PART I: SYNTHESIS OF A-RING MODIFIED ALLOCOLCHICINOIDS VIA LEWIS ACID CATALYZED CONJUGATE ADDITION REACTIONS; PART II: PREPARATION OF BENZOCYCLOHEPTADIENYNOL-Co2(CO)6 COMPLEXES

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PART I: SYNTHESIS OF A-RING MODIFIED ALLOCOLCHICINOIDS VIA LEWIS ACID CATALYZED CONJUGATE ADDITION REACTIONS;
PART II: PREPARATION OF BENZOCYCLOHEPTADIENYNOL–Co₂(CO)₆ COMPLEXES

By

Mariam Alaa Mehdi

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

Windsor, Ontario, Canada
2016

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PART I: SYNTHESIS OF A-RING MODIFIED ALLOCOLCHICINOIDS VIA LEWIS ACID CATALYZED CONJUGATE ADDITION REACTIONS;
PART II: PREPARATION OF BENZOCYCLOHEPTADIENYNOL–Co₂(CO)₆ COMPLEXES

by

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April 1st, 2016
I. Co-Authorship Declaration

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

This thesis also incorporates the outcome of a joint research undertaken under the supervision of Professor James R. Green. The collaboration is covered in Chapter 2 of "Part I" and Chapter 2 of "Part II" of the thesis. In all cases, the key ideas, primary contributions, experimental designs, data analysis and interpretation, were performed by the author, and the contribution of co-authors was primarily through the provision of guidance and advice when needed,

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II. Declaration of Previous Publication

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<td><strong>Chapters 1 and 2</strong> Novel Analogue of Colchicine Induces Selective Pro-Death Autophagy and Necrosis in Human Cancer Cells/ Larocque, K.; Ovadj, P.; Djurdjevic, S.; Mehdi, M.; Green, J. R.; Pandey, S. <em>PLoS ONE</em> 2014, 9 (1): e87064.</td>
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ABSTRACT

PART I

The chemistry of propargyliumdicobalt cations, known as the Nicholas reaction, has witnessed widespread use in organic synthesis mainly owing to the high stabilization of the carbocations, accompanied by their compatibility with numerous nucleophiles. However, there is a considerable shortage of studies regarding the factors affecting the stability and reactivity of the involved cations.

In this project, we investigated the chemistry of a novel Nicholas carbocation, namely the benzo-homologue of the dehydrotropylium cation, known as a benzodehydrotropylium–Co$_2$(CO)$_6$ cation. To obtain the desired cation, preparation of the requisite alcohol precursor involved the key ring-closure of the cycloheptyne via an intramolecular Sakurai reaction. Additionally, heterocyclic-based cycloheptadienynol–Co$_2$(CO)$_6$ complexes were also prepared. A Lewis acid mediated ionization of the parent alcohol complex led to the in situ generation of the benzodehydrotropylium–Co$_2$(CO)$_6$ ion, which was trapped with several nucleophiles, where the preferred site of substitution was the site remote to the dicobalt alkyne unit. Computational studies using NICS (1) values estimated the ion's aromaticity to be one third of that of tropylium ion, which is comparable to that of the dehydrotropylium–Co$_2$(CO)$_6$ ion previously studied in our group.
PART II

Allocolchicinoids are a well-recognized family of compounds (including both natural and synthetic derivatives) which possess a 6-7-6 tricyclic core. Many of them are known to have antitumor activity where they act by the same mode of action as the natural alkaloid colchicine, that is to say by inhibiting the cellular tubulin assembly process.

Particular attention has been devoted by our group to a series of allocolchicinoids bearing a modified A-ring substitution pattern, which is different from the one seen in the naturally-derived allocolchicine. Biological studies have shown their potency in targeting cancer cells. Considering the dibenzocycloheptanone as the core of the allocolchicine, we present herein our results on getting to allocolchicinoids based on an approach that constructs the B-ring via catalytic conjugate addition reaction chemistry, ultimately leading to the synthesis of allocolchicinoids of interest. The viability of this strategy is demonstrated by the preparation of differently substituted C-ring substrates. This work also reports the formal synthesis of allocolchicine iso-NSC 51046, and the first total syntheses of two novel allocolchicines.
DEDICATION

To my mom...for her love, warmth, support, and years of encouragement,

and to all my family.
ACKNOWLEDGEMENTS

I would like to start by extending my sincerest gratitude to my advisor Dr. James Green who gave me the opportunity to join his research group. I have been very lucky to have a supervisor who cares so much about his students and their work. His exceptional mentorship, patience, and guidance throughout the past years will always be remembered and appreciated.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARATION OF CO-AUTHORSHIP/PREVIOUS PUBLICATIONS</td>
<td>iii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>vii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xiii</td>
</tr>
<tr>
<td>LIST OF SCHEMES</td>
<td>xiv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xvii</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xix</td>
</tr>
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</table>

## PART I: PREPARATION OF BENZO- AND HETERO-FUSED CYCLOHEPTADIONYL–Co₂(CO)₆ COMPLEXES VIA INTRAMOLECULAR SAKURAI REACTION: GENERATION AND REACTIVITY OF BENZODEHYDROTROPYLUM–Co₂(CO)₆ ION

### CHAPTER 1 INTRODUCTION

1.1 Nicholas Reaction

1.2 Angle Strained Alkynes

1.3 Preparation of Cycloheptynes and Benzocycloheptynes by Nicholas Reaction

   Chemistry

1.3.1 Cycloheptynedicobalt Complexes

1.3.2 Benzocycloheptynedicobalt Complexes
1.4 Preparation of Cycloheptynes and Benzocycloheptynes by Other Methods ........................................ 13
   1.4.1 Cycloheptynedicobalt Complexes ........................................ 13
   1.4.2 Benzocycloheptynedicobalt Complexes ................................ 17
1.5 Origin of Current Project and Proposed Research ........................................ 20
   1.5.1 Dehydrotropylium–Co₂(CO)₆ Ion ........................................ 20
   1.5.2 Tropylium Ion and Annulation Effect ................................... 24
   1.5.3 Benzodehydrotropylium–Co₂(CO)₆ Cation ................................ 26

CHAPTER 2 RESULTS AND DISCUSSION ........................................... 27
2.1 Towards the Synthesis of Target Benzodehydrotropylium-Co₂(CO)₆ ion .... 27
   2.1.1 Retrosynthetic Analysis ................................................. 27
   2.1.2 Preparation of Cycloheptadienynol–Co₂(CO)₆ Complex: Cation Precursor ........................................ 28
2.2 Hetero-Fused Cycloheptadienynol–Co₂(CO)₆ Complexes .............................. 33
2.3 Generation of Benzodehydrotropylium–Co₂(CO)₆ Ion and its Reactivity .... 40
2.4 Computational Assessment of the Cation's Aromaticity ................................ 47

CHAPTER 3 CONCLUSIONS ................................................................ 53

CHAPTER 4 EXPERIMENTAL DATA .................................................. 55
   4.1 General Methods ............................................................... 54
   4.2 Experimental Methods ....................................................... 55

REFERENCES .................................................................................... 81
PART II:
AN ENANTIOSELECTIVE FORMAL SYNTHESIS OF A-RING MODIFIED ALLOCOLCHICINOIDs VIA LEWIS ACID CATALYZED CONJUGATE ADDITION REACTIONS

CHAPTER 1  INTRODUCTION ................................................................................................. 87
  1.1 Colchicine and Allocolchicinoids .............................................................................. 87
    1.1.1 (−)-Colchicine ................................................................................................. 87
    1.1.2 Allocolchicinoids .............................................................................................. 89
  1.2 Literature Overview and Previous Syntheses .......................................................... 91
    1.2.1 Preparation of Allocolchicine Derivatives from Natural Colchicine ............. 91
    1.2.2 Total Syntheses of N-Acetylcolchinol ............................................................. 93
    1.2.3 Methods for Allocolchicine Synthesis ............................................................. 96
    1.2.4 Syntheses of NCME or NSC 51046 ................................................................. 98
  1.3 Modified Allocolchicinoids ...................................................................................... 101
  1.4 Arene-Enone Conjugate Addition Reactions ......................................................... 104
  1.5 Origin of Current Project and Proposed Research ................................................. 106

CHAPTER 2  RESULTS AND DISCUSSION ............................................................................. 108
  2.1 General Synthetic Strategy ...................................................................................... 108
  2.2 Lewis Acid Catalyzed Alkylation of Electron-Rich Arenes ...................................... 113
    2.2.1 Reaction Scope ............................................................................................... 117
  2.3 Heterocyclic Analogues ......................................................................................... 123
  2.4 Completion of Enantioselective Synthesis of Allocolchicines ............................... 124
  2.5 Targeting Dibenzocycloheptanone Precursor en route to NSC 51046
    Synthesis ............................................................................................................. 128
LIST OF FIGURES

Figure 1.1 Categories of various cycloalkynes based on their occurrence. .......... 7

Figure 1.2 Selected examples of organic compounds with benzocycloheptane-based
skeleton. ................................................................. 10

Figure 1.3 Tropylium cation (51) and dehydrotropylium–Co₂(CO)₆ cation (52) ...... 20

Figure 1.4 Tropylium cation (51) and examples of annulated tropylium ions (56-62) 25

Figure 1.5 Structure of benzodehydrotropylium–Co₂(CO)₆ cation. ...................... 26

Figure 2.1 Optimized geometry of cation (63) with basis set B3LYP/6-311+G(d,p),
and selected measured bond lengths in Å. .................................................. 48

Figure 2.2 NICS (1) values of both rings of cation (63). ................................. 49

Figure 2.3 Literature NICS (1) values of (structures from left to right): tropylium ion,
dehydrotropic–Co₂(CO)₆ ion, benzotropylium ion, and benzene (at
B3LYP/6-311+G(d,p) level, except benzene). ............................................ 50

Figure 1.6 Structure of (−)-(aR, 7S) colchicine and its numbering system. ........... 87

Figure 1.7 Numbering system of allocolchicinoids. ....................................... 89

Figure 1.8 Common allocolchicinoids. ......................................................... 90

Figure 1.9 Examples of C-ring modified allocolchicines. .................................. 101

Figure 1.10 Examples of B-Ring modified allocolchicines. ............................. 102

Figure 1.11 Heterocyclic allocolchicinoids. .................................................. 103
LIST OF SCHEMES

**Scheme 1.1** Equilibrium of hydration/dehydration process of Co$_2$(CO)$_6$–complexed propargylic alcohols with their enyne complex. ........................................ 1

**Scheme 1.2** The Nicholas Reaction. ................................................................. 2

**Scheme 1.3** Generation of propargyliumdicobalt cation from enyne–Co$_2$(CO)$_6$ complex. ................................................................. 3

**Scheme 1.4** Reactivity of acyclic propargylic/allylic cations with nucleophiles. ........ 5

**Scheme 1.5** Reactivity of cyclic propargylic/allylic cations with nucleophiles. ........ 6

**Scheme 1.6** Preparation of cycloheptyne by argon-matrix irradiation. ................. 8

**Scheme 1.7** Synthesis of cycloheptyne-Co$_2$(CO)$_6$ complexes via intramolecular Nicholas reaction. ................................................................. 11

**Scheme 1.8** Preparation of benzocycloheptynedicobalt complexes via intramolecular Nicholas reaction. ................................................................. 12

**Scheme 1.9** Synthesis of cycloheptynedicobalt complexes via ring closing metathesis by Green. ................................................................. 13

**Scheme 1.10** Synthesis of cycloheptynedicobalt complexes via ring closing metathesis by Young *et al.* ................................................................. 14

**Scheme 1.11** [5+2] Cycloaddition reactions in the synthesis of cyclic and bicyclic cycloheptyne–Co$_2$(CO)$_6$ complexes. ........................................ 15

**Scheme 1.12** Diels-Alder reaction in cycloheptynedicobalt synthesis. ................. 16

**Scheme 1.13** Synthesis of cycloheptynedicobalt complexes using intramolecular Michael-type reaction. ................................................................. 17

**Scheme 1.14** Carbonylative Heck reaction. ................................................................. 18
Scheme 1.15  Benzotropone skeleton formation via rhodium(I)-catalyzed [3+2] annulation reaction. ................................................................. 19

Scheme 1.16  Formation of 4,5-benzotropones. ................................................................. 20

Scheme 1.17  Synthesis of cycloheptadienynol–Co$_2$(CO)$_6$ complex (cation precursor). 21

Scheme 1.18  Generation and precipitation of dehydrotropylium–Co$_2$(CO)$_6$ complex ion (52): $^1$H NMR resonances assignment and dimerization by-products .... 22

Scheme 1.19  Generation and reactivity of dehydrotropylium–Co$_2$(CO)$_6$ complex ion. ................................................................. 23

Scheme 2.1  Proposed retrosynthetic approach to the formation of the benzodehydrotropylium–Co$_2$(CO)$_6$ ion. ................................................................. 28

Scheme 2.2  Subjecting 2-bromobenzaldehyde to a Sonogashira reaction followed by desilylation to install the intended terminal alkyne group. ...................... 29

Scheme 2.3  Formation of the enyne followed by complexation to form the dicobalt-alkyne moiety. ................................................................. 29

Scheme 2.4  Proposed mechanism of formation of cycloheptadienynol–Co$_2$(CO)$_6$ complex via BF$_3$-mediated Sakurai reaction. ............................................. 30

Scheme 2.5  A series of transformations to obtain the benzodehydrotropylium–Co$_2$(CO)$_6$ ion precursor. ................................................................. 31

Scheme 2.6  Formation of the substitution products upon nucleophilic attack on either $\alpha$- or $\gamma$-sites of the in situ generated cation. ................................................. 41

Scheme 2.7  Formation of the elimination by-product. ............................................................. 43

Scheme 2.8  Summary of reactions of carbocation (63) with various nucleophiles. .... 44
Scheme 1.20 Obtaining allocolchicine by derivatization of colchicine. .......................... 91

Scheme 1.21 Obtaining compound ZD6126 (104) by derivatization of colchicine. 92

Scheme 1.22 The first asymmetric synthesis of N-acetylcolchinol, (NAC), by
Sawyer and Macdonald. ................................................................. 93

Scheme 1.23 Kocienski’s asymmetric synthesis of NAC. ............................................. 94

Scheme 1.24 Retrosynthesis of NAC by Leonard et al. ................................................ 95

Scheme 1.25 Wulff’s total synthesis of (−)-allocolchicine (101). ................................. 96

Scheme 1.26 Formal synthesis of allocolchicine (101) by Fagnou and Leblanc. ...... 97

Scheme 1.27 Retrosynthesis of NCME (rac-103) by DeShong and Seganish. ........... 98

Scheme 1.28 Green’s synthesis of allocolchicine NCME via Nicholas reaction
chemistry. ....................................................................................... 100

Scheme 1.29 Construction of 6,7,6-tricyclic compounds via Lewis acid mediated
cycloalkylation by Majetich et al. .................................................. 105

Scheme 2.9 Proposed retrosynthetic approach to dibenzoheptanone and
ultimately to allocolchicine iso-NSC 51046 (118). ................................. 109

Scheme 2.10 Two proposed routes to construct the tricyclic core of allocolchicinoids
via intramolecular conjugate addition reaction. ...................................... 110

Scheme 2.11 Suzuki-Miyuara cross-coupling reaction. ............................................. 111

Scheme 2.12 Preparation of alkynone cyclization precursor (Route A). ................. 111

Scheme 2.13 Preparation of alkenone cyclization precursor (Route B). ................. 113

Scheme 2.14 Proposed cyclization mechanism. ...................................................... 114

Scheme 2.15 Preparation of C-ring thiophene-based cycloheptanone (138h). ....... 123
Scheme 2.16 Completion of enantioselective formal synthesis of \textit{iso}-NSC 51046 (118). ........................................................................................................ 126

Scheme 2.17 Completion of enantioselective total synthesis of allocolchicinoids (144) and (145). .............................................................. 127

Scheme 2.18 Preparation of acyclic enone (146a) as cyclization reaction precursor. 128

Scheme 2.19 A plausible mechanism for the Lewis acid induced rearrangement of cycloheptanone. ................................................................. 131

Scheme 2.20 Examples by Majetich demonstrating the substituents' effect in the formation of spiro-fused enone compound (151). ....................... 135
LIST OF TABLES

Table 2.1  Appending the alkyne group for various substrates via Sonogashira reaction. ................................................................. 34

Table 2.2  Products of desilylation reactions using potassium carbonate in methanol. 35

Table 2.3  Formation of acyclic enynes of various heterocyclic substrates and their subsequent complexation with Co$_2$(CO)$_8$. ............................................ 36

Table 2.4  Cyclization reactions of various substrates via BF$_3$–mediated Sakurai reaction. ........................................................................... 39

Table 2.5  Attempts to induce the cyclization using alkynone as substrate. .......... 112

Table 2.6  Screening Lewis acids as catalysts for conjugate addition reaction. ..... 115

Table 2.7  Optimization of cyclization reaction catalyzed by BF$_3$-OEt$_2$. ............ 116

Table 2.8  Suzuki-Miyaura cross-coupling reaction. ........................................ 118

Table 2.9  Synthesis of allylic alcohol compounds ($136a$-$g$). .......................... 119

Table 2.10  Oxidation reaction to form acyclic enones. ....................................... 120

Table 2.11  Cyclization of enones using BF$_3$-OEt$_2$. ......................................... 121

Table 2.12  Screening Lewis acids for cyclization of ($137h$) to ($138g$). .............. 124

Table 2.13  Screening Lewis acids as catalysts for conjugate addition reaction of ($146$). ......................................................................................... 129

Table 2.14  Screening Lewis acids as catalysts for conjugate addition reaction of ($146b$). ......................................................................................... 133
# LIST OF ABBREVIATIONS

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<th>Symbol</th>
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EtOAc        ethyl acetate
EtOH         ethanol
Et₃SiH       triethylsilane
ESI          Electrospray Ionization
GIAO         gauge independent atomic orbital
HRMS         High Resolution Mass Spectrometry
HPLC         High Performance Liquid Chromatography
h            hour
IR           Infrared Spectroscopy
J            coupling constant
LDA          Lithium diisopropylamide
L.A.         Lewis acid
Me           methyl
m/e          mass/charge ratio
mol          mole
mmol         millimole
m            multiplet
mp           melting point
Mes          mesityl
NMO          4-methylmorpholine N-oxide
NMR          Nuclear Magnetic Resonance
Nu           nucleophile
OMe          methoxy
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<thead>
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<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>pyridine</td>
</tr>
<tr>
<td>ppm</td>
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</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
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<tr>
<td>q</td>
<td>quartet</td>
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<tr>
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<td>methyl</td>
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<td>acetonitrile</td>
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<tr>
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<td>2-(3-nitrophenyl)-1,3,2-dioxaborolane-4,5-dicarboxylic acid</td>
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<td>triplet of doublet</td>
</tr>
<tr>
<td>Tf</td>
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PART I

CHAPTER 1: INTRODUCTION

1.1 Nicholas Reaction

For many years, the use of propargylic cations as electrophilic synthons has been limited owing to the relatively low ability of the alkynyl function to impart stabilization to the generated positive charge. This severe limitation has been overcome by the discovery of Nicholas and Pettit\(^1\) in 1971 when they initially reported the use of dicobalt hexacarbonyl (Co\(_2\)(CO)\(_6\)) unit as a protecting group for the C–C triple bond. During their development of this chemistry, the authors noted the facile acid-promoted hydration/dehydration equilibrium between the dicobalt hexacarbonyl-complexed propargyl alcohols (1) and their corresponding 1,3–enynes (2) (Scheme 1.1).\(^2,3\)

\[\text{R}(-\text{OH})\text{Co}^\text{III}(\text{CO})_3\text{R}^1\text{Co}^\text{III}(\text{CO})_3\text{R}^2\rightleftharpoons \text{Co}_2(\text{CO})_6\text{R}^1\text{R}^2\]

**Scheme 1.1** Equilibrium of hydration/dehydration process of Co\(_2\)(CO)\(_6\)–complexed propargylic alcohols with their enyne complex.
This observation led to the postulation that the dicobalt hexacarbonyl group is capable of stabilizing propargyl carbocation. Stemming from this pioneering finding, Nicholas et al.\textsuperscript{2} developed the first substitution reaction involving a dicobalt hexacarbonyl-complexed propargylic alcohol (3) in the presence of strong protic acid and electron-rich benzene compounds. The generation of a cation (3a), propargylic to an alkyne–Co\textsubscript{2}(CO)\textsubscript{6} group, usually by ionization of an oxygen-based function by a protic or Lewis acid, followed by the trapping of that cation by nucleophiles, is commonly known as the Nicholas reaction (Scheme 1.2).

![Scheme 1.2 The Nicholas Reaction.](image)

Generation of the propargylumdicobalt cation is not restricted to the acid-promoted ionization of a propargylic alcohol complex. Alternatively, Smit and Caple\textsuperscript{4} reported that the carbocation could be generated from different precursors, namely 1,3-enyne–Co\textsubscript{2}(CO)\textsubscript{6} complexes (4) and an electrophile (Scheme 1.3). Subsequently, a mild
oxidative demetalation can regenerate the alkyne functionality of the resulting substituted products (5).

![Scheme 1.3 Generation of propargyliumdicobalt cation from enyne–Co₂(CO)₆ complex.](image)

**Cation Stability**

The remarkable thermodynamic and kinetic stability of [propargylium–Co₂(CO)₆]⁺ cations is evidenced by their convenient isolation and long-term storability as salts. Owing to their exceptional stability, the salts of such cations have been isolated by Connor and Nicholas⁵ as stable, dark red solids upon treatment of the Co₂(CO)₆–complexed propargylic alcohols with excess HF-SbF₅ or tetrafluoroboric acid etherate. The authors also studied the thermodynamic stability of a group of cobalt-coordinated propargylium cations by determining the pK’s for ionization of their corresponding alcohol complexes. It was reported that the cations' measured pK⁺ value ranges from −6.8 to −7.4 (−5.5 as reported in another reference⁶), which in fact is comparable to that of the well-known stable cation, triphenylmethyl (trityl, Ph₃C⁺) cation, whose pK⁺ is −6.6. It was also noted that the pK⁺ values of the studied propargylic carbocations were essentially identical, regardless of the substituents at the cation center.⁵
Furthermore, the stability of the cations have been also confirmed through spectroscopic studies. By comparing the IR spectra of the cationic species and the parent alcohol complex, a noticeable increase in the IR absorption frequencies of the CO ligands of the cationic complex was evident ($\Delta \nu \sim 40$-60 cm$^{-1}$) when compared to those of the alcohol complex. This shift denotes a significant charge delocalization onto the cobalt carbonyl unit, a feature that can be rationalized by the increased C–O bonding resulting directly from reduced d (Co)$\rightarrow$$\pi^*$($\text{CO}$) donation in the electron-poor cation.$^5$

**Reactivity and Regioselectivity of Propargyliumdicobalt Cations**

The alkyne–Co$_2$(CO)$_6$ complexes are readily prepared by stirring octacarbonyldicobalt(0), which is commercially available, and the alkyne-containing substrates, to form $\eta^2$-hexacarbonylalkynedicobalt complexes. The reaction normally proceeds at room temperature in many different types of organic solvents such as: diethyl ether, tetrahydrofuran, and dichloromethane. A wide scope of alkynes can undergo this complexation process, including terminal alkynes, symmetrical and unsymmetrical disubstituted alkynes, diynes, triynes, and cyclic alkynes.$^7$ The resultant complexes are purified by chromatography on alumina or silica gel, to afford the products as dark brown, or maroon-red colour oils or solids; they have remarkable stability if stored at low temperatures.

The versatility of the Nicholas reaction largely arises from the compatibility of the generated propargylic electrophilic synthon with a wide range of nucleophilic partners, including both inter- and intramolecular processes.$^8$ Our group and several others have expanded the scope of this reaction by exploring a range of nucleophilic partners such as...
electron-rich arenes,\textsuperscript{9} alkenes,\textsuperscript{10} ketones,\textsuperscript{11} hydrides,\textsuperscript{12} allylmetaloids,\textsuperscript{13} and enol derivatives including carbon and heteroatom-based ones.\textsuperscript{14,15} In addition, heteroatomic nucleophiles like ROH, RNH\textsubscript{2}, RSH, PR\textsubscript{3} are also compatible.\textsuperscript{16-18}

When the generated cation, propargylic to an alkyne–Co\textsubscript{2}(CO)\textsubscript{6} group, is in an acyclic system, the nucleophilic substitution tends to occur exclusively at the propargylic site,\textsuperscript{19} unless the cation is also allylic (6), in which case the substitution has been found to occur predominantly at the terminus remote to the alkyne–Co\textsubscript{2}(CO)\textsubscript{6} unit, i.e. \(\gamma\)-site (7, Scheme 1.4). This bias towards (E)-1,3–enynes was first addressed by Padmanabhan and Nicholas\textsuperscript{19a} in 1982, where it has been attributed to the considerable steric hindrance of the Co\textsubscript{2}(CO)\textsubscript{6} moiety and not to any hypothetical stabilizing conjugative interaction between the C=C double bond and the alkyne complex. Some exceptions have been encountered in literature, such as cases where the nucleophilic attack reactions are entropically driven towards the \(\alpha\)-site.\textsuperscript{20} Some oxygen-based nucleophiles proceed through \(\alpha\)-site attack pathway to give the corresponding propargylic substitution products.\textsuperscript{19a,21}

\[
\begin{array}{c}
\text{Lewis acid/or protic acid} \\
\text{Nu} \\
\text{Nu} \\
\end{array}
\]

\textbf{Scheme 1.4} Reactivity of acyclic propargylic/allyl cations with nucleophiles.
The site selectivity studies were expanded further when our group targeted allylic cations derived from cyclic precursor, namely cycloheptynes based ring systems (Scheme 1.5). To gain access to the cation of interest, the requisite precursor (i.e. the cyclic allylic acetate alkynedicobalt complex (9)) was obtained readily by ring closing metathesis.

\[ \text{9} \quad \text{BF}_3\text{-OEt}_2 \quad \text{Nu} \quad \text{10} \quad \text{Nu} \quad \text{11} \]

**Scheme 1.5** Reactivity of cyclic propargylic/allylic cations with nucleophiles.

The results of Nicholas reactions on the cation derived from the cyclic precursor (9) showed preferential reaction at the terminus remote (i.e. γ-) to the alkynedicobalt function (10), with increasing amounts of α-product (11) for reaction partners with greater nucleophilicity. Heteroatom-based nucleophiles, which react reversibly, gave γ-products (10) exclusively. The thermodynamic preference for the γ-product has been ascribed to the conjugative enyne stabilization in γ-product. Also, kinetically, this product is believed to be favoured since it exhibits less steric hindrance at the γ-position.\(^{22}\)
1.2 Angle Strained Alkynes

A recurring theme in organic synthesis is the development of efficient ways to synthesize medium-sized cycloalkynes.\textsuperscript{23} Since the triple bond prefers a linear geometry, cycloalkynes often have limited stability.\textsuperscript{24} An eight-membered ring alkyne (13), (Figure 1.1), is the smallest ring size that can tolerate this deformed geometry and still be isolated as a stable molecule.\textsuperscript{25} It has been generally accepted that the C–C≡C bond angle in cyclooctyne deviates 17° from the idealized 180° angle of a triple carbon-carbon bond.

In contrast to the isolable medium-sized cycloalkynes, their smaller homologues (i.e. five-, six-, and seven-membered cycloalkynes, 14-16) are non-isolable; they are however capable of existing as transient and highly reactive reaction intermediates that oligomerize rapidly.\textsuperscript{28} The occurrence of these unstable cycloalkynes has been confirmed experimentally by careful generation in solution and in a matrix. For example, irradiation
of cyclopropenone compound (19) in an argon matrix at 17 K provided (14) readily and allowed the measurement of the vibrational spectrum of cycloheptyne (Scheme 1.6).\textsuperscript{29}

![Scheme 1.6](image)

**Scheme 1.6** Preparation of cycloheptyne by argon-matrix irradiation.

To gain access to the aforementioned cycloalkynes "in-solution", these highly reactive intermediates were generated in situ in a fast reaction at very low temperatures and in the absence of any reactive reagents that might interfere with the triple bond of the alkyne. Once formed, these transient species could be trapped with specific reagents, hence enabling the measurement of the kinetic stability of the cycloalkynes of interest. For instance, in dilute dichloromethane solution at $-25 \, ^\circ C$, cycloheptyne possess a half-life of less than a minute, but it can be increased to one hour at $-78 \, ^\circ C$.\textsuperscript{30} Under analogous conditions, the lifespan of cyclohexyne at $-110 \, ^\circ C$ is only a few seconds. Finally, no experimental data supports the existence of cyclic alkynes with lower ring sizes (i.e. five-, four-, and three-membered ones).

In the vast majority of cycloheptynes and smaller cycloalkynes, the strain of bending the formally $sp$-hybridized carbon atoms substantially away from $180^\circ$ would be accompanied with a great energetic cost. This situation may be alleviated by resorting to transition metal complexes of these cycloheptynes, particularly the dicobalt hexacarbonyl complexes.\textsuperscript{31} Upon complexation of a carbon-carbon triple bond to a $\text{Co}_2(\text{CO})_6$ unit, there
are two critical features of the newly formed organometallic complex that are worth highlighting: 1) a significant added stabilization to the cation generated at the propargylic site, and 2) the normally linear digonally hybridized triple bond bends to ca. 140°. These specific features have made it possible for chemists to derive reactive intermediates and cyclic alkynes which would otherwise not accessible in their metal-free counterparts.

