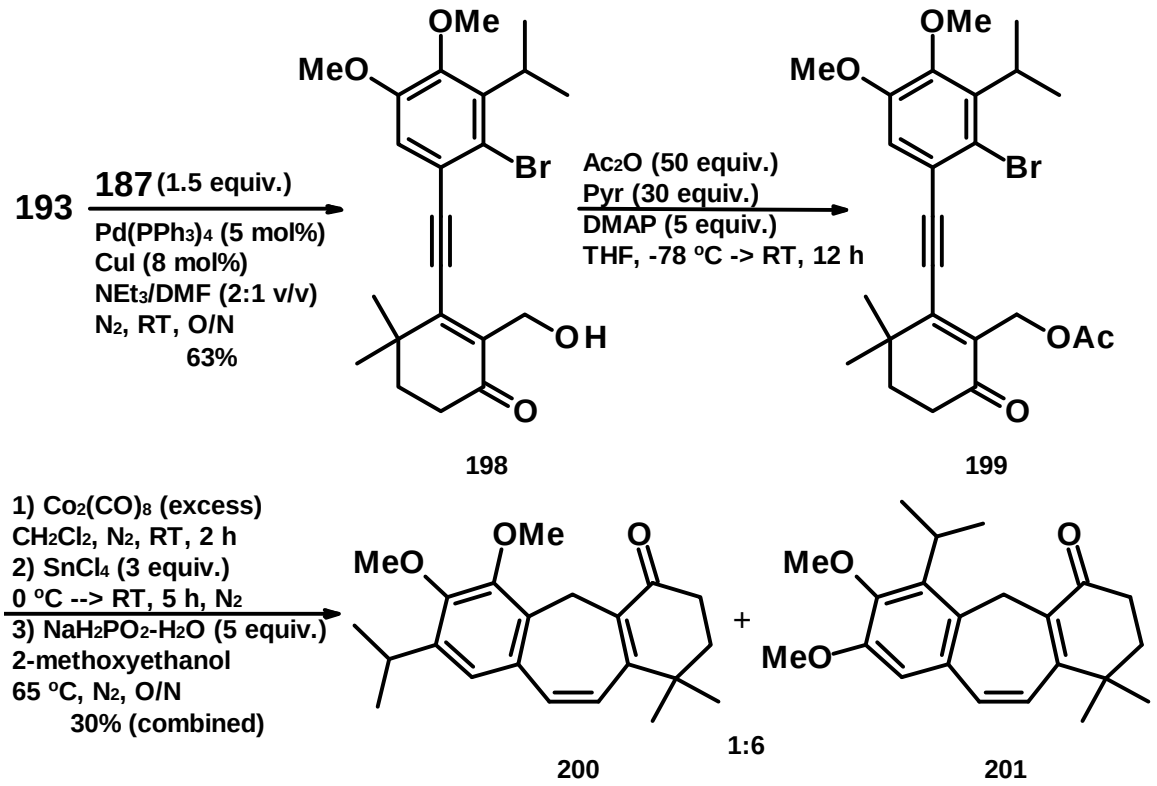
Scheme 2.19: One-pot complexation, cyclization, and decomplexation of **195**.

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 Bu_2BOTf 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 $Co_2(CO)_8$ at ambient conditions in CH_2Cl_2 (enough to make a solution with concentration ~7×10^{-3} M), the reaction flask was submerged into an ice bath to cool to 0 ^oC, and the stirring solution was then treated with $SnCl_4$. 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 $NH_4^+Cl^-$ (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%.

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 $SnCl_4$ to 1.5 equivalents, and/or the amount of excess $Co_2(CO)_8$ 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.

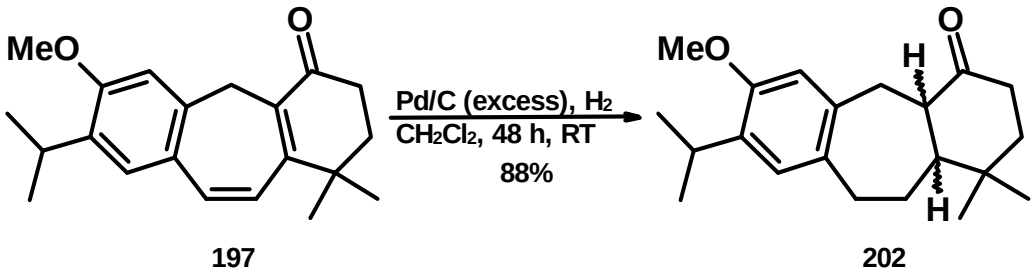


Scheme 2.20: Synthetic route towards the barbatusol skeleton.

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 H_2 gas through the reaction flask containing excess Pd/C, a set of inseperable diastereomers was isolated. This constituted a formal synthesis of pisiferin[123], 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 CCl_4 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**.



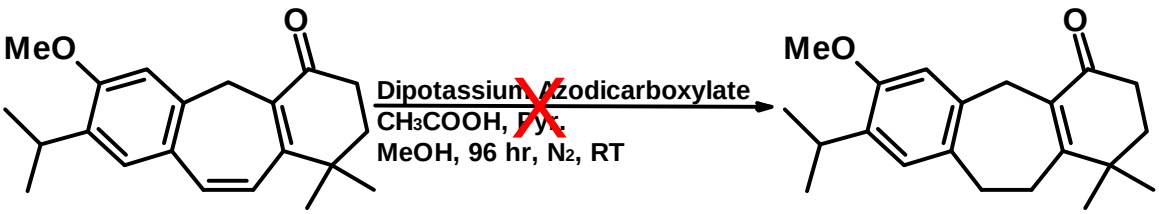
197 202

Scheme 2.21: Non-selective hydrogenation of **197** using Pd/C.

In a report published by the Sarpong group[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 *p*-toluenesulphonyl hydrazide in 1,2-dichloroethane at elevated temperatures). The reduction of carbon-carbon π systems by diimide occurs stereoselectively and stereospecifically[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 et. al.*[56] studied the relative rates of a large number of substituted alkenes toward reduction by diimide generated from triethylamine and *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 $TsNHNH_2$ 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[74,149]. The dipotassium azodicarboxylate

was synthesized according to work published by *Groves & Ma*[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[2] (**Scheme 2.22**). The reduction was allowed to stir over the of course 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[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[117].



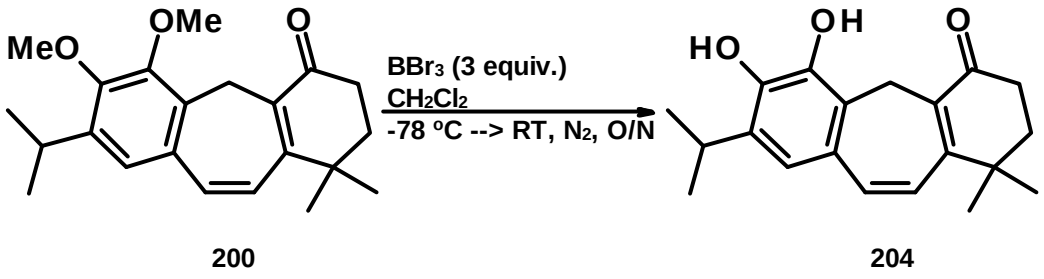
197 **203**

Scheme 2.22: Selective hydrogenation of **197** using $K^{+-}O_2CN{=}NCO_2^{-}K^{+}$ 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® 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.

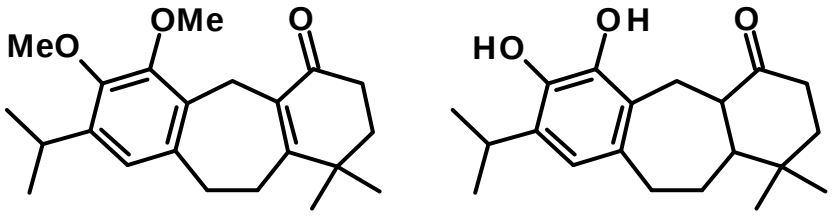
Probing further into literature revealed that BBr_3 is a well-known, selective, versatile reagent for aromatic methyl ethers' demethylation, and would make for a good alternative[40,128,157] (**Scheme 2.23**). Unfortunately due to time constraints, this reaction was not attempted.



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[120], and constitute a formal synthesis. Full hydrogenation of **204** would afford rosmaridiphenol (**102, Figure 2.2**), and a total synthesis.



122 **102**

Figure 2.2: Intermediate **122** in Majetich's total synthesis of (±)-barbatusol; and rosmaridiphenol (**102**).

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-enyne-$Co_2(CO)_6$ complexes, which readily underwent an intramolecular vinylogous Nicholas reaction, indeed, proved to be a powerful method for the assembly of 6,7,*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, $SnCl_4$ 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. $SnCl_4$ 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 BF_3•OEt_2, affording both elimination and cyclized products. Finally, $SnCl_4$ 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 ^oC to -78 ^oC 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.

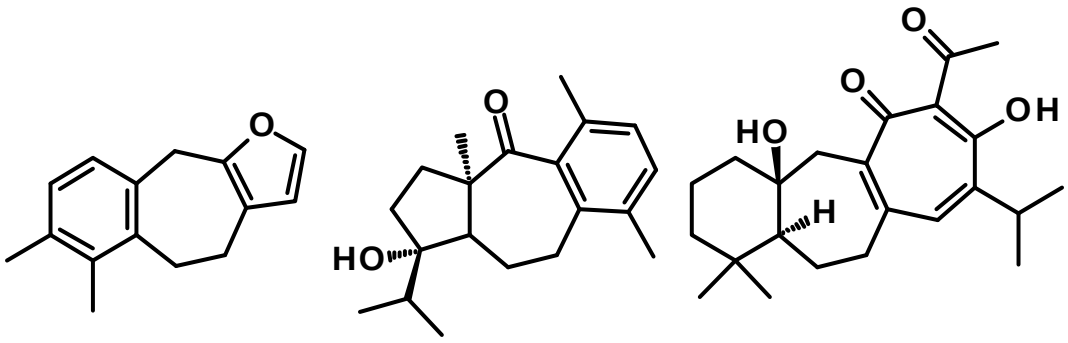
Reductive decomplexation proved quite facile. Subjecting a cyclized-$Co_2(CO)_6$ complexed product to hydrosilylation conditions, followed by *in situ* protodesilylation with TFA afforded an overall reduced tricyclic product. Repeating the same procedure, with the modification that protodesilylation 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 $Co_2(CO)_6$ 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-$Co_2(CO)_6$ 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-

icetexapentan-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

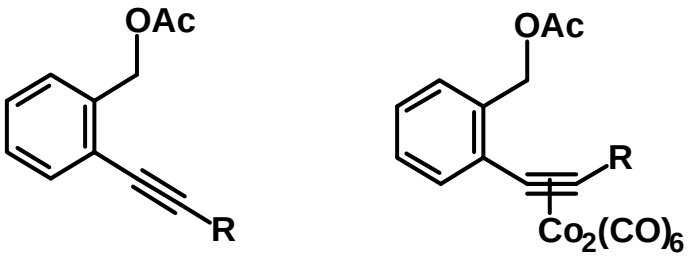
By virtue of being science, in the act of solving questions, it in fact, creates more of them. These questions, however, are what spur the progress of science, and the work outlined in the previous chapters is of no exception. There lay many future possibilities and developments involving vinylogous Nicholas reaction chemistry in the synthesis of cycloheptyne-$Co_2(CO)_6$ 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 **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 **146** pave way for the potential synthesis of some pallescensins[25,27] (in particular, pallescensin E[26] (**205, Figure 3.1**)), a class of furanosesquiterpenoids isolated from the marine sponge *Disidea pallescens*. The brown algae of the family *Dictyotaceae* are a prolific source of diterpenes. A specimen of *Dictyota divaricata* contains diterpenes of several structures, including isodolastane diterpene **206**[156] (**Figure 3.1**), which could be obtained from cyclization of **152** (n = 1). Finally, *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 *Perovskia atriplicifolia*. Possessing a rearranged 9 (10->20)-abeoabietane, perovskatone A (**207, Figure 3.1**) is the first 6,7,7-tricyclic C_{23} diterpeniod found in a natural source.



205 **206** **207**

Figure 3.1: Structures of pallescensin E (**205**), (8S*, 9S*, 12R*)-9-hydroxyisodolasta-1,3,5-(14)-trien-13-one (**206**), and perovskatone A (**207**).

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 S_N1 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.



208 209

Figure 3.2: Model structures for the kinetic study of generated benzylic and Nicholas cations (R = alkyl).

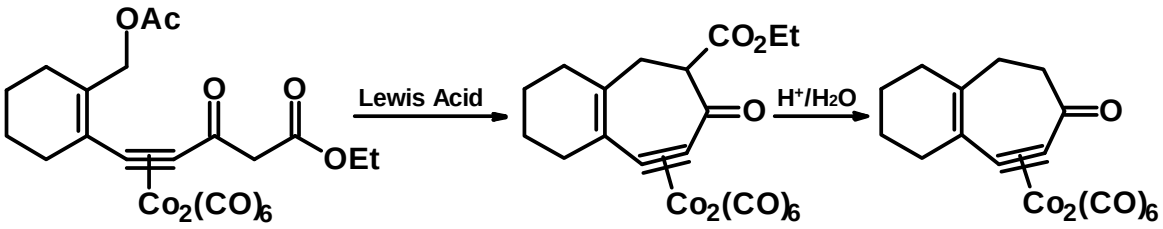
Further information about structural parameters could be gained from X-ray analyses. This would provide useful information on complexes such as **153g**, **153h**, and **153i**. Comparing experimental data to the theoretical DFT calculations performed would be interesting in determining exactly how much 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.*[81], in their study of Lewis acids, determined that for boron-based Lewis acids, BF_3•OEt_2 surpasses only BH_3 in terms of reactivity. Both BCl_3 and BBr_3 were placed ahead of BF_3•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

successes with aluminum-based Lewis acids[129,134] in their work with alkyne-$Co_2(CO)_6$ 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_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[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.



210 211 212

Scheme 3.1: Cyclization of complexed β-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 ^{o}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 (CH_2Cl_2, DMF, Et_2O, 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 *Heck*[79]. The chemicals were used as supplied without further purification unless specifically stated, with the exception of BF_3•OEt_2 and $TiCl_4$, 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 N_2 pressure where necessary. Reactions carried out at -78 ^{o}C were performed

using an acetone/dry ice bath, while those carried out at 0 ^{o}C used a water/ice bath. Reactions carried out at temperatures in between 0 ^{o}C and -78 ^{o}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.

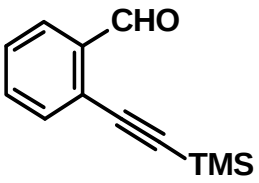
Melting points were measured with a Thomas Hoover, Uni-Melt® capillary point apparatus. ^{1}H-NMR and ^{13}C-NMR spectroscopy was carried out in deuterated solvents, and performed on 300 MHz and/or 500 MHz Bruker Avance spectrometers at room temperature, with 7.27 ppm (residual $CHCl_3$) and 77.0 ppm in $CDCl_3$, 7.15 ppm (residual C_6H_6) and 128.0 ppm in C_6D_6, and 5.32 (residual CH_2Cl_2) and 54.0 in CD_2Cl_2 as the reference chemical shifts for ^{1}H-NMR and ^{13}C-NMR, respectively. All chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (Me_4Si) 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 ^{o}C in order to minimize decomposition.

4.2. EXPERIMENTAL DATA

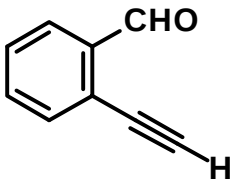
2-(Trimethylsilyl)ethynyl benzaldehyde (135) (GENERAL PROCEDURE A)



$Pd(PPh_3)_4$ (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[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®, the solution dissolved in Et_2O (75 mL), and then extracted with $NH_4^+Cl^-$ (aq., sat., 2 x 75 mL), followed by brine (1

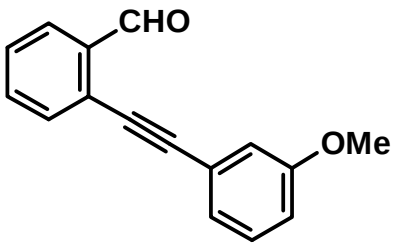
x 75 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Kugelrohr distillation, b.p. 125 °C, 0.1 Torr (lit., 98 °C[1] at 0.2 Torr) afforded **135** as a yellow oil (3.2094 g, 15.882 mmol, 90%), which was characterized as spectroscopically identical to reported values[1].