1.3 Preparation of Cycloheptynes and Benzocycloheptynes by Nicholas Reaction Chemistry

Since its discovery just over four decades ago, the chemistry of cycloheptyneco$_2$(CO)$_6$ complexes (i.e., the Nicholas reaction) has proven to be especially intriguing and widely used in organic transformations owing to the reliable site of reactivity of the cations, their ready generation and significant stability, coupled with their ability to engage in reaction with a broad spectrum of nucleophiles. The intermediacy of these complexes has proven to be particularly reliable in the construction of cycloheptynedicobalt complexes.$^{32}$

Additionally, Nicholas reaction chemistry has proven its efficiency in preparation of benzo-fused seven-membered ring compounds, in spite of the scarcity of methods developed for quick access for those ring systems. Benzocycloheptanes and benzocycloheptanones are of remarkable importance since they are commonly encountered in a variety of natural and pharmacologically relevant products including icetexanes,$^{33}$ (−)-colchicine and its analogue (−)-allocolchicine,$^{34}$ and purpurogalline,$^{35}$ to name a few (Figure 1.2).
1.3.1 Cycloheptynedicobalt Complexes

In 1986, the early efforts by Schreiber et al.\textsuperscript{36} paved the way for the synthesis of this class of compounds. Their reported methodology employed a Lewis acid mediated reaction of propargyl ether dicobalt hexacarbonyl complexes bearing a remote allylsilane (23), to afford a cycloalkyne complex with an exocyclic vinyl group (24). By varying the length of the carbon tether in the substrate, eight and even six-membered rings were formed analogously. Another related preparation of this class of compounds was developed by our group,\textsuperscript{37} where our initial efforts were primarily driven by the developed knowledge about the $\gamma$-carbonyl cation–Co$_2$(CO)$_6$ complexes and their potential use as successful precursors for cycloheptyne formation. With that in mind, and following experimentation with different substrate designs, a series of allylsilane containing propargylic acetates (25) were deemed to be suitable precursors. In the presence of BF$_3$-OEt$_2$, they readily underwent facile intramolecular cyclization via...
Nicholas reaction to give cycloheptenyne (26), bearing an endocyclic alkene function, in respectable yields (84-89 %). (Scheme 1.7).

Scheme 1.7 Synthesis of cycloheptyne–Co₂(CO)₆ complexes via intramolecular Nicholas reaction.
1.3.2 Benzocycloheptynedicobalt Complexes

The use of acyclic alkynedicobalt complexes and Nicholas reaction chemistry have been established as powerful means for rapid preparation of cycloheptyne–Co$_2$(CO)$_6$ complexes. Only a limited number of ring fused versions of these cycloheptyne complexes are known; of these, our group has a special academic interest in gaining access to benzocycloheptyne complexes. Ding and Green$^{38}$ reported an effective utilization of Nicholas reaction in the synthesis of a series of benzocycloheptynedicobalt complexes in addition to other heterocyclic analogues. In their synthetic approach, the design of the precursor was based on exploiting the ability of propargyldicobalt cations to react with electron rich arenes via intramolecular Nicholas reaction to afford the benzo-fused cycloheptyne complexes. By subjecting the precursor (27) to BF$_3$-OEt$_2$, the intended benzocycloheptyne-dicobalt complex was successfully formed (28, Scheme 1.8). Substrates with electron rich benzene rings underwent the cyclization reaction more rapidly (compared to the unsubstituted counterparts). In addition, the reaction scope also included successful preparation of hetero-fused cycloheptyne complexes, including thienyl, furyl and indole systems.

Scheme 1.8 Preparation of benzocycloheptynedicobalt complexes via intramolecular Nicholas reaction.
1.4 Preparation of Cycloheptynes and Benzocycloheptynes by Other Methods

1.4.1 Cycloheptynedicobalt Complexes

By Ring Closing Metathesis

Nicholas reaction chemistry is not the sole method to access cycloheptynedicobalt complexes. Rapid access to cycloheptynyne–Co$_2$(CO)$_6$ complexes is available via ring closing metathesis (RCM) chemistry. Green$^{39}$ reported the first RCM reactions on alkyne-cobalt complexes, where hexacarbonyldicobalt complexes of cycloheptynynes (30a) were cleanly obtained by the ring closing metathesis of the corresponding acyclic dienes (29a), using Grubbs' catalyst, (Cy$_3$P)$_2$Cl$_2$Ru=CHPh in good to excellent yields (Scheme 1.9).

Scheme 1.9 Synthesis of cycloheptynedicobalt complexes via ring closing metathesis by Green.$^{39}$
Two years later, Young’s group\textsuperscript{40} reported the use of analogous chemistry to obtain cycloheptyne–Co\textsubscript{2}(CO)\textsubscript{6} complexes (among other medium-sized rings). The construction of the seven-membered ring of cycloheptyne was achieved by the metathesis of dienes (29b) that were linked by a Co\textsubscript{2}(CO)\textsubscript{6}–complexed alkyne, in the presence of Grubbs I pre-catalyst (Cy\textsubscript{3}P)\textsubscript{2}Cl\textsubscript{2}Ru=CHPh (Scheme 1.10).

![Scheme 1.10](image)

**Scheme 1.10** Synthesis of cycloheptynedicobalt complexes via ring closing metathesis by Young et al.\textsuperscript{40}

The first attempted reaction was carried out with dienene substrate (29b), where \( R_1 = \text{H} \) and \( R_2 = \text{OH} \), but it failed to metathesize under the given conditions. This result prompted a structural modification by incorporating a protecting group for the alcohol, namely OTBDS, which in fact resulted in successful RCM, and the cyclic product was obtained in 80 % yield. A variety of cycloheptynedicobalt complexes (30b) were synthesized with variable propargylic substituents to furnish the RCM product in yields ranging from moderate to excellent.
By Cycloaddition Reactions

Cycloheptynedicobalt complexes have also been prepared by means of cycloaddition reactions. Tanino and co-workers\(^1\) used propargylic cationic species to develop a [5+2] cycloaddition protocol to generate cyclic (34) and bicyclic (34a) cycloheptyn–Co\(_2\)(CO)\(_6\) adducts (Scheme 1.11). Under the influence of EtAlCl\(_2\), hexacarbonyldicobalt propargyl cation (32), i.e. the five-carbon entity or pentadienyl cation surrogate, reacted with enol triisopropylsilyl ethers (31 and 31a) via Nicholas reaction to initially construct silyloxonium ions (33), which in turn underwent intramolecular cyclization to furnish the cycloheptyn–Co\(_2\)(CO)\(_6\) complexes in good yields (34 and 34a).

![Scheme 1.11](image)

Scheme 1.11 [5+2] Cycloaddition reactions in the synthesis of cyclic and bicyclic cycloheptyn–Co\(_2\)(CO)\(_6\) complexes.
**By Diels-Alder Reaction**

Iwasawa group\(^{42}\) has demonstrated that cycloheptynedicobalt complexes can also be generated by silica gel mediated Diels-Alder reactions \((\text{Scheme 1.12})\). When placed on silica gel column under inert atmosphere, furan-enynone complex \((35)\) underwent an intramolecular Diels–Alder reaction providing a mixture of the starting alkyne–Co\(_2(CO)_6\) complex and the desired cyclized alkyne–Co\(_2(CO)_6\) complex \((36)\) in equilibrium. The alkene in the furan ring of the Diels-Alder adduct was then rapidly subjected to hydrogenation with H\(_2\) and Pd/C to furnish reduced \((37)\) as a stable complex in 62 % yield (over two steps).

\[
\text{35} \xrightarrow{\text{silica gel}} \text{36} \xrightarrow{\text{H\(_2\), Pd/C, EtOAc, 0 \^{\circ}C}} \text{37 (62 %)}
\]

**Scheme 1.12** Diels-Alder reaction in cycloheptynedicobalt synthesis.

**By Michael Reaction**

Iwasawa\(^{43}\) also reported another strategy that's suited for the stereoselective synthesis of medium-sized cyclic compounds, including seven-membered ring ones. Through the intermediacy of alkyne–dicobalt hexacarbonyl complex precursors \((38)\) containing silyl enol ether and electron-deficient alkene moieties on opposite ends of the molecule, an intramolecular Michael-type reaction was promoted with a Lewis acid in the
presence of 2,6-di-(tert-butyl) pyridine (DTBP) to afford a mixture of cyclized silyl enol ether (39) and its hydrolyzed ketone (40) in a combined yield of 73 % (Scheme 1.13).

Scheme 1.13 Synthesis of cycloheptynedicobalt complexes using intramolecular Michael-type reaction.

1.4.2 Benzocycloheptynedicobalt Complexes

By Carbonylative Heck Reaction

A novel approach was reported by Iwasawa and Satoh\textsuperscript{44} which involved the unique usage of the carbonylative Heck-type coupling reaction in the synthesis of a benzocycloheptynedicobalt complex (43), (Scheme 1.14). In order to carry out the palladium catalyzed Heck-type coupling step, hexacarbonylalkynedicobalt complex (41) was subjected to ligand exchange with 1,1-bis(diphenylphosphino)methane (dppm) to produce the more thermally stable alkyne–Co\textsubscript{2}(CO)\textsubscript{4}-dppm complex (42). In addition, the optimal carbonyl source was found to be diphenylacetylene–Co\textsubscript{2}(CO)\textsubscript{6}.
By Rhodium(I)-Catalyzed [3 + 2] Annulation Reaction

An elegant approach has been reported by Murakami\textsuperscript{45} involving the development of rhodium(I) catalyzed [3 + 2] annulation reactions to form benzotropones. In the main proposal, reacting 2-cyanophenylboronic acid (45), as a three-carbon component, with an internal alkyne or strained alkene afforded the five-membered ring indenone derivative (41 to 93 % yield) in the presence of 5 mol % of [Rh(OH)(cod)]\textsubscript{2} catalyst. However, in one case, when ethyl 2-hexynoate (44) was used as the alkyne substrate, its reaction with 2-cyanophenylboronic acid (45) under similar reaction conditions resulted in the unexpected formation of benzotropone (46) as the major product (64 %) instead of the five-membered ring indenone derivative (Scheme 1.15).
Scheme 1.15 Benzotropone skeleton formation via rhodium(I)-catalyzed [3+2] annulation reaction.

Cyclization of bis-silyl enol ethers with 1,2-dialdehydes

A series of 4,5-benzotropones have been prepared by Langer and co-workers\textsuperscript{46} through two related pathways (Scheme 1.16). The first one involved a TiCl\textsubscript{4}-mediated cyclization of 1,3-bis-silyl enol ethers (47) with phthalic dialdehyde (48). Alternatively, the same 1,2-dialdehyde compound (48) could react with (2,4-dioxobutylidene) triphenylphosphoranes (49) via a Knoevenagel/Wittig reaction to afford similar benzotropones (50).
1.5 Origin of Current Project and Proposed Research

1.5.1 Dehydrotropylium–Co$_2$(CO)$_6$ Ion

Tropylium ion (also known as cycloheptatrienyl cation), is a well-recognized seven-membered ring cyclic cation which depicts a classical example of a Hückel-type aromatic compound with 6π-electrons (51), (Figure 1.3). Given the significance of this cationic species, our group has studied and reported the generation and reactivity of the dehydrotropylium–Co$_2$(CO)$_6$ cation (52).

![Tropylium cation (51) and dehydrotropylium–Co$_2$(CO)$_6$ cation (52).](image)

Figure 1.3 Tropylium cation (51) and dehydrotropylium–Co$_2$(CO)$_6$ cation (52).
The primary objective of the study was to provide a better understanding of the stabilization of propargyldicobalt cations by investigating whether (52) demonstrates greater stability than un-functionalized propargyldicobalt cations, and whether its nominal 6\(\pi\)-electron system shows evidence of aromaticity.\(^{48}\) The dehydrotropylium–Co\(_2\)(CO)\(_6\) cation was accessed from the corresponding cycloheptadienynol–Co\(_2\)(CO)\(_6\) complex precursor (54), which was in turn derived from [(diacetoxy)cycloheptenyne] dicobalt complex (53), a compound previously prepared in our group via ring-closing metathesis chemistry.\(^{39}\) The RCM adduct underwent a series of transformations, as shown in (Scheme 1.17), including acid-induced alkene isomerization, MnO\(_2\) oxidation, and DIBAL-H reduction, to give the target alcohol (54) with the desired \(\pi\)-conjugated system.

**Scheme 1.17** Synthesis of cycloheptadienynol–Co\(_2\)(CO)\(_6\) complex (cation precursor).
Reaction of alcohol (54) with HBF$_4$ (in CH$_2$Cl$_2$ at -78 °C) followed by the addition of Et$_2$O (or alternatively subjecting a solution of (54) in Et$_2$O to HBF$_4$ at -78 °C) afforded the dehydrotropylium ion–Co$_2$(CO)$_6$ complex (52) as a dark solid precipitate. The resultant precipitate was sufficiently stable to be analyzed by $^1$H NMR spectroscopy. In addition to the detection of the desired cation, NMR analysis also revealed the presence of two regioisomers of radical dimers (55a and 55b) whose structures are given below (Scheme 1.18).$^{48}$

![Scheme 1.18](image)

**Scheme 1.18** Generation and precipitation of dehydrotropylium–Co$_2$(CO)$_6$ complex ion (52): $^1$H NMR resonances assignment and dimerization by-products.

Perhaps the most noteworthy aspect of the spectrum is that all three chemically distinct protons have resonances that appear upfield from those of the classical tropylium ion as measured by Cox *et al.*$^{49}$ (δ 9.16 ppm in CH$_2$Cl$_2$). In regards to the protons in the two
propargylic sites of the complex, they are more downfield (in comparison to the rest of the ring), which is indicative of slightly reduced positive charge possession. In view of the brief stability of cation (52) as evidenced by its gradual decomposition in solution even at temperatures as low as -20 °C, this made $^{13}$C NMR analysis for the cation unattainable.$^{48}$

Reactivity studies of cation (52) showed that in the presence of reactive nucleophiles ($N > 1$ on the Mayr$^{50}$ scale), nucleophilic addition reactions took place predominantly at the propargylic site ($\alpha$-site) of the cobalt-complexed alkynyl unit in the cationic species. In the presence of less reactive nucleophiles ($N < 1$) however, cation (52) underwent a different reaction pathway where dimerization products were formed instead (Scheme 1.19).

![Scheme 1.19 Generation and reactivity of dehydrotropylium–Co$_2$(CO)$_6$ complex ion.](attachment:scheme_1.19.png)
To assess the aromaticity (or the lack thereof) of the generated cation, three different computational methods were evaluated: the harmonic oscillator model of aromaticity (HOMA), by evaluation of homodesmotic reactions involving cation (52), and by the nucleus-independent chemical shift, NICS (1) method. Upon examining the results gained from each of the three methods, it was concluded that values obtained from homodesmotic reactions and NICS(1) calculations presented a more accurate depiction of the aromaticity measure, where both suggested that cation (52) possess ca. 25 % the aromaticity of tropylium ion (51). On the other hand, the value obtained by HOMA method was considered to be less reliable and hence was disregarded in the aromaticity assessment.48

1.5.2 Tropylium Ion and Annulation Effect

Several decades ago, Pettit and co-workers51 disclosed interesting observations when they reported that the annulation of benzo- or heterocyclic derived π-systems significantly affect the properties of the parent ionic species. Tropylium ion (51), which is a representative of the nonbenzenoid aromatic 6π-electron system, has a good thermodynamic stability,47 where its pK<sub>R+</sub> is 4.7. A significant destabilization of tropylium ion is brought about by benzo-annulation as demonstrated by benzotropylium ion (56), (Figure 1.4) (pK<sub>R+</sub> = 1.7)52 and dibenzotropylium ion (57) (pK<sub>R+</sub> = −3.7)53. This suggests that the benzotropylium cation is about 10<sup>3</sup> times less stable than a tropylium cation.44
Conversely, an appreciable stabilization is evident when a tropylium ion was annulated with azulene; cyclohepta[α]-azulenylium ion (58), has been synthesized and its enhanced stabilization was measured to be \( pK_{R^+} = 7.3 \). A similar trend has been observed when tropylium ion was annulated to a furan (59) or thiophene ring (60) where an increase in stability was obtained (\( pK_{R^+} = 6.7 \) and 6.0, respectively). Two novel tropylium ions were studied by Pedaja and Gronowitz, which involved annulating a benzo-fused tropylium ion to a thienyl ring in one case, and a selenolo-ring in another. Using potentiometric titration methods, the authors measured the corresponding \( pK_{R^+} \) values of these ions and were found to be 3.8 for benzo[4,5]thieno[2,1-b]tropylium ion (61) and 3.4 for benzo[4,5]selenolo[2,1-b]tropylium ion (62). These values signified that the stabilities of these "hybrid" ions were lower than the thienotropylium ion, but higher than that of the benzotropylium ion. All these experimental data provide strong evidence that combining more than one \( \pi \)-system could endow new properties to the original \( \pi \)-system.
1.5.3 Benzodehydrotropylium–Co$_2$(CO)$_6$ Cation

In view of our group’s long-standing and sustained interest in developing preparation methods of benzocycloheptyne–Co$_2$(CO)$_6$ complexes to enable formation of various synthetic targets, it seemed to us of primary interest to further expand the utility of benzocycloheptyne complexes by investigating the formation and underlying reactivity of the benzo-homologue of the dehydrotropylium cation, also known as benzodehydrotropylium–Co$_2$(CO)$_6$ cation (Figure 1.5). Encouraged by the fruitful results obtained by Amiralaei and Green$^{48}$ in their previous work on preparation of Co$_2$(CO)$_6$ complex of dehydrotropylium ion, we chose to extend the cation-related studies to include the benzo-fused analogue ion as well. It was envisioned that benzodehydrotropylium–Co$_2$(CO)$_6$ cation would have a crucial role in acquiring better understanding of this novel class of ions, including their preparative methods, generation, associated reactivity towards nucleophiles, and finally the aromatic character.

![Figure 1.5](image-url)  

**Figure 1.5** Structure of benzodehydrotropylium–Co$_2$(CO)$_6$ cation.
CHAPTER 2: RESULTS AND DISCUSSION

2.1 Towards the Synthesis of Target Benzodehydrotropylium–Co$_2$(CO)$_6$ ion

2.1.1 Retrosynthetic Analysis

In literature, there are a limited number of methodologies that provide access to benzo-annulated cycloheptyne compounds. To prepare the desired benzodehydrotropylium–Co$_2$(CO)$_6$ ion, a synthesis plan was developed which involved two main parts. The first one aimed to provide a reasonable synthetic route to the cation precursor compound; this in turn would lead to initiating the second part which entailed generating the corresponding cationic species and examining the possibility of trapping it with nucleophiles of choice. The retrosynthetic strategy followed to prepare the benzodehydrotropylium–Co$_2$(CO)$_6$ ion is envisaged in (Scheme 2.1). The central step involves forming the cycloheptadienynol complex, which is perceived as the direct precursor to the intended cation (63).
Scheme 2.1 Proposed retrosynthetic approach to the formation of the benzodehydro-
tropylium–Co$_2$(CO)$_6$ ion.

2.1.2 Preparation of Cycloheptadienynol–Co$_2$(CO)$_6$ Complex: Cation

Precursor

The starting point of the synthetic plan was the assembly of 2-bromobenzaldehyde (64) and (trimethylsilyl)acetylene (65) under appropriate Sonogashira-type reaction conditions, i.e. palladium(0) as a catalyst and copper(I) as co-catalyst, to give the trimethylsilyl-protected alkyne (66) in 85 % yield (Scheme 2.2). Subsequently, the obtained alkyne (66) underwent desilylation by potassium carbonate in methanol to give the terminal alkyne species (67) quantitatively.
Scheme 2.2 Subjecting 2-bromobenzaldehyde to a Sonogashira reaction followed by desilylation to install the intended terminal alkyne group.

The latter compound was in turn submitted to another Sonogashira-type cross coupling reaction with 2-bromo-3-(trimethylsilyl)-1-propene (68) to afford the requisite enyne substrate (69) in 71 % yield. The next step proceeded smoothly, where the prepared alkyne was subjected to complexation with dicobalt octacarbonyl, and the corresponding dicobalt hexacarbonyl-alkyne complex (70) was obtained in a very good yield (80 %). Having the intended substrate in hand, the stage was set for attempting the cyclization, which is the key step to obtain the benzocycloheptyne precursor.

Scheme 2.3 Formation of the enyne followed by complexation to form the dicobalt-alkyne moiety.
To promote the ring-closing process, it was necessary to utilize an appropriate Lewis acid to mediate the reaction. Stemming from the fact that most of our previous group's work has relied on using boron trifluoride as the preferred Lewis acid, and due to its minimized tendency to induce decomposition in related cobalt complexes, it was envisioned that it would be a logical starting point for this current work as well. To our delight, the cyclization reaction proceeded smoothly in the presence of 1 equiv. of BF$_3$-OEt$_2$ and the desired cyclic product (71) was obtained in 75 % yield.

![Scheme 2.4](image)

**Scheme 2.4** Proposed mechanism of formation of cycloheptadienynol–Co$_5$(CO)$_6$ complex via BF$_3$-mediated Sakurai reaction.

The ring closing step, which qualifies as a 7-exo-trig process, could be best described as an intramolecular Hosomi-Sakurai reaction.$^{59}$ Upon the initial complexation of the Lewis acid to the oxygen, the carbonyl's carbon is activated by enhancing its
electrophilicity. The allylic silane serves as a nucleophile (through its terminal carbon) where it attacks the electron poor carbonyl resulting in the formation of the seven-membered ring of the cycloheptadienynol–Co$_2$(CO)$_6$ complex (71).

After successfully achieving the key cyclization reaction, the next objective was to further derivatize the cycloheptadienynol–Co$_2$(CO)$_6$ complex in hand, with the intent to construct the 6π-electron system in the cycloheptyne ring of the complex. This was a crucial requirement for the benzodehydrotrropylium complex ion to be generated from its relevant precursor. Having stated this, a series of transformations were designed for this purpose (Scheme 2.5).

**Scheme 2.5** A series of transformations to obtain the benzodehydrotrropylium–Co$_2$(CO)$_6$ ion precursor.

The first step involved converting the benzylic alcohol to the corresponding ketone using a mild oxidant, MnO$_2$, to give the intended oxidized product (72) in sub-
optimal yields (43% brsm). Although the desired product was obtained, it cannot be
denied that some drawbacks ascribed to this particular oxidation conditions rendered the
reaction slow and not highly efficient. The main drawback was the incomplete conversion
of the reactant even when adding a large excess of MnO₂ and increasing the reaction time.
In addition, some inevitable decomposition was observed (even though it could be
minimized by keeping the temperature close to 0 °C) which again contributed to low
yields. Due to the presence of cobalt moiety in the substrate, the choices of oxidants were
rather limited. The use of conventional oxidants such as Swern conditions was avoided
due to the potential risk of removal of the organometallic unit. Despite the low yields, a
reasonable amount of the ketone could be generated.

The isolated ketone (72) was then subjected to acid-catalyzed alkene
isomerization which indeed proved to be effective in furnishing the rearranged enone with
the endocyclic alkene (73) in 88 % yield. Now that the alkene and ketone were
conjugated in the cycloheptadienynone–Co₂(CO)₆ complex (73), this constituted the π-
system skeleton needed for the cation's precursor.

The last transformation involved reducing the ketone to the corresponding
secondary alcohol (74) using hydride-based reducing agent, DIBAL-H. After isolating the
crude benzo-fused cycloheptadienynol–Co₂(CO)₆ complex, it was purified using silica
gel-based column chromatography. The proton NMR spectrum of the purified alcohol
revealed the occurrence of an alkene isomerization, converting (74) → (75), where the
latter isomer bore a double bond that was in conjugation with the 6π-electron system of
the annulated arene. This acid-induced isomerization indicated that the obtained isomer
possessed higher stability than the previous compound, which in fact seems to be a logical rationale, given the significant contribution of conjugation in enhancing stability.

On a side note, by examining the final structure of the alcohol precursor (75), it could be noted that there is a methyl group on the carbon bearing the hydroxyl which does not truly contribute to the aromaticity considerations of the cation. The justification for the presence of this "extra" methyl group is that the original design of the synthesis presented the need for a synthetic handle which was necessary for the cyclization process.

2.2 **Hetero-Fused Cycloheptadienynol–Co$_2$(CO)$_6$ Complexes**

Considering that the established preparative method worked well for the formation of benzene annulated cycloheptyne complex, we sought to prove the viability of this method in preparing other bicyclic ring systems, namely heteroaryl-based compounds. To demonstrate the flexibility of our methodology, three different π-excessive heterocyclic ring systems were investigated which were: thiophene, furan, and indole; in addition, the electron rich methoxy-aryl substrate was also included in the reaction scope study.

To obtain the relevant precursors for hetero-fused and methoxy-aryl cycloheptadienynol–Co$_2$(CO)$_6$ complexes, a synthetic protocol analogous to the one reported earlier (when preparing the precursor for benzo-fused cycloheptyne complex ion) was attempted.

The synthesis of the intended substrates was initiated by installing an alkyne moiety through subjecting the corresponding bromo-arylaldehydes (76a-d) and TMS-acetylene to Sonogashira reaction (Table 2.1).
Table 2.1  Appending the alkyne group for various substrates via Sonogashira reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76a</td>
<td>77a</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>76b</td>
<td>77b</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>76c</td>
<td>77c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>76d</td>
<td>77d</td>
<td>98</td>
</tr>
</tbody>
</table>
The reactions proceeded with great success and the resultant compounds (77a-d) underwent desilylation under the appropriate reaction conditions (K₂CO₃ in methanol, or TBAF) to furnish the terminal alkynes needed for the next coupling reaction. A summary of the results is shown in Table 2.2.

**Table 2.2** Products of desilylation reactions using potassium carbonate in methanol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77a</td>
<td><img src="image1.png" alt="Image" /> 78a</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>77b</td>
<td><img src="image2.png" alt="Image" /> 78b</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>77c</td>
<td><img src="image3.png" alt="Image" /> 78c</td>
<td>72</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>77d</td>
<td><img src="image4.png" alt="Image" /> 78d</td>
<td>95</td>
</tr>
</tbody>
</table>

ᵃ Desilylation was achieved using TBAF (1.0 M in THF).
In the presence of 2-bromo-3-(trimethylsilyl)-1-propene and (78a-d), the Sonogashira reaction was employed again to obtain the acyclic enynes (79a-d), which in turn were subjected to complexation with Co$_2$(CO)$_8$ (Table 2.3). Indeed, the desired alkyne–Co$_2$(CO)$_6$ complexes (80a-d) were readily obtained in excellent yields, and this set the stage for running the cyclization reaction, namely, the seven-membered ring closure.

**Table 2.3** Formation of acyclic enynes of various heterocyclic substrates and their subsequent complexation with Co$_2$(CO)$_8$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product/ (Yield)</th>
<th>Product/ (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78a</td>
<td>MeO-CHO</td>
<td>MeO-CHO</td>
</tr>
<tr>
<td></td>
<td>78a</td>
<td>79a (73 %)</td>
<td>80a (75 %)</td>
</tr>
<tr>
<td>2</td>
<td>78b</td>
<td>MeO-CHO</td>
<td>MeO-CHO</td>
</tr>
<tr>
<td></td>
<td>78b</td>
<td>79b (63 %)</td>
<td>80b (77 %)</td>
</tr>
</tbody>
</table>
With the prepared precursors complexes in hand, the next transformation involved formation of the cycloheptynes via the Sakurai reaction. Once again, BF$_3$ was the first Lewis acid to be selected as a suitable mediator for the 7-exo-trig process. The success of the cyclization process was variable from one substrate to another. Substrate (80a), bearing an electron-donating methoxy group on its benzene ring underwent a rapid cyclization and the intended product, (81a), was isolated in 72 % yield. In addition, the C3-substituted thienyl-based substrate (80b) was also readily converted to the thiophene-fused cycloheptyne complex (81b) in 90 % yield. Cyclization was also successfully accomplished when C3-substituted furan substrate (80c) was subjected to analogous conditions. Despite the fact that the starting material was fully consumed during the reaction progress (clearly shown by TLC analysis), some decomposition was apparent which led to relatively reduced overall yield of (81c, 60 %). The final heteroaryl substrate
that we examined was the C3-substituted indole (80d) which also resulted in the formation of the intended cyclic product (81d). However, the percentage yield was significantly reduced (54 % yield) due to occurrence of some decomposition of the isolated product.

The ring closing step in all the given substrates was generally rapid, and the reaction time ranged from 5 minutes to 1 hour. The cyclized products (81a-d) were conveniently isolated following aqueous work-up with saturated sodium bicarbonate solution, solvent removal, and silica gel flash chromatography. The results are presented in (Table 2.4).
Table 2.4 Cyclization reactions of various substrates via BF$_3$–mediated Sakurai reaction.

![Cyclization mechanism](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80a</td>
<td><img src="image" alt="Product 81a" /></td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>80b</td>
<td><img src="image" alt="Product 81b" /></td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>80c</td>
<td><img src="image" alt="Product 81c" /></td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>80d</td>
<td><img src="image" alt="Product 81d" /></td>
<td>54</td>
</tr>
</tbody>
</table>
Having established that the proposed ring formation method was indeed widely applicable to heteroreryl-fused systems as well, it is worth noting that in principle, each of the formed bicyclic alcohol compounds (81a-d) could likely be readily converted to the corresponding ring-fused dehydrotropylium–Co$_2$(CO)$_6$ complex ion. This could potentially generate a reasonable library of novel Nicholas cations that could be further evaluated through reactivity studies with nucleophiles of choice.

2.3 Generation of Benzodehydrotropylium–Co$_2$(CO)$_6$ Ion and its Reactivity

Accessing the benzodehydrotropylium ion now became feasible in light of the availability of its requisite alcohol precursor. It was our belief that upon treatment of the alcohol (75) with a Lewis acid, the cationic species (63) could be readily generated in situ, which could then be trapped with nucleophiles of choice via an intermolecular Nicholas reaction. Once again, boron trifluoride was our choice of Lewis acid reagent, mainly due to the successful results achieved in generating the dehydrotropylium cation in previous work in our lab. Based on previous reports, it has been shown that the reaction of the Nicholas cation with different nucleophiles roughly obeyed Mayr's linear free enthalpy equation:

$$\log k (20 \degree C) = s (E + N);$$

where $E$ is an electrophilicity parameter, $N$ is a nucleophilicity parameter, and $s$ is a nucleophile-specific slope parameter. On the basis of this model, nucleophile/electrophile combinations with $(E + N \geq 5)$ are expected to proceed with a reasonable rate at room temperature. As such, [propargylium–Co$_2$(CO)$_6$]$^+$ cations which have $E$ values ranging between $-1.2$ and $-2.2$
are expected to undergo a reaction with nucleophiles with \((N > -3)\). Therefore, several nucleophiles possessing a range of strengths were studied, particularly as reflected by Mayr’s \(N\) values of nucleophilicity scale, in an attempt to obtain an experimental measure of the cation's electrophilicity and reactivity pattern.

Once the ion is generated, two different reactivity pathways were potentially possible: substitution and elimination. To start with the substitution pathway, ionization of the hydroxyl group leads to formation of a cation in the propargylic site (C-7) i.e. \(\alpha\)- to the alkyne-cobalt unit. By resonance, this positive charge can be delocalized to C-9 i.e. \(\gamma\)-site with respect to the cobalt-alkyne unit. This creates two potential cationic sites for nucleophiles, which would ultimately lead to two possible substitution products (\(82a\) and \(82b\)) as shown in (Scheme 2.6).

**Scheme 2.6** Formation of the substitution products upon nucleophilic attack on either \(\alpha\)- or \(\gamma\)-sites of the in situ generated cation.
The general synthetic protocol of the intermolecular Nicholas reaction employed the addition of BF$_3$-OEt$_2$ (3 equiv.) to a dichloromethane solution of parent alcohol (75, 1 equiv.) and nucleophile of interest (5 equiv.) at 0 °C. Under these reaction conditions, cation (63) readily reacted with allyltrimethylsilane (Mayr $N$ value = 1.79) to give primarily the corresponding C-9 (i.e. $\gamma$–site) substitution product (84a) in addition to a minor amount of C-7 (\alpha–site) substitution product (84b) (combined yield 83 %; 84a:84b ($\gamma$:\alpha) = 6:1). Moreover, the reactivity pattern of the more nucleophilic 2-methallyltrimethylsilane ($N = 4.41$) was analogous to that of allyltrimethylsilane (combined yield 68 %; 85a:85b ($\gamma$:\alpha) = 6:1). Among the nucleophiles investigated was the trimethylsilyl enol ether of acetophenone ($N = 6.22$), which underwent a reaction with the cation to afford a mixture of C-9 ($\gamma$–site) substitution product (86a, major) alongside a smaller proportion of C-7 (\alpha-site) product (86b) (combined yield 55 %; 86a:86b ($\gamma$:\alpha) = 4:1). On the other hand, $N$-methylpyrrole ($N = 5.85$) gave exclusively the C-9 ($\gamma$–site) product (87) in 81 % yield with no observable \alpha-site product.

Intermolecular trapping of the generated cation with the desired nucleophile was not the only anticipated outcome of the reaction. In some cases, the cation underwent elimination as shown in (Scheme 2.7), forming the exo-alkene compound (83). With nucleophiles such as thiophene ($N = –1.01$), 1,3,5-trimethoxybenzene ($N = 3.40$), and 2-methoxypropene ($N = 5.41$), the elimination product (83) was the only one obtained.
A reversed reactivity pattern was obtained when an oxygen-based nucleophile was tested. Methanol was the nucleophile of choice, and it predominantly reacted at the \( \alpha \)-site of the carbocation to give a propargylic substituted product as the major compound (88a), while forming only a minor amount of the \( \gamma \)-substitution product (88b) (combined yield 54 \%\; 88a:88b (\( \alpha:\gamma \)) = 3:1). The results of the Nicholas reaction of cation (63) with various nucleophilic species are summarized in (Scheme 2.8).
Scheme 2.8 Summary of reactions of carbocation (63) with various nucleophiles.

*a These nucleophiles include: 1,3,5-trimethoxybenzene, thiophene, and 2-methoxypropene.
Theoretically, the stabilization in the $\gamma$-substituted product could be ascribed to two main sources: first, the conjugation between the $\pi$-systems of the alkene function and the complexed alkyne unit (in the seven-membered ring), and secondly the lack of steric bulk, since the dicobalt hexacarbonyl group and the incoming nucleophile are positioned far apart from one another. On the other hand, conjugation is also a major player in stabilizing the $\alpha$–product. As a matter of fact, it is thought to be of a more pronounced effect since the double bond of the $\alpha$–substituted product is in conjugation with the $6\pi$-system of the fused benzene ring. This point can be validated by examining the outcome of the reaction scheme presented earlier (Scheme 2.5), where the alcohol precursor (74) unambiguously underwent an acid-induced isomerization (on silica gel) to the more conjugated alkene (75). That is to say that the thermodynamic product is actually the $\alpha$–substituted product.

Having established that $\alpha$–product is thermodynamically favoured, results deduced from the reactivity studies clearly support that substitution reactions involving the Nicholas cation (63) cation and various carbon-based nucleophiles were not under thermodynamic control; this was evident by the predominance of the formation of the $\gamma$–product (either as the major or exclusive product). However, a reversed pattern was observed when using an oxygen-based nucleophile, methanol, which delivered a higher ratio of $\alpha$-product (Scheme 2.8). This suggests that the nucleophilic substitution by MeOH was most likely operating under thermodynamic control, that is to say that the attack occurred reversibly under the given reaction conditions. This behaviour can be attributed to the presence of an easily protonated oxygen in the product formed initially, hence providing a pathway for cation re-formation.
By reviewing the relevant literature,\textsuperscript{19,22} Nicholas reactions of a cation that is both propargylic to an alkyne–Co$_2$(CO)$_6$ group and also allylic have been well known to favour the $\gamma$-site attack (i.e. the terminus remote to the alkyne–Co$_2$(CO)$_6$ unit) over $\alpha$-site for most nucleophiles (especially for lower reactivity nucleophiles) for reasons that are not exactly well-understood. This observation has been proven to be consistent in acyclic\textsuperscript{19} and cyclic systems\textsuperscript{22} as well. Stemming from these facts, we see that the reactivity/selectivity pattern in cation (63) is no exception. Despite the inability of drawing a clear-cut trend that relates the nucleophilicity (Mayr's $N$ value) to the resultant $\gamma$:$\alpha$ substitution ratio, it's evident that the $\gamma$-product is the preferred product. Additionally, the reactivity studies of the benzodehydrotr Typography Error typotropylium cation clearly indicated the relatively strong electrophilicity of the cation as proved by its ability to react with nucleophiles ranging from moderate (Mayr's $N$ value = 1.79), to ones that are more nucleophilic ($N = 6.22$). However, it can be argued that the results of Nicholas reaction with the selected nucleophiles was not truly conclusive since it lacked a wider scope of nucleophiles, including heteroatomic-based ones which could absolutely provide a better evidence for reactions reversibility (as witnessed by the methanol nucleophile).

The rationale behind the preference for nucleophiles to attack the remote site of the cation (63) could also be backed up by investigating the sterics involved in the cation system. Namely, the presence of the methyl group in the propargylic site (i.e. C-7) is likely inhibiting addition to the $\alpha$–position of the cation.
2.4 Computational Assessment of the Cation's Aromaticity

The concept of aromaticity is undoubtedly among the most fundamental tools for understanding organic chemistry. Among the available criteria, the nucleus independent chemical shift (NICS), which was first introduced by Schleyer et al.\textsuperscript{59} in 1996, has recently became the most widely used magnetic index of aromaticity, mainly due to its simplicity and efficiency.\textsuperscript{60} This method allows the evaluation of aromaticity, anti-aromaticity, and non-aromaticity of monocyclic systems and individual rings in polycyclic systems (local aromaticities). By definition, NICS is the magnetic shielding tensor measured for an arbitrary "ghost atom" which is placed in the middle of the ring of interest; this measures NICS (0) value.\textsuperscript{59} Other known key modifications in the calculation of NICS include placing the aforementioned "ghost atom" 1 Å above the molecular plane of the ring to avoid any potential interaction with the σ-framework electrons; this give NICS (1) values.\textsuperscript{61} Rings with an aromatic character have a significant negative NICS values as a result of the diatropic ring current, whereas rings with anti-aromatic character give rise to positive NICS values due to the existence of paratropic ring current; non-aromatic systems have NICS values of zero.

In the quest for a better understanding of this concept, we wished to investigate whether benzodehydrotriprylium–Co\textsubscript{2}(CO)\textsubscript{6} ion possessed any aromaticity, and whether this could lead us to draw conclusions about the potential ion's stabilization (computational studies were conducted by Dr. Eric Bushnell in Professor James Gauld's group).
In this study, the geometries of the benzodehydrotropylium–Co$_2$(CO)$_6$ ion were first optimized at the B3LYP/6-311+ G(d,p) level of theory (Figure 2.1).

![Figure 2.1 Optimized geometry of cation (63) with basis set B3LYP/6-311+G(d,p), and selected measured bond lengths in Å.](image)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond Length (in Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C2</td>
<td>1.364</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.403</td>
</tr>
<tr>
<td>C3-C4</td>
<td>1.415</td>
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<tr>
<td>C5-C6</td>
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<tr>
<td>C6-C7</td>
<td>1.437</td>
</tr>
<tr>
<td>C7-C1</td>
<td>1.441</td>
</tr>
</tbody>
</table>

**Figure 2.1** Optimized geometry of cation (63) with basis set B3LYP/6-311+G(d,p), and selected measured bond lengths in Å.

**NICS (1) Studies**

The NICS measurements were obtained by calculating NMR shielding values at the gauge independent atomic orbital (GIAO) HF/6-311+G(d,p)//B3LYP/6-311+G(d,p)
level. By examining the optimized structure generated for the benzodehydrotropylium complex (63), it was noted that the cobalt-cobalt vertex and the cycloheptadienyl unit were not perpendicular to one another, hence it was legitimate to place an arbitrary atom at two different locations\(^\text{48}\): 1 Å above and 1 Å below the center of the ring, and therefore, two different NICS (1) values may be computed. Given that the cation has two annulated rings, this would give rise to a total of four NICS (1) values. For the benzene ring, the two NICS (1) values were -9.4491 and -8.4815, and those measured for the seven-membered ring were -4.8798 and -2.0318. Since the environments at points 1 Å above and below the ring centres are not equivalent in the cycloheptyne ring, the averaged values were used for NICS (1) values which were calculated to be -3.5 (A-ring) and -8.96 (B-ring) as seen in the structure below (Figure 2.2).

**Figure 2.2** NICS (1) values of both rings of cation (63).
To put these measurements in perspective, the literature values of NICS (1) reported for some known aromatic rings are shown below (Figure 2.3).

![Diagram of aromatic rings](image)

**Figure 2.3** Literature NICS (1) values of (structures from left to right): tropylium ion, dehydrotropylium-Co\(_2\)(CO)\(_6\) ion, benzotropylium ion, and benzene (at B3LYP/6-311+G(d,p) level, except benzene).

The instant conclusion that can be drawn is that the negative sign of NICS (1) values of (63) is clearly indicative of the presence of "slight" aromatic character in the cation. To be more specific, it can also be noted that the aromaticity of the benzene-ring of the cation, i.e. B-ring, whose average NICS (1) is ca. −9.0, is reasonably comparable to that of the monocyclic benzene (−10.40, computed at the same level of theory\(^6^2\)). On the other hand, the average NICS (1) values of the A-ring is −3.5, which suggests that aromaticity of this annulated seven-membered ring is significantly reduced in comparison to the monocyclic tropylium cation (in literature, NICS (1) value of tropylium ion ranges from −9.2 to −11.2, depending on the basis set,\(^6^3\) however, it was previously measured in our group\(^4^8\) using B3LYP/6-311+G(d,p) basis set, and was found to be −10.5).
In summary, by establishing that the aromaticity of the benzodehydrotropylium–Co$_2$(CO)$_6$ ion (63) is highly influenced by the local ring current of the seven-membered ring, it can be reasonably stated that cation (63) is closely comparable to the computed aromaticity of dehydrotropylium–Co$_2$(CO)$_6$ ion complex (NICS (1) values of −3.5 and −2.92 respectively). The slight increase in aromaticity of (63) may be attributed to the annulation to the benzene ring which itself has a significant local aromaticity. Furthermore, its NICS (1) measurements suggests that (63) possess roughly 33% of the aromaticity of tropylium cation.

**Bond Length Alternation**

Bond length equalization is characteristic for aromatic compounds, whereas large bond length alternation ($\Delta r$) is found in anti-aromatic compounds; the bigger the ($\Delta r$) of a specific ring is, the less aromatic the system becomes. Bond lengths in the seven-membered ring of the bicyclic cation were computed as depicted in (Figure 2.1). With the exclusion of the carbon-carbon triple bond (C1-C2) due to its understandable deviation from ideal benzenoid bond length of 1.397 Å, bond length calculations show moderate bond length alternation, from 1.385 Å (C4-C5) to 1.437 Å (C6-C7), giving $\Delta r = 0.052$ Å (at the B3LYP/6-311+G(d,p) level), where $\Delta r$ here refers to the difference between the longest and shortest bond in the seven-membered ring (A-ring).

In the previous work of Amiralaei and Green, the bond length calculations of dehydrotropylium–Co$_2$(CO)$_6$ complex ion were implemented to further assess the system's aromaticity using HOMA (the harmonic oscillator model of aromaticity) method. In brief, HOMA is one of the most simple and common structure-based indices.
of aromaticity measurements. It takes into account both deviations from ideal aromatic bond lengths (EN) and bond alternation (GEO) according to the following relationship: \[ \text{HOMA} = 1 - \text{EN} - \text{GEO} \]

HOMA values calculated for dehydrotriplyium–Co$_2$(CO)$_6$ complex cation were shown to be not useful in quantitative evaluations of the ion's aromaticity. Based on this result, we envisioned that the aromaticity assessment of our current system, cation (63), using HOMA values will be highly inaccurate; hence, no further bond length-based calculations were carried out.
CHAPTER 3: CONCLUSIONS

In this study, we investigated the chemistry of a novel Nicholas carbocation, namely the benzo-homologue of the dehydrotropylium complex cation, known as benzodehydrotropylium–Co₂(CO)₆ cation. The required alcohol precursor, benzo-cycloheptadienynol–Co₂(CO)₆ complex, was prepared from commercially available starting materials. The desired benzo-fused dehydrotropylium–Co₂(CO)₆ complex cation was generated in situ upon ionization of the parent alcohol precursor with a Lewis acid (namely BF₃·OEt₂). Due to the delocalization of the positive charge in the seven-membered ring through resonance, this created two possible electrophilic sites in the molecule. The cation was trapped with a number of nucleophiles ranging in nucleophilicity from moderate to strong (N = 1.79 to 7.54 on the Mayr scale) which reacted with the carbocation through intermolecular Nicholas reactions. The main feature of reactivity was that nucleophiles predominantly attacked the γ-site of the cation, that is the site remote to the cobalt-alkyne unit, to give the γ-substituted products as the major ones, mixed with a minor ratio of α-product (the outcome of the attack on the α-site). An oxygen-based nucleophile, methanol, was the only exception, where it formed the α-product as the major one, which was ascribed to possible reversibility of the reaction hence leading to the formation of the thermodynamic product. On the other hand, a few nucleophiles did not react with the cation and instead the elimination product was isolated. Finally, the aromaticity of benzodehydrotropylium–Co₂(CO)₆ cation was assessed using computational methods, namely NICS (1) values. The calculated NICS (1) value of the seven-membered ring was found to be −3.5 which is indicative of modest
aromatic character. It can be said that it is ca. one third the aromaticity of tropylium cation and reasonably close to that of the dehydrotropylium–Co$_2$(CO)$_6$ cation.

The synthetic methodology for preparing annulated cycloheptyne–Co$_2$(CO)$_6$ complexes was proven to be of a decent applicability. In addition to the facile formation of benzene annulated cycloheptyne complex (i.e. the cation's alcohol precursor), the chemistry of seven-membered ring formation was further extended to other analogues. Heteroaryl-based systems (thiophene, furan, and indole) were also capable of participating in the formation of the corresponding fused cycloheptyne complexes.
CHAPTER 4: EXPERIMENTAL

General Methods and Materials: All reagents, unless otherwise noted, were purchased from Aldrich. Trimethylsilylacetylene was purchased from GFS Chemicals. Dicobalt octacarbonyl was purchased from Strem. 3-Bromo-2-formylfuran was purchased from Frontier Scientific. All reactions were run under a nitrogen atmosphere using oven-dried glassware (110 °C, > 1h). All reaction solvents were directly obtained from solvent purification system (Innovative Technologies). Commercial BF$_3$-OEt$_2$ was distilled and stored under nitrogen. The term “conventional workup” refers to extraction of the product from the aqueous layer with an organic solvent (such as dichloromethane or diethyl ether), drying of the combined organic layers with anhydrous magnesium sulfate and filtration of the resultant mixture, followed by evaporation of the volatiles under reduced pressure to obtain the crude product(s).

Instrumentation: Flash chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ sheets from Silicycle. Preparative TLC was carried out over silica gel GF-254 plates from Silicycle. Low-resolution mass spectra were recorded at 20eV on a Varian CP-3800/1200L GC/MS. High-Resolution Mass Spectrometry (HRMS) results were obtained by means of a Direct Insertion Probe-Electron Ionization method (70 eV), on a Waters/ Micromass GCT (GC-EI/CI Time of Flight Mass Spectrometer) performed at the McMaster Regional Centre for Mass Spectrometry. Proton nuclear magnetic resonance (¹H NMR) data were obtained either on Bruker Avance 300 or 500 MHz spectrometers.
Chemical shifts are reported in delta (δ) units, parts per million (ppm), relative to the singlet at 7.26 ppm for chloroform-d₆, unless otherwise indicated. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (¹³C NMR) data were obtained on Bruker Avance 75 or 125 MHz spectrometers. Infrared Spectroscopy (IR) data were recorded on a Burker Vector 22 FT-IR spectrophotometer using KBr plates. The reported IR data reflects the frequencies of the distinctive functional group stretches only.

2-Bromo-3-(trimethylsilyl)-1-propene (68)

![Chemical structure of 2-Bromo-3-(trimethylsilyl)-1-propene (68)](image)

Compound (68) was prepared using the method reported by Trost et al. The product showed spectroscopic data identical with the literature (isolated in 71% yield).

3-Bromothiophene-2-carbaldehyde (76b)

![Chemical structure of 3-Bromothiophene-2-carbaldehyde (76b)](image)

Compound (76b) was prepared from 3-bromothiophene in a sequence involving selective lithiation with LDA at the 2-position and formylation using excess DMF. The experimental procedure followed was adapted from literature.
(3-Bromothiophene was distilled under nitrogen prior to use; diisopropylamine was freshly distilled with CaH$_2$ under nitrogen before use). 3-Bromothiophene (0.501 g, 3.067 mmol) was added dropwise to a stirred solution of lithium diisopropylamide (LDA) [prepared by addition of n-butyllithium (1.8 M in THF, 1.70 mL, 3.067 mmol) to diisopropylamine (0.433 mL, 3.067 mmol)] in anhydrous THF (10 mL) at 0 °C and the resulting mixture was stirred for a further 30 min at this temperature. Then, DMF (0.47 mL, 0.448 g, 6.133 mmol) was added dropwise over a period of 20 min. The mixture was stirred further until TLC analysis indicated that all the starting material had been consumed (ca. 3 h) when an excess of 20% aqueous ammonium chloride was added to it. Extraction of the mixture with ether gave 3-bromo-thiophene-2-carbaldehyde as dark oil. The product showed spectroscopic data identical with the literature$^{68}$ (77 % yield).

3-Bromo-1-methyl-1H-indole-2-carbaldehyde (76d)

![Diagram of 3-Bromo-1-methyl-1H-indole-2-carbaldehyde (76d)](attachment:image)

To a solution of 1-methylindole-2-carbaldehyde (0.507 g, 3.185 mmol) in anhydrous THF was added N-bromosuccinimide (NBS) (0.60 g, 3.371 mmol) portion-wise. The solution was stirred for 2 h at room temperature. Then, a 2.0 M aqueous NaOH solution was added to the reaction mixture, followed by the addition of brine solution. Next, the mixture was subjected to a conventional extractive workup using ethyl acetate, to afford (76d) as yellow solid. No chromatographic purification was needed; the product
obtained was found to be pure enough to be used in subsequent reactions (> 98 % purity). The product showed spectroscopic data identical with the literature\(^\text{69}\) (0.743 g, 98 % yield), mp 86-88 °C (lit. mp 86-89 °C).\(^\text{69b}\)

2-Ethynylbenzaldehyde (67)

\[
\text{CHO} \\
\text{CH}_2=\text{C}(\text{CHO})
\]

\textbf{67}

Compound (67) was prepared using the method reported by Fujii and Ohno.\(^\text{70}\) The product showed spectroscopic data identical with the literature (96 % yield from 2-bromobenzaldehyde); mp 60–61.5 °C (lit. mp 60-61 °C).\(^\text{70}\)

2-Ethynyl-5-methoxybenzaldehyde (78a)

\[
\text{CHO} \\
\text{MeO} \\
\text{CH}_2=\text{C}(\text{CHO})
\]

\textbf{78a}

Compound (78a) was prepared using the method reported by Fujii and Ohno.\(^\text{70}\) The product showed spectroscopic data identical with the literature (77 % yield from 2-bromo-5-methoxybenzaldehyde), mp 96-97 °C (lit. 98 °C).\(^\text{70}\)
3-Ethynylthiophene-2-carbaldehyde (78b)

(3-Bromothiophene-2-carbaldehyde (76b) was subjected to Sonogashira coupling method following a procedure that was adapted from Eberbach,\textsuperscript{71} to give 3-((trimethylsilyl) ethynyl)thiophene-2-carbaldehyde (77b) in 82 % yield. To a solution of 77b (0.1092 g, 0.525 mmol) in methanol (3 mL) was added a catalytic amount (unweighed) of anhydrous potassium carbonate at room temperature. The reaction was stirred until starting material has been completely consumed, as judged by TLC using 2:1 petroleum ether/Et\textsubscript{2}O (30 min). The reaction mixture was concentrated under reduced pressure until most of the methanol has evaporated. To the resulting oily crude product was added water and Et\textsubscript{2}O (1:1), and a conventional work-up was performed. The crude product was purified by flash chromatography (2:1 petroleum ether/Et\textsubscript{2}O) to give (78b) as yellow oil (0.071 g, 99 % yield). The product showed spectroscopic data identical to literature.\textsuperscript{71}

3-Ethynylfuran-2-carbaldehyde (78c)
(3-Bromofuran-2-carbaldehyde (76c) was subjected to Sonogashira coupling method following a procedure that was adapted from Eberbach,\textsuperscript{72} to give 3-((trimethylsilyl) ethynyl)furan-2-carbaldehyde (77c) in 85% yield. To a solution of 77c (0.191 g, 0.99 mmol) in methanol (4.6 mL), anhydrous potassium carbonate (0.127 g) was added in one portion. The reaction was stirred until starting material has been completely consumed; judged by TLC using 5:1 petroleum ether/ether (5–10 min). The reaction mixture was concentrated under reduced pressure until most of the methanol has evaporated. The resulting oily crude product was washed with water/ether (1:1) solution. The organic ether layer was washed with saturated NH\textsubscript{4}Cl aqueous solution and brine solution. The combined organic layer was dried with anhydrous MgSO\textsubscript{4}. After removing the volatiles, compound (78c) was afforded as brown solid (0.103 g, 86% yield), mp 45-46 °C (lit.\textsuperscript{72} mp 45 °C). The product showed spectroscopic data identical to a previous report in literature.

3-Ethynyl-1-methyl-1H-indole-2-carbaldehyde (78d)

\[
\begin{align*}
\text{Br} & \quad \text{CHO} \\
\text{N} & \quad \text{SiMe}_3 \\
\text{Pd(PPh}_3)_4 & \quad \text{CuI, Et}_3\text{N} \\
\rightarrow & \quad \text{CHO} \\
\text{SiMe}_3 & \quad \text{V} \\
\text{TBAF} & \\
76d & \quad 77d \\
\end{align*}
\]

3-Bromo-1-methyl-1H-indole-2-carboxaldehyde 76d (0.570 g, 2.39 mmol, 1 equiv.) and trimethylsilylacetylene (0.38 g, 3.87 mmol, 1.6 equiv.) were dissolved in degassed triethylamine (30 mL). This solution was stirred at room until a clear homogenous solution was obtained. Then, Pd(PPh\textsubscript{3})\textsubscript{4} (0.138 g, 5 mol %) and CuI (0.045
g, 10 mol %) were added quickly to the reaction mixture. The solution was stirred for 1.5 h at 60 °C. After cooling the reaction to room temperature, a saturated solution of aqueous ammonium chloride was added and the mixture was subjected to a conventional work-up using diethyl ether. The dark oil was purified by flash chromatography (5:1 petroleum ether/Et₂O) to give pure 1-methyl-3-trimethylsilylethynyl-1H-indole-2-carboxaldehyde (77d) as yellow solid (0.601 g, 98 %). The spectroscopic data were identical to a former report by Barluenga et al.⁷³

A solution of 77d (0.741 g, 2.90 mmol) in anhydrous THF (25 mL) was treated with a solution of TBAF (1.0 M in THF, 2.9 mL, 1 equiv.) at room temperature. When the reaction was judged complete by TLC (5 min), it was quenched with a saturated solution of ammonium chloride and subjected to conventional work-up using diethyl ether. No further purification was required. Compound (78d) was collected as a yellow solid (0.5122 g, 95 % yield), mp 122-123 °C. IR (KBr) νmax 3284, 2102, 1669, 1476 cm⁻¹;

\[ ^1H\text{ NMR} \] (500 MHz, CDCl₃) δ 10.21 (s, 1H), 7.84 (dt, J = 1.0, 8.0, 1H), 7.47 (apparent td, J = 1.0, 8.0, 1H), 7.40 (apparent dt, J = 1.0, 8.5, 1H), 7.26 (td, J = 1.0, 7.5, 1H), 4.09 (s, 3H), 3.53 (s, 1H); \[ ^1H\text{ NMR} \] (500 MHz, CD₂Cl₂) δ 10.20 (s, 1H), 7.82 (d, J = 8.1, 1H), 7.49-7.43 (m, 2H), 7.26 (td, J = 7.0, 1.0, 1H), 4.07 (s, 3H), 3.61 (s, 1H); \[ ^13C\text{ NMR} \] (75 MHz, CDCl₃) δ 182.3, 139.3, 136.5, 128.0, 127.8, 122.1, 121.9, 110.6, 110.3, 84.7, 74.8, 31.8; \[ \text{HRMS} \] m/e for C₁₂H₁₉NO calcd 183.0684, found 183.0684.
2-(3-((Trimethylsilyl)methyl)but-3-en-1-yn-1-yl)benzaldehyde (69)

![Chemical Structure](image)

**General Procedure A:** (THF and diisopropylamine were well-degassed with a stream of nitrogen for 1 h prior to use in Sonogashira coupling). 2-Ethynylbenzaldehyde (67, 0.543 g, 4.18 mmol) and 2-bromo-3-(trimethylsilyl)-1-propene (68, 0.807 g, 4.18 mmol) were dissolved in a (5:1) solvent mixture of diisopropylamine/THF (40 mL). This solution was stirred at room temperature until a clear homogenous solution was obtained. Then, Pd(PPh\textsubscript{3})\textsubscript{4} (0.241 g, 5 mol %) and CuI (0.080 g, 10 mol %) were added quickly to the reaction mixture. The solution was stirred for 2 h at room temperature. A saturated aqueous solution of ammonium chloride was added and the mixture was subjected to a conventional work-up using diethyl ether. The dark oil was purified by flash chromatography (25:1 petroleum ether/Et\textsubscript{2}O) to give pure product 69 (0.719 g, 71 %) as a yellow oil. **IR** (KBr) \(\nu_{\text{max}}\) 2927, 1700, 1599 cm\(^{-1}\); **\(^1\)H NMR** (500 MHz, CDCl\textsubscript{3}) \(\delta\) 10.53 (d, \(J=\ 0.5\), 1H), 7.91 (m, 1H), 7.53 (m, 2H), 7.41 (m, 1H), 5.37 (d, \(J=\ 2.0\), 1H), 5.18 (d, \(J=\ 1.5\), 1H), 1.79 (d, \(J=\ 0.5\), 2H), 0.11 (s, 9H); **\(^13\)C NMR** (75 MHz, CDCl\textsubscript{3}) \(\delta\) 192.0, 135.9, 133.9, 133.2, 128.6, 128.4, 127.3, 127.2, 120.8, 98.7, 83.8, 28.1, -1.5; **HRMS** \(m/e\) for C\textsubscript{15}H\textsubscript{18}OSi calcd 242.1127, found 242.1130.
5-Methoxy-2-(3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)benzaldehyde (79a)

![Chemical Structure](image)

**Procedure A** was followed using 2-ethynyl-5-methoxybenzaldehyde (78a, 0.147 g, 1.1 equiv) and 2-bromo-3-(trimethylsilyl)-1-propene (68, 0.1616 g, 0.836 mmol). Flash chromatography (5:1 petroleum ether/Et₂O) gave pure product 79a (0.166 g, 73 %) as a yellow oil. **IR** (KBr) νmax 2955, 2200, 1690, 1601, 1493 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 10.49 (s, 1H), 7.45 (d, J= 8.5, 1H), 7.39 (d, J= 3.0, 1H), 7.10 (dd, J= 3.0, 8.5, 1H), 5.33 (s, 1H), 5.14 (s, 1H), 3.86 (s, 3H), 1.78 (s, 2H), 0.11 (s, 9H); **¹³C NMR** (125 MHz, CD₂Cl₂) δ 191.3, 159.8, 137.2, 134.5, 132.0, 128.6, 121.3, 119.6, 109.8, 96.9, 83.6, 55.7, 27.9, -2.0; **HRMS** m/e for C₁₆H₂₀O₂Si calcd 272.1233, found 272.1239.

3-(3-((Trimethylsilyl)methyl)but-3-en-1-yn-1-yl)thiophene-2-carbaldehyde (79b)

![Chemical Structure](image)

**Procedure A** was followed using 3-ethynlthiophene-2-carbaldehyde (78b, 0.1425 g, 1.05 mmol) and 2-bromo-3-(trimethylsilyl)-1-propene (68, 0.2035 g, 1.05
mmol). The reaction mixture was stirred for 2 h at 50 °C. Flash chromatography (2:1 petroleum ether/ether) afforded compound 79b (0.165 g, 63 % yield) as yellow oil. IR (KBr) ν max 2955, 2925, 2195, 1668, 1418, 1248 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.12 (d, J= 1.0, 1H), 7.66 (dd, J= 1.0, 5.0, 1H), 7.15 (d, J= 5.0, 1H), 5.38 (d, J= 1.5, 1H), 5.20 (d, J= 1.5, 1H), 1.78 (s, 2H), 0.11 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 183.1, 143.4, 134.0, 131.6, 128.2, 121.3, 110.3, 98.3, 80.5, 28.1, -1.5; HRMS m/e for C₁₃H₁₆OSSi calcd 248.0691, found 248.0673.