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 Et_2O (1 x 75 mL) and dH_2O (2 x 75 mL), the organic layer dried over $MgSO_4$, 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 °C[142]). The compound was spectroscopically identical to reported values[142].

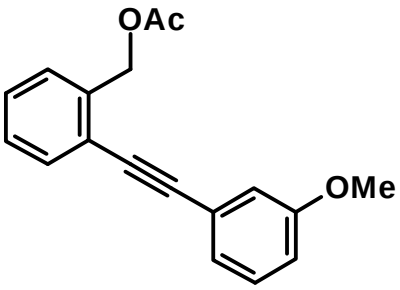
2-[(3-Methoxyphenyl)ethynyl] benzaldehyde (137a) (GENERAL PROCEDURE C)



$Pd(PPh_3)_4$ (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[44]. 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 Et_2O (75 mL), and subsequently extracted with $NH_4^+Cl^-$ (aq., sat., 2 x 75 mL), followed by brine (1 x 75 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography (25:1 hexanes:Et_2O) afforded the product **137a** as a yellow oil (0.8583 g, 3.646 mmol, 84%), which was characterized as spectroscopically identical to reported values[152].

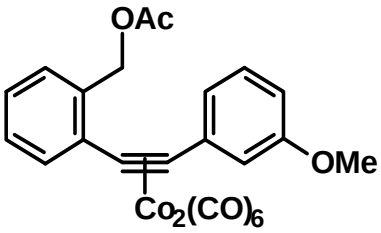
2-[(Methoxyphenyl)ethynyl]benzyl acetate (138a) (GENERAL PROCEDURE D)



In a round bottom flask, compound **137a** (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[165,197] (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 $NH_4^+Cl^-$ (aq., sat., 75 mL)

and extracted with Et_2O (3 x 75 mL). The collected organic fractions were extracted further with $NH_4^+Cl^-$ (aq., sat., 1 x 75 mL) and brine (1 x 75 mL). The organic fraction was then dried over $MgSO_4$, filtered, the solvent removed under pressure, and finally flash chromatography (15:1 hexanes:Et_2O), afforded compound **138a** as a pale yellow oil (0.8677 g, 3.098 mmol, 85%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{18}H_{16}O_3$ calculated 280.1099 (M^+), found 280.1100.

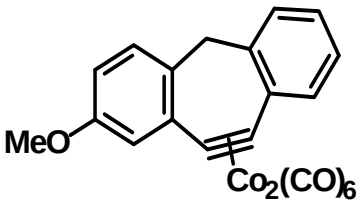
2-[(Methoxyphenyl)ethynyl]benzyl acetate dicobalt hexacarbonyl (139a) (GENERAL PROCEDURE E)



In a round bottom flask, compound **138a** (0.8677 g, 3.098 mmol) and dicobalt octacarbonyl (excess) were dissolved in dry CH_2Cl_2 (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_2O mixture, which eluted compound **139a** as a dark brown solid (1.6404 g, 2.8985 mmol, 94%). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67 (dd, 1H, J = 7.8, J = 1.4), 7.43 (dd, 1H, J = 7.4, J = 1.4),

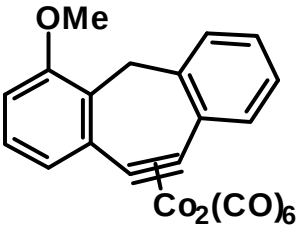
7.34-7.40 (m, 2H), 7.30 (apparent t, 1H, J = 8.0), 7.07 (ddd, 1H, J = 7.6, J = 1.6, J = 0.9), 7.01-7.02 (m, 1H), 6.91 (ddd, 1H, J = 8.2, J = 2.5, J = 0.9), 5.13 (s, 2H), 3.83 (s, 3H), 2.04 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 199.1, 170.5, 159.8, 140.0, 136.1, 134.5, 132.4, 129.9, 129.6, 128.8, 128.4, 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 $C_{24}H_{16}Co_2O_9$ calculated 509.9560 ($M-2CO^+$), found 509.9543.

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



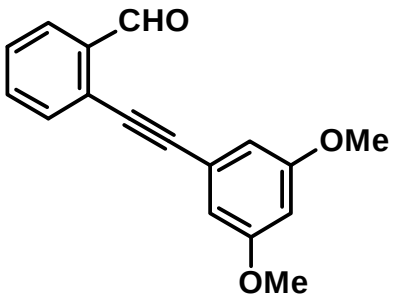
Compound **139a** (0.2279 g, 0.4027 mmol) was dissolved in dry CH_2Cl_2 to a concentration of $7x10^{-3}$ M (57.5 mL) under a nitrogen atmosphere, and cooled down to 0 °C. $SnCl_4$ (141 μL, 1.21 mmol) was added dropwise. The reaction was allowed to warm to room temperature over the course of 15 h, at 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_2O (2 x 75mL). The organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (15:1 hexanes:Et_2O) 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 $C_{22}H_{12}Co_2O_7$ calculated 449.9349 ($M-2CO^+$), found

449.9361.



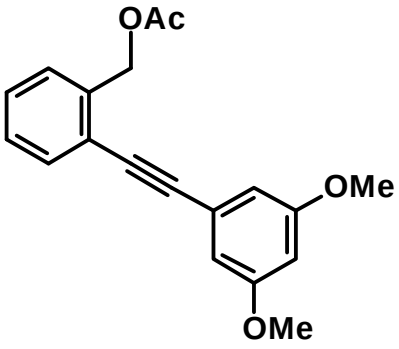
Compound **140a'** was isolated as the minor product (and the first band off the column) as a dark maroon solid (0.0286 g, 0.0565 mmol, 14%). The combined yield was 66%, with a 3.7:1 para:ortho attack (i.e., major:minor products). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.68-7.70 (m, 1H), 7.36-7.38 (m, 1H), 7.32-7.34 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{22}H_{12}Co_2O_7$ calculated 477.9298 ($M\text{-}CO^+$), found 477.9301.

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



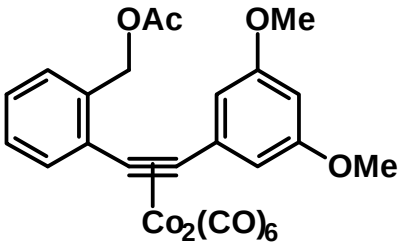
Compound **136** (0.6020 g, 4.629 mmol) was subjected to General Procedure C along with 1-bromo-3,5-dimethoxybenzene (1.4997 g, 6.9439 mmol), with the modification that $Pd(PPh_3)_2Cl_2$ (0.0975 g, 0.139 mmol, 3 mol%) was used as catalyst instead of $Pd(PPh_3)_4$, and the reaction flask was placed in an oil bath set to a temperature of 60 ^{o}C instead of room temperature for overnight (20 h). The product **137b** was isolated using flash chromatography (10:1 hexanes:Et_2O) as a yellow solid (0.9732 g, 3.657 mmol, 79%), with a m.p. 75-77 ^{o}C (lit., m.p. 76-77 ^{o}C[116]), and which was characterized as spectroscopically identical to reported values[116].

2-[(3.5-Dimethoxyphenyl)ethynyl]benzyl acetate (138b)



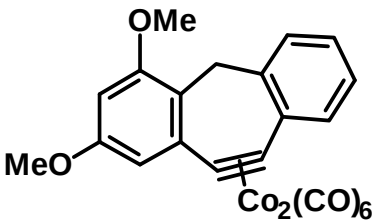
Compound **138b** was synthesized according to General Procedure D from **137b** (0.9732 g, 3.657 mmol). The product was isolated as a pale yellow oil (0.9656 g, 3.114 mmol, 85%) via flash chromatography (7:1 hexanes:Et_2O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.55-7.58 (m, 1H), 7.40-7.43 (m, 1H), 7.28-7.37 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{18}O_4$ calculated 310.1205 (M^+), found 310.1205.

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



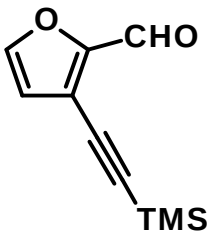
Compound **138b** (0.9656 g, 3.114 mmol) was complexed using General Procedure E to afford product **139b** (1.7463 g, 2.9302 mmol, 94%) as a dark brown solid. The product was eluted from a column of silica using 7:1 hexanes:Et_2O. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67 (dd, 1H, J = 7.3, J = 1.85), 7.42 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{18}Co_2O_{10}$ 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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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, 1138; HRMS: m/e for $C_{23}H_{14}Co_2O_8$ calculated 479.9454 ($M-2CO^+$), found 479.9455.

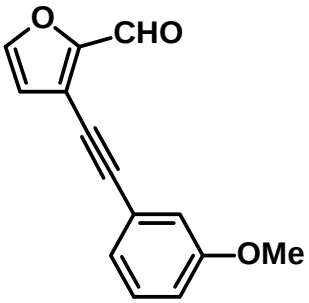
3-[(Trimethylsilyl)ethynyl]furan-2-carbaldehyde (142)



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:Et_2O), with a m.p. of 49-50 ^oC (lit., m.p. 50 ^oC[42]), and characterized as spectroscopically identical to reported values[42].

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

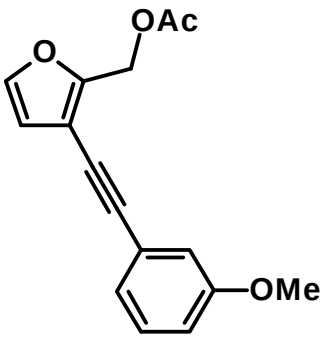
Compound **143** was synthesized using a tandem desilylation/Sonogashira reaction. $Pd(PPh_3)_4$ (0.2208 g, 0.1911 mmol, 3 mol%) and CuI (0.0607 g, 0.318 mmol, 5 mol%) were placed in a round bottom flask, and put under vacuum for 10 minutes. The flask was then



purged with nitrogen. This was repeated two times more[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). NEt_3 (42.5 mL) (which had been bubbled through with N_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®, dissolved in Et_2O (75 mL), and extracted with $NH_4^+Cl^-$ (aq., sat., 2 x 75 mL), followed by brine (1 x 75 mL). The organic fraction was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography (10:1 hexanes:Et_2O) eluted the product (**143**) as a pale yellow oil (1.1380 g, 5.0340 mmol, 79%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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), 6.93 (dd, 1H, J = 8.4, J = 2.6), 6.65-6.66 (m, 1H), 3.80 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{14}H_{10}O_3$ calculated 226.0630 (M^+), found 226.0626.

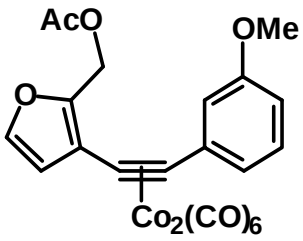
[3-((3-Methoxyphenyl)ethynyl)furan-2-yl]methyl acetate (145a)

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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{16}H_{14}O_4$ calculated 270.0892 (M^+), found 270.0885.

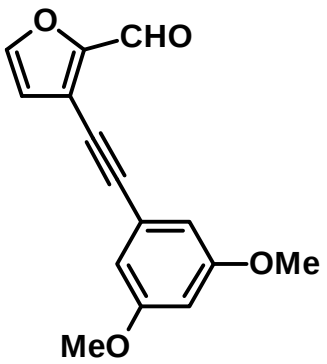
[3-((3-Methoxyphenyl)ethynyl)furan-2-yl]methyl acetate dicobalt hexacarbonyl (146a)



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:Et_2O) eluted the complexed product. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{22}H_{14}Co_2O_{10}$ calculated 471.9403 ($M-3CO^+$), found 471.9389.

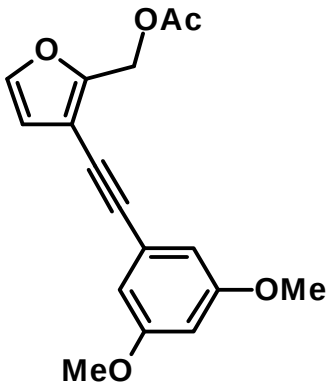
3-[(3,5-Dimethoxyphenyl)ethynyl]furan-2-carbaldehyde (144a)

[(3,5-Dimethoxyphenyl)ethynyl]trimethylsilane (**156c**) (0.9212 g, 3.935 mmol) was subjected to tandem desilylation/Sonogashira chemistry according to General Procedure G



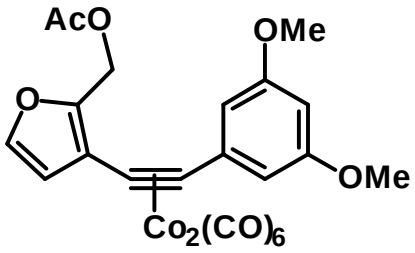
with 3-bromo-2-formylfuran (1.1977 g, 6.8861 mmol) and $Pd(PPh_3)_2Cl_2$ (0.0828 g, 0.118 mmol, 3 mol%) as the catalyst. The product (**144a**) was isolated with flash chromatography (7:1 hexanes:Et_2O) as a light yellow solid (0.8263 g, 3.227 mmol, 82%) with a m.p. of 88-88.5 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{15}H_{12}O_4$ calculated 256.0736 (M^+), found 256.0731.

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



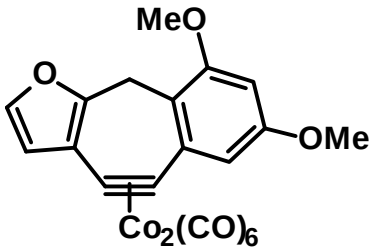
Compound **144a** (0.8263 g, 3.227 mmol) was treated according to General Procedure D. The product (**145b**) was isolated using flash chromatography (5:1 hexanes:Et_2O) as a colourless solid (0.8552 g, 2.850 mmol, 88%) with m.p. 58.5-60 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): 7.39 (d, 1H, J = 1.9), 6.66 (d, 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{17}H_{16}O_5$ 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:Et_2O) after washing the column with 100% hexanes to remove any excess, uncomplexed $Co_2(CO)_8$. The product (1.5958 g, 2.7235 mmol, 96%) was a dark brown solid in appearance. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{23}H_{16}Co_2O_{11}$ calculated 529.9458 (M^+), found 529.9470.

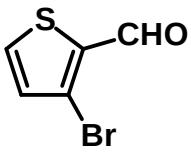
Compound 147b



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:Et_2O) as a maroon solid (0.0232 g, 0.0441 mmol, 17%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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,

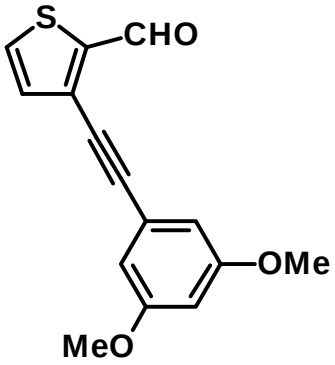
2086, 2016, 1995, 1561, 1318, 1141; HRMS: m/e for $C_{21}H_{12}Co_2O_9$ calculated 469.9247 (M-$2CO^+$), found 469.9245.

3-Bromothiophene-2-carbaldehyde (141b)



Compound **141b** was synthesized (with slight modifications) according to reported procedures by *Fuller et. al.*[52]. 3-Bromothiophene (2.5412 g, 15.695 mmol) was added dropwise to a stirred solution of LDA [prepared by addition of *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 $NH_4^+Cl^-$ (aq., sat., 30 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, 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[52]) afforded the product as a yellow oil (2.2360 g, 11.774 mmol, 75%), which was spectroscopically identical to reported values[52].