3-(3-((Trimethylsilyl)methyl)but-3-en-1-yn-1-yl)furan-2-carbaldehyde (79c)

![Diagram](image)

Procedure A was followed using 3-ethynylfuran-2-carbaldehyde (78c, 0.0737 g, 0.61 mmol) and 2-bromo-3-(trimethylsilyl)-1-propene (68, 0.1185 g, 0.61 mmol). Flash chromatography (5:1 petroleum ether/ Et₂O) gave compound 79c (0.0939 g, 66 % yield) as yellow oil. IR (KBr) ν max 2956, 1683, 1420, 1250 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.77 (d, J= 1.0, 1H), 7.61 (apparent dd, J= 1.5, 2.8, 1H), 6.58 (d, J= 3.0, 1H), 5.38 (d, J= 1.5, 1H), 5.21 (d, J= 1.5, 1H), 1.77 (d, J= 0.5, 2H), 0.10 (s, 9H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 176.2, 153.0, 148.0, 128.6, 121.4, 120.0, 115.5, 99.8, 77.5, 28.1, -1.7; HRMS m/e calcd for C₁₃H₁₆O₂Si: 232.0920; found: 232.0925.
1-Methyl-3-(3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)-1H-indole-2-carbaldehyde

(79d)

Procedure A was followed using 3-ethynyl-1-methyl-1H-indole-2-carbaldehyde (78d, 0.512 g, 2.79 mmol) and 2-bromo-3-(trimethylsilyl)-1-propene (68, 0.539 g, 2.79 mmol). The reaction mixture was stirred for 30 min at room temperature. Flash chromatography (5:1 petroleum ether/Et₂O) gave pure product 79d (0.595 g, 72 %) as a yellow oil. IR (KBr) νₘₐₓ 2954, 2200, 1668, 1476 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.18 (s, 1H), 7.83 (d, J= 8.0, 1H), 7.46 (td, J= 1.0, 7.5, 1H), 7.37 (d, J= 8.5, 1H), 7.24 (apparent dd, 1H), 5.39 (d, J= 2.0, 1H), 5.17 (s, 1H), 4.08 (s, 3H), 1.84 (s, 2H), 0.14 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 182.4, 139.6, 135.4, 128.8, 127.8, 127.7, 122.3, 121.6, 119.7, 112.2, 110.5, 99.3, 79.2, 31.8, 28.3, -1.5; HRMS m/e for C₁₈H₂₃NOSi calcd 295.1392, found 295.1384.
Hexacarbonyl [μ-η⁴-(2-(3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)benzaldehyde)]
dicobalt (70)

General Procedure B: Compound 69 (0.132 g, 0.55 mmol) was dissolved in anhydrous Et₂O and cooled to 0 °C in an ice bath. An unweighed amount of dicobalt octacarbonyl (excess) was added and the reaction was stirred while maintaining the temperature at 0 °C. After 1.5 h, the mixture was concentrated under reduced pressure in a cold water bath. The crude brown-coloured material was purified on a plug of silica (using 100% hexanes to remove the unreacted dicobalt octacarbonyl, and then switching to 100% diethyl ether to elute the final product). Compound (70) was obtained as dark brown oil (0.230 g, 80 % yield). IR (KBr) ν_max 2925, 2852, 2092, 2055, 2022, 1693, 1593 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.37 (s, 1H), 7.94 (d, J= 7.8, 1H), 7.68 (d, J= 7.5, 1H), 7.61 (td, J= 1.25, 7.5, 1H), 7.46 (t, J= 7.7, 1H), 5.48 (d, J= 1.0, 1 H), 5.35 (d, J= 1.0, 1H), 1.72 (d, J= 1.0, 2H), 0.10 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 199.0, 191.1, 143.7, 141.5, 134.7, 133.5, 132.6, 128.2, 117.3, 101.9, 88.6, 26.5, -0.8; HRMS m/e for C₂₁H₁₈Co₂O₇Si [M⁺ - 2CO] calcd 471.9587, found 471.9604.
Hexacarbonyl[μ-η^4-(5-methoxy-2-(3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)benzaldehyde)]dicobalt (80a)

![Image of compound 80a]

A solution of 79a (0.155 g, 0.57 mmol) in anhydrous Et_2O (40 mL) was subjected to Procedure B to afford product 80a (0.238 g, 75 % yield) as a dark brown oil. IR (KBr) ν_max 2959, 2090, 2055, 1689, 1599, 1481 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 10.36 (s, 1H), 7.60 (d, J= 8.5, 1H), 7.43 (d, J= 2.5, 1H), 7.18 (dd, J= 2.5, 8.5, 1H), 5.48 (s, 1H), 5.34 (s, 1H), 3.89 (s, 3H), 1.71 (s, 2H), 0.10 (s, 9H); ^13C NMR (75 MHz, CDCl_3) δ 199.2, 190.9, 159.7, 143.8, 135.2, 133.8, 133.5, 122.5, 117.3, 110.6, 101.6, 89.1, 55.8, 26.4, -0.8; HRMS m/e for C_{22}H_{20}Co_2O_8Si [M^+ - 4CO] calcld 445.9795, found 445.9785.

Hexacarbonyl [μ-η^4-(3-(3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)thiophene-2-carbaldehyde)]dicobalt (80b)

![Image of compound 80b]

A solution of 79b (0.0165 g, 0.066 mmol) in anhydrous Et_2O (15 mL) was subjected to Procedure B to afford product 80b (0.0273 g, 77 % yield) as a dark brown
oil. \textbf{IR} (KBr) \textit{v} \textsubscript{max} 2957, 2925, 2855, 2092, 2056, 2026, 1721, 1664, 1461 cm\textsuperscript{-1}; \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \textit{\delta} 10.08 (s, 1H), 7.71 (d, \textit{J} = 5.0, 1H), 7.23 (d, \textit{J} = 5.0, 1H), 5.48 (s, 1H), 5.33 (s, 1H), 1.77 (s, 2H), 0.11 (s, 9H); \textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\textsubscript{3}) \textit{\delta} 198.8, 182.4, 147.3, 143.5, 137.2, 134.7, 132.9, 117.0, 99.9, 81.4, 26.3, -0.9; \textbf{HRMS} \textit{m/e} for C\textsubscript{19}H\textsubscript{16}Co\textsubscript{2}O\textsubscript{7}Si [M\textsuperscript{+} - CO] calcd 505.9101, found 505.9100.

**Hexacarbonyl [\mu-\eta\textsuperscript{4}-(3-(3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)furan-2-carbaldehyde)] dicobalt (80c)**

\begin{center}
\includegraphics[width=0.2\textwidth]{80c}
\end{center}

A solution of 79c (0.0305 g, 0.131 mmol) in anhydrous Et\textsubscript{2}O (35 mL) was subjected to \textit{Procedure B} to afford product 80c (0.058 g, 85 \% yield) as a dark brown oil. \textbf{IR} (KBr) \textit{v} \textsubscript{max} 2958, 2949, 2956, 2026, 1679, 1477, 1251 cm\textsuperscript{-1}; \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \textit{\delta} 9.84 (d, \textit{J} = 0.6, 1H), 7.65 (apparent dd, \textit{J} = 0.6, 1.8, 1H), 6.64 (d, \textit{J} = 1.8, 1H), 5.46 (d, \textit{J} = 0.9, 1H), 5.29 (d, \textit{J} = 0.9, 1H), 1.78 (d, \textit{J} = 0.6, 2H), 0.10 (s, 9H); \textbf{\textsuperscript{13}C NMR} (125 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \textit{\delta} 199.0, 176.2, 147.9, 146.6, 143.5, 136.1, 116.5, 115.6, 100.1, 77.9, 26.0, -1.3; \textbf{HRMS} \textit{m/e} for C\textsubscript{19}H\textsubscript{16}Co\textsubscript{2}O\textsubscript{8}Si [M\textsuperscript{+} - CO] calcd 489.9329, found 489.9312.
Hexacarbonyl[μ-η⁴-(1-methyl-3-((trimethylsilyl)methyl)but-3-en-1-yn-1-yl)-1H-indole-2-carbaldehyde]dicobalt (80d)

A solution of 79d (0.0918 g, 0.311 mmol) in CH₂Cl₂ (30 mL) was subjected to Procedure B to afford product 80d (0.146 g, 81 % yield) as a dark green oil. IR (KBr) νmax 2926, 2854, 2088, 2053, 2025, 1728, 1667, 1472 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.52 (s, 1H), 7.90 (d, J = 8.0, 1H), 7.41-7.48 (m, 2H), 7.23-7.24 (m, 1H), 5.58 (s, 1H), 5.39 (d, J = 1.0, 1H), 4.12 (s, 3H), 1.73 (s, 2H), 0.11 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 199.7, 182.5, 127.9, 122.5, 121.7, 117.2, 110.9, 91.6, 84.8, -0.5; HRMS m/e for C₂₉H₂₁Co₂NO₇Si [M⁺ - 3CO] calcd 496.9904, found 496.9911.

Hexacarbonyl [μ-(8,9-dehydro-7-methylene-6,7-dihydro-5H-benzo[7]annulen-5-ol)]dicobalt (71)

![Chemical structure image](image-url)
**General Procedure C:** To a solution of 70 (0.2177 g, 0.410 mmol) in anhydrous CH$_2$Cl$_2$ (25 mL) at 0 °C was added BF$_3$-OEt$_2$ (0.051 mL, 0.41 mmol, 1.0 equiv). After stirring for 20 min at the same temperature, saturated NaHCO$_3$(aq) was added to the mixture and a conventional extractive workup using CH$_2$Cl$_2$ followed. After the removal of volatiles under reduced pressure, the crude dark oil was purified by flash chromatography (2:1 petroleum ether/Et$_2$O) to afford alcohol (71) as dark brown solid (0.1415 g, 75 % yield). IR (KBr) $\nu_{\text{max}}$ 3438, 2090, 2055, 2022, 1633 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J=7.5$, 1H), 7.31-7.41 (m, 3H), 5.86 (s, 1H), 5.70 (s, 1H), 4.98 (q, $J=4.0$, 1H), 3.11 (d of 0.5 ABq, $J=8.0$, 14.5, 1H), 2.88 (0.5 ABq, $J=14.5$, 1H), 1.76 (d, $J=4.0$, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.2, 143.0, 141.3, 135.8, 134.3, 129.4, 129.2, 128.5, 123.4, 88.4, 88.0, 73.3, 41.3; HRMS $m/e$ for C$_{18}$H$_{10}$Co$_2$O$_7$ [M$^+$] calcd 455.9090, found 455.9085.

Hexacarbonyl [µ-(8,9-dehydro-3-methoxy-7-methylene-6,7-dihydro-5H-benzo[7]annulen-5-ol)]dicobalt (81a)

![81a]

Following Procedure C, a solution of compound 80a (0.1445 g, 0.259 mmol) in anhydrous CH$_2$Cl$_2$ (30 mL) was treated with BF$_3$-OEt$_2$ (32.8 µL, 0.259, 1.0 equiv). The reaction was judged to be complete after 5 min where all the starting material was consumed (by TLC). The crude compound was purified by flash chromatography (5:1
petroleum ether/Et₂O) to afford pure compound 81a (0.0901 g, 72 % yield) as dark brown solid. IR (KBr) ν max 3413, 2923, 2088, 2051, 2021 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J= 8.4, 1H), 6.92 (dd, J= 2.7, 8.4, 1H), 6.89 (d, J= 2.7, 1H), 5.84 (s, 1H), 5.67 (d, J= 0.9, 1H), 4.91 (dd, J= 4.5, 7.5, 1H), 3.85 (s, 3H), 3.09 (d of 0.5 ABq, J= 7.8, 14.5, 1H), 2.88 (0.5 ABq, J= 14.5, 1H), 1.84 (d, J= 4.5, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 199.4, 159.9, 143.1, 135.9, 127.4, 123.1, 114.7, 114.5, 88.8, 88.6, 73.3, 55.5, 41.7; HRMS m/e for C_{19}H_{12}Co₂O₈ [M⁺] calcd 485.9196, found 485.9202.

**Hexacarbonyl [μ-(7,8-dehydro-6-methylene-6H-cyclohepta[b]thiophen-8-ol)]dicobalt (81b)**

![81b]

A solution of compound 80b (0.0165 g, 0.031 mmol) in anhydrous CH₂Cl₂ (8 mL) was treated with BF₃-OEt₂ (3.48 µL, 0.031 mmol, 1.0 equiv) as described in Procedure C. The crude compound was purified by flash chromatography (2:1 petroleum ether/Et₂O) to afford pure compound 81b (0.0131 g, 91 % yield) as brown oil. IR (KBr) ν max 3398, 2926, 2855, 2090, 2055, 2022, 1715, 1625 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, J= 5.5, 1H), 7.25 (d, J= 5.0, 1H), 5.85 (s, 1H), 5.70 (s, 1H), 5.05 (m, 1H), 3.00 (d of 0.5 ABq, J= 14.0, 1H), 2.87 (0.5 ABq, J= 14.0, 1H), 2.04 (d, J= 6.5, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 199.2, 143.5, 142.3, 133.4, 130.9, 125.7, 124.2, 89.3, 82.3, 68.2, 41.7; HRMS m/e for C₁₆H₈Co₂O₇S [M⁺] calcd 461.8655, found 461.8652.
Hexacarbonyl $[\mu-(7,8\text{-dehydro-6-methylene-6H-cyclohepta}[b]\text{furan-8-ol})]$dicobalt (81c)

A solution of compound 80c (0.041 g, 0.079 mmol) in anhydrous CH$_2$Cl$_2$ (15 mL) was treated with BF$_3$-OEt$_2$ (9.8 µL, 0.079 mmol, 1.0 equiv) as described in Procedure C. The crude compound was purified by flash chromatography (2:1 petroleum ether/Et$_2$O) to afford pure compound 81c (0.0208 g, 60 % yield) as brown oil. IR (KBr) $\nu$$_{\text{max}}$ 3390, 2094, 2056, 2026 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 (s, 1H), 6.62 (s, 1H), 5.85 (s, 1H), 5.70 (s, 1H), 5.02 (m, 1H), 2.99 (dd, $J$ = 6.0, 14.0, 1H), 2.77 (d, $J$ = 14.5, 1H), 1.85 (d, $J$ = 7.0, 1H); HRMS $m/e$ for C$_{16}$H$_8$Co$_2$O$_8$ [$M^+$ - 2CO] calcd 389.8985, found 389.8989.

Hexacarbonyl $[\mu-(9,10\text{-dehydro-5-methyl-8-methylene-5,6,7,8-tetrahydrocyclohepta}[b]\text{indol-6-ol})]$dicobalt (81d)
A solution of compound 80d (0.0664 g, 0.114 mmol) in anhydrous CH$_2$Cl$_2$ (15 mL) was treated with BF$_3$-OEt$_2$ (14.0 µL, 0.114 mmol, 1.0 equiv) as described in Procedure C. The crude compound was purified by flash chromatography (2:1 petroleum ether/Et$_2$O) to afford pure compound 81d (0.0132 g, 54 % yield) as black/dark green solid. IR (KBr) $\nu_{\text{max}}$ 3561, 2921, 2086, 2036, 2000, 1720 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J$= 8.0, 1H), 7.38 (d, $J$= 8.0, 1H), 7.34 (td, $J$= 1.0, 7.0, 1H), 7.27 (td, $J$= 1.0, 7.0, 1H), 5.91 (s, 1H), 5.71 (d, $J$= 1.5, 1H), 5.22 (apparent dd, $J$= 1.5, 2.0, 1H), 3.84 (s, 3H), 3.15 (d of 0.5 ABq, $J$= 5.5, 14.0, 1H), 2.90 (0.5 ABq, $J$= 14.0, 1H), 1.70 (d, $J$= 10.0, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.9, 142.1, 138.3, 137.7, 128.4, 123.7, 123.3, 121.0, 119.8, 110.1, 109.6, 92.1, 83.0, 63.5, 40.3, 29.6; HRMS m/e for C$_{21}$H$_{13}$Co$_2$NO$_7$ [M$^+$] calcd 508.9356, found 508.9352.

**Hexacarbonyl [μ-(8,9-dehydro-7-methylene-6,7-dihydro-5H-benzo[7]annulen-5-one)]dicobalt (72)**

\[\text{Hexacarbonyl [μ-(8,9-dehydro-7-methylene-6,7-dihydro-5H-benzo[7]annulen-5-one)]dicobalt (72)}\]

To a solution of alcohol 71 (0.248 g, 0.544 mmol) in anhydrous CH$_2$Cl$_2$, manganese oxide (MnO$_2$) powder (0.2364 g, 2.720 mmol, 5 equiv.) was added in one portion at -5 °C. Following stirring for 1 h at this temperature, the solution was filtered to remove the excess solid. The filtrate was concentrated under reduced pressure and was subjected to flash chromatography (5:1 petroleum ether/ Et$_2$O) to give the sequential
elution of ketone 72 (0.0691 g, 28 % yield, 43 % based on recovered 71) and starting material 71 (0.0868 g, 35 % recovery). IR (KBr) \( \nu_{\text{max}} \) 2926, 2095, 2057, 2026, 1682, 1596 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.75 (d, \( J = 7.5 \), 1H), 7.68 (dd, \( J = 1.5, 7.7 \), 1H), 7.56 (td, \( J = 1.5, 7.7 \), 1H), 7.41 (td, \( J = 1.0, 7.7 \), 1H), 5.77 (s, 1H), 5.75 (s, 1H), 3.76 (s, 2H); \(^{13}\)C NMR (125 MHz, CD\(_2\)Cl\(_2\)) \( \delta \) 198.8, 198.3, 139.1, 138.6, 136.8, 133.4, 132.6, 128.9, 128.4, 122.3, 87.8, 87.4, 51.9; HRMS \( m/e \) for \( \text{C}_{18}\text{H}_{8}\text{Co}_2\text{O}_7^[\text{M}^+] \) calcd 453.8934, found 453.8914.

**Hexacarbonyl [\( \mu-(8,9\text{-dehyro-7-methyl-5H-benzo[7]annulen-5-one}) \) dicobalt (73)**

\[ \text{Co}_2(\text{CO})_6 \quad \text{H}_2\text{SO}_4 \text{(cat)} \quad \text{CH}_2\text{Cl}_2, 0^\circ\text{C} \quad \text{Co}_2(\text{CO})_6 \]

72

To a stirred ice cold solution of 72 (80.9 mg, 0.20 mmol) in anhydrous CH\(_2\)Cl\(_2\) (10 mL) was added \( \text{H}_2\text{SO}_4 \) (3 drops in 2 mL of anhydrous CH\(_2\)Cl\(_2\)) in a dropwise fashion over a period of 20 min. Following stirring for 2 h at 0 °C, water was added, and the mixture was subjected to a conventional extractive workup using dichloromethane. The isolated crude extract was subjected to flash chromatography (5:1 petroleum ether/Et\(_2\)O) to afford pure 73 (70.8 mg, 88 % yield). IR (KBr) \( \nu_{\text{max}} \) 2918, 2095, 2057, 2031, 1730, 1605, 1582 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.25 (dd, \( J = 1.2, 8.1 \), 1H), 7.87 (dd, \( J = 1.2, 7.6 \), 1H), 7.66 (td, \( J = 1.2, 7.5 \), 1H), 7.53 (td, \( J = 1.2, 7.5 \), 1H), 6.67 (d, \( J = 1.2, 1\)H), 2.43 (d, \( J = 1.2, 3\)H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \( \delta \) 198.5, 189.3, 149.5, 137.8, 136.7, 133.6, 133.5,
132.4, 131.4, 129.1, 85.4, 83.7, 23.6; **HRMS** *m/e* for C₁₈H₈Co₂O₇ [M⁺] calcd 453.8934, found 453.8941.

**Hexacarbonyl [µ-(8,9-dehydro-7-methyl-7H-benzo[7]annulen-7-ol)]dicobalt (74)**

![Diagram](image)

Compound 73 (52 mg, 0.11 mmol) was dissolved in anhydrous CH₂Cl₂ (7 mL) and the solution was cooled to -78 °C. DIBAL-H (0.46 mL of a 1.0 M solution in THF, 0.46 mmol, 4 equiv.) was added dropwise and the solution was stirred for 1 h at the same temperature. Then, a saturated aqueous solution of NH₄Cl was added and the reaction mixture was subjected to a conventional extractive workup using dichloromethane. Removal of the volatiles under reduced pressure afforded a crude mixture which was subjected to flash chromatography (5:1 petroleum ether/Et₂O) to afford alcohol compounds 74 and 75 (inseparable by chromatography) and the elimination product 83 (14.0 mg, 29 % yield). The isolated mixture containing (74) and (75) was mixed with silica in hexanes. After stirring for 1 h, the silica was filtered off and the collected filtrate was concentrated under reduced pressure to afford alcohol (75) exclusively (35.5 mg, 68 % yield from ketone 73). **Compound 75: IR (KBr) ν<sub>max</sub> 3448, 2924, 2853, 2092, 2055, 1650 cm⁻¹.**
2024, 1723 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.67 (m, 1H), 7.34 (m, 2H), 7.18 (m, 1H), 6.38 (d, \(J= 12.5\), 1H), 6.13 (d, \(J= 12.5\) Hz, 1H), 2.23 (s, 1H), 1.54 (s, 3 H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 199.3, 139.6, 135.9, 135.4, 133.0, 131.2, 128.8, 128.2, 125.4, 90.8, 88.0, 71.6, 22.7; HRMS \textit{m/e} for C\(_{18}\)H\(_{10}\)Co\(_2\)O\(_7\) [M\(^+\) - 2CO] calcd 399.9192, found 399.9196. Resonances from (83) could be detected at: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.68 (m, 1H), 7.28 (m, 2H), 7.13 (m, 1H), 6.37 (d, \(J= 7.5\), 1H), 6.32 (d, \(J= 7.5\), 1H), 5.69 (s, 1H), 5.61 (s, 1H).

**General Procedure D:** To a solution of (75) in anhydrous dichloromethane at 0 °C, an excess amount of the nucleophile (5-8 equiv.) was added. Then, BF\(_3\)-OEt\(_2\) (3 equiv.) was added dropwise while maintaining the temperature at 0 °C. The solution was stirred for 30 min (TLC monitoring). The reaction was quenched with a saturated aqueous sodium bicarbonate solution, and was followed with a conventional aqueous workup using dichloromethane. The crude mixture was purified by flash chromatography (100:1 petroleum ether/Et\(_2\)O) to afford the final product.

**Hexacarbonyl [μ-(8,9-dehydro-5-allyl-7-methyl-5H-benzo[7]annulene)]dicobalt (84a and 84b)**

\[
\begin{align*}
84a & \quad \begin{array}{c}
\text{Co}_2(\text{CO})_6
\end{array} \\
84b & \quad \begin{array}{c}
\text{Co}_2(\text{CO})_6
\end{array}
\end{align*}
\]
A solution of alcohol compound 75 (11.41 mg, 0.0250 mmol) in CH₂Cl₂ (7 mL) was subjected to Procedure D using allyltrimethylsilane (22.81 mg, 0.201 mmol, 8 equiv.) to afford a (6:1) mixture of 84a and 84b (9.943 mg, 83 % total yield 84a + 84b).

IR (KBr) v_max 2924, 2854, 2088, 2048, 2015, 1445, 1102 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (major product, 84a) δ 7.68 (d, J= 6.5, 1H), 7.30-7.35 (m, 2H), 7.20 (d, J= 7.5, 1H), 5.73-5.79 (m, 2H), 5.06-5.13 (m, 2H), 3.13 (m, 1H), 2.66 (m, 2H), 2.14 (s, 3H); resonances from the minor product (84b) could be detected at 6.37 (d, J= 12.0, 1H), 5.86 (d, J= 12.0, 1H), 3.65 (br s, 2H); ¹³C NMR (75 MHz, CDCl₃) (major product, 84a) δ 199.7, 139.3, 137.4, 136.5, 135.4, 132.9, 131.4, 128.5, 127.0, 126.2, 117.0, 92.8, 89.4, 38.2, 29.7, 23.0; resonances from the minor product (84b) could be detected at 49.5, 118.7, 129.8, 133.9, 140.3; HRMS m/e for C₂₁H₁₄Co₂O₆ [M⁺] calcd 479.9454, found 479.9440.

**Hexacarbonyl [μ-(8,9-dehydro-7-methyl-5-(2-methylallyl)-5H-benzo[7]annulene)] dicobalt (85a and 85b)**

A solution of alcohol compound 75 (25.6 mg, 0.056 mmol) in CH₂Cl₂ (10 mL) was subjected to Procedure D using methallyltrimethylsilane (36.1 mg, 0.280 mmol, 5 equiv.) to afford a (6:1) mixture of 85a and 85b (18.25 mg, 66 % total yield 85a + 85b).
IR (KBr) ν<sub>max</sub> 2956, 2922, 2852, 2094, 2055, 2011, 1601, 1463 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) (major product, 85a) δ 7.69 (d, J= 7.5, 1H), 7.29-7.35 (m, 2H), 7.21 (d, J= 7.5, 1H), 5.71 (d, J= 4.5, 1H), 4.86 (s, 1H), 4.77 (s, 1H), 3.23 (apparent t, J= 4.5, 1H), 2.60-2.66 (m, 2H), 2.13 (s, 3H), 1.68 (s, 3H); resonances from the minor product (85b) could be detected at 6.37 (d, J= 12.0, 1H), 5.94 (d, J= 12.0, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (major product, 85a) δ 199.2, 143.1, 139.5, 135.3, 133.1, 131.2, 128.6, 127.1, 126.0, 113.3, 94.5, 89.0, 42.3, 40.9, 23.1, 22.3; HRMS m/e for C<sub>22</sub>H<sub>16</sub>Co<sub>2</sub>O<sub>6</sub> [M<sup>+</sup> - 2CO] calcd 437.9713, found 437.9720.

**Hexacarbonyl[µ-(8,9-dehydro-2-(7-methyl-5H-benzo[7]annulen-5-yl)-1 phenylethanone]dicobalt (86a and 86b)**

A solution of alcohol compound 75 (30.10 mg, 0.066 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was subjected to **Procedure D** using trimethyl((1-phenylvinyl)oxy)silane (76.86 mg, 0.396 mmol, 6 equiv.) to afford a 4:1 mixture of 86a and 86b (estimated yield based on <sup>1</sup>H NMR spectrum is 55 % total yield 86a + 86b). IR (KBr) ν<sub>max</sub> 2923, 2853, 2088, 2050, 2017, 1688, 1449 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) (major product, 86a) δ 8.00 (d, J= 7.5, 2H), 7.15-7.70 (m, 7H), 5.84 (d, J= 5.5, 1H), 4.03 (m, 1H), 3.53 (m, 1H), 3.46 (d, J= 5.0, 1H), 2.12 (s, 3H); resonances from the minor product (86b) could be detected at 6.69
(s, 1H), 6.35 (d, J= 12.0, 1H), 6.29 (d, J= 12.0, 1H), 3.43 (d, J= 5.0, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) (major product, 86a) δ 199.9, 197.9, 140.7, 138.8, 137.4, 137.1, 135.3, 131.7, 130.8, 129.8, 129.2, 128.9, 128.3, 127.7, 127.2, 89.0, 83.3, 44.5, 29.6, 23.3; HRMS m/e for C$_{26}$H$_{16}$Co$_{2}$O$_{7}$[M$^+$ - 6CO] calcd 389.9865, found 389.9844.

**Hexacarbonyl [μ-(8,9-dehydro-1-methyl-3-(7-methyl-5H-benzo[7]annulen-5-yl)-1H-pyrrole)]dicobalt (87)**

![Chemical Structure](image)

A solution of alcohol compound 75 (10.20 mg, 0.0224 mmol) in CH$_2$Cl$_2$ (5 mL) was subjected to Procedure D using N-methylpyrrole (9.085 mg, 0.112 mmol, 5 equiv.) to afford product 78 (9.358 mg, 81 % yield). IR (KBr) $\nu_{\text{max}}$ 3434, 2918, 2090, 2051, 2021, 1641 cm$^{-1}$; $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.71 (dd, J = 1.5, 7.5, 1H), 7.28 (m, 1H), 7.21 (td, J = 1.8, 7.5, 1H), 6.64 (apparent t, J = 2.1, 1H), 6.34 (m, 1H), 6.30 (m, 1H), 6.25 (m, 1H), 6.19 (td, obscured, 1H), 4.38 (d, J = 2.1, 1H), 3.20 (s, 3 H), 2.21 (t, J = 2.8, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ 199.5, 139.7, 137.1, 136.3, 132.8, 132.7, 130.2, 128.7, 127.2, 126.5, 122.0, 108.1, 106.9, 92.8, 89.4, 41.8, 33.5, 22.8; HRMS m/e for C$_{23}$H$_{15}$Co$_{2}$NO$_6$[M$^+$ - 2CO] calcd 462.9665, found 462.9662.
Hexacarbonyl [{(8,9-dehydro-7-methoxy-7-methyl-7H-benzo[7]annulene)}dicobalt (88a and 88b)]

A solution of alcohol compound 75 (17.4 mg, 0.0381 mmol) in 10 mL of (1:1) CH₂Cl₂/MeOH solvent was subjected to Procedure D to afford a 3:1 mixture of 88a and 88b (9.7 mg, 54% total yield 88a + 88b). IR (KBr) v_max 3395, 2924, 2091, 2053, 2020, 1576, 1081 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) (major product, 88a) δ 7.69 (m, 1H), 7.34 (m, 2H), 7.22 (m, 1H), 6.47 (d, J = 12.5, 1H), 6.05 (d, J = 12.5, 1H), 3.42 (s, 3H), 1.49 (s, 3H); resonances from the minor product (88b) could be detected at 7.74-7.79 (m, 2H), 6.61 (d, J = 12.5, 1H), 6.12 (dd, J = 1.0, 5.5, 1H), 4.53 (d, J = 6.0, 1H), 3.21 (s, 3H), 1.50 (s, 3H); ¹³C NMR (75 MHz, CD₂Cl₂) (major product, 88a) δ 199.7, 138.2, 136.0, 132.2, 131.6, 129.6, 128.7, 128.1, 127.7, 88.0, 78.2, 50.9, 28.2; resonances from the minor product (88b) could be detected at 133.3, 128.3, 81.0, 56.3, 29.7; ¹³C NMR (75 MHz, CDCl₃) δ 199.3, 138.1, 136.0, 132.1, 131.6, 131.5, 129.8, 128.8, 128.0, 91.0, 78.4, 51.1, 28.5; resonances from the minor product (88b) could be detected at 133.3, 81.2, 53.4, 29.7; HRMS m/e for C₁₉H₁₂Co₂O₇ [M⁺ - CO] calcd 441.9298, found 441.9299.
REFERENCES


[38] Ding, Y.; Green, J. R. Synlett 2005, 2, 271–274.