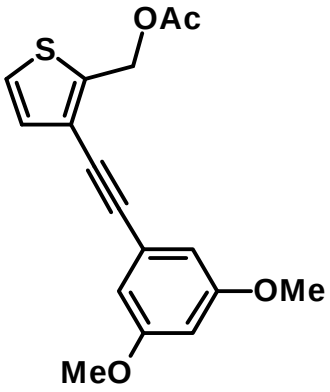
3-[(3,5-Dimethoxyphenyl)ethynyl]thiophene-2-carbaldehyde (144b)



[(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_2O) as a colourless solid

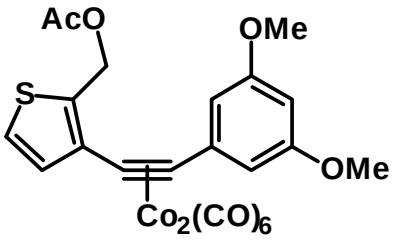
(0.6715 g, 2.468 mmol, 77%) with m.p. 94.5-95 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.21 (d, 1H, J = 0.7), 7.67 (dd, 1H, J = 0.7, J = 5.0), 7.23 (d, 1H, J = 5.0), 6.68 (d, 2H, J = 2.3), 6.50 (t, 1H, J = 2.2), 3.79 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): 183.0, 160.7, 143.7, 134.0, 131.6, 130.8, 123.2, 109.6, 102.7, 96.2, 81.1, 55.5; IR (Pt/diamond): 3008, 2964, 2835, 2209, 1659, 1585, 1203; HRMS: m/e for $C_{15}H_{12}O_3S$ calculated 272.0507 (M^+), found 272.0512.

[3-((3,5-Dimethoxyphenyl)ethynyl)thiophen-2-yl]methyl acetate (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_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{17}H_{16}O_4S$ calculated 316.0769 (M^+), found 316.0756.

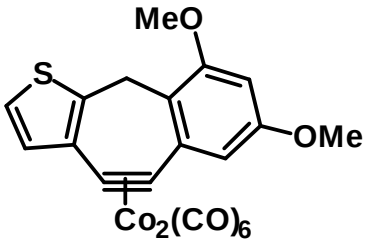
[3-((3,5-Dimethoxyphenyl)ethynyl)thiophen-2-yl]methyl acetate dicobalt hexacarbonyl (146c)



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

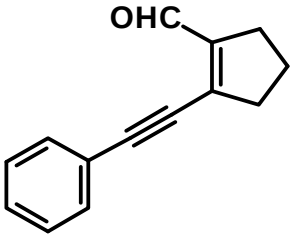
hexanes:Et_2O), after removing excess, uncomplexed $Co_2(CO)_8$ with 100% hexanes. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.31 (d, 1H, J = 5.2), 7.15 (d, 1H, J = 5.2), 6.67 (d, 2H, J = 2.3), 6.46 (t, 1H, J = 2.2), 5.23 (s, 2H), 3.80 (s, 6H), 2.03 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 199.0, 170.5, 160.9, 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 $C_{23}H_{16}Co_2O_{10}S$ 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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{12}Co_2O_8S$ calculated 513.8968 ($M-CO^+$), found 513.8949.

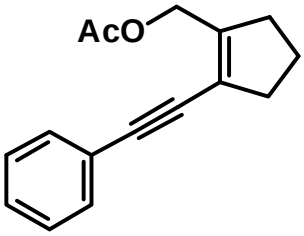
2-(Phenylethynyl)cyclo-pent-1-enecarbaldehyde (150a)



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

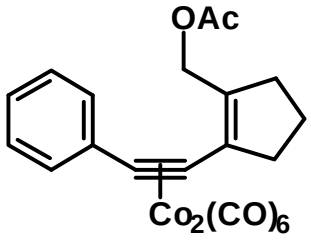
temperature of 75 °C. It was isolated by preparative TLC (25:1 hexanes:Et_2O) as a yellow oil (0.6907 g, 3.522 mmol, 72%). ^{1}H-NMR (500 MHz, $CDCl_3$): 10.16 (s, 1H), 7.49 (apparent dd, 2H, J = 7.6, J = 1.8), 7.33-7.38 (m, 3H), 2.79 (t, 2H, J = 7.9), 2.64 (t, 2H, J = 7.9), 1.98 (apparent pentet, 2H, J = 7.9); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{14}H_{12}O$ 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 prepartative TLC (15:1 hexanes:Et_2O) as a yellow oil (0.5531 g, 2.303 mmol, 89%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{16}H_{16}O_2$ calculated 240.1150 (M^+), found 240.1145.

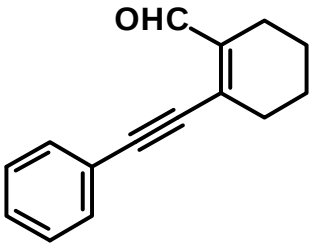
[2-(Phenylethynyl)cyclopent-1-enyl]methyl acetate dicobalt hexacarbonyl (152a)



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

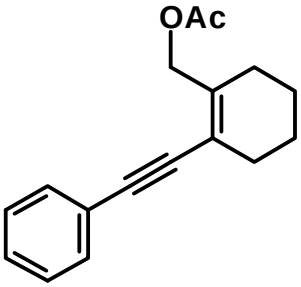
hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.44-7.47 (m, 2H), 7.30-7.37 (m, 3H), 4.63 (s, 2H), 2.79 (t, 2H, J = 7.8), 2.56 (t, 2H, J = 7.9), 2.03 (apparent pentet, 2H, J = 7.9), 2.00 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 199.4, 170.8, 138.5, 137.6, 137.2, 129.3, 128.9, 127.9, 93.1, 84.7, 61.2, 39.9, 36.3, 21.9, 20.9; IR (KBr): 3077, 2957, 2848, 2089, 2050, 2021, 1745, 1231; HRMS: m/e for $C_{22}H_{16}Co_2O_8$ calculated 497.9560 ($M\text{-}CO^+$), 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 ^{o}C using an oil bath. The product was isolated using preparative TLC (25:1 hexanes:Et_2O) as a yellow oil (0.4687 g, 2.231 mmol, 82%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{14}O$ calculated 210.1045 (M^+), found 210.1045.

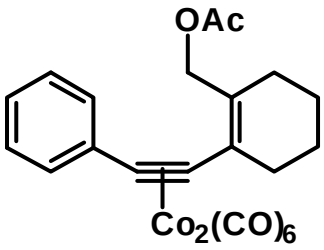
[2-(Phenylethynyl)cyclohex-1-enyl]methyl acetate (151b)



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:Et_2O) as a yellow oil (0.4889 g, 1.924 mmol, 86%). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.43-7.45 (m, 2H), 7.29-7.33 (m, 3H),

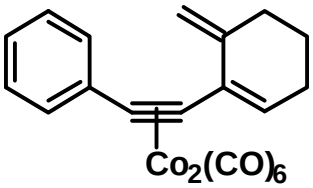
4.90 (s, 2H), 2.31 (m, 2H), 2.18 (m, 2H), 2.10 (s, 3H), 1.66-1.71 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.3, 139.1, 131.6, 128.4, 128.2, 123.5, 120.1, 93.2, 88.2, 66.7, 30.3, 27.2, 22.3, 22.1, 21.1; IR (KBr): 3058, 2934, 2861, 1740, 1228; HRMS: m/e for $C_{17}H_{18}O_2$ calculated 254.1307 (M^+), 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_2O). ^{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 $C_{23}H_{18}Co_2O_8$ calculated 483.9767 ($M-2CO^+$), found 483.9759.

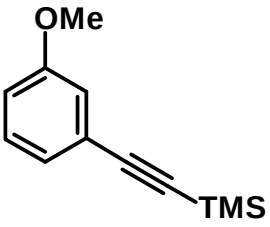
[(6-Methylenecyclohex-1-enyl)ethynyl]benzene dicobalt hexacarbonyl (154a)



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

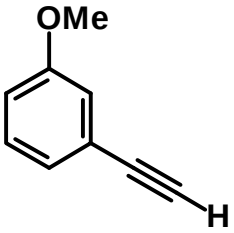
(s, 1H), 4.73 (s, 1H), 2.48 (t, 2H, J = 6.4), 2.35 (apparent q, 2H, J = 5.7), 1.83 (apparent pentet, 2H, J = 6.3); ^{13}C-NMR (75 MHz, $CDCl_3$): 199.9, 140.5, 138.5, 136.8, 135.2, 130.2, 128.7, 127.8, 112.9, 94.9, 93.6, 32.9, 29.8, 27.7, 22.9; IR (KBr): 2940, 2828, 2087, 2047, 2015, 1633; HRMS: m/e for $C_{21}H_{14}Co_2O_6$ 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].

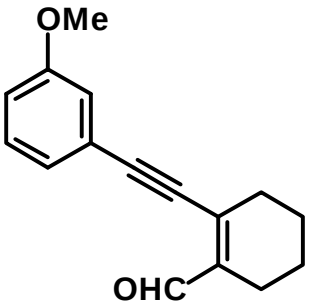
Ethynyl-3-methoxybenzene (148b) (GENERAL PROCEDURE H)



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_2Cl_2 (48.0 mL), and the reaction flask was cooled to 0 ^{o}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_2O (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].

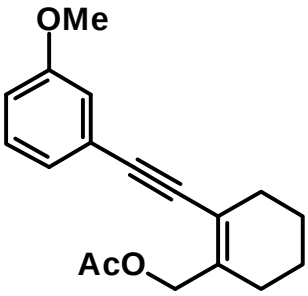
2-[(3-Methoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150c)

Compound **150c** was synthesized according to General Procedure C from **148b** (0.4596 g



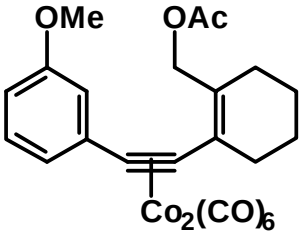
3.480 mmol) and 2-bromocyclohex-1-ene-1-carbaldehyde **149b** (0.9918 g, 5.220 mmol). The product was isolated as a yellow oil (0.6204 g, 2.584 mmol, 74%) via preparative TLC (20:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 10.32 (s, 1H), 7.26 (apparent t, 1H, J = 8.0), 7.07 (d of t, 1H, J = 7.6, 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{16}H_{16}O_2$ calculated 240.1150 (M^+), found 240.1158.

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



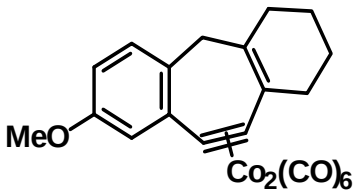
Compound **150c** (0.6204 g, 2.584 mmol) was subjected to General Procedure D. The product **151c** was isolated as a pale yellow oil (0.6542 g, 2.302 mmol, 89%) via preparative TLC (10:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.22 (apparent t, 1H, J = 8.0), 7.03 (d of t, 1H, J = 7.6, J = 1.0), 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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): 3002, 2935, 2861, 2198, 1738, 1596, 1230; HRMS: m/e for $C_{18}H_{20}O_3$ calculated 284.1412 (M^+), found 284.1415.

[2-((3-Methoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152c)



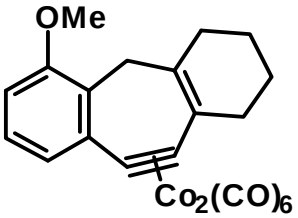
Compound **151c** (0.6542 g, 2.302 mmol) was subjected to complexation as outlined in General Procedure E. The complexed product **152c** was isolated as a dark brown solid (1.2123 g, 2.1269 mmol, 92%) by flash chromatography (10:1 hexanes:Et_2O), after washing through excess, uncomplexed $Co_2(CO)_8$ 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 $C_{24}H_{20}Co_2O_9$ calculated 430.0026 ($M-5CO^+$), found 430.0021.

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



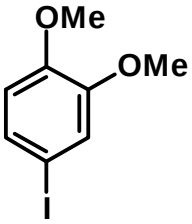
Complexed compound **152c** (0.0322 g, 0.0565 mmol) was subjected to General Procedure F, with the use of BF_3•OEt_2 (21 μL, 0.17 mmol) as Lewis acid. The reaction was complete in 1.5 h, as monitored by TLC. The regioisomers were separable by flash chromatography using 100% hexanes. The major product **153c** (0.0195 g, 0.0382 mmol, 68%) eluted as the second band, and as a dark maroon solid. ^{1}H-NMR (500

MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{22}H_{16}Co_2O_7$ calculated 481.9625 ($M\text{-}CO^+$), 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%. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{22}H_{16}Co_2O_7$ calculated 481.9611 ($M\text{-}CO^+$), found 481.9624.

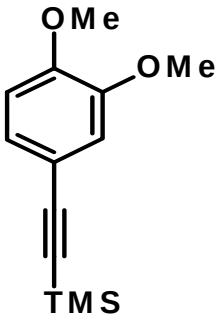
4-Iodo-1,2-dimethoxybenzene (155b) (GENERAL PROCEDURE I)



Compound **155b** was synthesized according methods reported by *Karade et. al.*[94] Veratrole (2.5000 g, 18.107 mmol), I_2 (2.7574 g, 10.864 mmol), and DIB (6.4155 g, 19.918 mmol) were ground using a pestle and mortar for approximately 30 minutes, or until a noticeable colour change (from violet to an orange-yellow) was observed. The completion of the reaction was verified by TLC, at which point the mixture was washed with $Na_2S_2O_3$ (aq., sat., 75 mL), and extracted with CH_2Cl_2 (2 x 75 mL). The organic fractions were combined and dried using $MgSO_4$.

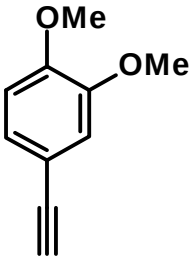
Filtration, followed by removal of the solvent under reduced pressure, and finally Kugelrohr distillation at 0.1 Torr afforded compound **155b** (4.4454 g, 16.841 mmol, 93%) as a yellow oil, which was characterized as spectroscopically identical to reported values[94].

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



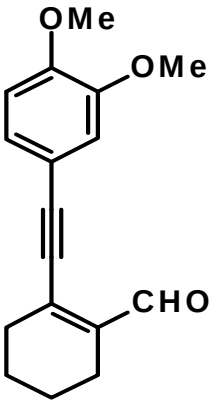
Compound **156b** was synthesized from 4-iodo-1,2-dimethoxybenzene (**155b**) (1.7822 g, 6.7516 mmol) according to General Procedure A. Compound **156b** was isolated as a yellow oil (1.5212 g, 6.4979 mmol, 96%) using flash chromatography (10:1 hexanes:Et_2O) for the final purification step , and was characterized as spectroscopically identical to reported values[135].

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_2O), with a m.p. of 72-73 ^oC (lit., 70-71 ^oC[135]), and was characterized as spectroscopically identical to reported values[135].

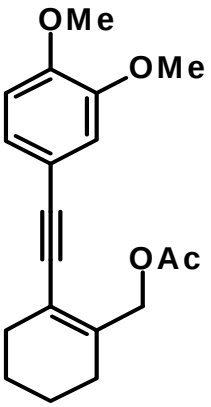
2-[(3,4-Dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150d)



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_2O), and was characterized as

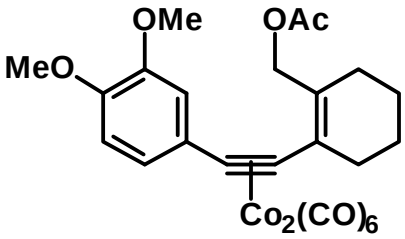
spectroscopically identical to reported values[84].

[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_2O), as a pale yellow oil (1.1207 g, 3.5674 mmol, 89%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{19}H_{22}O_4$ calculated 314.1518 (M^+), found 314.1513.