PART II

CHAPTER 1: INTRODUCTION

1.1 Colchicine and Allocolchicinoids

1.1.1 (−)-Colchicine

(aR,7S)-Colchicine [(-)-colchicine] (100), (Figure 1.6), the principal alkaloid of the poisonous plant meadow saffron (Colchicum autumnale), is one of the oldest known natural products. It was first isolated in its pure state by Pelletier and Caventou\textsuperscript{1} in the 19\textsuperscript{th} century, but it was not until 1959 when Eschenmoser and co-workers\textsuperscript{2} reported the first successful total synthesis of colchicine. For thousands of years, colchicine has been considered a well-known ancient remedy for treating acute gout, Mediterranean fever, and liver cirrhosis.\textsuperscript{3} In 2009, colchicine became officially approved by FDA and was patented as brand-name "Colcrys".\textsuperscript{4}

![Figure 1.6 Structure of (−)-(aR, 7S) colchicine and its numbering system.](image-url)


Colchicine has gained increased interest due to its antitumor activity; it was shown to be effective in inhibiting the proliferation of cancer cells in mice and inducing tumor regression.\textsuperscript{5-7} Like other tubulin-binding natural products such as taxol and epothilones, colchicine exhibits great pharmaceutical potential and has experienced a renaissance in interest in the last few years.\textsuperscript{8} The mechanism of action of this alkaloid involves binding to the intracellular protein tubulin (which is the main constitutive protein of microtubules), hence disrupting the microtubule-dependent functions in the cell. Due to the essential role of the mitotic spindle in cell division, the microtubule dynamic is still regarded as one of the most relevant drug targets for the treatment of cancer.\textsuperscript{5} Tubulin consists of $\alpha$– and $\beta$– protein subunits which combine to form a heterodimer. These heterodimers polymerize in a helical fashion to form long tubes known as microtubules.\textsuperscript{9} Microtubules are known to be responsible for a multitude of cellular functions including: formation of the cytoskeleton to maintain the cellular shape, transport systems for moving material around inside the cell, and most importantly, the formation of the mitotic spindle during cell division. Colchicine (100) disrupts these activities by binding to the tubulin heterodimer and preventing polymerization to form microtubules. This leads to the termination of the cell cycle in the G2/M phase, ultimately resulting in apoptotic cell death.\textsuperscript{8}

Despite colchicine's intriguing anti-proliferative properties, and following many years of clinical research, its high cytotoxicity in chemotherapy has precluded further development of the drug as a potential antitumor agent. It was found that its therapeutic effects are only observed at toxic or nearly toxic doses, hence rendering it clinically unusable for cancer treatment.\textsuperscript{10} Nevertheless, owing to its unique tricyclic-based
structure, colchicine has became a useful structural reference for the search of other tubulin-targeting antitumor compounds. This prompted researchers to find alternative structural analogues that possess similar structural features to the parent alkaloid but also provide a lower systemic toxicity. \(^5\)

### 1.1.2 Allocolchicinoids

Among several classes of structurally related compounds, allocolchicinoids; or allocolchicines, (the terms will be used interchangeably hereafter), have been identified as promising candidates for further development (Figure 1.7). These are compounds with an altered C-ring, where the tropolone ring has been replaced by an aryl moiety. \(^{11}\)

![Figure 1.7 Numbering system of allocolchicinoids.](image)

There is a myriad of naturally occurring allocolchicinoids (Figure 1.8) such as (–)-allocolchicine (101, isolated from Colchicum cornigerum and Colchicum autumnale), \(^{12}\) (–)-colchibiphenyl (105) and (–)-androhibiphenyl (106) (both from Colchicum ritchii), \(^{13}\) and (–)-jerusalemine (107, derived from Colchicum decaisnei). \(^{14}\) In addition, there are also semi-synthetic congeners such as N-acetylcholcholin (NAC,
and its water-soluble form known as ZD6126 (104), and synthetic ones such as N-acetylcolchinol-O-methylether (103, NCME or NSC 51046).\(^{16}\)

Like colchicine, allocolchicinoids such as allocolchicine (101) and N-acetylcolchinol ZD6126 (104) have also shown anticancer activity owing to their ability to arrest cellular mitosis by inhibiting tubulin polymerization.\(^{17}\) Most importantly, they possess the added feature of owning reduced toxicity compared to colchicine, the parent alkaloid. This has led to an increasing interest in the development of synthetic protocols to provide allocolchicine and its derivatives for biological evaluation.

**Figure 1.8** Common allocolchicinoids.
1.2 Literature Overview and Previous Syntheses

1.2.1 Preparation of Allocolchicine Derivatives from Natural Colchicine

For a long time, allocolchicine derivatives have been typically obtained by synthetic transformation of colchicine (100), which itself is isolated on a commercial scale for treating acute gout. This resulted in limiting the range of structural variation of novel derivatives which possess reduced toxicity. Several approaches have been reported for the partial synthesis of allocolchicine or derivatives. For example, N-acetylcolchicinol (102) has been obtained by treatment of colchicine with 30 % hydrogen peroxide.\textsuperscript{18} Thereafter, an O-methylation under standard conditions provided N-methyl ether acetylcolchicinol (102) with a total yield of 33 %. Alternatively, a different method to derive (102) with a total yield of 40 % over two steps, featured photooxygenation of colchicine followed by triphenylphosphine-assisted rearrangement to give (102).\textsuperscript{19}

![Scheme 1.20 Obtaining allocolchicine by derivatization of colchicine.](image-url)
Another example in this field is the work of Davis and co-workers\textsuperscript{17a} who reported the synthesis of compound ZD6126 (104) by deriving it from natural colchicine (100), using a series of three transformations as shown in (Scheme 1.21).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1_21.png}
\caption{Obtaining compound ZD6126 (104) by derivatization of colchicine.}
\end{figure}

1.2.2 Total Syntheses of \textit{N}-Acetylcolchinol

\textit{N}-Acetylcolchinol, (NAC, 102) is an allocolchicine derivative whose popularity is mainly attributed to its phosphate pro-drug, (ZD6126, 104). Sponsored by the AstraZeneca company, the results of Phase I clinical trials showed that ZD6126 has promising properties as a novel vascular targeting agent for the therapy of solid tumors.\textsuperscript{20}
In fact, it induced tumor cells necrosis in in-vivo mouse models of a number of human cancer cell lines (such as lung, breasts, and ovarian tumor). Unfortunately, a few years later, further studies were ceased in Phase II clinical trials due to cardiotoxicity and critical side effects observed in humans when the required dose of the drug was administered. In view of this pharmaceutical potential, much attention has been dedicated to developing effective ways of obtaining NAC (102) itself.

**Sawyer and Macdonald's Method**

In 1988, Sawyer and Macdonald\(^{21}\) performed the first total synthesis of racemic NAC (102). Using thallium (III) to mediate an intramolecular non-phenolic coupling reaction of the protected 1,3-diarylpropyl acetamide (108), the seven membered B-ring was constructed and the biaryl linkage was created simultaneously.

\[ \text{Scheme 1.22 The first asymmetric synthesis of N-acetylcolchinol, (NAC), by Sawyer and Macdonald.}^{21} \]
Stemming from Sawyer and Macdonald's synthetic strategy, Kocienski and co-workers\textsuperscript{22} developed an asymmetric version of the synthesis of NAC (102). The key distinction was the use of phenyliodonium bis(trifluoroacetate) as an oxidant in the final step.

\textbf{Scheme 1.23} Kocienski's asymmetric synthesis of NAC.\textsuperscript{22}

\textbf{Using Biaryl Reductive Coupling}

In 2007, Leonard \textit{et al.}\textsuperscript{23} reported an alternative synthetic approach to (S)-N-acetylcolchinchinol. The authors devised a modified Ziegler-Ullmann process as the key step in the total synthesis of allocolchicine (102) by allowing the formation of the biaryl product, which in turn was readily cyclized under basic conditions. With the tricyclic core system in hand, the asymmetric hydrogenation of the enamide (109) was achieved using ruthenium catalyst, namely FerroTANE-based catalyst. The retrosynthetic analysis is given in (\textbf{Scheme 1.24}).
1.2.3 Methods for Allocolchicine Synthesis

Wulff's Method

The first total synthesis of (−)-(7S)-allocolchicine (101) was performed in 2003 by Wulff's group at the University of Michigan, by employing Diels-Alder reaction for constructing the C-ring around the A-B-framework (Scheme 1.25). The key step was employing the bicyclic diene (110) to undergo a regioselective Diels-Alder reaction in the presence of methyl propiolate as dienophile. The diene was first protected with TBDMS group which the authors propose as a necessary step not only for alcohol protection, but also as a major player in regiocontrol during the DA cycloaddition reaction. To complete the synthesis of dibenzoheptanone compound, a sequence of deprotection and oxidation steps were conducted, which gave (111), which in turn was asymmetrically reduced with (+)-TarB-NO₂/LiBH₄. Inversion of stereochemistry at C7 with concomitant introduction
of the requisite nitrogen functionality was achieved by Mitsunobu reaction with \( \text{Zn(N}_3\text{)}_2\text{-2Py} \) as azide source, generating the desired natural \((-\text)-\text{allocolchicine (101)}\).

![Chemical structures](image)

**Scheme 1.25** Wulff's total synthesis of \((-\text)-\text{allocolchicine (101)}\).\(^{24}\)

**Fagnou and Leblanc's Method**

In 2005, Fagnou and Leblanc\(^ {25}\) reported an enantioselective formal synthesis of \((-\text)-\text{allocolchicine (101)}\). Their novel approach involved employing a palladium-catalyzed intramolecular direct arylation of aryl chloride (112) to forge the key A-C biaryl carbon-carbon bond needed to the construct seven-membered ring (i.e. B ring) of allocolchicine's tricyclic core (113). Deprotection of the OMOM group followed by employing Wulff's method to introduce the acetamide group at C7 completed the formal total synthesis of the natural product (101).
Unlike Wulff who established the chiral center in the allocolchicine after constructing the tricyclic core, Fagnou's strategy was to introduce the molecule's chirality in the early stages of the synthesis before forming the tricyclic framework. This method presented itself as a new and unique strategy in the asymmetric allocolchicinoid synthetic work.

1.2.4 Syntheses of NCME or NSC 51046

Several total syntheses of allocolchicine have been reported in literature, however, there are considerably fewer methods for synthesis of NCME (103). In fact, this allocolchicinoid possesses tubulin inhibition activity that is greater than that of colchicine itself, yet researchers have only recently started to show some synthetic interest.
DeShong Synthesis

In 2006, DeShong's group\(^\text{27}\) from the University of Maryland published a novel and versatile approach to the allocolchicine carbocyclic skeleton. First, the A-C biaryl ring system was accessed using a palladium catalyzed siloxane coupling method; this was followed by ring expansion reaction of substituted MOM-protected phenanthrol (114) as the key step for the construction of tricyclic skeleton of N-acetylcolchinol-O-methyl ether. The authors implemented this strategy to accomplish the first total synthesis of racemic NCME (103).

\[\text{rac-103} \rightarrow \text{MeO} \quad \text{MeO} \quad \text{OMOM} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \rightarrow \text{MeO} \quad \text{MeO} \quad \text{CHO} \quad \text{MeO} \quad \text{OMe} \quad \text{OMe} \]

\[\quad \rightarrow \quad \text{MeO} \quad \text{MeO} \quad \text{CHO} \quad \text{MeO} \quad \text{OMe} \quad \text{Br} \rightarrow \text{Si(OEt)}_3 \quad \text{OMe} \]

Scheme 1.27 Retrosynthesis of NCME (\textit{rac-103}) by DeShong and Seganish.\(^\text{27}\)
Green's Synthesis of NCME and iso-NSC 51046 via Nicholas Reaction Chemistry

Central to the Green group's research interests is the synthesis of 6,7,6-containing compounds, primarily by utilizing Nicholas reaction chemistry for the construction of the seven-membered ring core. From previous research performed by Green's group, it was evident that intramolecular Nicholas reactions constitute a reliable approach towards the synthesis of dibenzocycloheptanone, ultimately leading to achieving an enantioselective synthesis of N-acetyl-O-methylcolchinol (NSC 51046 or NCME, 103).

In the synthesis of Djurdjevic and Green28 (Scheme 1.28), the biaryl propargyl acetate hexacarboxyldicobalt complex (115a) underwent a Lewis acid intramolecular Nicholas reaction to afford dibenzocycloheptadienyne–Co₂(CO)₆ complex (116a). This latter compound was in turn readily reductively decomplexed by hydrosilylation-acidic desilylation method, followed by hydroboration and oxidation reactions to afford the C-7 ketone (117). Compound (117a) was subsequently subjected to a sequence of transformations that were analogous to those previously employed by Wulff24 in his asymmetric total synthesis of (103).
In addition, this approach was further extended to prepare a novel allocolchicine analogue (118), namely (S)-3,8,9,10-tetramethoxy (A-ring) regioisomer of NSC 51046 (103). Compound (118) will be referred to as *iso*-NSC 51046 hereafter, and will be presented in more detail in **CHAPTER 2** (*vide infra*).
1.3 Modified Allocolchicinoids

Besides the synthesis of conventional allocolchicine derivatives, novel targets that include allocolchicinoids analogues with modified B-, C-, and B,C-ring systems have also been synthesized and tested for biological activity. Some relevant selected examples will be discussed in the following section.

Boyer and Hanna have developed a synthetic strategy which was based on a conceptually similar approach to Wulff’s work in synthesizing allocolchicine derivatives. Using [4+2]–cycloaddition, structural analogues of allocolchicine were obtained with an altered position of the ester group in the C-ring, namely at the C-10 and C-11 positions (Figure 1.9; 119a/b and 120, respectively). In their most recent work, Boyer's group were involved in the synthesis of allocolchicinoids derivatives with B- and C-ring variations via sequential enyne-metathesis/Diels-Alder reactions. These compounds were evaluated for their tubulin assembly inhibition effects. Some of the noteworthy results of these evaluations revealed that allocolchicine (119a) with methyl ester at C-10 had a comparable biological activity in comparison to natural colchicine alkaloid. However, complete activity loss was observed for allocolchicine (120) with a methyl ester at C-11 of the C-ring.

![Figure 1.9](image_url)  
Figure 1.9 Examples of C-ring modified allocolchicines.
Seitz and co-workers\textsuperscript{32} have synthesized two series of novel B-ring modified allocolchicinoid congeners that mimic the structure of (S)-\textit{N}-acetylcolchinol-\textit{O}-methyl ether (103, NCME). The first series of NCME variants (121) included a nitrogen containing eight membered B-ring, whereas in the second series (122), the seven-membered B-ring of NCME was modified by annulation with a heterocyclic ring system. These novel heterocyclic-fused seven membered B-ring allocolchicinoids were found to be highly potent antimicrotubule agents.

\textbf{Figure 1.10} Examples of B-ring modified allocolchicines.

Recently, Fedorov and co-workers\textsuperscript{33-35} reported the synthesis and biological assessment of a group of heterocyclic allocolchicine variants in which the C-ring of the parent allocolchicine is fused to an indole, furan-, or pyrrolo-derived core. Selected examples are shown in (\textbf{Figure 1.11}).
**Figure 1.11** Heterocyclic allocolchicinoids.

The indole-derived allocolchicine analogues (123a) and (123b) are considered the first examples of heteroarene-based allocolchicines. Biological evaluation studies revealed that these individual derivatives exhibited pronounced anti-proliferative activity, and were also capable of inducing apoptosis in different lymphoma cells. Although their unspecific cytotoxicity was found to be low, they were effective in very small nanomolar concentration (and even in sub-nanomolar levels).

In their most recent work, Fedorov *et al.* also reported the synthesis of pyrrolo-allocolchicinoids of type (124), which are in fact constitutional isomers of (123a) and (123b). They, too, possessed anti-proliferative and pro-apoptotic activities which were very comparable to that of the indole-based analogues (123a/b). The authors also extended their studies where they reported a semi-synthetic route to furan-based allocolchicinoids. After preparing a set of furan-based allocolchicinoids of type (125), in vitro studies showed that the most potent compound is when R = CH$_2$-OH, where it was found to be a more effective tubulin inhibitor than colchicine.
1.4 Arene-Enone Conjugate Addition Reactions

In addition to allocolchicines derivatives, the 6,7-ring framework is a commonly encountered motif in many other natural products. Amongst the remarkable number of approaches available in literature, conjugate addition chemistry lends itself as a valuable and versatile means to access 6,7-bicyclic systems. Several methodologies have been developed in which activated arenes were used as Michael donors in conjugate addition reactions. Of note, the work of Majetich\textsuperscript{36} provides excellent and relevant examples that fit very well in this topic.

The Majetich group has elaborately employed Lewis acid mediated cycloalkylation reactions in the synthesis of natural products based on 6,7-ring systems. Their debut work\textsuperscript{36a} in this area was reported in 1993, where they prepared the [6-7-6] tricyclic compounds via Lewis acid catalyzed intramolecular alkylation of electron-rich arenes with conjugated dienones (Scheme 1.29). Two series of arene-dienones were employed (2-arene-dienones and 4-arene-dienones), and they were both shown to be effective in providing the corresponding 6,7,6-fused tricycles.
Scheme 1.29 Construction of 6,7,6-tricyclic compounds via Lewis acid mediated cycloalkylation by Majetich et al.\textsuperscript{36a}

These results prompted Majetich to apply the aforementioned approach in synthesizing a significant number of natural products, such as (±)-barbatusol, (±)-pisiferin, (±)-deoxofaveline, (±)-xochitlolone, and (±)-faveline.\textsuperscript{36b} Despite the versatility of Majetich’s Friedel-Crafts alkylation method, the published cases to date required either stoichiometric or super-stoichiometric amounts of Lewis acid; in addition, the 6,7,6-systems of the allocolchicines derivatives have not been among the reported synthetic targets.

Another relevant example in literature was provided by the Chen group.\textsuperscript{37} In their recent work, Chen et al. reported the synthesis of dibenzocycloheptenones, the core structure of allocolchicine, via a stoichiometric ICl–mediated electrophilic iodocyclization.
1.5 Origin of Current Project and Proposed Research

The search for novel allocolchicinoids with improved antitumor properties remains an ongoing quest for synthetic chemists. With the exception of our group's previous work\textsuperscript{28} (Djurđević and Green's synthesis), allocolchicinoid analogues with a modified A-ring are non-existent in literature. As stated earlier, Green's approach using Nicholas reaction chemistry was successfully implemented in preparing two allocolchicinoids derivatives (NSC 51046 and \textit{iso}-NSC 51046), whose biological properties were underexplored for the most part.

Dr. Siyaram Pandey, a prominent biochemist in our Department of Chemistry and Biochemistry, became interested in studying the biological properties (namely the anticancerous activity) of these two closely related allocolchicine derivatives. In a recent publication, Pandey\textsuperscript{38} and his group have reported the detailed findings of their study of these compounds. NSC 51046 was found to be non-selective as it induced apoptosis in both BxPC-3 and PANC-1 pancreatic cancer cells and in normal human fibroblasts. Interestingly, it was found that \textit{iso}-NSC 51046 was able to induce pro-death autophagy in these pancreatic cancer cells and E6-1 leukemia cells but not in normal human fibroblasts.

Unlike colchicine and NSC 51046, \textit{iso}-NSC 51046 did not appear to affect tubulin polymerization, indicating that it has a different molecular target. It also caused increased reactive oxygen species (ROS) production in mitochondria isolated from pancreatic cancer cells. Furthermore, in vivo studies revealed that it was well tolerated in mice.\textsuperscript{38} These findings suggested that a small change in the structure of the parent allocolchicine
derivative can presumably change the mechanism of action and improve selectivity. This may also lead to better selective treatments in cancer therapy.

Despite the significance of the aforementioned Nicholas reaction synthetic approach, there were two main drawbacks in using this method, particularly if the synthesis was carried on a larger scale. The first issue is attributed to the use of excess (greater than stoichiometric) amounts of dicobalt octacarbonyl reagent, which may pose an environmental concern if the synthesis was scaled-up. The other shortcoming was the length of the synthesis. The overall total synthesis was carried out in 11 steps and afforded the allocolchicine in an overall yield of 14%. Specifically, there were a total of 8 steps required to arrive at the dibenzocycloheptanone, followed by an additional 3 steps to furnish the end product.

Conjugate addition reactions (both intermolecular and intramolecular) are amongst the most efficient tools for C-C formation in organic synthesis. However, in most cases strong Brønsted or Lewis acid reagents are required in stoichiometric or excess amounts, and many of them require the use of rare (hence cost ineffective) metals. Herein we report the construction of tricyclic framework of various allocolchicinoids via intramolecular Michael-type Friedel-Crafts alkylation to form the seven-membered ring. This process requires an appropriate Lewis acid that's capable of catalytic turnover.

On the basis of our group's continuing interest in constructing 6-7-6 tricyclic core systems, and given the biological significance of allocolchicine analogues that were alluded to earlier, we envisioned that a short, atom-economical, catalytic, and overall more efficient synthesis of the relevant dibenzocycloheptanone (en route to iso-NSC 51046 synthesis and other A-ring modified allocolchicines) would be worth investigating.
CHAPTER 2: RESULTS AND DISCUSSION

In continuation of our group's interest in the synthesis of seven-membered ring containing compounds, herein we report a short and efficient synthesis of allocolchicine derivatives under mild conditions. From a synthetic perspective, the dibenzo-cycloheptanone represents a key intermediate en route to numerous allocolchicine analogues. Having stated that, the key step in this synthetic approach can be viewed as the construction of the seven membered B-ring using an appropriate catalyst. The methodology will also be expanded to other related substrates with variable substituents.

2.1 General Synthetic Strategy

Multiple strategies to access the tricyclic fused ring system of allocolchicinoids analogues have been developed to date. To access the desired dibenzocycloheptanone, the synthetic strategy depicted in (Scheme 2.9) was investigated. The synthetic plan first features a facile preparation of the biarylcarboxaldehyde by means of Suzuki-Miyaura coupling chemistry. Conversion of the biarylcarboxaldehyde into the corresponding alkenones or alkynones could be accomplished by nucleophilic addition of the proper Grignard reagent followed by alcohol oxidation to the corresponding ketone. At this point, closure of the cycloheptane (or cycloheptene) would be assessed by screening several Lewis acids, primarily to seek a Lewis acid reagent that can effectively catalyze the ring closure process using a minimum catalytic loading. Once obtained, the cycloheptanone can be readily converted to the corresponding allocolchicine, such as allocolchicine iso-NSC 51046 (118) shown in (Scheme 2.9) as a general example, by implementing a series of previously reported protocols.
Scheme 2.9 Proposed retrosynthetic approach to dibenzoheptanone and ultimately to allocolchicine iso-NSC 51046 (118).

From a synthetic point of view, two plausible routes can provide access to the intended dibenzocycloheptanone (117b) as depicted in (Scheme 2.10). The synthetic scheme following (Route A) involves obtaining the biaryl compound (128) which may be further derivatized to get the alkynone cyclization precursor (130). Catalyzed by the proper Lewis or Brønsted acid, it was envisioned that the ring closure step could potentially take place to yield the dibenzocycloheptenone B-ring (131). This step would be followed by subsequent reduction of the C=C bond which in turn forms the intended dibenzocycloheptanone species (117b). Alternatively, (Route B) was also proposed as another means of reaching the cycloheptanone. Through the steps indicated in (Scheme
2.10), the biaryl compound could be converted to the corresponding enone substrate (133). The next step would involve subjecting the acyclic enone to the proper catalytic condition (Lewis or Brønsted acid) to directly furnish the intended cycloheptanone (117b). If completed successfully, this would constitute the tricyclic core of a group of the allocolchicinoids (which will be discussed later in this section).

Scheme 2.10 Two proposed routes to construct the tricyclic core of allocolchicinoids via intramolecular conjugate addition reaction.

Our initial proposal was to obtain the desired tricyclic framework via ring closure of corresponding alkynone (128). To access the cyclization precursor, the first synthetic task involved obtaining a biaryl carboxaldehyde by utilizing the Suzuki-Miyaura coupling reaction. This specific step was duplicated from the previous allocolchicine synthesis reported by our group (Djurđević and Green).^{28} Using the Fürstner^{39} conditions, the
Suzuki cross-coupling reaction of 5-methoxy-2-bromobenzaldehyde (126) and 3,4,5-trimethoxyphenylboronic acid (127) furnished the desired biaryl product (128) in 88 % yield (Scheme 2.11).

Scheme 2.11 Suzuki-Miyuara cross-coupling reaction.

To proceed further with the preparation of the precursor required for (Route A) synthetic pathway, the biarylcarboxaldehyde substrate (128) was then subjected to reaction with ethynylmagnesium bromide to afford the corresponding propargylic alcohol (129) in 97 % yield. The latter compound was converted to the corresponding ketone using MnO$_2$ oxidation to attain the intended acyclic alkynone (130) in 57 % yield (Scheme 2.12).

Scheme 2.12 Preparation of alkynone cyclization precursor (Route A).
With substrate (130) in hand, a number of protocols were investigated to carry out the key conjugate addition reaction towards the construction of the seven membered ring. To achieve this, a Lewis acid is necessary to catalyze the cyclization, namely the 7-endo-dig process. The first attempt to induce the cyclization reaction was using "carbophilic" or "π-electrophilic" Lewis acid.

The use of gold (I) and (III) salts has dramatically increased in organic syntheses due to their unique Lewis acidic nature. Specifically, gold (III) compounds have been used as potential Lewis acids by virtue of their ability to activate π–bonds under extremely mild conditions. In light of the versatility and fascinating reactivity of gold catalysis in modern organic transformations, we chose AuCl₃ as the first catalyst. The soft, carbophilic Au(III) Lewis acid didn't prove to be effective in promoting cyclization of the alkynone. Upon adding 10 mol % loading of AuCl₃, an immediate degradation of the starting material was evident. A similar observation was noted when using GaCl₃, which is known to be as both a powerful σ– and π–Lewis acid, under similar reaction conditions (Table 2.5).

Table 2.5 Attempts to induce the cyclization using alkynone as substrate.

<table>
<thead>
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<th>Lewis acid</th>
<th>Catalyst loading</th>
<th>Conditions</th>
<th>Observations</th>
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</thead>
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<td>AuCl₃</td>
<td>10 mol %</td>
<td>CH₂Cl₂, rt</td>
<td>immediate decomposition</td>
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<tr>
<td>GaCl₃</td>
<td>10 mol %</td>
<td>CH₂Cl₂, rt</td>
<td>immediate decomposition</td>
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</tbody>
</table>
Faced with the inability to prepare the desired cycloheptanone via (Route A), our attention was turned to the alternative approach (Route B), starting with the same starting materials (126 and 127), and following an analogous strategy to assemble of the biaryl unit via the Suzuki cross-coupling reaction. The corresponding allylic alcohol (132) was generated as a result of the nucleophilic attack of a vinyl Grignard reagent on the relatively electron deficient carbon of the aldehyde (128). Subsequently, the allylic alcohol was subjected to oxidation to give the enone (133) which is the intended precursor for the cyclization reaction (Scheme 2.13).

Scheme 2.13 Preparation of alkenone cyclization precursor (Route B).

2.2 Lewis Acid Alkylation of Electron-Rich Arenes

In the given enone (133), the electron-rich trioxygenated A-ring (nucleophilic species) and the α, β-unsaturated ketone (Michael acceptor, i.e. electrophile) are the two components of the conjugate addition process. To achieve the B-ring closure, the cyclization can proceed only if activated by an appropriate Lewis acid as suggested in the proposed mechanism (Scheme 2.14). In view of the availability of a wide array of Lewis
acidic metal reagents, it was deemed logical to assess two types of Lewis acids: carbophilic (or π-selective) and oxophilic.

![Chemical structure](image)

**Scheme 2.14** Proposed cyclization mechanism.

Attempts at cyclization reactions of (133) by the use of π-selective Lewis acids met with limited success (*Table 2.6*). The use of 10 mol % loading of gold (III) chloride (AuCl₃) enabled the complete consumption of the starting material, however it led to a poor yield (31 %) and extensive baseline material. On the other hand, treating the same substrate with the carbophilic gold (I) Lewis acid (AuCl(SMe)₂) in the presence of AgBF₄ gave similar results. It's worth noting that in the absence of Au(I), the reaction progress appeared to be unaffected, which suggested that the Ag(I) was in fact the active catalytic species in the cyclization reaction. Other metal salts were also explored, and they showed somewhat limited effectiveness in promoting the conjugate addition reaction. Both FeCl₃
and InCl$_3$ gave only a small amount of (117b). Furthermore, Sc(OTf)$_3$, an oxophilic Lewis acid, led to the complete decomposition of the substrate once added to the reaction mixture. Likewise, PtCl$_4$ also resulted in unproductive decomposition when 30 mol % loading was introduced to the substrate. Conversely, using SnCl$_4$ gave relatively respectable yields (based on the percent conversion) but it lacked the catalytic turnover which rendered the reagent less useful in our studies.

**Table 2.6** Screening Lewis acids as catalysts for conjugate addition reaction.

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Catalytic loading</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AuCl$_3$</td>
<td>10 mol %</td>
<td>acetonitrile [0.003 M], rt, 3h</td>
<td>31</td>
</tr>
<tr>
<td>AuCl(SMe)$_2$+</td>
<td>5 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt, 24h</td>
<td>23</td>
</tr>
<tr>
<td>AgBF$_4$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AgBF$_4$</td>
<td>5 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt, 24h</td>
<td>25</td>
</tr>
<tr>
<td>FeCl$_3$</td>
<td>45 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt, 24h</td>
<td>15</td>
</tr>
<tr>
<td>InCl$_3$</td>
<td>10 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt, 24h</td>
<td>11</td>
</tr>
<tr>
<td>SnCl$_4$</td>
<td>50 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt, 3h</td>
<td>51</td>
</tr>
<tr>
<td>GaCl$_3$</td>
<td>10 mol %</td>
<td>CH$_2$Cl$_2$ [0.002 M], rt, 3h</td>
<td>52</td>
</tr>
<tr>
<td>Sc(OTf)$_3$</td>
<td>10 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt</td>
<td>(a)</td>
</tr>
<tr>
<td>PtCl$_4$</td>
<td>30 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], rt</td>
<td>(a)</td>
</tr>
</tbody>
</table>

*Immediate decomposition of starting material.*
Given the limited success achieving a truly catalytic cyclization reaction, a test reaction was run using the most conventional and commonly used Lewis acid in the Green lab, BF$_3$-OEt$_2$. There has been wide success in previous projects in our group with employing boron trifluoride to mediate the formation of 7-membered rings (albeit being used in stoichiometric amounts). In view of these facts, the first cyclization reaction was conducted using 1.5 equiv. of BF$_3$-OEt$_2$ to a dichloromethane solution of enone. To our surprise, the reaction furnished the intended cyclized product in good yield (75%). This outcome encouraged additional experiments with lower loadings of the Lewis acid to bring the cyclization reaction to the catalytic domain.