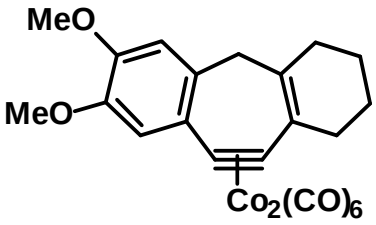
[2-((3,4-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152d)



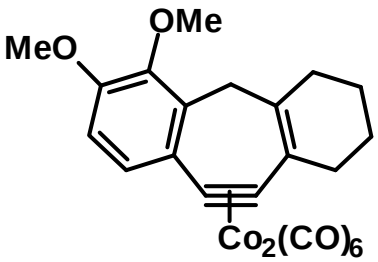
Compound **151d** (1.1207 g, 3.5674 mmol) was complexed according to General Procedure E. After washing the column of silica with 100% hexanes to remove excess, uncomplexed $Co_2(CO)_8$, the product **152d** was eluted using 5:1 hexanes:Et_2O, and isolated as a dark brown solid (2.0001 g, 3.3336 mmol, 93%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 199.6, 170.8, 149.0, 148.9, 133.4, 132.0, 130.7, 122.1, 112.5, 111.4, 94.0,

91.4, 65.3, 56.0, 55.9, 33.4, 28.3, 23.4, 22.2, 20.7; IR (KBr): 2935, 2834, 2086, 2045, 2014, 1742, 1509, 1228; HRMS: m/e for $C_{25}H_{22}Co_2O_{10}$ calculated 571.9928 ($M\text{-}CO^+$), found 571.9925.

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



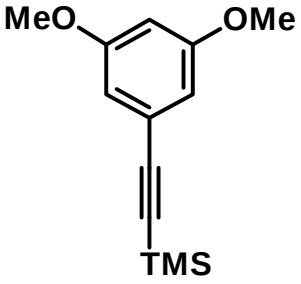
Compound **152d** (1.0023 g, 1.6705 mmol) was reacted according to General Procedure F, using $BF_3 \bullet OEt_2$ (635 μL, 5.01 mmol) as Lewis acid. The product was obtained as a pair of regioisomers, **153d** (0.7280 g, 1.348 mmol, 81%) as the major product, and **153d'** (0.0823 g, 0.152 mmol, 9%) 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_2O). ^{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 $C_{23}H_{18}Co_2O_8$ calculated 511.9716 ($M\text{-}CO^+$), found 511.9711.



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-

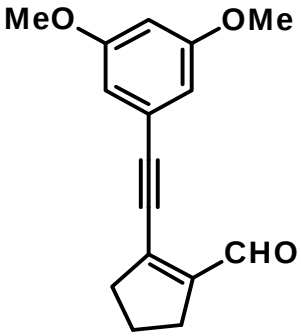
NMR (500 MHz, $CDCl_3$): 7.39 (d, 1H, J = 8.6), 6.87 (d, 1H, J = 8.7), 3.90 (s, 3H), 3.84 (s, 3H), 3.34 (s, 2H), 2.31-2.36 (m, 4H), 1.67-1.79 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): 200.2, 153.4, 145.7, 136.3, 131.2, 131.1, 130.9, 128.2, 110.9, 95.2, 90.4, 61.4, 55.9, 33.8, 33.2, 30.6, 23.1, 22.8; IR (KBr): 2962, 2917, 2849, 2085, 2048, 2017, 1463, 1283; HRMS: m/e for $C_{23}H_{18}Co_2O_8$ 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 °C[21]), and which was characterized as spectroscopically identical to reported values[21].

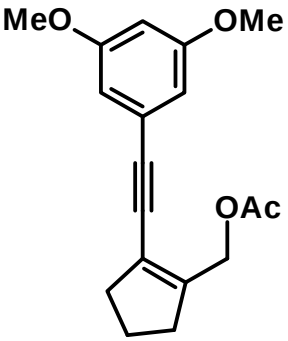
2-[(3,5-Dimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150e)



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:Et_2O), with a m.p. of 120-122 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): 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

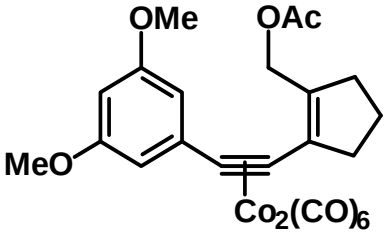
(apparent pentet, 2H, J = 7.6); ^{13}C-NMR (75 MHz, $CDCl_3$): 188.9, 160.7, 148.2, 143.0, 123.3, 109.6, 102.9, 100.9, 82.8, 55.5, 38.9, 29.7, 22.2; IR (KBr): 3080, 2995, 2936, 2838, 2190, 1669, 1587, 1156; HRMS: m/e for $C_{16}H_{16}O_3$ calculated 256.1099 (M^+), found 256.1096.

[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_2O). ^{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.

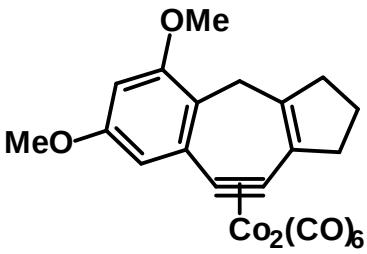
[2-((3,5-Dimethoxyphenyl)ethynyl)cyclopent-1-enyl]methyl acetate dicobalt hexacarbonyl (152e)



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_2O) 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 $C_{24}H_{20}Co_2O_{10}$ calculated 473.9925 (M-4CO$_+$), found 473.9930.

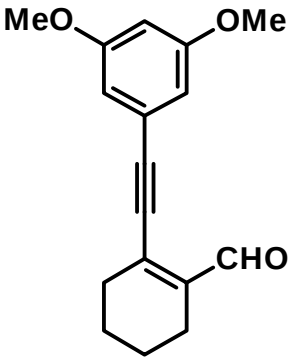
Compound 153e



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_2O) 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 $C_{22}H_{16}Co_2O_8$ calculated 525.9509 (M^+), found 525.9510.

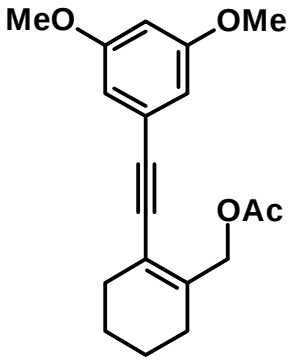
2-[(3,5-Dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150f)

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 ^{o}C overnight (20 h) using



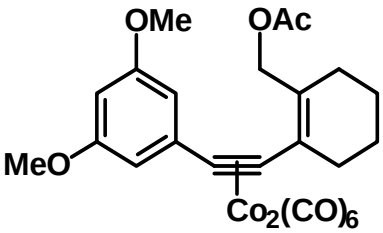
an oil bath instead of leaving it at room temperature. The coupled product (**150f**) was isolated as a yellow oil (0.9252 g, 3.425 mmol, 90%) following flash chromatography (10:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 10.30 (s, 1H), 6.60 (d, 2H, J = 2.2), 6.47 (t, 1H, J = 2.1), 3.78 (s, 6H), 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, 2937, 2838, 2197, 1672, 1594, 1421, 1208; 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)



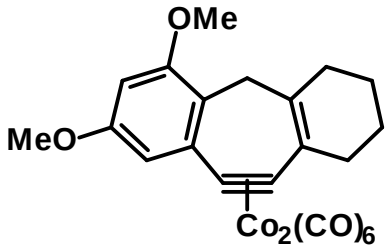
Compound **150f** (0.9252 g, 3.425 mmol) was subjected to reduction and acetylation according to General Procedure D. Product **151f** was isolated as a yellow oil (0.9761 g, 3.107 mmol, 91%) following flash chromatography (5:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.58 (d, 2H, J = 2.3), 6.42 (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:Et_2O) following removal of excess, uncomplexed $Co_2(CO)_8$ with 100% hexanes. The product was isolated as a dark brown solid (1.7135 g, 2.8559 mmol, 92%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{22}Co_2O_{10}$ calculated 543.9979 ($M-2CO^+$), found 543.9975.

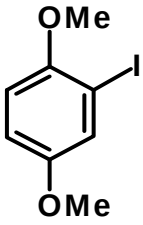
Compound 153f



Compound **152f** (0.0783 g, 0.130 mmol) was reacted according to General Procedure F using BF_3•OEt_2 (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:Et_2O) as a maroon solid (0.0601 g, 0.111 mmol, 85%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 200.0, 159.2, 156.7, 140.1, 138.2, 130.5,

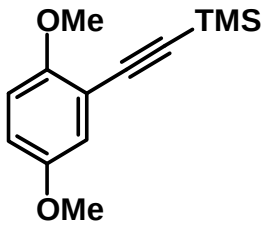
118.2, 108.0, 98.8, 95.2, 90.4, 55.9, 55.4, 33.7, 31.8, 30.4, 23.0, 22.8; IR (KBr): 3020, 2086, 2046, 2015, 1600, 1279; HRMS: m/e for $C_{23}H_{18}Co_2O_8$ calculated 539.9666 (M^+), found 539.9669.

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



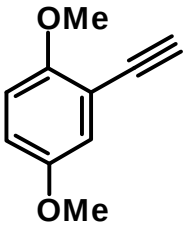
1,4-Dimethoxybenzene (2.0000 g, 14.486 mmol) was subjected to General Procedure I. Compound **155d** was isolated as a yellow oil (3.4415 g, 13.038 mmol, 90%), and was characterized as spectroscopically identical to reported values[94].

[(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 ^oC, and spectroscopically identical to reported values[198].

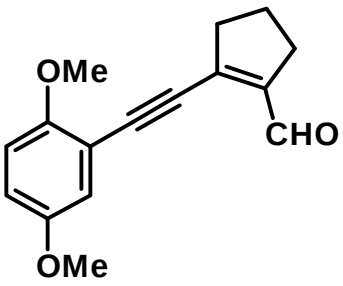
2-Ethynyl-1,4-dimethoxybenzene (148d)



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 ^oC, and spectroscopically identical to reported values[198].

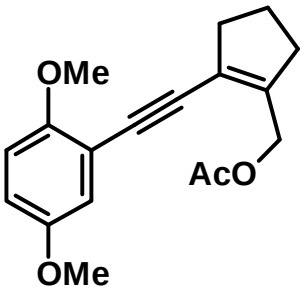
2-[(2,5-Dimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150g)

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,



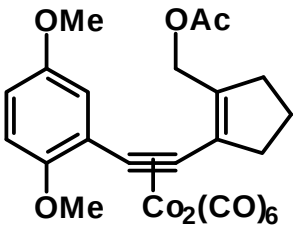
6.0373 mmol). Product **150g** was isolated as a cream-coloured solid (0.8184 g, 3.196 mmol, 79%) following flash chromatography (10:1 hexanes:Et_2O), with a m.p. of 109-110 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): 10.21 (s, 1H), 6.97 (d, 1H, J = 3.0), 6.92 (dd, 1H, J = 9.0, J = 3.1), 6.83 (d, 1H, J = 9.1), 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{16}H_{16}O_3$ calculated 256.256.1099 (M^+), found 256.1087.

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



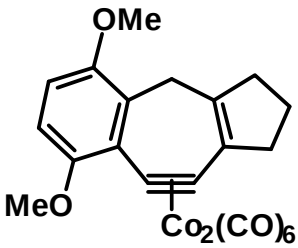
Compound **150g** (0.8184 g, 3.196 mmol) was subjected to reduction and acetylation according to General Procedure D. Product **151g** was isolated as a colourless solid (0.8595 g, 2.864 mmol, 90%) following flash chromatography (7:1 hexanes:Et_2O), with m.p. 63-65 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): 6.95 (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 = 8.0), 2.09 (s, 3H), 1.96 (apparent pentet, 2H, J = 7.8); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{18}H_{20}O_4$ 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:Et_2O) following removal of excess, uncomplexed $Co_2(CO)_8$ with 100% hexanes. The product was isolated as a dark brown solid (1.5256 g, 2.6035 mmol, 91%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 199.8, 170.9, 153.6, 150.6, 137.7, 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 $C_{24}H_{20}Co_2O_{10}$ calculated 529.9822 ($M-2CO^+$), found 529.9818.

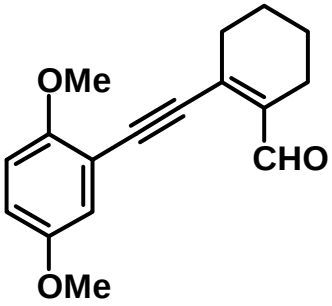
Compound 153g



Compound **152g** (0.0502 g, 0.0857 mmol) was reacted according to General Procedure F using BF_3•OEt_2 (32 μL, 0.26 mmol) and at -40 ^{o}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:Et_2O) as a maroon solid (0.0028 g, 0.0053 mmol, 6%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$, partial): 200.3, 135.5,

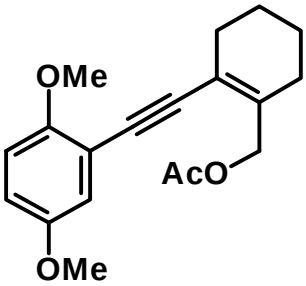
112.3, 108.5, 56.6, 54.6, 39.1, 35.3, 28.1, 22.7; IR (KBr): 2919, 2850, 2086, 2048, 2024, 1650, 1464, 1263; HRMS: m/e for $C_{22}H_{16}Co_2O_8$ calculated 469.9611 ($M-2CO^+$), found 469.9628.

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_2O), and with a m.p. of 75-76 ^oC. ^1H-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.

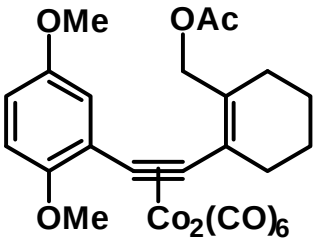
[2-(2,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151h)



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_2O), and with m.p. 54-56 ^oC. ^1H-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}C-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.

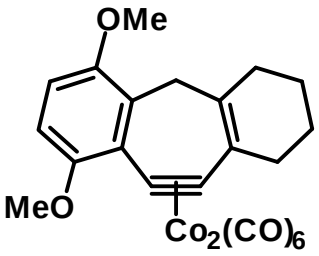
[2-(2,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152h)



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_2O) 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}H-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}C-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 $C_{25}H_{22}Co_2O_{10}$ calculated 543.9979 ($M-2CO^+$), found 543.9979.

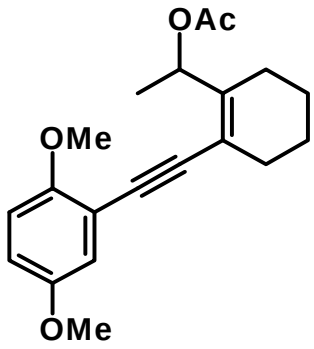
Dicobalt hexacarbonyl[μ-((10,11-η:10,11-η)-10,11-didehydro-2,3,4,5-tetrahydro-6,9-dimethoxy-1*H*-dibenzo[*a*,*d*]cycloheptene)] (153h)

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



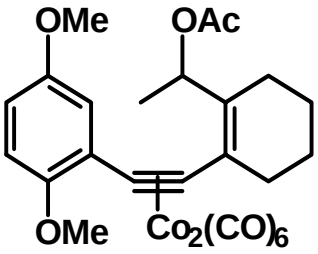
TLC analysis. The cyclized product (**153h**) was isolated by flash chromatography (15:1 hexanes:Et_2O) as a maroon solid (0.2405 g, 0.4454 mmol, 82%). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.92 (d, 1H, J = 9.0), 6.74 (d, 1H, J = 9.0), 3.87 (s, 3H), 3.82 (s, 3H), 3.34 (s, 2H), 2.30-2.36 (m, 4H), 1.73-1.78 (m, 2H), 1.66-1.71 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{23}H_{18}Co_2O_8$ calculated 539.9666 (M^+), found 539.9669.

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



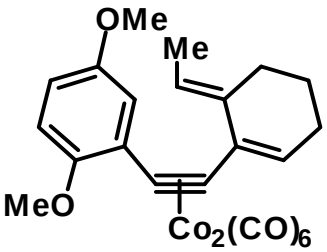
Compound **150h** (0.4632 g, 1.715 mmol) was subjected to General Procedure D, where DIBAL-H was substituted with MeLi (1.6 M in Et_2O, 2.1 mL, 3.4 mmol). The product (**151hh**) was isolated as a yellow oil (0.4671 g, 1.423 mmol, 83%) following preparative TLC (7:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-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 $C_{20}H_{24}O_4$ calculated 328.1675 (M^+), found 328.1672.