Table 2.7 Optimization of cyclization reaction catalyzed by BF$_3$-OEt$_2$.

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Catalyst loading</th>
<th>Conditions</th>
<th>Yield/ conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF$_3$-OEt$_2$</td>
<td>1.5 equiv</td>
<td>CH$_2$Cl$_2$ [0.005 M], 24h, 0°C-rt</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>50 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], 24h, 0°C-rt</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>25 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], 12h, 0°C-rt</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>10 mol %</td>
<td>CH$_2$Cl$_2$ [0.005 M], 3h, 0°C-rt</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>10 mol %</td>
<td>CH$_2$Cl$_2$ [0.002 M], 3h, 0°C-rt</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>5 mol %</td>
<td>CH$_2$Cl$_2$ [0.002 M], 4h, 0°C-rt</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>3 mol %</td>
<td>CH$_2$Cl$_2$ [0.002 M], 24h, 0°C-rt</td>
<td>90% conversion$^{(a)}$; 65% yield</td>
</tr>
</tbody>
</table>

$^{(a)}$ Incomplete conversion.
Indeed, the results were comparably successful even when using sub-stoichiometric amount of Lewis acid, where good yields were maintained at 25 mol % and only slightly compromised at 10 mol % loadings (Table 2.7). To further validate our original proposal in developing an atom-economic and "genuinely" catalytic synthesis, the catalyst loading was reduced further. Upon exposure to 5 mol % of BF$_3$-OEt$_2$ catalyst, complete conversion from (133) to (117b) was realized with an isolated yield of 75 %. Lower amounts of the catalyst resulted in incomplete conversion and thus it was determined that the lower limit of the BF$_3$-OEt$_2$ was 5 mol %. In addition, the concentration of the reaction mixture was noted to play a significant role. In fact, the optimal yield was obtained when running the reaction under high dilution conditions (0.0002 M) in the presence of the Lewis acid. It's also worth noting that the reaction outcome may be slightly jeopardized if the reaction time was longer than 4 hours, possibly due to gradual product decomposition that could be taking place.

### 2.2.1 Reaction Scope

Having established the optimized conditions of the cycloalkylation reaction, the next stage was to explore the reaction's scope and to investigate substituent effects on the ring closure step in particular. Using Suzuki coupling reaction, a series of biaryl compounds were readily prepared (135a-g) in yields ranging from 74 to 94 %. The results are summarized in (Table 2.8).
Table 2.8  Suzuki-Miyaura cross-coupling reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Product/ Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>135a/ 86 %</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CO_2Me</td>
<td>H</td>
<td>135b/ 81 %</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>135c/ 94 %</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>135d/ 91 %</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>135e/ 79 %</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>-OCH_2O-</td>
<td></td>
<td>135f/ 86 %</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>135g/ (45 %)^a</td>
</tr>
</tbody>
</table>

^a Yield in parentheses is based on recovered starting material (134g).

In accordance with the reaction sequence provided earlier in (Scheme 2.13), the addition of vinylmagnesium bromide to the corresponding aldehydes (135a-g) readily afforded the allylic alcohol compounds (136a-g). The reaction conditions were analogous in all substrates and a summary of the formed compounds is given in (Table 2.9).
Table 2.9 Synthesis of allylic alcohol compounds (136a-g)

The resultant allylic alcohols were subsequently oxidized to the corresponding ketones. Some substrates were oxidized with manganese (IV) oxide (MnO₂) as a mild oxidant (entries 2, 4, and 7; Table 2.10). In other cases, oxidation with MnO₂ was less successful, with low yields being obtained; hence we resorted to other choices of oxidants, namely tetrapropylammonium perruthenate (TPAP) in combination with N-methylmorpholine N-oxide (NMO), to give the corresponding enones in respectable yields (entries 1, 3, 5, and 6; Table 2.10).
Table 2.10 Oxidation reaction to form acyclic enones.

![Reaction diagram]

where [O] = TPAP (cat), NMO or MnO₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>[O]</th>
<th>Product/ Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>TPAP (cat.), NMO</td>
<td>137a/ 80 %</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CO₂Me</td>
<td>H</td>
<td>MnO₂</td>
<td>137b/ 90 %</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>TPAP (cat.), NMO</td>
<td>137c/ 66 %</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>MnO₂</td>
<td>137d/ 70 (81 %) (^a)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>TPAP (cat.), NMO</td>
<td>137e/ 70%</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>-OCH₂O-</td>
<td>TPAP (cat.), NMO</td>
<td>137f/ 68 %</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>MnO₂</td>
<td>137g/ 95 %</td>
</tr>
</tbody>
</table>

\(^a\) Yields in parentheses are based on recovered starting material (136d).

After preparing a series of various enones (137a-g), these substrates were submitted to the previously optimized conditions: BF₃·OEt₂ (5 mol %) and 0.002 M concentration or closely related conditions. The results are summarized in (Table 2.11).
Table 2.11 Cyclization of enones using BF$_3$-OEt$_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>Conditions</th>
<th>Product/Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH$_2$Cl$_2$ [0.002 M], 12h, 0°C-rt</td>
<td>138a/ 81 %</td>
</tr>
<tr>
<td>2$^{(a)}$</td>
<td>H</td>
<td>CO$_2$Me</td>
<td>H</td>
<td>CH$_2$Cl$_2$ [0.002 M], 48h, 0°C-rt</td>
<td>138b/ 68 %</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>CH$_2$Cl$_2$ [0.001 M], 48h, 0°C-rt</td>
<td>138c/ 68 %</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>CH$_2$Cl$_2$ [0.002 M], 48h, 0°C-rt</td>
<td>138d/ 81 %</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>CH$_2$Cl$_2$ [0.001 M], 12h, 0°C-rt</td>
<td>138e/ 70 %</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>-OCH$_2$O-</td>
<td></td>
<td>CH$_2$Cl$_2$ [0.002 M], 72h, 0°C-rt</td>
<td>138f/ 63 %</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>CH$_2$Cl$_2$</td>
<td>(b)</td>
</tr>
</tbody>
</table>

$^a$ Reaction complete using 10 mol% of BF$_3$-OEt$_2$

$^b$ No reaction. Immediate decomposition of the reaction mixture

The presence of either electron donating or electron withdrawing substituents on the C-ring was well tolerated. Benzyloxy-substituted (137d) afforded (138d, 81 % yield, 48 h, Table 2.11, entry 4). The methylenedioxy-substituted (137f) successfully converted into (138f, 63 %, 72 h, Table 2.11, entry 6). Among the most interesting cases was the
ester-substituted substrate. The acyclic alkenone (137b) was successfully cyclized to the corresponding benzosuberone (138b). Even though an incomplete consumption of (137b) at the 5 mol % loading of BF₃-OEt₂ was observed, complete conversion to the intended product was realized by doubling the amount of BF₃-OEt₂ to 10 mol % (138b, 68 %, 48 h, Table 2.11, entry 2). The significance of this particular substrate is mainly owing to the fact that (138b) can be regarded as the precursor of the A-ring isomer of the natural occurring alkaloid (−)-allocolchicine (101). Furthermore, by using 5 mol % of BF₃-OEt₂, the fluorinated product (138c) was obtained in 47 % yield in 48 h at 0.002 M, but the yields were improved when the concentration was dropped to 0.001 M (138c, 68%, 48 h, Table 2.11, entry 3). Placing a methoxy substituent in C-5 position of the C-ring did not adversely affect the yields of cyclization either. The cyclization product was readily obtained in 70 % yield when subjected to 5 mol % of BF₃-OEt₂ (138e, Table 2.11, entry 5). Also, among the targeted examples was a substrate devoid of C-ring substitution (137a, Table 2.11, entry 1). Optimal yields of the cyclized compound (138a) were realized in 81 % yield using 5 mol % BF₃-OEt₂, and complete conversion required relatively long reaction time (12 h). Regarding the last entry (137g, entry 7, Table 2.11), it can be observed that the presence of a methoxy substituent in R¹ position led to the deactivation of the 7-endo-trig cyclization process. Despite attempting this reaction multiple times, it was evident that the starting material underwent complete degradation instantly once the Lewis acid was added. This was also reinforced by the appearance of deep dark purple color which is usually indicative of decomposition.
2.3 Heterocyclic Analogues

Given the recent prominence of heterocyclic-based allocolchicinoids as potential antitumor agents\textsuperscript{32-35} (by mimicking the colchicine mode of action), we wanted to prove the viability of our methodology in accessing heterocyclic analogues of cycloheptanones. Following our established approach, the preparation of thiophene-based cycloheptanone was initiated by assembling the 3,4,5-trimethoxyphenylboronic acid (127) and 2-bromo-3-thiophenecarboxaldehyde (134h) to yield the heterocyclic biaryl system (135h) in 40 % yield. In accordance with the vinyl Grignard addition protocols applied earlier with other substrates, the allylic alcohol compound (136h) was obtained in 85 % yield, which was subsequently oxidized with MnO\textsubscript{2} to give the thiophene-based enone in 71 % yield (Scheme 2.15).

Scheme 2.15 Preparation of C-ring thiophene-based cycloheptanone (138h).
Lewis acid mediated cyclization of (137h) was first attempted using BF$_3$-OEt$_2$. The thiophene-based enone was fully converted to the cyclic compound (138g) in the presence of a full equivalent of the Lewis acid (61 % yield). However, BF$_3$-OEt$_2$ proved to be not effective in catalytic loadings (incomplete conversion) as shown in (Table 2.12). Fortunately, GaCl$_3$ provided a decent catalytic turnover in the 7-endo-trig cyclization process. After adding 0.25 equivalent of Ga(III), the reaction proceeded smoothly and the product was obtained in 70 % yield.

**Table 2.12** Screening Lewis acids for cyclization of (137h) to (138g).

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Catalytic loading</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF$_3$-OEt$_2$</td>
<td>20 mol %</td>
<td>CH$_2$Cl$_2$, 12h</td>
<td>incomplete conversion</td>
</tr>
<tr>
<td>BF$_3$-OEt$_2$</td>
<td>40 mol %</td>
<td>CH$_2$Cl$_2$, 12h</td>
<td>incomplete conversion</td>
</tr>
<tr>
<td>BF$_3$-OEt$_2$</td>
<td>1 equiv.</td>
<td>CH$_2$Cl$_2$, 4h</td>
<td>61</td>
</tr>
<tr>
<td>GaCl$_3$</td>
<td>25 mol %</td>
<td>CH$_2$Cl$_2$, 24h</td>
<td>70</td>
</tr>
</tbody>
</table>

2.4 Completion of Enantioselective Synthesis of Allocolchicines

After successfully arriving at the intended cycloheptanone, there remained 3 steps to complete the synthesis of allocolchicine compound iso-NSC 5146 (118). As shown previously (Scheme 1.28), these synthetic steps had already been successfully established in the previous work of Green.$^{28}$ Hence, the preparation of (117b) constitutes a formal synthesis of (118). In view of the success of using Wulff's$^{24}$ approach in our group's
previous synthesis of allocolchicinoids, it was logical to adopt a similar approach in this current work. The asymmetric reduction of the ketone was achieved using Singaram\textsuperscript{44} and co-workers' method where the substrate was exposed to reducing agent \( \text{LiBH}_4 \) in the presence of 2-(3-nitrophenyl)-1,3,2-dioxaborolane-4\( R,5\)\( R \)-dicarboxylic acid [(+)\textendash\textsuperscript{TarB-NO}_2, 139] as a chiral Lewis acid (Scheme 2.16). The reduction of (117\textsuperscript{b}) under these conditions proceeded with an excellent yield (97\%) and high enantioselectivity (99 \% ee), as determined by means of HPLC with a chiral stationary phase. To incorporate the correct stereochemistry of the molecule, the chirality at C-7 of (140) was inverted (\( R \)- to \( S \)-) using a Mitsunobu reaction; the nucleophilic displacement of the hydroxy group by an azide (\( \text{Zn(N}_3\text{)}_2 \)-2Py as azide source) was crucial to introduce the nitrogen function needed in the molecule. The reaction proceeded smoothly giving (141) in 77 \% yield. Subsequently, the reduction of (141) to the corresponding amine was achieved via hydrogenolysis using Lindlar's catalyst. This step was followed promptly by acetylation of the amine to afford the acetamide functionality at C-7 of the intended allocolchicine. The enantiomeric purity of (118) was measured to be 98\% ee. After a single recrystallization, the purified compound was obtained, and it showed identical physical properties to the previously synthesized allocolchicine (mp, spectroscopic data).\textsuperscript{28}
Scheme 2.16 Completion of enantioselective formal synthesis of \textit{iso}-NSC 51046 (118).

Two other dibenzocycloheptanones, unsubstituted (138a) and ester-substituted C-ring (138b) substrates, were chosen for further derivatization, where they were subjected to analogous conditions to arrive at the corresponding allocolchicine (Scheme 2.17). Singaram's method\textsuperscript{44} worked smoothly and the benzylic chiral alcohols were obtained in 98\% (142a) and 80\% (142b) yield and 99\% ee for both (142a) and (142b). The subsequent step (Mitsunobu reaction) proved to be effective in giving the azide containing compounds in 72\% (143a) and 77\% (143b) yield. Subjecting the formed azides to hydrogenolysis using Lindlar's catalyst followed by acetylation gave the corresponding allocolchicines (71\% yield of (144) and 57\% yield of (145)) in high enantiomeric excess (98\% ee for (144) and 99\% ee for (145)). Since these allocolchicine
derivatives have not been reported in literature previously, this work constitutes total syntheses of two novel allocolchicines analogues of the iso-NSC 51046 series.

\[ R = H, \textbf{138a} \quad R = \text{CO}_2\text{Me}, \textbf{138b} \]

\[ R = H, \textbf{142a} \quad R = \text{CO}_2\text{Me}, \textbf{142b} \quad (98\%, 99\% \text{ ee}) \]

\[ R = H, \textbf{143a} \quad R = \text{CO}_2\text{Me}, \textbf{143b} \quad (72\%) \]

\[ R = H, \textbf{144} \quad (71\%, 98\% \text{ ee}) \]

\[ R = \text{CO}_2\text{Me}, \textbf{145} \quad (57\%, 99\% \text{ ee}) \]

**Scheme 2.17** Completion of enantioselective total synthesis of allocolchicinoids (144) and (145).
2.5 Targeting Dibenzocycloheptanone Precursor en route to NSC 51046 Synthesis

Encouraged by the results obtained in synthesis of iso-NSC 51046, it was envisioned that providing access to compounds with "allocolchicine-like" trimethoxy arrangement is very desirable mainly since they provide greater resemblance to the naturally occurring family of allocolchicines. Targeting the precursors needed for synthesis of the natural alkaloid (−)-allocolchicine is recognized as logical, since it serves to provide a more generalized substrate scope and complements the applicability of our Nicholas chemistry-based methodology.

Following an analogous sequence of transformations in preparing the previously reported cyclization precursors, the corresponding enone substrate (146a) was synthesized via Suzuki cross-coupling reaction, followed by reaction with vinylmagnesium bromide to afford the allylic alcohol which was subsequently subjected to oxidation to obtain the enone of interest (Scheme 2.18).

Scheme 2.18 Preparation of acyclic enone (146a) as cyclization reaction precursor.
To carry out the ring closing step, a set of Lewis acid mediated conjugate addition protocols were surveyed to achieve an efficient synthesis of dibenzocycloheptanone (117a) bearing a 2,3,4-trimethoxy substituted A-ring. The complete list of results is summarized in (Table 2.13).

Table 2.13 Screening Lewis acids as catalysts for conjugate addition reaction of (146a).

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Catalyst Loading</th>
<th>Solvent</th>
<th>Yield/conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF₃-OEt₂</td>
<td>1.0 equiv</td>
<td>CH₂Cl₂</td>
<td>74 %</td>
</tr>
<tr>
<td>BF₃-OEt₂</td>
<td>20 mol %</td>
<td>CH₂Cl₂</td>
<td>(a)</td>
</tr>
<tr>
<td>BF₃-OEt₂</td>
<td>50 mol %</td>
<td>CH₂Cl₂</td>
<td>50 % conv.</td>
</tr>
<tr>
<td>InCl₃</td>
<td>30 mol %</td>
<td>CH₂Cl₂, 24h, rt</td>
<td>45 % conversion</td>
</tr>
<tr>
<td>FeCl₃</td>
<td>25 mol %</td>
<td>CH₂Cl₂, 24h, rt</td>
<td>29 % conversion</td>
</tr>
<tr>
<td>AuCl₃</td>
<td>30 mol %</td>
<td>CH₂Cl₂</td>
<td>50 % conversion</td>
</tr>
<tr>
<td>GaCl₃</td>
<td>50 mol %</td>
<td>CH₂Cl₂, rt</td>
<td>72%</td>
</tr>
<tr>
<td>GaCl₃</td>
<td>25 mol %</td>
<td>CH₂Cl₂, Δ</td>
<td>62 %</td>
</tr>
<tr>
<td>GaCl₃</td>
<td>10 mol %</td>
<td>CH₂Cl₂, Δ</td>
<td>50 % conversion</td>
</tr>
</tbody>
</table>

*a* No conversion was obtained; only starting material was recovered.
While BF₃-OEt₂ proved to be superior to other Lewis acids in the synthesis of iso-NSC 51046 and other substrates with analogous A-ring substitution pattern, it wasn't shown to be effective at catalytic loadings for the current system. The first attempt to induce the cyclization reaction was by using BF₃-OEt₂. Starting with 1.0 equiv. of Lewis acid, the conversion was complete in 48h with 74 % yield of a compound initially assigned as (117a). However, the catalytic turnover didn't occur and hence, using sub-stoichiometric amounts of BF₃-OEt₂ led to incomplete conversion. InCl₃, FeCl₃, and AuCl₃ also showed low potential for catalysis. In the continuing search for suitable catalytic Lewis acid metal reagent, gallium trichloride was tested next. We were delighted to see that it showed a potential to give catalytic turnover to the process, and gave acceptable yields at 25 mol % loading in refluxing methylene chloride (62 %, 48 h, Table 2.13).

Having the end product in hand, a quick comparison of the experimental data (spectroscopic information and the melting point) of the newly formed cyclized compound with those previously reported in literature revealed that the identity of the cyclic compound was assigned incorrectly. In fact, the obtained data were unambiguously identical to those of compound (117b). To better understand the reaction outcome, a plausible mechanism was proposed that accounts for the formation of the spirocyclic compound via an ipso-cyclization. As shown in (Scheme 2.19), once the Lewis acid complexes to the oxygen of the enone, two reaction pathways are potentially possible: I) a 6-endo trig ipso-cyclization and II) an 8-endo-trig cyclization.
Scheme 2.19 A plausible mechanism for the Lewis acid induced rearrangement of cycloheptanone.
Due to the presence of three electron-donating methoxy substituents on the A ring, electronic effects will presumably play a major role in the reaction outcome. To start with the carbon in the *ipso* position (a), the *ortho*–methoxy group (*i.e. ortho relative to ipso-carbon*) can donate electron density to it through resonance effects. In addition, the high electron content in the *ipso* position is even further amplified due to the presence of another EDG in the *para*-position (methoxy group). This means that the *ipso* position has become "doubly" activated to engage in pathway (I) cyclization to form the spiro 6-membered ring intermediate species via a 6-endo-trig path. On a similar note, position (b) (*i.e. carbon in the *meta* position relative to the 1,1’-diphenyl bond) is also activated by two methoxy groups through resonance effects. This leads to a high electron density on this position which can potentially undergo an 8-endo-trig cyclization (pathway II). In spite the fact that both the *ipso* and the *meta* positions on the A ring are equally activated (based on electronics), yet the formation of 8-membered ring sizes is known to be thermodynamically and kinetically unfavourable process. As a result, the outcome of the given reaction will be likely dominated by pathway (I) and the spirocyclic compound is thought to be the immediate product formed in the first step of the conjugate addition reaction. The *ipso* attack is followed by a skeletal rearrangement (1,2-aryl group migration) which results in ring expansion and, upon loss of a proton, affords the observed dibenzocycloheptanone.

An additional closely related analogue (bearing an 9,10,11-trimethoxy substituted A-ring and an unsubstituted C-ring) was investigated. After preparing the alkenone compound, we wanted to assess whether it was a suitable substrate for cyclization reaction.
This particular example proved to be the most stubborn case in undergoing the cyclization step. Upon subjecting the enone to an array of commercially available Lewis acids, we had limited success in achieving the sought after transformation. In most cases, the consumption of the starting material was not evident even after long reaction times, and one case resulted in immediate decomposition of the substrate.

Table 2.14 Screening Lewis acids as catalysts for conjugate addition reaction of (146b).

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Catalyst loading</th>
<th>Yield/ conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF₃·OEt₂</td>
<td>10 mol %</td>
<td>no reaction</td>
</tr>
<tr>
<td>BF₃·OEt₂</td>
<td>1 equiv.</td>
<td>no reaction</td>
</tr>
<tr>
<td>GaCl₃</td>
<td>25 mol %</td>
<td>side product (147)</td>
</tr>
<tr>
<td>AuCl₃</td>
<td></td>
<td>decomposition</td>
</tr>
<tr>
<td>AuClPPh₃+</td>
<td>10 mol %</td>
<td>no reaction</td>
</tr>
<tr>
<td>AgBF₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlCl₃</td>
<td>1 equiv.</td>
<td>45 % (138a)</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>excess</td>
<td>52 % (138a)</td>
</tr>
</tbody>
</table>
In an attempt to accomplish the reaction under the same conditions that were found to be optimal in the previous example (i.e. using GaCl₃), the intended product (138a) was not formed, but instead, an unexpected side-product was isolated. After carefully examining the NMR spectroscopic data of the compound, the absence of one singlet peak (which represents –OCH₃ protons) revealed that a demethoxylation process has been involved. We speculated that a quinone-like spiroconjugated compound (147) was the side product in hand.

During further testing of other Lewis acids, the aluminum based Lewis acid, AlCl₃, showed to be ultimately somewhat successful. By subjecting the enone substrate to an excess amount (6 equiv.) of AlCl₃ in nitrobenzene, we were delighted to finally see complete consumption of the starting material, and the product (138a) was obtained in 52 % yield. It's worth noting that this Lewis acid did not appear to have catalytic turnover, where the lowest loading required to fully drive the reaction to completion was 1 equiv; the yield was slightly compromised (45 %) presumably due to the longer reaction time. On the other hand, both BF₃-OEt₂ and AuClPPh₃ (with AgBF₄) were not able to promote the cyclization reaction as seen in (Table 2.14). Also, AuCl₃ led to complete degradation of starting material. It's worth highlighting that the location of the methoxy groups in the cyclic compound was analogous to the case reported earlier, where similar aryl migration was expected to have occurred resulting in the formation of the rearranged cycloheptanone in lieu of the predicted cyclized species (Scheme 2.19).

The formation of spirocyclic compounds in intramolecular arene-enone reactions has been encountered in several cases in literature.⁷,⁴² Perhaps the most relevant example was the one reported by Majetich et al.⁶b during their investigations of the substituents'
effect on the outcome of cycloalkylation of dienones with activated arenes (Scheme 2.20). When the methoxy substituent was located at the 3' position of the arene (148), the reaction pathway went through 7-endo trig cyclization to furnish the dibenzocycloheptane product (149). However, placing the methoxy group on position 2' (150) dictated a different reaction pathway, where an ipso-attack formed a cyclohexane intermediate, followed by demethylation to ultimately give the spiro-fused enone (151). The authors attributed the different outcomes of the two reactions to the stability of the involved cations in each case; that is to say that the six-membered ring formation led to carbocation (150a) is more stabilized than the cation formed by cycloheptane formation (150b).

Scheme 2.20 Examples by Majetich\textsuperscript{36b} demonstrating the substituents' effect in the formation of spiro-fused enone compound (151).
CHAPTER 3: CONCLUSIONS AND FUTURE OUTLOOK

3.1 Conclusions

We have elaborated a conveniently short, efficient, atom-economical, and more environmentally benign synthetic route to iso-(aR,7S)-(−)-N-acetycolchinol or iso-NSC 51046 (an A-ring isomer of allocolchicine NSC 51046), exploiting a Lewis acid catalyzed Friedel-Crafts intramolecular cyclalkylation. In the key step, the seven-membered ring (B-ring) was efficiently constructed under mild conditions, where BF$_3$-OEt$_2$ was found to be a privileged catalyst in this process. A 7-step asymmetric synthesis of iso-NSC 51046 from commercially available 5-methoxy-2-bromobenzaldehyde and 3,4,5-trimethoxyphenylboronic acid was accomplished in 20% overall yield. In comparison, this is considered a significant improvement over our group's previous method which provided an 11-step synthesis for an overall yield of 14% of iso-NSC 51046. Specifically, there were a total of 8 steps required to arrive at the dibenzocycloheptanone followed by an additional 3 steps to furnish the end product. As a result, the current methodology makes the present route better suited to larger scale syntheses, and it paves the way to a rather broad variety of new allocolchicinoids. The synthetic accessibility and significant antitumor activity exhibited by the new colchinoids described here make them promising objects for more detailed biological investigations. We consider the A-ring modified allocolchicinoids of type iso-NSC 51046 as promising lead in the search for novel anticancer agents with improved properties.
3.2 Future Outlook

Having a group of synthesized dibenzoheptanones in hand (138c-g), it can be envisioned that an analogous chemistry can be extended to these substrates to ultimately attain a reasonable library of compounds of the iso-NSC 51046 series. They can be subsequently submitted for biological evaluations.

In 1991, Barry M. Trost\textsuperscript{43} introduced the concept of "atom economy" in an attempt to prompt synthetic organic chemists to adopt 'greener chemistry'. Simply stated, atom economy is a calculation which measures “how much of the reactants remain in the final product"\textsuperscript{43} Hence, a chemical transformation is considered to have an ideal atom economy if all reactant atoms are found in the end product. By examining our proposed Lewis acid catalyzed cyclization (which is the key transformation in the synthesis), it is evident that there are no "wasted" atoms in the process, and all the atoms of the acyclic enone are seen in the produced dibenzocycloheptanone, which makes this process atom economical. To increase the efficiency of our reported protocol in preparing the tricyclic core of allocolchicinoids, we foresee that the ring-closing process can be made even "greener". One major consideration would be to replace the chlorinated solvent (dichloromethane) with greener solvent alternatives that can still solvate the reaction substrates and the involved catalyst. The careful choice of alternative solvents should mainly avoid ones that contain "basic" or nucleophilic atoms which can potentially pair with the Lewis acid. Solvents such as hexanes or cyclohexane seem to be logical choices and worth investigating in the future.
CHAPTER 4: EXPERIMENTAL

General Methods and Materials: All reagents, unless otherwise noted, were purchased from Aldrich. 2,3,4-Trimethoxyphenylboronic acid was purchased from Alfa Aesar. All reactions were run under a nitrogen atmosphere using oven-dried glassware (110 °C, > 1h). All reaction solvents (except 1,2-dimethoxyethane, DME) were directly obtained from solvent purification system (Innovative Technologies). Commercial BF$_3$-OEt$_2$ was distilled and stored under nitrogen. The term “conventional workup” refers to the extraction of the product from the aqueous layer with an organic solvent (such as dichloromethane or diethyl ether), drying the combined organic layers with anhydrous magnesium sulfate and filtration of the resultant mixture, followed by evaporation of the volatiles under reduced pressure to obtain the crude product(s).

Instrumentation: Flash chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ sheets from Silicycle. Preparative TLC was carried out over silica gel GF-254 plates from Silicycle. High-Resolution Mass Spectrometry (HRMS) results were obtained by means of a Direct Insertion Probe-Electron Ionization method (70 eV), on a Waters/Micromass GCT (GC-EI/CI Time of Flight Mass Spectrometer) performed at the McMaster Regional Centre for Mass Spectrometry. Proton nuclear magnetic resonance ($^1$H NMR) data were obtained either on Bruker Avance 300 or 500 MHz spectrometers. Chemical shifts are reported in delta ($\delta$) units, parts per million (ppm), relative to the singlet at 7.26 ppm for chloroform-d, unless otherwise indicated. Coupling constants are
reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (\(^{13}\)C NMR) data were obtained on Bruker Avance 75 MHz or 125 MHz spectrometers. Infrared Spectroscopy (IR) data were recorded on a Bruker alpha-ATR FT-IR spectrometer. The reported IR data (neat) reflects the frequencies of the distinctive functional group stretches only. Melting points were measured with a Thomas Hoover, Uni-Melt\textsuperscript{©} capillary point apparatus.

\textbf{3',4',5'-Trimethoxy-[1,1'-biphenyl]-2-carbaldehyde (135a)}

![Chemical structure of 135a]

Title compound was prepared according to the procedure reported by Kundu,\textsuperscript{45} starting with 2-bromobenzaldehyde (2.0 g, 10.81 mmol) and 3,4,5-trimethoxy-phenylboronic acid (2.52 g, 11.89 mmol) to yield 2.56 g of compound (135a) as a white solid (86 % yield), mp 92-93 °C (lit. 102-106 °C). The spectroscopic data matched the ones reported in the literature.\textsuperscript{45}
Methyl 2-formyl-3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carboxylate (135b)

![Chemical Structure of 135b](image)

Prepared according to the Fürstner method, where methyl 4-bromo-3-formylbenzoate (1.40 g, 5.78 mmol) afforded the title compound (135b) as a colorless powder (1.54 g, 81% yield), 137-139 °C. IR (neat) \( v_{\text{max}} \) 2942, 2839, 1719, 1689, 1119, 765.6 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 10.03 (s, 1H), 8.65 (d, \( J = 2.0, 1H \)), 8.28 (dd, \( J = 1.5, 8.0, 1H \)), 7.56 (d, \( J = 8.0, 1H \)), 6.57 (s, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.89 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 191.5, 166.1, 153.3, 149.7, 138.5, 133.9, 132.4, 130.8, 129.8, 129.1, 107.3, 61.0, 56.3, 52.5; HRMS \( m/e \) for C\(_{18}\)H\(_{18}\)O\(_6\) calcd 330.1103, found 330.1100.