1-[2-((2,5-Dimethoxyphenyl)ethynyl)cyclohex-1-enyl]ethyl acetate dicobalt hexacarbonyl (152hh)



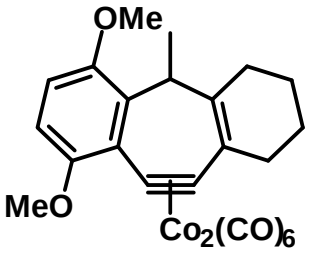
Compound **151hh** (0.4671 g, 1.423 mmol) was subjected to complexation according to General Procedure E. The complexed compound (**152hh**) was isolated via flash chromatography (7:1 hexanes:Et_2O) following removal of excess, uncomplexed $Co_2(CO)_8$ with 100% hexanes. The product was isolated as a dark brown solid (0.8023 g, 1.307 mmol, 92%). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.01 (d, 1H, J = 3.0), 6.86 (dd, 1H, J = 8.9, J = 3.1), 6.74 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{24}Co_2O_{10}$ calculated 474.0288 ($M-5CO^+$), found 474.0270.

Compounds 154b and 153hh



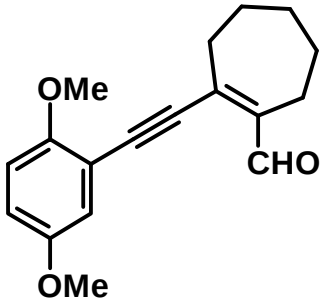
Compound **152hh** (0.7070 g, 1.151 mmol) was reacted according to General Procedure F using BF_3•OEt_2 (438 μL, 3.45 mmol). The reaction was complete after 1 h, as assessed by TLC analysis. The cyclized product (**153hh**) and its elimination isomer (**154b**) were inseparable by flash chromatography, and hence, eluted as one band using a 25:1 hexanes:Et_2O solvent mixture. The products were isolated as a green-maroon solid (0.5102 g, 0.9210 mmol, 80%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-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 ^{1}H-NMR spectra, and calculated to be 1.0:3.0 in favour of the elimination product (i.e., cyclized **153hh**:elimination **154b**). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{20}Co_2O_8$ (sample containing both isomers) calculated 525.9873 (M-CO^{+}), found 525.9872.

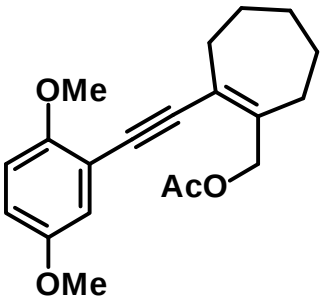
2-[(2,5-Dimethoxyphenyl)ethynyl]cyclohept-1-enecarbaldehyde (150i)



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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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),

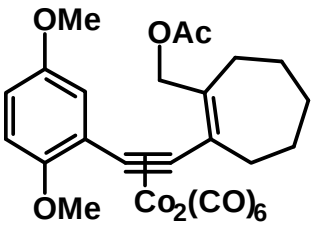
2.52-2.54 (m, 2H), 1.81 (apparent pentet, 2H, J = 5.9), 1.68 (apparent pentet, 2H, J = 5.7), 1.46 (apparent pentet, 2H, J = 6.0); ^{13}C-NMR (125 MHz, $CDCl_3$): 193.0, 154.9, 153.2, 148.2, 145.9, 117.6, 116.9, 112.0, 111.9, 96.8, 92.0, 56.4, 55.8, 37.4, 32.3, 25.8, 24.3; IR (KBr): 2999, 2922, 2852, 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)



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_2O). ^{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, 32.4, 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.

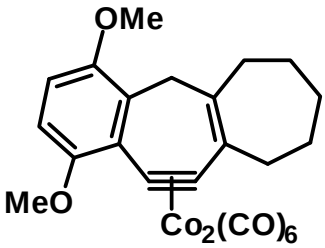
[2-((2,5-Dimethoxyphenyl)ethynyl)cyclohept-1-enyl]methyl acetate dicobalt hexacarbonyl (152i)



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

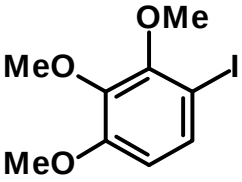
hexanes:Et_2O) following removal of excess, uncomplexed $Co_2(CO)_8$ with 100% hexanes. The product was isolated as a dark brown-green solid (0.6867 g, 1.118 mmol, 85%). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.01 (d, 1H, J = 3.0), 6.86 (dd, 1H, J = 8.9, J = 3.1), 6.75 (d, 1H, J = 8.9), 4.52 (s, 2H), 3.81 (s, 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 $C_{26}H_{24}Co_2O_{10}$ 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)



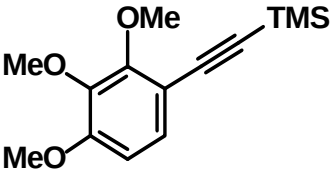
Compound **152i** (0.2234 g, 0.3638 mmol) was reacted according to General Procedure F using BF_3•OEt_2 (138 μL, 1.09 mmol). The reaction was complete after 1 h, as assessed by TLC analysis. The cyclized product (**153i**) was isolated by flash chromatography (15:1 hexanes:Et_2O) as a maroon solid (0.1687 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 $C_{24}H_{20}Co_2O_8$ calculated 553.9822 (M^+), found 553.9802.

1-Iodo-2,3,4-trimethoxybenzene (155e)



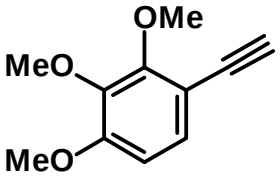
Compound **155e** was synthesized according to General Procedure I from 1,2,3-trimethoxybenzene (5.0000 g, 29.748 mmol). The product was isolated as a yellow oil (8.1235 g, 27.633 mmol, 93%), and was characterized as spectroscopically identical to reported values[153].

[(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 values[55].

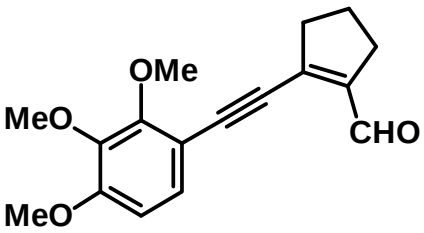
1-Ethynyl-2,3,4-trimethoxybenzene (148e)



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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{11}H_{12}O_3$ calculated 192.0786 (M^+), found 192.0781.

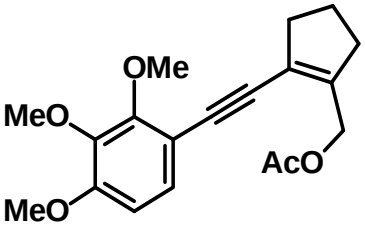
2-[(2,3,4-Trimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150j)

Compound **148e** (0.9223 g, 4.802 mmol) was subjected to Sonogashira coupling with 2-



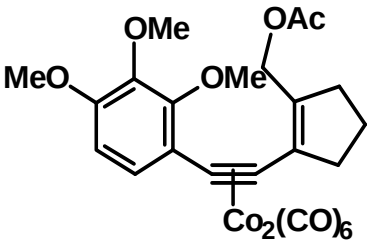
bromocyclopent-1-ene-1-carbaldehyde (**149a**) (1.2606 g, 7.2025 mmol) according to General Procedure C. Flash chromatography (2:1 hexanes:Et_2O) afforded the product (**150j**) as a pale yellow solid (1.1881 g, 4.1524 mmol, 86%) with m.p. of 74-76 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): 10.19 (s, 1H), 7.17 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{17}H_{18}O_4$ calculated 286.1205 (M^+), found 286.1214.

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



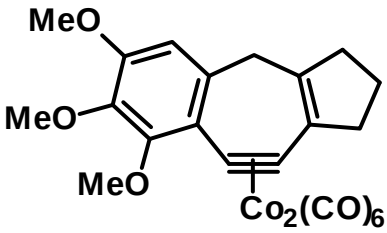
Compound **150j** (1.1881 g, 4.1524 mmol) was treated according to General Procedure D. Flash chromatography (2:1 hexanes:Et_2O) afforded **151j** as a pale yellow oil (1.2573 g, 3.8083 mmol, 92%). ^1H-NMR (500 MHz, $CDCl_3$): 7.10 (d, 1H, J = 8.9), 6.60 (d, 1H, J = 8.9), 4.88 (s, 2H), 3.95 (s, 3H), 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{22}O_5$ 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_2O 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 $C_{25}H_{22}Co_2O_{11}$ calculated 448.0131 (M-6CO$^+$), found 448.0139.

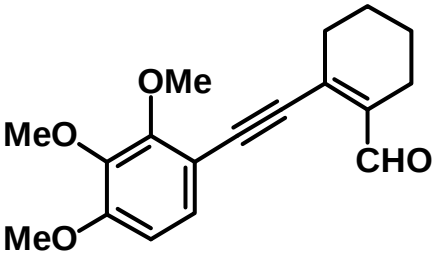
Compound 153j



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_2O) 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,

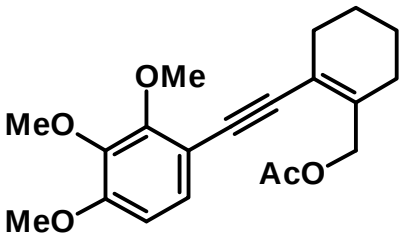
38.8, 38.0, 35.5, 22.6; IR (Pt/diamond): 2931, 2850, 2083, 2025, 2009, 1993, 1588, 1487, 1319, 1120; HRMS: m/e for $C_{23}H_{18}Co_2O_9$ calculated 499.9716 ($M\text{-}2CO^+$), found 499.9699.

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:Et_2O) 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 ^oC. ^1H-NMR (300 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{18}H_{20}O_4$ calculated 300.1362 (M^+), found 300.1355.

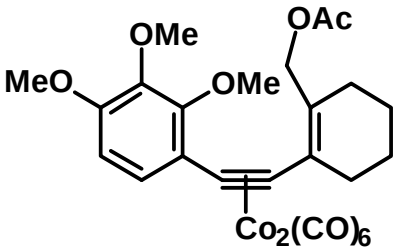
[2-((2,3,4-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151k)



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:Et_2O). ^1H-NMR (500 MHz, $CDCl_3$): 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

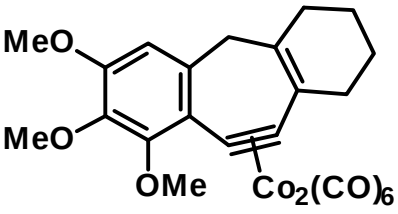
(m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.3, 154.7, 154.3, 142.3, 138.4, 127.9, 120.4, 110.8, 107.4, 91.0, 89.2, 66.8, 61.3, 61.2, 56.2, 30.3, 27.1, 22.3, 22.1, 21.1; IR (KBr): 2940, 2839, 2196, 1746, 1494, 1234; HRMS: m/e for $C_{20}H_{24}O_5$ calculated 344.0624 (M^+), found 344.0627.

[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_2O). ^{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 $C_{26}H_{24}Co_2O_{11}$ calculated 462.0288 (M-6CO$^+$), found 462.0298.

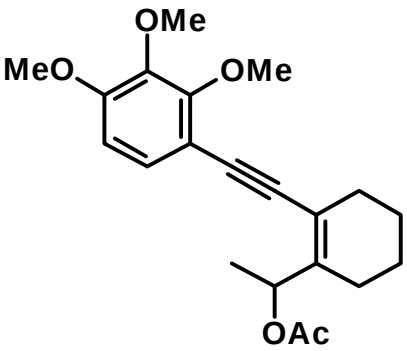
Compound 153k



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

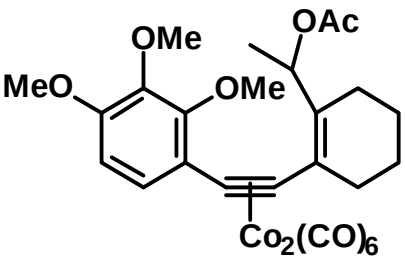
solid following flash chromatography using neutralized silica (20:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.48 (s, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.18 (s, 2H), 2.35 (t, 2H, J = 6.3), 2.28 (t, 2H, J = 6.2), 1.67-1.78 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): 200.5, 154.3, 153.9, 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 $C_{24}H_{20}Co_2O_9$ calculated 513.9873 ($M-2CO^+$), found 513.9852.

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



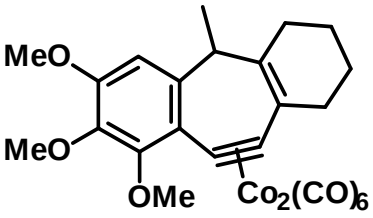
Compound **150k** (0.7450 g, 2.482 mmol) was subjected to General Procedure D, where DIBAL-H was substituted with MeLi (1.6 M in Et_2O, 3.1 mL, 5.0 mmol). The product (**151kk**) was isolated as a yellow/orange oil (0.7888 g, 2.202 mmol, 89%) following flash chromatography (2:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{26}O_5$ calculated 358.1780 (M^+), found 358.1777.

1-[2-((2,3,4-Trimethoxyphenyl)ethynyl)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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{27}H_{26}Co_2O_{11}$ calculated 588.0241 (M-2CO$^+$), found 588.0226.

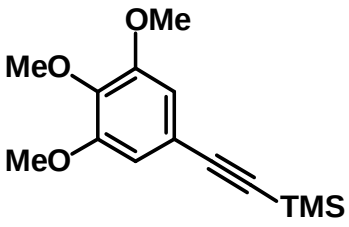
Compound 153kk



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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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,

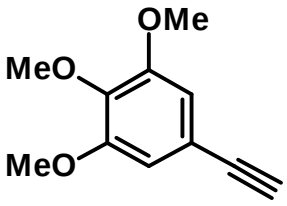
1319, 1259; HRMS: m/e for $C_{25}H_{22}Co_2O_9$ calculated 555.9979 ($M-CO^+$), found 555.9996.

[(3,4,5-Trimethoxyphenyl)ethynyl]trimethylsilane (156f)



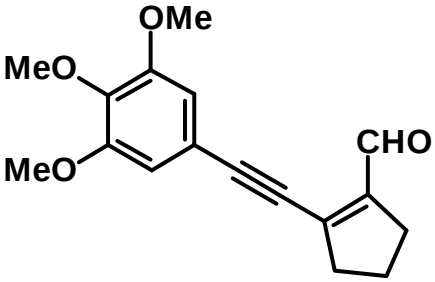
Compound **156f** was synthesized according to General Procedure A from 5-iodo-1,2,3-trimethoxybenzene (**155f**) (1.5110 g, 5.1399 mmol). The product was isolated as a cream-coloured solid (1.3208 g, 5.0008 mmol, 97%), with a m.p. of 55-56 ^oC, and spectroscopically identical to reported values[41].

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 ^oC (lit., 68-68.5 ^oC[95]), and spectroscopically identical to reported values[95].

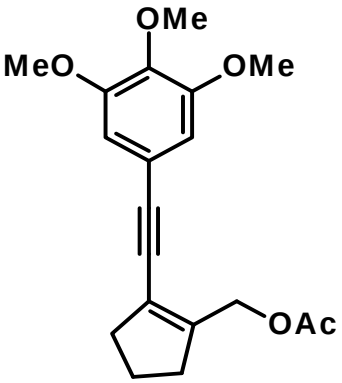
2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclopent-1-enecarbaldehyde (150l)



Compound **148f** (0.2514 g, 1.309 mmol) was subjected to General Procedure C with 2-bromocyclopent-1-ene-1-carbaldehyde (**149a**) (0.3436 g, 1.963 mmol). Preparative TLC (2:1 hexanes:Et_2O) afforded the product as a yellow solid (0.3109 g, 1.087 mmol, 83%) with a m.p. of 131-133 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{17}H_{18}O_4$

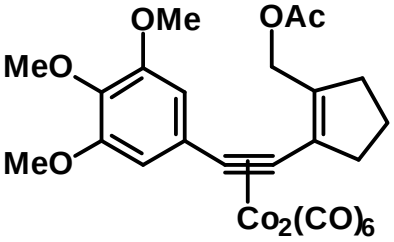
calculated 286.1205 (M^+), found 286.1206.

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



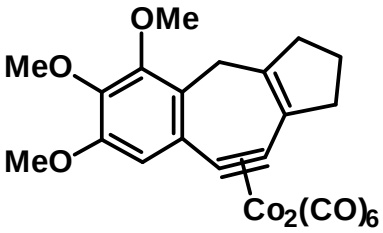
Compound **150l** (0.3099 g, 1.083 mmol) was subjected to General Procedure D. The product compound (**151l**) was isolated as a yellow oil (0.3093 g, 0.9368 mmol, 89%) via preparative TLC (2:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.64 (s, 2H), 4.84 (s, 2H), 3.82 (s, 6H), 3.81 (s, 3H), 2.58 (t, 2H, J = 7.7), 2.47 (t, 2H, J = 7.8), 2.05 (s, 3H), 1.92 (apparent pentet, 2H, J = 7.7); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{22}O_5$ calculated 330.1467 (M^+), found 330.1464.

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



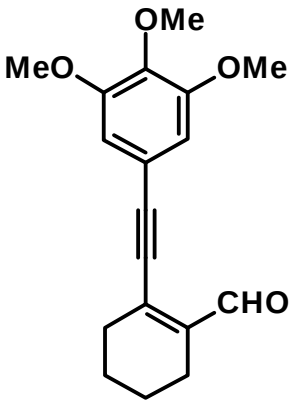
Compound **151l** (0.3093 g, 0.9368 mmol) was complexed using General Procedure E to afford product **152l** (0.5156 g, 0.8370 mmol, 89%) as a dark brown solid following flash chromatography (1:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.71 (s, 2H), 4.72 (s, 2H), 3.90 (s, 3H), 3.88 (s, 6H), 2.81 (t, 2H, J = 7.8), 2.56 (t, 2H, J = 7.9), 2.04 (apparent pentet, 2H, J = 7.8), 2.02 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{22}Co_2O_{11}$ 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 BF_3•OEt_2 (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:Et_2O) as a dark maroon solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{23}H_{18}Co_2O_9$ calculated 527.9666 (M-CO^+), found 527.9654.

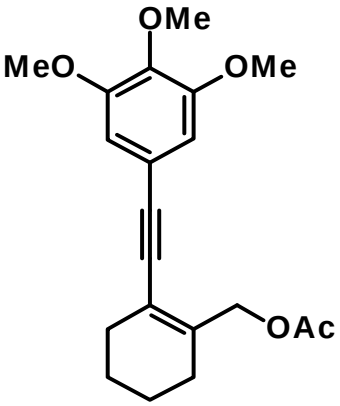
2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150m)



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:Et_2O) was used to isolate **150m** as a cream-coloured solid (0.4510 g, 1.503 mmol, 85%), with a m.p. of 121-123 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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,

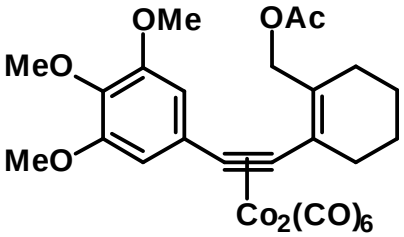
22.0, 21.2; IR (KBr): 2933, 2195, 1664, 1238; HRMS: m/e for $C_{18}H_{20}O_4$ calculated 300.1362 (M^+), found 300.1361.

[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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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.

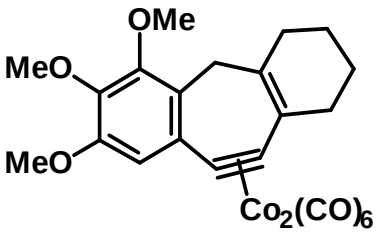
[2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152m)



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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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,

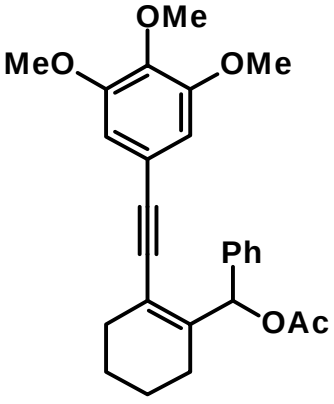
1742, 1232; HRMS: m/e for $C_{26}H_{24}Co_2O_{11}$ calculated 574.0084 ($M-2CO^+$), found 574.0071.

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



Compound **152m** (0.3033 g, 0.4814 mmol) was cyclized according to General Procedure F with BF_3•OEt_2 (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:Et_2O) as a dark maroon solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{20}Co_2O_9$ calculated 541.9822 ($M-CO^+$), found 541.9821.

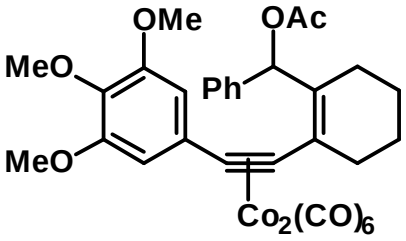
Phenyl[2-((3,4,5-trimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate (151mm)



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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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

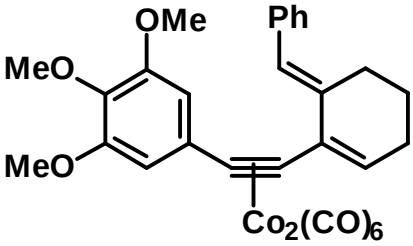
(s, 2H), 3.90 (s, 6H), 3.89 (s, 3H), 2.33-2.41 (m, 2H), 2.22 (s, 3H), 1.92-1.98 (m, 2H), 1.55-1.73 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): 169.8, 153.2, 142.6, 139.5, 138.8, 128.4, 127.5, 125.7, 119.1, 118.7, 108.8, 93.5, 88.2, 76.3, 61.1, 56.3, 30.2, 23.8, 22.2, 22.0, 21.3; IR (KBr): 3062, 3004, 2939, 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)

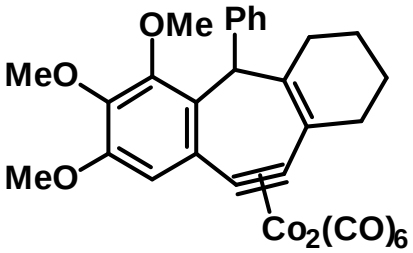


Compound **151mm** (0.2826 g, 0.6725 mmol) was complexed using General Procedure E to afford product **152mm** (0.4118 g, 0.5833 mmol, 87%) as a dark brown solid following flash chromatography (1:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.18-7.20 (m, 3H), 6.94 (s, 1H), 6.87-6.89 (m, 2H), 6.36 (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 $C_{32}H_{28}Co_2O_{11}$ 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-1*H*-dibenzo[*a*,*d*]cycloheptene)] (153mm)



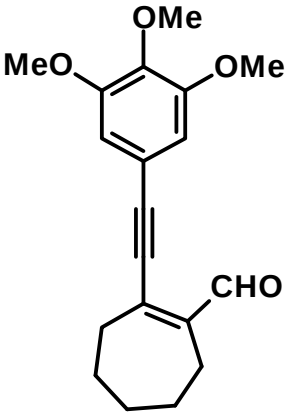
Compound **152mm** (0.1300 g, 0.1841 mmol) was reacted according to General Procedure F using BF_3•OEt_2 (70 μL, 0.55 mmol). The reaction was complete after 1 h, as assessed by TLC analysis. The cyclized product (**153mm**) was separated from its elimination isomer (**154c**) by flash chromatography (10:1 hexanes:Et_2O). 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%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{30}H_{24}Co_2O_9$ 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. ^{1}H-NMR

(500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{30}H_{24}Co_2O_9$ calculated 562.0237 ($M-3CO^+$), found 562.0240.

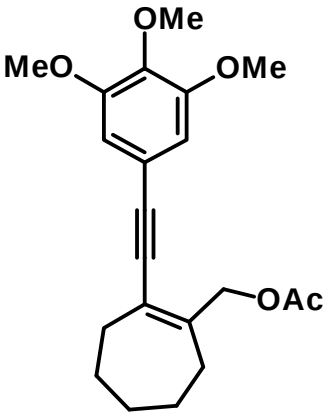
2-[(3,4,5-Trimethoxyphenyl)ethynyl]cyclohept-1-enecarbaldehyde (150n)



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:Et_2O) isolated the product as a cream-coloured solid (0.3408 g, 1.085 mmol, 86%), with a m.p. of 115-116 ^oC. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{22}O_4$ calculated 314.1518 (M^+), found 314.1526.

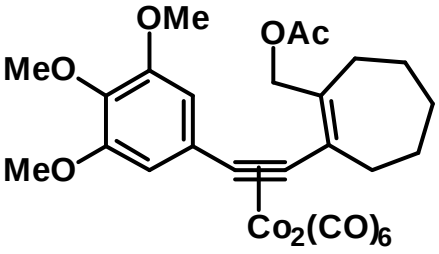
[2-((3,4,5-Trimethoxyphenyl)ethynyl)cyclohept-1-enyl]methyl acetate (151n)

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:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.66 (s, 2H), 4.90 (s,



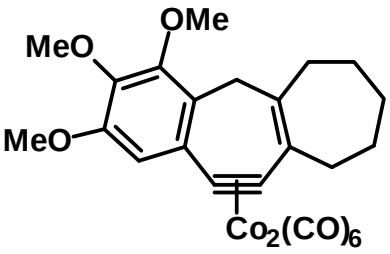
2H), 3.86 (s, 6H), 3.85 (s, 3H), 2.48-2.50 (m, 2H), 2.31-2.33 (m, 2H), 2.10 (s, 3H), 1.79 (apparent pentet, 2H, J = 5.8), 1.61 (apparent pentet, 2H, J = 5.4), 1.53 (apparent pentet, 2H, J = 5.5); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.3, 153.4, 145.1, 138.8, 125.9, 118.7, 108.7, 94.0, 88.8, 68.0, 61.1, 56.3, 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 $C_{21}H_{26}O_5$ calculated 358.1780 (M^+), found 358.1776.

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



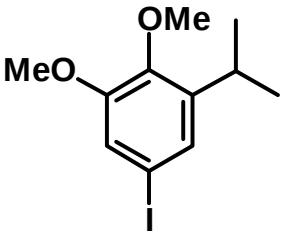
Compound **151n** (0.3498 g, 0.9766 mmol) was complexed using General Procedure E to afford product **152n** (0.5788 g, 0.8987 mmol, 92%) as a dark green solid following flash chromatography (1:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.64 (s, 2H), 4.69 (s, 2H), 3.89 (s, 3H), 3.86 (s, 6H), 2.62-2.64 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{27}H_{26}Co_2O_{11}$ 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_2O) 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 $C_{25}H_{22}Co_2O_9$ 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 ^{o}C, and aqueous H_2O_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 ^{o}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 *p*TsOH (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].

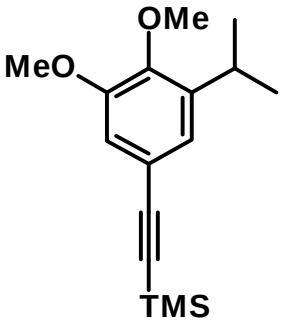
The ester was then dissolved in THF (45.0 mL), and the solution cooled to 0 ^{o}C. MeMgBr (3.0 M in Et_2O, 97.4 mL, 292 mmol) was added slowly to the reaction flask, which was then stirred at that temperature for 30 minutes before it was allowed to warm up to room temperature. Once at room temperature, the reaction flask was placed in an oil bath set at 60 ^{o}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_2O (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.

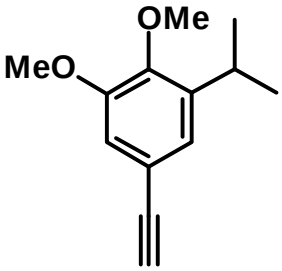
As the last step, this compound was dissolved in methanol (150 mL) along with Wilkinson's catalyst (0.5700 g, 0.6161 mmol). H_2 was bubbled through the solution, which was stirring at room temperature. The reaction was done after 1.5 days, as assessed by ^{1}H-NMR. The solvent was removed under reduced 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%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{11}H_{15}IO_2$ calculated 306.0117 (M^+), found 306.0122.

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



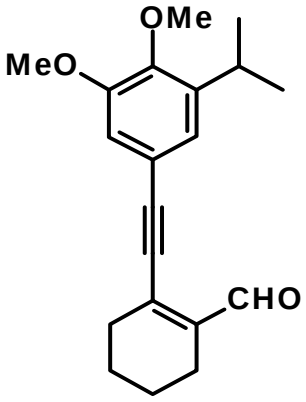
Compound **156g** was synthesized from 5-iodo-1-isopropyl-2,3-dimethoxybenzene (**155g**) (2.2563 g, 7.3732 mmol) according to General Procedure A. Compound **156g** was isolated by flash chromatography (10:1 hexanes:Et_2O) for the final purification step as a pale yellow oil (2.0005 g, 7.2441 mmol, 98%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{16}H_{24}O_2Si$ 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:Et_2O) as a pale yellow oil (1.3196 g, 6.4650 mmol, 89%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{13}H_{16}O_2$ calculated 204.1150 (M^+), found 204.1145.

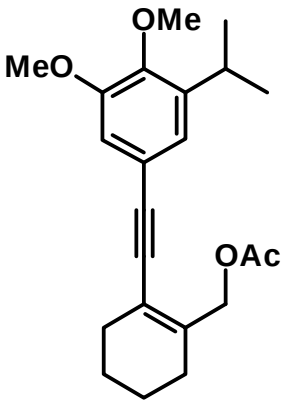
2-[(3-Isopropyl-4,5-dimethoxyphenyl)ethynyl]cyclohex-1-enecarbaldehyde (150o)



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%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{20}H_{24}O_3$ calculated 312.1725 (M^+), found

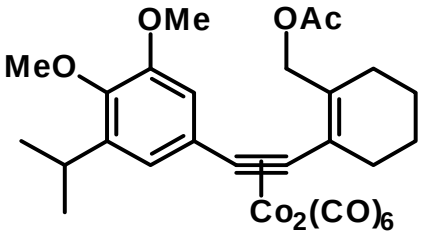
312.1727.

[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:Et_2O) as a pale yellow oil (1.7960 g, 5.0421 mmol, 90%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{22}H_{28}O_4$ calculated 356.1988 (M^+), found 356.1990.

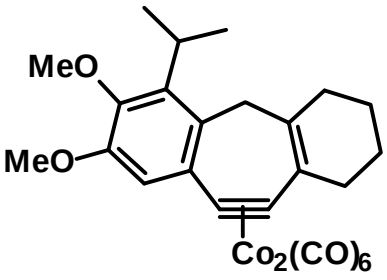
[2-((3-Isopropyl-4,5-dimethoxyphenyl)ethynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (152o)



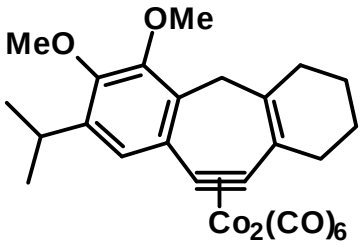
Compound **151o** (1.7960 g, 5.0421 mmol) was complexed according to General Procedure E. After washing the column of silica with 100% hexanes to remove excess, uncomplexed $Co_2(CO)_8$, the product (**152o**) was eluted using 5:1 hexanes:Et_2O, and isolated as a dark brown solid (2.8905 g, 4.5021 mmol, 89%). ^{1}H-NMR (500 MHz, $CDCl_3$): 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,

6H, J = 7.1); ^{13}C-NMR (75 MHz, $CDCl_3$); 199.7, 170.8, 152.5, 146.1, 142.7, 133.8, 133.5, 131.8, 119.9, 110.8, 94.5, 91.3, 65.2, 61.0, 55.8, 33.4, 28.3, 26.9, 23.5, 23.4, 22.2, 20.8; IR (KBr): 2962, 2936, 2869, 2834, 2086, 2048, 2019, 1743, 1464, 1308, 1230; HRMS: m/e for $C_{28}H_{28}Co_2O_{10}$ calculated 558.0499 ($M-3CO^+$), found 558.0486.