4-Fluoro-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-carbaldehyde (135c)

![Chemical Structure of 135c](image)
(The preparation method of this compound was adapted from a literature protocol).46

To a 100 mL oven-dried flask, was added 3,4,5-trimethoxyphenylboronic acid (1.3 g, 5.07 mmol), 2-bromo-5-fluorobenzaldehyde (1.13 g, 5.58 mmol), Pd(PPh₃)₄ (0.4 g, 6 mol %), and Na₂CO₃ (1.13 g, 2 equiv.). Then, the flask was evacuated and refilled with nitrogen gas (x 3). The flask was then placed under nitrogen and 52 mL of degassed dioxane/water/ethanol was added via syringe (5:1:1). The reaction mixture was heated at reflux for 12 h. After cooling the reaction to room temperature, the dioxane was removed under reduced pressure. The resulting residue was then dissolved in dichloromethane and washed with water/brine. The organic layer was separated, and dried with anhydrous magnesium sulfate. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (3:1 hexanes/diethyl ether) to afford compound (135c) as a white solid (1.53 g, 94 % yield), mp 132-134°C. IR (neat) ν_max 2956, 1675, 1582, 1486, 1237, 1127 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.85 (d, J = 3.0, 1H), 7.51 (dd, J = 2.8, 8.8, 1H), 7.39 (dd, J = 5.5, 8.5, 1H), 7.23 (td, J = 3.0, 8.0, 1H), 6.48 (s, 2H), 3.82 (s, 3H), 3.80 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 191.0, 162.0 (d, J_C,F = 247.5), 153.1, 142.0 (d, J_C,F = 3.0), 138.1, 135.3 (d, J_C,F = 6.1), 132.5 (d, J_C,F = 7.3), 132.3, 120.6 (d, J_C,F = 21.9), 113.3 (d, J_C,F = 22.0), 107.4, 60.8 (d, J_C,F = 1.4), 56.1 (d, J_C,F = 1.1); HRMS m/z for C₁₆H₁₅FO₄ calcd 290.0954, found 290.0949.
4-(Benzyloxy)-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-carbaldehyde (135d)

Prepared according to the Fürstner method, where 5-benzyloxy-2-bromobenzaldehyde (1.05 g, 3.6 mmol) afforded the title compound (135d) as a viscous yellow oil (1.24 g, 91% yield).  IR (neat) $\nu_{\text{max}}$ 2934, 2839, 1711, 1684, 1583, 1486, 1239, 1123 cm$^{-1}$;  $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.98 (s, 1H), 7.58 (d, $J$ = 3.0, 1H), 7.34-7.48 (m, 6H), 7.26 (dd, $J$ = 3.0, 8.5, 1H), 6.53 (s, 2H), 5.17 (s, 2H), 3.91 (s, 3H), 3.87 (s, 6H);  $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.3, 158.3, 153.1, 139.3, 137.8, 136.3, 134.6, 133.1, 131.9, 128.7, 128.2, 127.6, 121.9, 110.9, 107.5, 70.3, 61.0, 56.2;  HRMS $m/e$ for C$_{23}$H$_{22}$O$_5$ calcd 378.1467, found 378.1456.

3',4',5',5'-Tetramethoxy-[1,1'-biphenyl]-2-carbaldehyde (135e)
Prepared according to the Fürstner\textsuperscript{39} method, where 2-bromo-4-methoxybenzaldehyde (1.03 g, 4.79 mmol) afforded (135e) as a colorless solid (1.15 g, 79 % yield), mp 128-130 °C. \textbf{IR} (neat) \( \nu_{\text{max}} \) 2926, 1675, 1602, 1580, 1236, 1120 cm\(^{-1}\); \textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)) \( \delta \) 9.98 (s, 1H), 7.49 (d, \( J = 2.5 \), 1H), 7.38 (d, \( J = 8.5 \), 1H), 7.19 (dd, \( J = 3.0, 8.5 \), 1H), 6.53 (s, 2H), 3.91 (s, 6H), 3.88 (s, 6H); \textbf{\(^{13}\)C NMR} (125 MHz, CDCl\(_3\)) \( \delta \) 192.3, 159.2, 153.1, 139.1, 137.8, 134.7, 133.2, 131.8, 121.3, 109.7, 107.6, 61.0, 56.2, 55.7; \textbf{HRMS} \( m/e \) for C\(_{17}\)H\(_{18}\)O\(_5\) calcd 302.1154, found 302.1146.

\textbf{6-(3,4,5-Trimethoxyphenyl)benzo[d][1,3]dioxole-5-carbaldehyde (135f)}

![135f]

Prepared according to the Fürstner\textsuperscript{39} method, where 6-bromobenzo[d][1,3]dioxole-5-carbaldehyde (0.214 g, 0.934 mmol) afforded the title compound (135f) as a colorless powder (0.254g, 86 % yield) after column chromatography (3:1 hexanes/diethyl ether); mp: 154-155 °C. \textbf{IR} (neat) \( \nu_{\text{max}} \) 2956, 2916, 1674, 1580, 1120 cm\(^{-1}\); \textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)) \( \delta \) 9.79 (s, 1H), 7.45 (s, 1H), 6.86 (s, 1H), 6.53 (s, 2H), 6.09 (s, 2H), 3.90 (s, 3H), 3.87 (s, 6H); \textbf{\(^{13}\)C NMR} (125 MHz, CDCl\(_3\)) \( \delta \) 190.7, 153.0, 152.0, 147.8, 143.6, 133.1, 128.9, 110.1, 107.4, 106.2, 102.1, 61.0, 56.2; \textbf{HRMS} \( m/e \) for C\(_{17}\)H\(_{16}\)O\(_6\) calcd 316.0947, found 316.0942.
3,3',4,4',5'-Pentamethoxy-[1,1'-biphenyl]-2-carbaldehyde (135g)

![Chemical Structure](image)

Prepared according to the Fürstner\textsuperscript{39} method, where 6-bromo-2,3-dimethoxybenzaldehyde (1.433 g, 5.847 mmol) afforded (135g) as a yellow solid (0.67 g, 35 % yield, or 45 % brsm), mp 86-87.5 °C (Et\textsubscript{2}O). IR (neat) ν\textsubscript{max} 2934, 2836, 1690, 1584, 1565, 1484, 1225 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 10.03 (s, 1H), 7.13 (d, J= 8.5, 1H), 7.11 (d, J= 8.5, 1H), 6.47 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.85 (s, 6H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 191.9, 153.0, 152.7, 149.5, 137.6, 137.1, 134.1, 129.4, 126.1, 116.2, 107.1, 62.4, 61.1, 56.3; HRMS m/e for C\textsubscript{18}H\textsubscript{20}O\textsubscript{6} calcd 332.1260, found 332.1245.

3-(3,4,5-Trimethoxyphenyl)thiophene-2-carbaldehyde (135h)

![Chemical Structure](image)

Prepared according to the Fürstner\textsuperscript{39} method, where 3-bromothiophene-2-carbaldehyde (0.36 g, 1.884 mmol) afforded the title compound (135h) as an off-white
powder (0.206 g, 40 % yield) after column chromatography (3:1 hexanes/ diethyl ether); mp 127.5–129 °C. IR (neat) $\nu_{\text{max}}$ 2930, 1647, 1583, 1415, 1237, 1123 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.93 (s, 1H), 7.73 (apparent dd, $J$= 1.0, 5.0, 1H), 7.22 (d, $J$= 4.8, 1H), 6.66 (s, 2H), 3.91 (s, 3H), 3.89 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 184.4, 153.5, 151.6, 138.8, 138.6, 134.3, 130.7, 129.6, 107.0, 61.1, 56.4; HRMS m/e for: C$_{14}$H$_{14}$O$_4$S calcd 278.0613, found 278.0613.

2',3',4'-Trimethoxy-[1,1'-biphenyl]-2-carbaldehyde (135i)

![Image of 2',3',4'-Trimethoxy-[1,1'-biphenyl]-2-carbaldehyde (135i)]

Prepared according to the Fürstner$^{39}$ method, starting with 2-bromobenzaldehyde (1.59 g, 8.59 mmol) and 2,3,4-trimethoxyphenylboronic acid (2.00 g, 9.43 mmol) to afford compound 135i (1.83 g, 78 % yield) as a white solid (mp 95-96 °C; lit. mp 98-99 °C). The product showed spectroscopic data identical with the literature.$^{39}$

**General Procedure E:** A solution of the biaryl compound (1 equiv.) in anhydrous diethyl ether was cooled down in an ice-bath to 0 °C. Then, vinylmagnesium bromide solution (2.0 equiv. of 1.0 M in THF solution) was added in dropwise fashion while stirring. The reaction mixture was stirred further for 1-2 h (TLC control). Upon the complete consumption of the starting material, the reaction was quenched with a saturated
solution of ammonium chloride and extracted with diethyl ether (2 times). The organic layer was separated and dried with anhydrous magnesium sulfate. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography to afford the final product.

1-(3',4,4',5'-Tetramethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (132)

![Chemical structure of 132]

Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (132) as a yellow viscous oil (76% yield). IR (neat) \( \nu_{\text{max}} \) 3455, 2938, 1708, 1583, 1488, 1234, 1122, 728 cm\(^{-1} \); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.19 (d, \( J = 8.4 \), 1H), 7.10 (d, \( J = 2.4 \), 1H), 6.87 (dd, \( J = 2.4 \), 8.4, 1H), 6.54 (s, 2H), 6.05 (ddd, \( J = 5.3 \), 10.3, 17.1, 1H), 5.30 (d, \( J = 5.1 \), 1H), 5.22 (d, \( J = 17.1 \), 1H), 5.17 (d, \( J = 10.3 \), 1H), 3.88 (s, 6H), 3.84 (s, 3H), 3.83 (s, 3H), 1.99 (br s, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 159.3, 152.7, 141.1, 140.5, 136.9, 136.1, 133.8, 131.0, 115.0, 113.4, 111.8, 106.8, 71.3, 60.94, 60.93, 56.1, 56.09, 55.4; HRMS m/e for C\(_{19}\)H\(_{22}\)O\(_5\) calcd 330.1467, found 330.1463.
1-(3',4',5'-Trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136a)

Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136a) as a yellow solid (82% yield), mp 80-83°C. IR (neat) $\nu_{\text{max}}$ 3434, 2937, 1707, 1583, 1408, 1343, 1235, 1121, 998, 764 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.57 (dd, $J$= 1.5, 8.0, 1H), 7.40 (apparent dt, $J$= 1.5, 7.5, 1H), 7.33 (apparent dt, $J$= 1.5, 7.5, 1H), 7.57 (dd, $J$= 1.5, 7.5, 1H), 6.57 (s, 2H), 6.08 (ddd, $J$= 5.5, 10.5, 17.5, 1H), 5.32 (br s, 1H), 5.23 (apparent td, $J$= 1.5, 17.5, 1H), 5.18 (apparent td, $J$= 1.5, 10.5, 1H), 3.90 (s, 3H), 3.85 (s, 6H), 1.92 (d, $J$= 4.0, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.9, 141.3, 140.8, 139.9, 137.2, 136.4, 129.9, 128.1, 127.6, 127.1, 115.0, 106.8, 71.4, 61.1, 56.2; HRMS $m/e$ for C$_{18}$H$_{20}$O$_4$ calcd 300.1362, found 300.1366.

Methyl 2-(1-hydroxyallyl)-3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carboxylate (136b)
Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136b) as a yellow viscous oil (82 % yield). IR (neat) \(\nu_{\text{max}}\) 3473, 2947, 1718, 1583, 1232, 1120 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.25 (d, \(J=\ 1.5, \ 1\)H), 7.98 (dd, \(J=\ 1.5, \ 8.0, \ 1\)H), 7.35 (d, \(J=\ 8.0, \ 1\)H), 6.56 (s, 2H), 6.09 (ddd, \(J=\ 5.5, \ 10.5, \ 17.0, \ 1\)H), 5.34 (br m, 1H), 5.20-5.27 (m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.85 (s, 6H), 1.99 (d, \(J=\ 4.0, \ 1\)H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.8, 152.9, 145.7, 140.2, 137.5, 135.2, 130.1, 129.7, 128.6, 128.5, 115.6, 106.4, 71.1, 61.0, 56.2, 52.2; HRMS \(m/e\) for C\(_{20}\)H\(_{22}\)O\(_6\) calcd 358.1416, found 358.1431.

1-(4-Fluoro-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136c)

Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136c) as a yellow viscous oil (90 % yield). IR (neat) \(\nu_{\text{max}}\) 3459, 2936, 1709, 1580, 1485, 1403, 1232, 1118, 993 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.19-7.24 (m, 2H), 6.99 (ddd, \(J=\ 2.8, \ 8.3, \ 8.3\) (J\(_{H,F}\) 1H), 6.50 (s, 2H), 6.00 (ddd, \(J=\ 5.3, \ 10.3, \ 17.4, \ 1\)H), 5.26 (d, \(J=\ 5.0, \ 1\)H), 5.20 (apparent td, \(J=\ 1.4, \ 10.3, \ 1\)H), 5.15 (apparent td, \(J=\ 1.4, \ 17.4, \ 1\)H), 3.87 (s, 3H), 3.82 (s, 6H), 2.21 (br s, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 162.5 (d, \(J_{C,F} = \ 245\), 153.0, 142.3 (d, \(J_{C,F} = \ 6.7\), 140.2, 137.4, 137.1, 135.5, 131.5 (d, \(J_{C,F} = \ 8.2\), 115.5, 114.5 (d, \(J_{C,F} = \ 21.0\), 113.8
(d, $J_{C,F} = 22.5$), 106.9, 71.2, 61.0, 56.2; **HRMS m/e** for $C_{18}H_{19}FO_4$ calcd 318.1267, found 318.1259.

1-(4-(Benzyloxy)-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136d)

Title compound was prepared by following **General Procedure E.** Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136d) as a yellow viscous oil (80 % yield). **IR** (neat) $\nu_{\text{max}}$ 3455, 2935, 1606, 1583, 1487, 1233, 1123, 728 cm$^{-1}$; **$^1H$ NMR** (500 MHz, CDCl$_3$) $\delta$ 7.34-7.45 (m, 5H), 7.21 (d, $J$= 8.5, 1H), 7.19 (d, $J$= 2.5, 1H), 6.94 (dd, $J$= 2.5, 8.5, 1H), 6.54 (s, 2H), 6.04 (ddd, $J$= 5.5, 10.2, 17.2, 1H), 5.30 (br s, 1H), 5.23 (dt, $J$= 1.5, 17.0, 1H), 5.18 (dt, $J$= 1.5, 10.4, 1H), 5.11 (s, 2H), 3.89 (s, 3H), 3.84 (s, 6H), 1.98 (d, $J$= 3.5, 1H); **$^{13}C$ NMR** (125 MHz, CDCl$_3$) $\delta$ 158.5, 152.8, 141.1, 140.4, 137.0, 136.9, 136.0, 134.1, 131.0, 128.6, 128.1, 127.6, 115.0, 114.2, 113.0, 106.8, 71.3, 70.1, 61.0, 56.1; **HRMS m/e** for $C_{25}H_{26}O_5$ calcd 406.1780, found 406.1764.
1-(3',4',5',5'-Tetramethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136e)

![Chemical Structure](image)

Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136e) as a yellow viscous oil (80% yield). IR (neat) \(\nu_{\text{max}}\) 3447, 2936, 1707, 1607, 1583, 1488, 1235, 1122, 729 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.20 (d, \(J= 8.5\), 1H), 7.10 (d, \(J= 2.8\), 1H), 6.88 (dd, \(J= 2.8\), 8.5, 1H), 6.54 (s, 2H), 6.06 (ddd, \(J= 5.5\), 10.5, 17.0, 1H), 5.30 (br m, 1H), 5.24 (dt, \(J= 1.5\), 17.0, 1H), 5.19 (apparent td, \(J= 1.5\), 10.5, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (s, 6H), 1.90 (d, \(J= 3.5\), 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.4, 152.8, 141.2, 140.6, 137.0, 136.2, 133.9, 131.1, 115.1, 113.6, 111.9, 106.9, 71.5, 61.1, 56.2, 55.5; HRMS m/e for C\(_{19}\)H\(_{22}\)O\(_5\) calcd 330.1467, found 330.1458.

1-(6-(3,4,5-Trimethoxyphenyl)benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (136f)

![Chemical Structure](image)

Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded the product (136f) as an off-white
solid (72 % yield), mp 93-95 ºC. \( \text{IR (neat)} \ \nu_{\text{max}} 3254, 2967, 2938, 1582, 1479, 1227, 1115, 1010, 921, 849 \text{ cm}^{-1} \); \( \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \) \( \delta 7.01 \) (s, 1H), 6.73 (s, 1H), 6.52 (s, 2H), 6.03 (dd, \( J = 5.5, 11.0, 17.0, 1H \)), 5.98 (s, 2H), 5.16-5.25 (m, 3H), 3.88 (s, 3H), 3.84 (s, 6H), 1.86 (br s, 1H); \( \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3 \) \( \delta 152.8, 147.3, 146.8, 140.6, 137.1, 136.1, 135.1, 133.5, 114.8, 109.7, 107.0, 106.7, 101.3, 71.1, 60.9, 56.1; \) \( \text{HRMS } m/e \) for \( \text{C}_{19}\text{H}_{20}\text{O}_6 \) calcd 344.1260, found 344.1243.

\( \text{1-(3',3',4,4',5'-Pentamethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136g)} \)

![Diagram of 136g]

Title compound was prepared by following \textit{General Procedure E}. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136g) as a viscous pale-yellow oil (96 % yield). \( \text{IR (neat)} \ \nu_{\text{max}} 3520, 2939, 2836, 1582, 1484, 1454, 1404, 1124 \text{ cm}^{-1} \); \( \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \) \( \delta 6.98 \) (d, \( J = 8.0, 1H \)), 6.90 (d, \( J = 8.5, 1H \)), 6.48 (s, 2H), 6.21-6.27 (m, 1H), 5.13-5.19 (m, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.82 (s, 6H); \( \text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3 \) \( \delta 152.8, 152.1, 147.5, 142.2, 137.2, 136.2, 134.7, 133.7, 125.5, 114.1, 111.8, 106.8, 72.3, 61.1, 61.0, 56.2, 56.0; \) \( \text{HRMS } m/e \) for \( \text{C}_{20}\text{H}_{24}\text{O}_6 \) calcd 360.1573, found [M\(^+\) – H\(_2\)O] 342.1466.
1-(3-(3,4,5-Trimethoxyphenyl)thiophen-2-yl)prop-2-en-1-ol (136h)

![Chemical Structure of 136h]

Title compound was prepared from compound 135h (0.154 g, 0.555 mmol) by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136h) as a viscous colorless oil (0.141 g, 85% yield). IR (neat) vₐₓₘₐₓ 3447, 2937, 1583, 1502, 1453, 1240, 1124 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, J= 5.0, 1H), 7.06 (dd, J= 1.5, 5.0, 1H), 6.69 (s, 2H), 6.19 (ddd, J= 5.5, 10.0, 17.2, 1H), 5.53 (br s, 1H), 5.40 (dd, J= 1.0, 17.0, 1H), 5.26 (dd, J= 1.0, 10.0, 1H), 5.26 (dd, J= 1.0, 10.0, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.87 (s, 6H), 2.16 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 153.1, 140.6, 140.3, 139.8, 137.3, 131.7, 129.2, 124.7, 115.5, 106.1, 68.9, 61.0, 56.2; HRMS m/e for C₁₆H₁₈O₄S calcd 306.0926, found 306.0911.

1-(2',3',4,4'-Tetramethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136i)

![Chemical Structure of 136i]
Title compound was prepared by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136i) as a yellow viscous oil (70 % yield). IR (neat) \( \nu_{\text{max}} \) 3459, 2937, 2836, 1710, 1598, 1483, 1460, 1408, 1092, 1076, 1001, 804 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) (two diastereomers on NMR time scale, major isomer reported, 23 °C) \( \delta \) 7.13 (d, \( J= 8.5 \), 1H), 7.06 (d, \( J= 2.5 \), 1H), 6.88 (m, 2H), 6.75 (d, \( J= 8.5 \), 1H), 5.90 (ddd, \( J= 4.3, 10.6, 17.3 \), 1H), 5.33 (dt, \( J= 1.7, 17.2 \), 1H), 5.16 (dt, \( J= 1.7, 10.6 \), 1H), 5.03 (m, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.54 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 159.5, 153.2, 151.0, 143.0, 142.4, 139.1, 131.3, 129.3, 127.7, 125.5, 114.1, 113.6, 112.1, 108.1, 71.5, 61.1, 56.1, 55.2; HRMS m/e for C\(_{19}\)H\(_{22}\)O\(_5\) calcd 330.1467, found 330.1478.

1-(2',3',4'-Trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-ol (136j)

![Chemical Structure](image)

Title compound was prepared from compound 135i (1.83 g, 6.72 mmol) by following General Procedure E. Column chromatography (3:1 diethyl ether/hexanes) yielded compound (136j) as a yellow oil (1.46 g, 73 % yield). IR (neat) \( \nu_{\text{max}} \) 3350, 2932, 2840, 1598, 1461,1408,1289, 1092 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) (two diastereomers on NMR time scale, major isomer reported, 23 °C) \( \delta \) 7.53 (dd, \( J= 1.0, 8.0 \), 1H), 7.40 (apparent td, \( J= 1.0, 8.0 \), 1H), 7.33 (apparent td, \( J= 1.5, 7.5 \), 1H), 7.21 (dd, \( J= 1.5, 7.5 \), 1H), 7.15 (dd, \( J= 1.5, 7.5 \), 1H), 7.10 (dd, \( J= 1.5, 7.5 \), 1H), 7.05 (ddd, \( J= 4.3, 10.6, 17.3 \), 1H), 6.90 (m, 2H), 6.70 (d, \( J= 8.5 \), 1H), 6.60 (m, 2H), 6.50 (m, 2H), 6.40 (d, \( J= 8.5 \), 1H), 5.90 (dd, \( J= 4.3, 10.6 \), 1H), 5.80 (m, 2H), 5.70 (m, 2H), 5.60 (m, 2H), 5.50 (m, 2H), 5.40 (m, 2H), 5.30 (m, 2H), 5.20 (m, 2H), 5.10 (m, 2H), 5.00 (m, 2H), 4.90 (m, 2H), 4.80 (m, 2H), 4.70 (m, 2H), 4.60 (m, 2H), 4.50 (m, 2H), 4.40 (m, 2H), 4.30 (m, 2H), 4.20 (m, 2H), 4.10 (m, 2H), 4.00 (m, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.60 (s, 3H), 3.50 (s, 3H), 3.40 (s, 3H), 3.30 (s, 3H), 3.20 (s, 3H), 3.10 (s, 3H), 3.00 (s, 3H), 2.90 (s, 3H), 2.80 (s, 3H), 2.70 (s, 3H), 2.60 (s, 3H), 2.50 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.80 (s, 3H), 0.70 (s, 3H), 0.60 (s, 3H), 0.50 (s, 3H), 0.40 (s, 3H), 0.30 (s, 3H), 0.20 (s, 3H), 0.10 (s, 3H), 0.00 (s, 3H).
1H), 6.89 (d, J= 8.5, 1H), 6.77 (d, J= 8.5, 1H), 5.93 (ddd, J= 4.5, 11.0, 17.4, 1H), 5.32 (apparent dt, J= 2.0, 17.0, 1H), 5.16 (apparent dt, J= 1.5, 10.5, 1H), 5.06 (m, 1H), 3.94 (s, 6H), 3.54 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) (two diastereomers on NMR time scale, major isomer reported, 23 °C) δ 153.5, 150.8, 141.7, 139.2, 130.3, 128.3, 128.0, 127.5, 127.4, 125.4, 114.2, 108.1, 71.4, 61.4, 61.2, 56.2; HRMS m/e for C$_{18}$H$_{20}$O$_4$ calcd 300.1362, found 300.13.

**General Procedure F:** After dissolving the vinyl alcohol compound in anhydrous dichloromethane, an excess amount of activated manganese (IV) dioxide was added in one portion. After stirring the reaction mixture at room temperature for 1-3 h (TLC control), it was filtered through Celite which was washed with dichloromethane. The filtrate was concentrated under reduced pressure to yield the crude compound which was purified using flash chromatography to afford the α, β-unsaturated ketone compounds (137a-h and 146a-b).

1-(3',4,4',5'-Tetramethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (133)

![Chemical Structure](image)

To a solution of 132 (0.1435 g, 0.435 mmol) in anhydrous dichloromethane (20 mL) were added 4 Å molecular sieves, N-methylmorpholine N-oxide (0.153 g, 1.30
mmol). After stirring the solution for 5 minutes at room temperature, tetrapropylammonium perruthenate (0.010 g, 0.0028 mmol) was added. The reaction was stirred for 2 h, then it was filtered through Celite and washed with diethyl ether. After removing the volatiles under reduced pressure, the obtained crude sample was purified by column chromatography (1:1 diethyl ether/hexanes) to afford the product (133) as a yellow solid (0.107 g, 75 % yield), mp 99-100 °C. IR (neat) ν_{max} 2937, 2836, 1711, 1665, 1583, 1484, 1240, 1121, 1005, 821 cm^{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.38 (d, J= 8.5, 1H), 7.05-7.08 (m, 2H), 6.47 (s, 2H), 6.18 (dd, J= 10.5, 17.5, 1H), 6.00 (dd, J= 1.5, 17.5, 1H), 5.56 (dd, J= 1.5, 10.5, 1H), 3.86 (s, 6H), 3.82 (s, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 197.0, 158.9, 153.2, 140.1, 137.5, 135.8, 135.5, 133.4, 130.9, 128.8, 117.2, 113.1, 106.4, 61.0, 56.1, 55.6; HRMS m/e for C\textsubscript{19}H\textsubscript{20}O\textsubscript{5} calcd 328.1311, found 328.1307.

1-(3',4',5'-Trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (137a)

\[ \text{\includegraphics[width=1cm]{137a.png}} \]

137a

To a solution of 136a (0.0455 g, 0.151 mmol) in anhydrous dichloromethane (10 mL) were added 4 Å molecular sieves, N-methylmorpholine N-oxide (0.053 g, 0.455 mmol). After stirring the solution for 5 minutes at room temperature, tetrapropylammonium perruthenate (0.0033 g, 0.0095 mmol) was added. The reaction was stirred for 12 h, then it was filtered through Celite and washed with diethyl ether.
After removing the volatiles under reduced pressure, the obtained crude sample was purified by column chromatography (1:1 diethyl ether/hexanes) to afford the product (137a) as a yellow solid (80 % yield), mp 68-70 °C. \(\text{IR (neat)} \nu_{\text{max}} 2938, 2835, 1658, 1582, 1455, 1406, 1344, 1239, 1122, 994, 729 \text{ cm}^{-1};\) \(\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3) \delta \text{ 7.41-7.46 (m, 2H), 7.51-7.54 (m, 2H), 6.51 (s, 2H), 6.20 (dd, } J = 10.5, 17.5, 1H), 5.98 (dd, } J = 1.5, 17.5, 1H), 5.57 (dd, } J = 1.5, 10.5, 1H), 3.87 (s, 3H), 3.82 (s, 6H);\) \(\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3) \delta 197.3, 153.3, 140.7, 139.2, 137.8, 136.0, 135.8, 130.7, 129.6, 128.8, 128.7, 127.4, 106.4, 61.0, 56.1;\) \(\text{HRMS m/e for C}_{18}\text{H}_{18}\text{O}_4 \text{calcd 298.1205, found 298.1213.}\)

**Methyl 2-acryloyl-3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carboxylate (137b)**

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

**137b**

Title compound was prepared by following *General Procedure F*. Column chromatography (2:1 diethyl ether/hexanes) yielded the product (137b) as a yellow viscous oil (90 % yield). \(\text{IR (neat)} \nu_{\text{max}} 2937, 2839, 1719, 1661, 1598, 1284, 1092 \text{ cm}^{-1};\) \(\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3) \delta 8.18 (s, 1H), 8.17 (d, } J = 1.5, 1H), 7.54 (d, } J = 8.0, 1H), 6.52 (s, 2H), 6.23 (dd, } J = 10.5, 17.0, 1H), 5.99 (dd, } J = 1.0, 17.5, 1H), 5.65 (dd, } J = 1.0, 10.5, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.83 (s, 6H);\) \(\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3) \delta 196.5, 166.2, 153.4, 144.9, 139.2, 138.4, 135.8, 134.7, 131.5, 130.0, 129.9, 129.6, 129.2, 106.3, 61.0, 56.2, 52.4;\) \(\text{HRMS m/e for C}_{20}\text{H}_{20}\text{O}_6 \text{calcd 356.1260, found 356.1251.}\)
1-(4-Fluoro-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (137c)

To a solution of 136c (0.171 g, 0.538 mmol) in anhydrous dichloromethane (10 mL) were added 4 Å molecular sieves, N-methylmorpholine N-oxide (0.189 g, 1.614 mmol). After stirring the solution for 5 minutes at room temperature, tetrapropylammonium perruthenate (0.028 g, 0.081 mmol) was added. The reaction was stirred for 1 h, then it was filtered through Celite and washed with diethyl ether. After removing the volatiles under reduced pressure, the obtained crude sample was purified by column chromatography (1:1 diethyl ether/hexanes) to afford the product (137c) as a yellow solid (0.112 g, 66 % yield), mp 73-74.5 °C. IR (neat) \( \nu_{\text{max}} \) 2941, 2836, 1659,1575, 1482, 1453, 1304, 1241, 1122, 827 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.37 (m, 1H), 7.15-7.18 (m, 2H), 6.42 (s, 2H), 6.13 (dd, \( J = 10.5, 17.4, 1H \)), 5.94 (dd, \( J = 1.5, 17.4, 1H \)), 5.56 (dd, \( J = 1.5, 10.2, 1H \)), 3.81 (s, 3H), 3.77 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 195.7, 161.8 (d, \( J_{\text{C,F}} = 247 \)), 153.3, 140.6 (d, \( J_{\text{C,F}} = 6.1 \)), 137.9, 136.8, 136.8, 135.5, 134.7, 131.5 (d, \( J_{\text{C,F}} = 7.7 \)), 129.4, 117.6 (d, \( J_{\text{C,F}} = 21.1 \)), 115.4 (d, \( J_{\text{C,F}} = 22.7 \)), 106.5, 61.0, 56.1; HRMS m/e for C\(_{18}\)H\(_{17}\)FO\(_4\) calcd 316.1111, found 316.1107.
1-(4-(Benzyloxy)-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (137d)

Title compound was prepared by following General Procedure F. Column chromatography (1:1 diethyl ether/hexanes) yielded the product (137d) as a yellow solid (70 %, 81 % brsm), mp 97-98.5 °C. IR (neat) νmax 2964, 2935, 1712, 1674, 1585, 1488, 1228, 1190, 1123, 1001 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.46 (m, 6H), 7.12-7.16 (m, 2H), 6.47 (s, 2H), 6.18 (dd, J= 10.5, 17.5, 1H), 6.00 (dd, J= 1.5, 17.5, 1H), 5.57 (dd, J= 1.5, 10.5, 1H), 5.13 (s, 2H), 3.87 (s, 3H), 3.82 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 197.0, 158.2, 153.3, 140.2, 137.7, 136.6, 136.0, 135.6, 133.8, 131.1, 129.0, 128.8, 128.3, 127.7, 118.0, 114.4, 106.5, 70.4, 61.1, 56.2; HRMS m/e for C₂₅H₂₄O₅ calcd 404.1624, found 404.1609.