Compounds 153o and 153o'



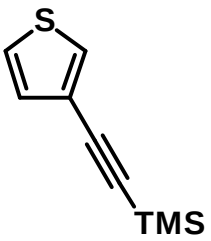
Compound **152o** (0.2042 g, 0.3180 mmol) was reacted according to General Procedure F. The product was obtained as a pair of regioisomers, **153o** (0.1361 g, 0.2338 mmol, 74%) and **153o'** (0.0098 g, 0.0168 mmol, 5%). The two regioisomers were separable by flash chromatography on neutralized silica (25:1 hexanes:Et_2O). The major product, **153o**, eluted as the first band, and was isolated as a maroon solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 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, $CDCl_3$): Irradiation at δ7.08 resonance gave enhancement of the δ3.88 resonance; ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{24}Co_2O_8$ 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'**). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.28 (s, 1H),

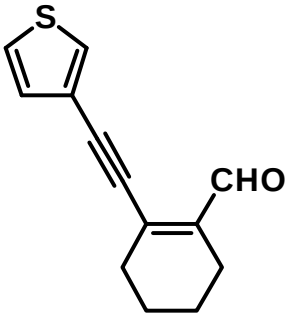
3.90 (s, 3H), 3.85 (s, 3H), 3.30 (septet, 1H, J = 7.2), 3.28 (s, 2H), 2.30-2.36 (m, 4H), 1.67-1.79 (m, 4H), 1.24 (d, 6H, J = 7.0); ^{13}C-NMR (125 MHz, $CDCl_3$): 200.1, 151.0, 149.5, 141.5, 136.6, 133.8, 131.0, 128.3, 125.2, 95.0, 90.6, 61.0, 60.6, 33.7, 33.0, 30.5, 26.9, 23.4, 23.0, 22.7; IR (Pt/diamond): 2961, 2920, 2849, 2084, 2043, 2010, 1407, 1306, 1226; HRMS: m/e for $C_{26}H_{24}Co_2O_8$ calculated 554.0186 ($M\text{-}CO^+$), found 554.0197.

3-(Trimethylsilylethynyl)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].

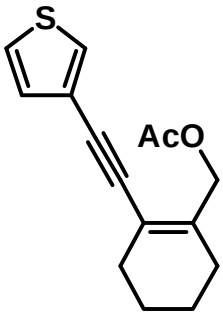
2-(Thiophen-3-ylethynyl)cyclohex-1-enecarbaldehyde (159)



3-(Trimethylsilylethynyl)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_2O) 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,

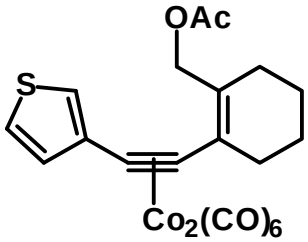
86.1, 32.4, 22.2, 22.0, 21.2; IR (KBr): 3320, 3106, 2936, 2861, 2834, 2201, 1668, 1596; HRMS: m/e for $C_{13}H_{12}OS$ calculated 216.0609 (M^+), found 216.0616.

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



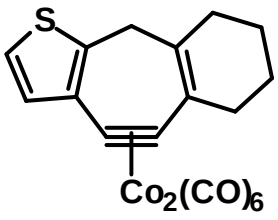
Compound **159** (0.3511 g, 1.625 mmol) was subjected to reduction and acetylation according to General Procedure D. The product (**160)** was isolated as a yellow oil (0.3957 g, 1.521 mmol, 94%) via preparative TLC (10:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.42 (d, 1H, J = 2.2), 7.27 (dd, 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{16}O_2S$ calculated 260.0871 (M^+), found 260.0876.

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



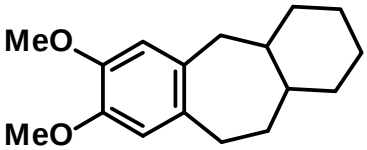
Compound **160** (0.3957 g, 1.521 mmol) was subjected to complexation procedures according to General Procedure E. The product (**161**) was isolated as a dark brown solid (0.7527 g, 1.379 mmol, 91%) via flash chromatography (10:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.32-7.34 (m, 2H), 7.06 (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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{16}Co_2O_8S$ calculated 461.9382 (M-3CO$^+$), found 461.9398.

Compound 162



Compound **161** (0.1230 g, 0.2253 mmol) was treated with BF_3•OEt_2 (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). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{12}Co_2O_6S$ calculated 457.9069 ($M\text{-}CO^+$), found 457.9088.

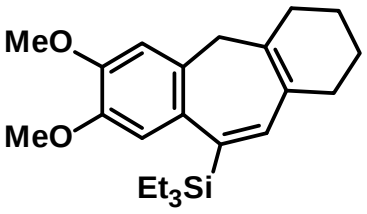
2,3,4,4a,5,10,11,11a-Octahydro-7,8-dimethoxy-1*H*-dibenzo[*a*,*d*]cycloheptene (165)



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 Et_2O (75 mL) and extracted with dH_2O (3 x 75 mL). The organic fraction was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Preparative TLC (15:1 hexanes:Et_2O) afforded compound **165** as a colourless solid of inseparable diastereomers (0.1980 g, 0.7610 mmol, 81%). ^{1}H-NMR (500 MHz, $CDCl_3$):

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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{17}H_{24}O_2$ calculated 260.1776 (M^+), found 260.1775.

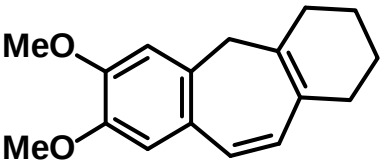
Compound 166



To a stirring 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 µL, 0.532 mmol) and triethylsilane (213µL, 1.33 mmol). The reaction was placed in an oil bath set at 65 ^{o}C, and allowed to stir for 6 h under a nitrogen atmosphere. Following the 6h, the reaction was cooled, dissolved in Et_2O (75 mL) and extracted with dH_2O (3 x 75 mL). The organic fraction was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Preparative chromatography (15:1 hexanes:Et_2O) 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 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): 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, $CDCl_3$): Pulsed $SiEt_3$ protons, saw aromatic; pulsed aromatic H, saw $SiEt_3$ protons; ^{13}C-NMR (125 MHz, $CDCl_3$): 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;

HRMS: m/e for $C_{23}H_{24}O_2Si$ calculated 370.2328 (M^+), found 370.2325.

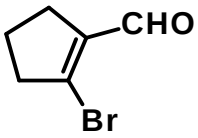
Compound 167



METHOD A: To a stirred solution of **166** (0.0849 g, 0.229 mmol) in degassed 1,2-dichoroethane (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 Et_2O (75 mL) and extracted with dH_2O (3 x 75 mL). The organic fraction was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Preparative TLC (15:1 hexanes:Et_2O) afforded compound **167** as a colourless solid (0.0570 g, 0.222 mmol, 97%), with a m.p. of 88-90 ^oC. **METHOD B:** Compound **153d** was decomplexed according to methods adapted from *Takai et. al.*[182]. 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 ^oC, 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 $MgSO_4$, filtered, and the organic solvent removed under reduced pressure. Preparative TLC afforded compound **167** as colourless crystals (0.1164 g, 0.4544 mmol, 76%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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:

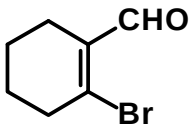
m/e for $C_{17}H_{20}O_2$ calculated 256.1463 (M^+), found 256.1457.

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



A stirred solution of CH_2Cl_2 (56.6 mL) and DMF (13.8 mL, 178 mmol) under a nitrogen atmosphere was cooled to 0 ^oC. 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_2O (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_2O) afforded compound **149a** as a yellow oil (3.9653 g, 22.656 mmol, 38%). The compound was spectroscopically identical to reported values[161].

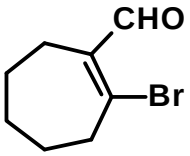
2-Bromocyclohex-1-ene-1-carbaldehyde (149b)



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_2O) as a yellow oil (14.2846 g, 75.5599 mmol, 74%), that was characterized with spectroscopically identical values to those reported[161].

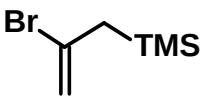
2-Bromocyclohept-1-ene-1-carbaldehyde (149c)

Cycloheptanone (5.0000 g, 44.574 mmol) was treated according to General Procedure J.



Compound **149c** was isolated using flash chromatography (15:1 hexanes:Et_2O) as a yellow oil (7.1250 g, 35.085 mmol, 79%), that was characterized with spectroscopically identical values to those reported[161].

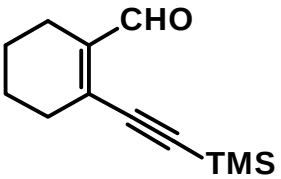
2-Bromo-3-(trimethylsilyl)-1-propene (171)



2,3-Dibromopropene was treated according to methods adapted from *Trost et. al.*[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 Et_2O (24.5 mL) containing NEt_3 (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 Et_2O, 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 $NH_4^+Cl^-$ (aq., sat.), the mixture was poured into a mixture of 500 mL of Et_2O 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 Et_2O. The combined organic layers were dried over $MgSO_4$, 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[186].

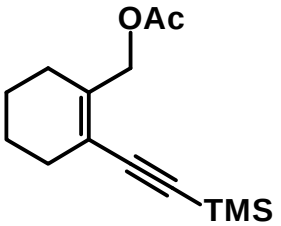
2-[(Trimethylsilyl)ethynyl]cyclohex-1-enecarbaldehyde (168a)

2-Bromocyclohex-1-ene-1-carbaldehyde (**149b**) (2.5314 g, 13.466 mmol) was subjected to



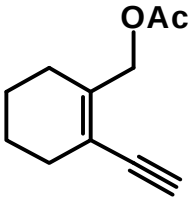
General Procedure C with trimethylsilylacetylene (2.6453 g, 26.932 mmol), and with THF in place of DMF. Compound **168a** was isolated as a yellow oil (2.3527 g, 11.415 mmol, 85%) via flash chromatography (20:1 hexanes:Et_2O). The material was spectroscopically identical to reported values[190].

[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_2O). ^{1}H-NMR (500 MHz, C_6D_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_6D_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 $C_{14}H_{22}O_2Si$ calculated 250.1389 (M^+), found 250.1386.

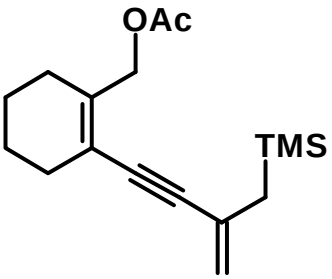
(2-Ethynylcyclohex-1-enyl)methyl acetate (170a)



Compound **169a** (1.6033 g, 6.4096 mmol) was desilylated according to General Procedure B (with the modification that 1.3 equivalents of KF•$2H_2O$ 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_2O). ^{1}H-NMR (500 MHz, C_6D_6): 4.84 (s, 2H), 2.98 (s, 1H), 2.03 (t, 2H, J = 6.0), 1.89 (t, 2H, J = 6.0),

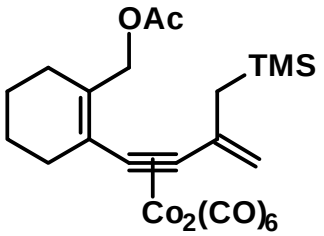
1.70 (s, 3H), 1.26-1.33 (m, 4H); ^{13}C-NMR (75 MHz, C_6D_6): 169.8, 140.7, 118.7, 82.4, 81.4, 65.9, 29.9, 26.6, 21.8, 21.7, 20.1; IR (Pt/diamond): 3286, 2932, 2861, 1736, 1366, 1227; HRMS: m/e for $C_{11}H_{14}O_2$ calculated 178.0994 (M^+), found 178.0998.

[2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohex-1-enyl]methyl acetate (172a)



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_2O). ^{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 $C_{17}H_{26}O_2Si$ calculated 290.1702 (M^+), found 290.1708.

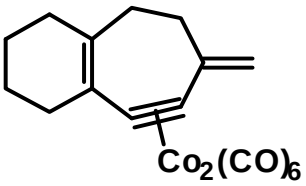
[2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohex-1-enyl]methyl acetate dicobalt hexacarbonyl (173a) (GENERAL PROCEDURE K)



Compound **172a** (1.4095 g, 4.8575 mmol) was dissolved in Et_2O (dry) (56.2 mL) along with excess $Co_2(CO)_8$. The solution was cooled to 0 ^{o}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_2O to elute the product as a maroon solid (2.5800 g, 4.4791 mmol, 92%). ^{1}H-NMR (500 MHz, C_6D_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_6D_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 $C_{23}H_{26}Co_2O_8Si$ calculated 408.0366 (M^+-6CO), found 408.0363.

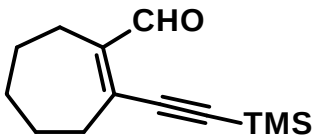
Compound 174a (GENERAL PROCEDURE L)



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_2Cl_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_6D_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

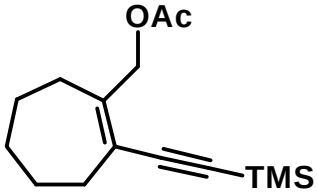
(m, 2H), 1.68-1.72 (m, 2H), 1.42-1.50 (m, 2H), 1.30-1.39 (m, 2H); ^{13}C-NMR (75 MHz, C6D_6): 200.3, 147.7, 140.5, 128.4, 118.9, 94.2, 89.1, 35.9, 33.7, 33.2, 30.2, 22.9, 22.6; IR (KBr): 2933, 2863, 2087, 2053, 1612, 1432, 1237; HRMS: m/e for $C_{18}H_{14}Co_2O_6$ calculated 415.9505 (M-CO^+), found 415.9513.

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



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_2O). ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{13}H_{20}OSi$ calculated 220.1283 (M^+), found 220.1274.

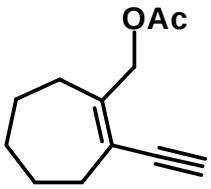
[2-((Trimethylsilyl)ethynyl)cyclohept-1-enyl]methyl acetate (169b)



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_2O). ^{1}H-NMR (500 MHz, C_6D_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); ^{13}C-NMR (125 MHz, C_6D_6): 169.6, 146.5, 125.6, 105.7, 98.3, 67.3,

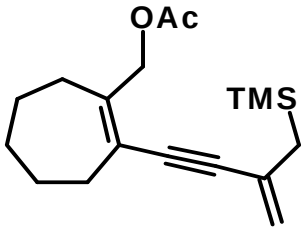
34.4, 32.1, 30.9, 25.9, 25.8, 20.0, -0.27; IR (Pt/diamond): 2922, 2851, 2136, 1740, 1375, 1226; HRMS: m/e for $C_{15}H_{24}O_2Si$ calculated 264.1546 (M^+), found 264.1547.

(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 $KF•2H_2O$ 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 chromatogrpahy (10:1 hexanes:Et_2O). ^{1}H-NMR (500 MHz, C_6D_6): 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); ^{13}C-NMR (125 MHz, C_6D_6): 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.

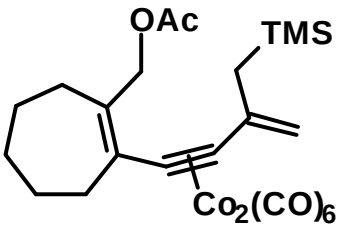
[2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohept-1-enyl]methyl acetate (172b)



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:Et_2O). ^{1}H-NMR (500 MHz, C_6D_6): 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); ^{13}C-NMR (75

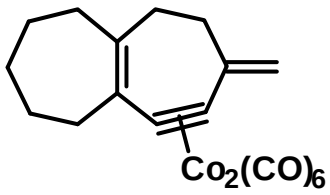
MHz, C_6D_6): 169.7, 144.8, 129.2, 125.9, 118.4, 96.4, 89.0, 67.5, 34.7, 32.2, 31.1, 28.1, 26.0, 26.0, 20.2, -1.8; IR (Pt/diamond): 2921, 2850, 1739, 1374, 1246; HRMS: m/e for $C_{18}H_{28}O_2Si$ calculated 304.1859 (M^+), found 304.1872.

[2-(3-((Trimethylsilyl)methyl)but-3-en-1-ynyl)cyclohept-1-enyl]methyl acetate dicobalt hexacarbonyl (173b)



Compound **172b** (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:Et_2O after all the excess, uncomplexed $Co_2(CO)_8$ had been washed off with 100% hexanes. ^{1}H-NMR (500 MHz, C_6D_6): 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); ^{13}C-NMR (75 MHz, C_6D_6): 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 $C_{24}H_{28}Co_2O_8Si$ calculated 422.0523 (M^+-6CO), found 422.0512.

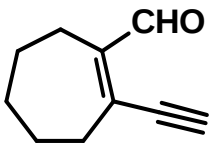
Compound 174b



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. ^{1}H-NMR (500 MHz, C_6D_6):

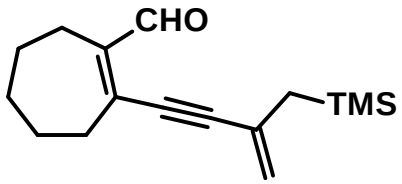
5.60 (s, 1H), 5.21 (s, 1H), 2.45-2.47 (m, 2H), 2.30-2.32 (m, 2H), 2.15-2.18 (m, 2H), 1.99-2.01 (m, 2H), 1.45-1.58 (m, 4H), 1.28 (apparent pentet, 2H, J = 5.7); ^{13}C-NMR (75 MHz, C_6D_6): 200.3, 147.6, 147.0, 133.9, 118.4, 95.4, 90.0, 39.2, 38.4, 34.7, 33.8, 32.2, 26.5, 26.1; IR (KBr): 2924, 2851, 2086, 2046, 2016, 1598, 1432, 1213; HRMS: m/e for $C_{19}H_{16}Co_2O_6$ 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_2O were used instead of 2.2 equivalents). The reaction was kept at 0 ºC 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 chromatogrpahy (10:1 hexanes:Et_2O). ^{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.

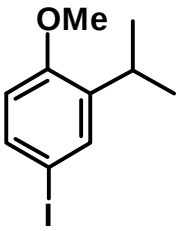
2-[3-((Trimethylsilyl)methyl)but-3-en-1-ynyl]cyclohept-1-enecarbaldehyde (180)



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:Et_2O). ^{1}H-NMR (300 MHz, C_6D_6): 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); ^{13}C-NMR (75 MHz, C_6D_6): 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 $C_{16}H_{24}OSi$ calculated 260.1596 (M^+), found 260.1590.

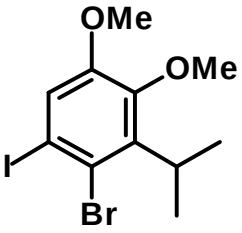
4-Iodo-2-isopropyl-1-methoxybenzene (186)



2-Isopropylanisole was synthesized using conditions reported by *Hassan et. al*[77]. 2-Isopropylphenol (0.6793 g, 4.992 mmol), K_2CO_3 (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 over night (20 h) at 40 ^{o}C. The reaction mixture was then diluted with Et_2O (100 mL) and washed with brine (3 x 100 mL). The organic portion was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography (15:1 hexanes:Et_2O) afforded 2-isopropylanisole as a yellow oil (0.6744 g, 4.493 mmol, 90%), which was characterized as spectroscopically identical to reported values[148]. 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[80].

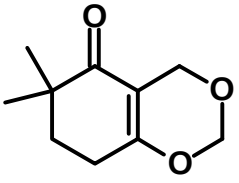
2-Bromo-1-iodo-3-isopropyl-4,5-dimethoxybenzene (187)

5-Iodo-1-isopropyl-2,3-dimethoxybenzene (**155g**) was brominated using conditions reported



by *Fürstner and Kennedy*[53]. To a stirred solution of compound **155g** (0.8493 g, 2.775 mmol) dissolved in glacial acetic acid (4.2 mL), Br_2 (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 $Na_2S_2O_3$ (aq., sat, 3 x 75 mL) and brine (1 x 75 mL), dried over $MgSO_4$, filtered, and the organic solvent removed under reduced pressure. Flash chromatography (10:1 hexanes:Et_2O) 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%). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.30 (s, 1H), 3.82 (s, 6H), 3.69 (m, 1H), 1.32 (d, 6H, J = 7.1); NOE (500 MHz, $CDCl_3$): Irradiation at δ7.30 resonance gave enhancement of the δ3.82 resonance; ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{11}H_{14}BrIO_2$ calculated 383.9222 (M^+), found 383.9218.

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



Compound **191** was synthesized according to methods adapted from *Majetich and Grove*[114] and *Smith et. al.*[177]. 1,3-Cyclohexanedione (10.0000 g, 89.2439 mmol) and *p*TsOH•H_2O (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[114].

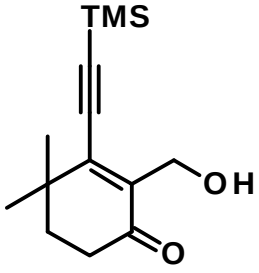
This compound was then dissolved in CH_2Cl_2 (118 mL), along with 1,3,5-trioxane (16.6528 g, 184.966 mmol) under a nitrogen atmosphere. The reaction flask was cooled to 0 ^{o}C, at which point BF_3•OEt_2 (20.8 mL, 164 mmol) was added dropwise over 5 minutes. The reaction was allowed to warm up to room temperature, and continue for another 16 h. Following this time, the mixture was filtered through Celite®, and subsequently rinsed twice with CH_2Cl_2. The solution was then cooled to 0 ^{o}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_2O) 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[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 ^{o}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 ^{o}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 ^{o}C for another hour. The reaction was warmed to -30 ^{o}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_2O (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[114].

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_2O). ^{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.

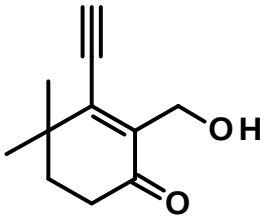
2-(Hydroxymethyl)-4,4-dimethyl-3-[(trimethylsilyl)ethynyl]cyclohex-2-enone (192)



Compound **192** was synthesized according to methods adapted from *Majetich and Grove*[114], and *Brummond and Gao*[14]. 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 $NH_4^+Cl^-$ (aq, sat.), and extraction of the aqueous layer with Et_2O (3 x 100 mL) was performed. The organic fractions were combined and extracted with $NH_4^+Cl^-$ (aq., sat., 1 x 100 mL) and brine (1 x 100 mL). The organic layer was then dried over $MgSO_4$, 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 $NaHCO_3$ (aq., sat.), and extracted with Et_2O (1 x 100 mL). The organic layer was then extracted with brine (2 x 100 mL), dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and flash chromatography (1:1 hexanes:Et_2O) afforded **192** (1.8928 g, 7.5670 mmol, 84%) as a pale yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{14}H_{22}O_2Si$ calculated 250.1389 (M^+), found 250.1387.

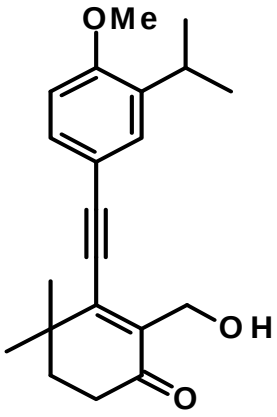
3-Ethynyl-2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (193)



Compound **192** (1.8928 g, 7.5670 mmol) was desilylated according to General Procedure B (with the modification that 1.3 equivalents of KF•2H_2O 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:Et_2O), with a m.p. of 83-84.5 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{11}H_{14}O_2$ calculated 178.0994 (M^+), found 178.0994.

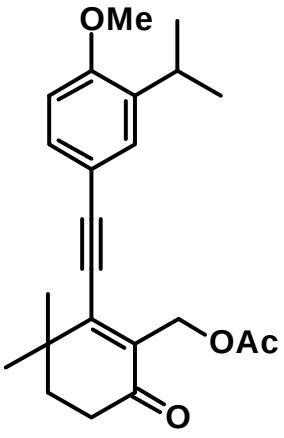
2-(Hydroxymethyl)-3-[(3-isopropyl-4-methoxyphenyl)ethynyl]-4,4-dimethylcyclohex-2-enone (194) (GENERAL PROCEDURE M)



$Pd(PPh_3)_4$ (0.1008 g, 0.08723 mmol, 5 mol%) and CuI (0.0266 g, 0.140 mmol, 8 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[44]. A solution of **186** (0.7225 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 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 Et_2O (75 mL), and then extracted with $NH_4^+Cl^-$ (aq., sat., 2 x 75 mL), followed by brine (1 x 75 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Preparative TLC (1:1 hexanes:Et_2O) afforded **194** as a thick yellow oil (0.3983 g, 1.221 mmol, 70%). ^{1}H-

NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{21}H_{26}O_3$ calculated 326.1882 (M^+), found 326.1882.

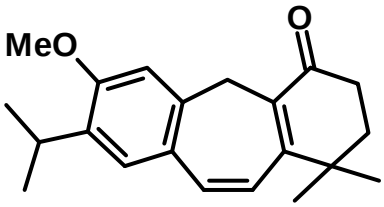
[2-((3-Isopropyl-4-methoxyphenyl)ethynyl)-3,3-dimethyl-6-oxocyclohex-1-enyl]methyl acetate (195) (GENERAL PROCEDURE N)



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 DMAP[165,197] (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 $NH_4^+Cl^-$ (aq., sat., 75 mL) and extracted with Et_2O (3 x 75 mL). The collected organic fractions were extracted further with $NH_4^+Cl^-$ (aq., sat., 1 x 75 mL) and brine (1 x 75 mL). The organic fraction was then dried over $MgSO_4$, filtered, the solvent removed under pressure, and finally preparative TLC (1:1 hexanes:Et_2O) 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. ^{1}H-NMR (500 MHz, $CDCl_3$): 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,

2H, J = 6.8), 1.99 (s, 3H), 1.90 (t, 2H, J = 6.8), 1.33 (s, 6H), 1.18 (d, 6H, J = 7.0); ^{13}C-NMR (75 MHz, $CDCl_3$): 196.3, 170.8, 158.4, 153.1, 137.6, 134.0, 131.4, 130.1, 113.8, 110.4, 108.7, 84.3, 59.7, 55.5, 36.1, 36.0, 34.1, 27.8, 26.7, 22.4, 21.0; IR (Pt/diamond): 2956, 2938, 2868, 2181, 1725, 1668, 1248; HR-MS: m/e for $C_{23}H_{28}O_4$ calculated 368.1988 (M^+), found 368.1998.

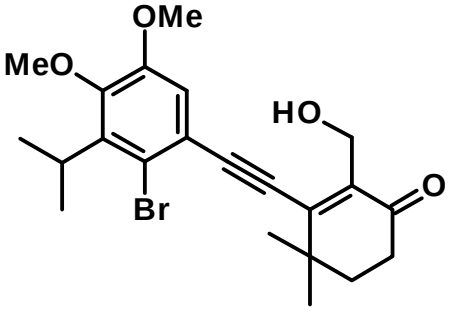
Compound 197



Compound **195** (0.2507 g, 0.6809 mmol) was dissolved in dry CH_2Cl_2 (97.2 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 reaction flask was submerged into an ice bath to cool the reaction to 0 ^oC. At this point, $SnCl_4$ (238 μL, 2.04 mmol) was added dropwise into the reaction, followed by *N,N*-diisoproplyethylamine (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 $NH_4^+Cl^-$ (aq., sat., 75 mL), as TLC analysis had shown the reaction to be complete. The organic portion was rinsed once more 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 quickly passed through a short column of silica to remove any excess impurities (100% hexanes, then 3:1 hexanes:Et_2O). The collected fraction (~0.16 g, ~0.27 mmol) was dissolved in degassed 2-methoxyethanol (4.1 mL) along with 5 equivalents of $NaH_2PO_2 \bullet H_2O$ (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 dH_2O (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_2O) isolated the product as a yellow oil (0.0592 g, 0.191 mmol, 28%). ^{1}H-NMR (500 MHz, CD_2Cl_2): 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, $CDCl_3$): 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; ^{13}C-NMR (75 MHz, CD_2Cl_2): 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 $C_{21}H_{26}O_2$ calculated 310.1933 (M^+), found 310.1932.

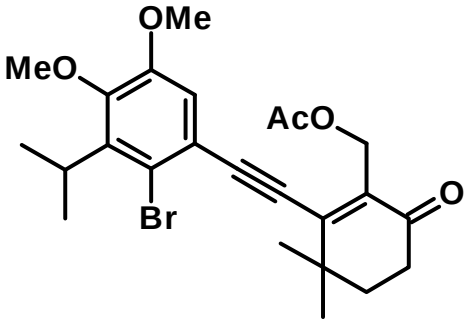
3-[(2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)ethynyl]-2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (198)



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:Et_2O) afforded **198** as a thick yellow oil (0.4777 g, 1.100 mmol, 63%). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.92 (s, 1H), 4.63 (d, 2H, J =

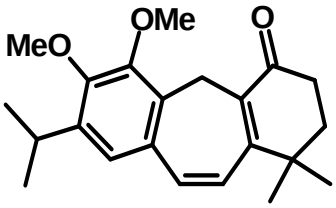
6.6), 3.85-3.87 (m, 6H), 3.65 (m, 1H), 3.12 (t, 1H, J = 7.2), 2.54 (t, 2H, J = 7.0), 1.93 (t, 2H, J = 7.0), 1.38 (s, 6H), 1.32 (d, 6H, J = 7.4); ^{13}C-NMR (125 MHz, $CDCl_3$): 199.7, 152.2, 148.5, 141.4, 138.7, 115.0, 105.8, 88.2, 61.2, 60.9, 56.0, 36.1, 36.0, 34.3, 27.8, 20.8; IR (Pt/diamond): 3428, 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_2O) 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.

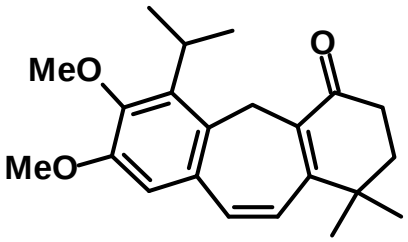
Compound 200 and 201



Compound **199** (0.1123 g, 0.6809 mmol) was dissolved in dry CH_2Cl_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

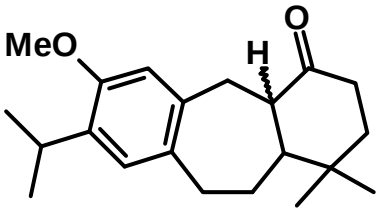
nitrogen atmosphere for 2 h. Following the allotted time, the solvent was removed under reduced pressure and the residue passed through a short column of silica. The excess $Co_2(CO)_8$ was eluted first with 100% hexanes, followed by the complexed product with a 1:1 hexanes:Et_2O mix. The product was concentrated on a rotary evaporator, and immediately dissolved in dry CH_2Cl_2 (33.7 mL). The reaction flask was then submerged into an ice bath to cool the reaction to 0 ^oC. 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_2O). The collected fractions were dissolved in degassed 2-methoxyethanol (3.6 mL) along with 5 equivalents of $NaH_2PO_2 \bullet H_2O$ (0.1038 g, 1.179 mmol). The solution was allowed to stir at 65 ^oC 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_2O (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_2O) isolated the products as colourless solids with **201** (0.0207 g, 0.0608 mmol) as the major isomer (top band), m.p. 103-105 ^oC, and **200** (0.0035 g, 0.010 mmol) as the minor isomer (bottom band), m.p. 151-152 ^oC (ratio of 1:5.9 **200**:**201**). Compound **200** is

spectroscopically identical to reported values[110].



201: ^{1}H-NMR (300 MHz, CD_2Cl_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 δ6.73 resonance gave enhancement of doublet at δ7.28 and methoxy protons at δ3.86; ^{13}C-NMR (75 MHz, CD_2Cl_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.

Compound 202



Compound **197** (0.0152 g, 0.0490 mmol) was dissolved in dry, anhydrous CH_2Cl_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®, the solvent removed under reduced pressure, and preparative chromatography (2:1 hexanes:Et_2O) 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.

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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*