1-(3',4',5,5'-Tetramethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (137e)
To a solution of 136e (0.0522 g, 0.158 mmol) in anhydrous dichloromethane (10 mL) were added 4 Å molecular sieves, N-methylmorpholine N-oxide (0.055 g, 0.474 mmol). After stirring the solution for 5 minutes at room temperature, tetrapropylammonium perruthenate (0.0035 g, 0.001 mmol) was added. The reaction was stirred for 30 min, and then it was filtered through Celite and washed with diethyl ether. After removing the volatiles under reduced pressure, the obtained crude sample was purified by column chromatography (1:1 diethyl ether/hexanes) to afford the product (137e) as a yellow solid (0.0365 g, 70% yield), mp 98-100 °C. IR (neat) νmax 2935, 1681, 1583, 1488, 1235, 1124, 998 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, J = 8.5, 1H), 7.07 (m, 2H), 6.47 (s, 2H), 6.19 (dd, J = 10.5, 17.5, 1H), 6.01 (dd, J = 1.5, 17.5, 1H), 5.57 (dd, J = 1.5, 10.5, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.83 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 197.0, 158.9, 153.2, 140.1, 137.5, 135.8, 135.5, 133.4, 130.9, 128.8, 117.2, 113.1, 106.4, 61.0, 56.1, 55.6; HRMS m/e for C₁₉H₂₀O₅ calcd 328.1311, found 328.1318.

1-(6-(3,4,5-Trimethoxyphenyl)benzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (137f)

![137f]

To a solution of 136f (0.0935 g, 0.271 mmol) in anhydrous dichloromethane (20 mL) were added 4 Å molecular sieves, N-methylmorpholine N-oxide (0.095 g, 0.814 mmol). After stirring the solution for 5 minutes at room temperature, tetrapropylammonium perruthenate (0.0143 g, 0.041 mmol) was added. The reaction was
stirred for 1 h at room temperature, and then it was filtered through Celite and washed with diethyl ether. After removing the volatiles under reduced pressure, the obtained crude sample was purified by column chromatography (2:1 diethyl ether/hexanes) to yield the product (137f) as colorless solid (68 %), mp 136-138 °C. IR (neat) $\nu_{\text{max}}$ 2937, 1662, 1575, 1479, 1244, 1233, 1117 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 7.04 (s, 1H), 6.91 (s, 1H), 6.46 (s, 2H), 6.10 (dd, $J$ = 10.3, 17.3, 1H), 6.07 (s, 2H), 5.97 (dd, $J$ = 1.8, 17.3, 1H), 5.46 (dd, $J$ = 1.8, 10.3, 1H), 3.79 (s, 6H), 3.78 (s, 3H); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) $\delta$ 194.9, 153.3, 149.7, 147.1, 136.9, 135.8, 135.7, 133.2, 127.1, 109.5, 108.8, 106.7, 102.1, 60.6, 56.0; HRMS $m/e$ for C$_{19}$H$_{18}$O$_6$ calcd 342.1103, found 342.1107.

1-(3',3',4',4',5'-Pentamethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (137g)

![137g]

Title compound was prepared by following General Procedure F. Column chromatography (2:1 hexanes/diethyl ether) yielded the product (137g) as a yellow oil (95 % yield). IR (neat) $\nu_{\text{max}}$ 2958, 2932, 2838, 1652, 1582, 1482, 1458, 1402, 1255, 1124 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.12 (d, $J$ = 8.5, 1H), 7.00 (d, $J$ = 8.5, 1H), 6.46 (s, 2H), 6.36 (dd, $J$ = 11.0, 17.5, 1H), 5.85 (d, $J$ = 10.5, 1H), 5.83 (d, $J$ = 17.5, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 197.4, 153.1, 152.1, 146.1, 138.1, 137.3, 135.1, 133.8, 132.9, 131.3, 125.3, 113.2, 106.4, 61.9, 61.0, 56.2, 56.1; HRMS $m/e$ for C$_{20}$H$_{22}$O$_6$ calcd 358.1416, found 358.1414.
**1-(3-(3,4,5-Trimethoxyphenyl)thiophen-2-yl)prop-2-en-1-one (137h)**

![struct_137h](image)

Title compound was prepared from compound **136h** (0.0840 g, 0.274 mmol) by following **General Procedure F**. Column chromatography (2:1 diethyl ether/hexanes) yielded the product (**137h**) as a yellow oil (0.0587 g, 71 % yield). **IR** (neat) $\nu_{\text{max}}$ 2956, 2915, 2871, 1643, 1583, 1497, 1127 cm$^{-1}$; **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J= 5.0$, 1H), 7.13 (d, $J= 5.0$, 1H), 6.59 (s, 2H), 6.41 (dd, $J= 9.5$, 17.0, 1H), 6.35 (dd, $J= 2.5$, 17.0, 1H), 5.56 (dd, $J= 2.5$, 9.5, 1H), 3.91 (s, 3H), 3.85 (s, 6H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta$ 184.6, 153.1, 146.5, 139.7, 138.2, 133.8, 131.7, 131.4, 131.36, 128.2, 106.8, 61.0, 56.2; **HRMS m/e** for C$_{16}$H$_{16}$O$_4$S calcd 304.0769, found 304.0756.

**1-(2',3',4,4'-Tetrahydroxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (146a)**

![struct_146a](image)

Title compound was prepared by following **General Procedure F**. Column chromatography (1:1 diethyl ether/hexanes) yielded the product (**146a**) as a yellow oil (73
% yield). **IR** (neat) \( \nu_{\text{max}} \) 2937, 2837, 1668, 1599, 1482, 1463, 1414, 1291, 1272, 1087, 1014 \( \text{cm}^{-1} \); **\(^1H\) NMR** (500 MHz, CDCl\(_3\)) \( \delta \) 7.30 (d, \( J = 8.5 \), 1H), 7.15 (d, \( J = 2.5 \), 1H), 7.07 (dd, \( J = 3.0 \), 8.5, 1H), 6.88 (d, \( J = 8.0 \), 1H), 6.68 (d, \( J = 8.5 \), 1H), 6.29 (dd, \( J = 10.3 \), 17.3, 1H), 6.10 (dd, \( J = 1.5 \), 17.5, 1H), 5.56 (dd, \( J = 1.5 \), 10.0, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.57 (s, 3H); **\(^13C\) NMR** (125 MHz, CDCl\(_3\)) \( \delta \) 195.1, 158.6, 153.5, 151.1, 142.1, 140.2, 135.2, 132.3, 129.3, 128.4, 126.9, 125.0, 117.1, 113.1, 107.2, 61.0, 60.4, 56.0, 55.5; **HRMS** \( m/e \) for C\(_{19}\)H\(_{20}\)O\(_5\) calcd 328.1311, found 328.1318.

**1-(2',3',4'-Trimethoxy-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (146b)**

![146b](image)

**146b**

Title compound was prepared from compound **136j** (1.31 g, 4.36 mmol) by following **General Procedure F**. Column chromatography (1:1 diethyl ether/hexanes) yielded the product (146b) as a yellow oil (1.17 g, 90 % yield). **IR** (neat) \( \nu_{\text{max}} \) 3057, 2937, 1668, 1599, 1500, 1464, 1406, 1292, 1268, 1214, 1095 \( \text{cm}^{-1} \); **\(^1H\) NMR** (500 MHz, CDCl\(_3\)) \( \delta \) 7.62 (apparent dd, \( J = 1.0 \), 8.0, 1H), 7.52 (td, \( J = 1.5 \), 7.5, 1H), 7.42 (td, \( J = 1.5 \), 7.5, 1H), 7.38 (apparent dd, \( J = 1.0 \), 8.0, 1H), 6.91 (d, \( J = 8.5 \), 1H), 6.70 (d, \( J = 8.5 \), 1H), 6.33 (dd, \( J = 10.5 \), 17.0, 1H), 6.09 (dd, \( J = 1.5 \), 17.5, 1H), 5.59 (dd, \( J = 1.5 \), 10.5, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.58 (s, 3H); **\(^13C\) NMR** (75 MHz, CDCl\(_3\)) \( \delta \) 195.4, 153.9, 151.1, 142.3, 139.4, 137.1, 135.5, 131.2, 130.8, 128.7, 128.5, 127.4, 127.2, 125.1, 107.3, 61.1, 60.6, 56.1; **HRMS** \( m/e \) for C\(_{18}\)H\(_{18}\)O\(_4\) calcd 298.1205, found 298.12.
**General Procedure G:** A dilute solution of α, β-unsaturated ketone compound (133, 146a, and 137a-h) in anhydrous dichloromethane (concentration = 0.002 M) was cooled to 0 °C. Then, a solution of boron trifluoride diethyl etherate (cat. loading 5 mol %) in dichloromethane, was slowly added to the reaction solution. Stirring was continued and the mixture was allowed to gradually warm to room temperature. Upon the complete consumption of the starting material (3-24 h), the reaction was quenched with a saturated solution of sodium bicarbonate and extracted with dichloromethane (twice). The organic layer was separated and dried with anhydrous magnesium sulfate. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography to afford the tricyclic ketone products (117b and 138a-g).

**3,8,9,10-Tetramethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-one (117b)**

![117b](image)

(117b) from (133): Compound 133 (0.0408 g, 0.12 mmol) was subjected to the reaction conditions given under *General Procedure G* (4 h). Column chromatography (2:1 diethyl ether/hexanes) afforded title compound (117b) as a colorless solid (0.0307 g, 75% yield); mp 123-124 °C (lit.28 123-125 °C). Spectral data are in agreement with those reported in literature.
(117b) from (146a): To a solution of 146a (0.0374 g, 0.114 mmol) in anhydrous dichloromethane (60 mL) was added GaCl₃ (4.0 mg, 2.3 x 10⁻⁵ mmol). The mixture was heated to reflux until disappearance of starting material was evident by TLC (48 h). Following the addition of water and a conventional extractive workup (dichloromethane), preparative TLC (1:1 diethyl ether/hexanes) afforded 117b (0.0232 g, 62 % yield).

8,9,10-Trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-one (138a)

![138a](image)

(138a) from (137a): Compound 137a (0.0408 g, 0.124 mmol) was subjected to the reaction conditions given under General Procedure G (12 h). Column chromatography (1:1 diethyl ether/hexanes) yielded the title compound (138a) as a viscous yellow oil (81 % yield). IR (neat) νmax 2958, 2923, 2853, 1679, 1455, 1259, 1109, 1019, 800 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.56-7.62 (m, 2H), 7.40-7.43 (m, 2H), 6.73 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.92-3.00 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 206.8, 152.4, 150.3, 142.2, 139.0, 138.8, 134.7, 132.0, 129.1, 128.4, 127.8, 125.6, 109.4, 61.5, 61.0, 56.2, 47.7, 20.6; HRMS m/e for C₁₈H₁₈O₄ calcd 298.1205, found 298.1200.
(138a) from (146b): To a solution of 146b (0.0280 g, 0.093 mmol) in anhydrous toluene (30 mL) was added 0.10 mL (0.093 mmol, 1 equiv.) of AlCl₃ (1.0 M in nitrobenzene). The mixture was heated to reflux until disappearance of starting material was evident by TLC (24 h). Following the addition of water and a conventional extractive workup, preparative TLC (1:1 diethyl ether/hexanes) afforded 138a (0.0125 g, 45 % yield).

Methyl 8,9,10-trimethoxy-5-oxo-6,7-dihydro-5H-dibenzo[a,c][7]annulene-3 carboxylate (138b)

Compound 137b (0.0794 g, 2.23 mmol) was subjected to the reaction conditions given under General Procedure G (the catalytic loading of BF₃·OEt₂ for this reaction was 10 mol %; reaction time 48 h). Column chromatography (2:1 diethyl ether/hexanes) yielded the title compound (138b) as a colorless solid (68 % yield), mp 109-110.5 °C; IR (neat) νmax 2935, 1728, 1676, 1237, 1108 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (d, J= 1.5, 1H), 8.21 (dd, J= 1.8, 8.1, 1H), 7.50 (d, J= 8.1, 1H) 6.73 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H), 2.97 (br m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 205.8, 166.1, 152.6, 150.4, 143.0, 142.8, 139.1, 133.7, 132.6, 129.8, 129.6, 129.4, 125.9, 109.4,
61.5, 61.0, 56.2, 52.4, 47.4, 20.5; **HRMS m/e** for C$_{20}$H$_{20}$O$_6$ calcd 356.1260, found 356.1260.

3-Fluoro-8,9,10-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-one (138c)

Compound 137c (0.0413 g, 0.131 mmol) was subjected to the reaction conditions given under **General Procedure G** (48 h) with the exception of a doubling of solvent volume. Column chromatography (1:1 diethyl ether/hexanes) afforded the title compound (138c) as a viscous yellow oil (68 % yield). **IR** (neat) $\nu_{\text{max}}$ 2936, 2838, 1680, 1480, 1452, 1410, 1342, 1251, 1196, 1105, 796 cm$^{-1}$; **$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 7.42 (dd, $J$ = 5.4, 8.4, 1H), 7.24-7.34 (m, 2H), 6.68 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.91-3.00 (m, 4H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta$ 205.2, 162.0 (d, $J_{C,F} = 248$), 152.5, 150.3, 142.2, 140.5 (d, $J_{C,F} = 6.4$), 135.0 (d, $J_{C,F} = 3.5$), 133.7, 131.2 (d, $J_{C,F} = 7.0$), 125.5, 119.0 (d, $J_{C,F} = 21.0$), 115.1 (d, $J_{C,F} = 22.7$), 109.3, 61.4, 60.9, 56.2, 47.3, 20.5; **HRMS m/e** for C$_{18}$H$_{17}$FO$_4$ calcd 316.1111, found 316.1102.
Compound 137d (0.0702 g, 0.174 mmol) was subjected to the reaction conditions given under General Procedure G (reaction time: 48 h). Column chromatography (1:1 diethyl ether/hexanes) yielded the title compound (138d) as a yellow solid (81 % yield); mp 109-111°C. IR (neat) ν_max 2928, 1851, 1675, 1600, 1453, 1411, 1108, 1008, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.46 (m, 2H), 7.41 (t, J= 7.3, 2H), 7.35-7.37 (m, 2H), 7.24 (d, J= 3.0, 1H), 7.19 (dd, J= 3.0, 8.5, 1H), 6.69 (s, 1H), 5.13 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 2.92-3.00 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3, 158.3, 152.3, 150.3, 141.8, 139.9, 136.5, 134.5, 131.8, 130.7, 128.7, 128.2, 127.6, 125.4, 119.6, 113.3, 109.2, 70.2, 61.5, 61.0, 56.2, 47.5, 29.7, 20.6; HRMS m/e for C₂₅H₂₄O₅ calcd 404.1624, found 404.1621.
2,8,9,10-Tetramethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-one (138e)

![Image of 138e]

Compound 137e (0.0600 g, 0.183 mmol) was subjected to the reaction conditions given under General Procedure G (12 h). Column chromatography (2:1 diethyl ether/hexanes) yielded the title compound (138e) as a colorless solid (70 % yield), mp 120-122 °C. IR (neat) ν\text{max} 2928, 1727, 1678, 1482, 1457, 1413, 1255, 1103, 1031 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.36 (m, 1H), 7.13 (m, 2H), 6.69 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 6H), 2.94 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 206.4, 159.1, 152.3, 150.3, 141.8, 139.8, 134.5, 131.6, 130.6, 125.4, 119.0, 112.2, 109.2, 61.4, 61.0, 56.2, 55.5, 47.5, 20.6; HRMS m/e for C\(_{19}\)H\(_{20}\)O\(_5\) calcd 328.1311, found 328.1310.

2,3,4-Trimethoxy-5H-benzo[3',4']cyclohepta[1',2':4,5]benzo[1,2-d][1,3]dioxol-7(6H)-one (138f)

![Image of 138f]
Compound 137f (0.0510 g, 0.149 mmol) was subjected to the reaction conditions given under General Procedure G (72 h). Column chromatography (2:1 diethyl ether/hexanes) yielded the title compound (138f) as a solid (63 % yield), mp 145-147 °C.

**IR** (neat) \(\nu_{\text{max}}\) 2922, 2851, 1730, 1655, 1498, 1478, 1457, 1250, 1101, 1021 cm\(^{-1}\);

\(\text{^1H NMR}\) (500 MHz, CDCl\(_3\) \(\delta\) 7.12 (s, 1H), 6.88 (s, 1H), 6.65 (s, 1H), 6.06 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.97 (m, 2H), 2.87 (m, 2H); \(\text{^13C NMR}\) (125 MHz, CDCl\(_3\) \(\delta\) 204.9, 152.3, 150.9, 150.1, 147.3, 142.0, 134.9, 134.4, 133.1, 125.7, 109.4, 109.1, 108.6, 101.9, 61.4, 60.9, 56.2, 47.3, 20.6; \(\text{HRMS}\) \(m/e\) for C\(_{19}\)H\(_{18}\)O\(_6\) calcd 342.1103, found 342.1105.

**7,8,9-Trimethoxy-5,6-dihydro-4H-benzo[3,4]cyclohepta[1,2-b] thiophen-4-one (138g)**

![Chemical Structure](image)

To a solution of 137h (12.6 mg, 0.0414 mmol) in anhydrous dichloromethane (30 mL) was added GaCl\(_3\) (1.8 mg, 0.010 mmol, 0.25 equiv.). The mixture was stirred for 48 h at room temperature. Following the addition of water and a conventional extractive workup (dichloromethane), preparative TLC (1:1 diethyl ether/hexanes) afforded 138g (8.80 mg, 70 % yield) as a pale yellow oil. **IR** (neat) \(\nu_{\text{max}}\) 2931, 1646, 1493, 1452, 1119 cm\(^{-1}\);

\(\text{^1H NMR}\) (500 MHz, CDCl\(_3\) \(\delta\) 7.66 (d, \(J=\) 5.5, 1H), 7.33 (d, \(J=\) 5.0, 1H), 6.93 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.06 (br s, 2H), 2.83 (m, 2H); \(\text{^13C NMR}\) (125
MHz, CDCl3) δ 195.4, 151.9, 150.8, 143.6, 142.8, 139.4, 132.7, 129.7, 129.68, 127.1, 108.7, 61.5, 61.0, 56.2, 43.1, 20.0; HRMS m/e for C16H16O4S calcd 304.0769, found 304.0763.

**2,3-Dimethoxy-2'H-spiro[cyclohexa[2,5]diene-1,1'-naphthalene]-4,4'(3'H)-dione (147)**

![147]

To a solution of 146b (0.0150 g, 0.050 mmol) in anhydrous dichloromethane (15 mL) was added GaCl₃ (2.2 mg, 0.0126 mmol). The mixture was stirred for 12 h at room temperature. Following the addition of water and a conventional extractive workup (dichloromethane), preparative TLC (1:1 diethyl ether/hexanes) afforded the spiro-conjugated compound (147) as a colorless solid (9.63 mg, 67 % yield), mp 135-137 °C. IR (neat) νmax 3453, 2931, 1685, 1654, 1597, 1491 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.12 (dd, J= 1.0, 8.0, 1H), 7.51 (td, J= 1.5, 7.5, 1H), 7.42 (td, J= 1.5, 7.5, 1H), 7.07 (dd, J= 0.5, 7.8, 1H), 6.79 (d, J= 10.0, 1H), 6.27 (d, J= 10.0, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 2.95 (m, 1H), 2.83 (m, 1H), 2.70 (m, 1H), 2.24 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 196.1, 184.1, 164.6, 147.0, 141.5, 138.8, 134.1, 132.6, 128.4, 128.1, 127.3, 126.9, 61.2, 60.9, 48.5, 34.3, 32.5; HRMS m/e for C17H16O4 calcd 284.1049, found 284.1051.
(R)-8,9,10-Trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-ol (142a)

A suspension of 3-nitrophenylboronic acid (1.002 g, 6.0 mmol), L-tartaric acid (0.900 g, 6.0 mmol), and CaH₂ (0.500 g, 11.9 mmol) in anhydrous THF (15 mL) was heated to reflux for 1.5 h. After cooling and allowing the solids to settle completely, the supernatant solution (ca. 8 mL) was added to ketone 138a (0.1207 g, 0.405 mmol) and the solution was allowed to stir for 1 h at room temperature. Then, lithium borohydride (0.2 mL of a 2.0 M solution in THF, 0.405 mmol) was added dropwise over a period of 30 min, and stirring was continued for another one hour at room temperature. The reaction was then quenched with NaOH (ca. 5 mL of a 10 % aqueous solution) and the reaction was subjected to a conventional extractive workup using water and diethyl ether. Column chromatography (2:1 Et₂O/hexanes) afforded 142a (0.1199 g, 99 %) as a yellow viscous oil (99 % ee, Chiralcel OD-H, 10 % i-PrOH/hexanes; flow rate: 0.5 mL/min, retention time: 20.0 min). [α]²²D +80.1° (c 0.625, CH₂Cl₂). IR (neat) νmax 3427, 2933, 1404, 1340, 1099, 1041, 1011, 764, 733 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.63 (d, J= 7.5, 1H), 7.37 (m, 3H), 6.79 (s, 1H), 5.21 (d, J= 4.5, 1H), 4.31 (m, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 2.87 (m, 1H), 2.41 (m, 1H), 1.81 (m, 2H); ¹³C NMR (125 MHz, DMSO-d₆) δ 151.9, 150.7, 143.0, 141.6, 137.7, 135.7, 127.9, 127.7, 127.1, 124.9, 123.9, 108.7, 68.9, 61.9, 60.9, 56.3, 41.9, 21.9; HRMS m/e for C₁₈H₂₀O₄ calcld 300.1360, found 300.1360.
(R)-Methyl 5-hydroxy-8,9,10-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulene-3-carboxylate (142b)

Singaram\textsuperscript{44} protocol: A suspension of 3-nitrophenylboronic acid (1.002 g, 6.0 mmol), L-tartaric acid (0.900 g, 6.0 mmol), and CaH\textsubscript{2} (0.500 g, 11.9 mmol) in anhydrous THF (15 mL) was heated to reflux for 1.5 h. After cooling and allowing the solids to settle completely, the supernatant solution (ca. 4 mL) was added to ketone 138b (0.024 g, 0.067 mmol) and the solution was allowed to stir for 1 h at room temperature. Then, lithium borohydride (0.03 mL of a 2.0 M solution in THF, 0.067 mmol) was added dropwise over a period of 30 min, and stirring was continued for another one hour at room temperature. The reaction was then quenched with NaOH (ca. 4 mL of a 10 % aqueous solution) and the reaction was subjected to a conventional extractive workup using water and diethyl ether. Column chromatography (2:1 Et\textsubscript{2}O/hexanes) afforded 142b (0.019 g, 80 %) as a colorless solid (99 % ee, Chiralcel OD-H, 10 % i-PrOH/hexanes; flow rate: 0.5 mL/min, retention time: 25.5 min), mp 131-133.5 °C; [α]\textsuperscript{22}\textsubscript{D} +128° (c 0.110, CH\textsubscript{2}Cl\textsubscript{2}). \textbf{IR} (neat) \nu\textsubscript{max} 3479, 2934, 1713, 1341, 1290, 1101 cm\textsuperscript{-1}; \textbf{\textsuperscript{1}H NMR} (DMSO-\textit{d}\textsubscript{6}) \& 8.26 (s, 1H), 7.94 (dd, \textit{J}= 1.5, 8.0, 1H), 7.52 (d, \textit{J}= 8.0, 1H), 6.85 (s, 1H), 5.40 (d, \textit{J}= 5.0, 1H), 4.30-4.34 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.88 (dd, \textit{J}= 6.0, 13.0, 1H), 2.38-2.48 (m, 1H), 1.82-1.88 (m, 1H), 1.72-1.79 (m, 1H), 1.52-1.56 (m, 1H), 1.08 (s, 1H), 0.88 (s, 1H), 0.85 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H), 0.79 (dd, \textit{J}= 6.0, 13.0, 1H), 0.71 (s, 1H), 0.70 (s, 1H), 0.68 (s, 1H), 0.67 (s, 1H).
$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 166.9, 152.1, 150.8, 143.7, 142.6, 142.3, 134.6, 128.8, 128.5, 128.2, 125.2, 108.9, 68.8, 62.0, 61.0, 56.5, 52.7, 41.8, 21.8; HRMS m/e for C$_{20}$H$_{22}$O$_6$ calcd 340.1311 [M–H$_2$O]$^+$, found 340.1299.

**(S)-7-Azido-2,3,4-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulene (143a)**

![Structure of 143a](image)

To a suspension of alcohol 142a (0.0436 g, 0.145 mmol), Zn(N$_3$)$_2$-(pyridine)$_2$ (0.0685 g, 0.217 mmol), and triphenylphosphine (0.1521 g, 0.580 mmol) in toluene (12 mL) was added diisopropyl azodicarboxylate (116µL, 0.580 mmol) in a dropwise fashion. After stirring for 4 h, the mixture was filtered through a plug of silica gel, and concentrated under reduced pressure. Column chromatography (5:1 hexanes/Et$_2$O) afforded compound (143a) as a yellow oil (0.034g, 72 % yield). [α]$^{22}_{D}$ =−87° (c 0.55, CH$_2$Cl$_2$). IR (neat) $\nu_{max}$ 2934, 2097, 1717, 1245,1342, 1110, 766, 747 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.54 (s, 1H), 7.30 (m, 3H), 6.74 (s, 1H), 4.47 (br s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.01 (s, 1H), 2.55 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.1, 150.9, 142.0, 138.9, 137.2, 135.5, 128.4, 127.9, 124.5, 108.2, 61.7, 61.1, 56.3, 39.1, 21.6; HRMS m/e for C$_{18}$H$_{19}$N$_3$O$_3$ calcd 325.1426, found 325.1414.
(S)-Methyl 5-azido-8,9,10-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulene-3-carboxylate (143b)

To a suspension of alcohol 142b (0.0844 g, 0.235 mmol), Zn(N3)2-(pyridine)2 (0.111 g, 0.353 mmol), and triphenylphosphine (0.247 g, 0.942 mmol) in toluene (18 mL) was added diisopropyl azodicarboxylate (188µL, 0.942 mmol) in a dropwise fashion. After stirring for 4 h, the mixture was filtered through a plug of silica gel, and concentrated under reduced pressure. Column chromatography (5:1 hexanes/Et2O) afforded compound (143b) as a yellow oil (0.0676 g, 77 % yield). [α]D -102° (c 0.490, CH2Cl2). IR (neat) vmax 3325, 2980, 2938, 2103, 1721, 1481, 1455, 1435, 1241, 1225, 1108 cm⁻¹; ¹H NMR (500 MHz, DMSO-d6) δ 8.07 (s, 1H), 8.01 (d, J= 8.0, 1H), 7.61 (d, J= 8.0, 1H), 6.91 (s,1H), 4.70 (br s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 (s, 6H), 2.80 (br, 1H), 2.54 (m, 1H), 2.02 (m, 1H), 1.21 (m, 1H); ¹³C NMR (125 MHz, DMSO-d6) δ 166.4, 152.3, 150.9, 142.5, 137.7, 134.1, 129.6, 129.2, 129.1, 124.3, 109.0, 61.9, 60.9, 56.4, 52.7, 38.6, 21.6; HRMS m/e for C₂₀H₂₁N₃O₅ calcd 383.1481, found 383.1481.
(S)-N-(8,9,10-Trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-yl)acetamide

(144)

Title compound was prepared from azide 143a (0.0333 g, 0.10 mmol) according to the reductive amination/acylation protocol of Wulff and co-workers. Column chromatography (19:1 CH$_2$Cl$_2$/MeOH) yielded 144 (0.0248 g, 71% yield) in 98% ee (Chiralcel OD-H, 10 % i-PrOH/ hexanes; flow rate: 0.5 mL/min, retention time: 22.4 min). A single recrystallization afforded (144), in > 99% ee, as colorless crystals, mp 218-220.6 °C; [α]$^22_D$ −35.0° (c 0.355, CHCl$_3$). IR (neat) $\nu_{\text{max}}$ 3279, 2933, 1635, 1546, 1108, 1054, 770, 749; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.43 (d, $J$= 8.0, 1H), 7.34-7.37 (m, 4H), 6.84 (s, 1H), 4.52 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.92 (m, 1H), 2.18 (m, 1H), 1.97 (m, 1H), 1.88 (s, 3H), 1.77 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 169.0, 152.2, 150.8, 141.7, 140.3, 138.9, 135.9, 128.5, 128.0, 127.5, 124.4, 123.9, 108.9, 62.0, 61.0, 56.4, 48.9, 23.2, 22.3; HRMS $m/e$ for C$_{20}$H$_{23}$NO$_4$ calcd 341.1627, found 341.1616.
(S)-Methyl 5-acetamido-8,9,10-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulene-3-carboxylate (145)

\[
\text{MeO} \quad \text{NHAc} \\
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe}
\]

145

Title compound was prepared from azide 143b (0.0674 g, 0.175 mmol) according to the reductive amination/acylation protocol of Wulff and co-workers.\textsuperscript{24} Column chromatography (19:1 CH\textsubscript{2}Cl\textsubscript{2}/ MeOH) yielded 145 (0.033 g, 57% yield) in 99 % ee (Chiralcel OD-H, 10 % i-PrOH/hexanes; flow rate: 0.5 mL/min, retention time: 29.5 min). A single recrystallization afforded (145), in > 99% ee, as colorless crystals, mp 205-207.5 °C; \([\alpha]\textsubscript{D}\textsuperscript{22} = -136.7^\circ\) (c 0.1550, CHCl\textsubscript{3}). IR (neat) \(\nu\text{max} 3266, 2928, 1720, 1643, 1298, 1103, 1012 \text{ cm}^{-1}\); \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \(\delta\) 8.61 (d, \(J= 8.5, 1\text{H})\), 7.95 (m, 2H), 7.55 (d, \(J= 7.5, 1\text{H})\), 6.93 (s, 1H), 4.52 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.92 (m, 1H), 2.18 (m, 1H), 1.97 (m, 1H), 1.88 (s, 3H), 1.77 (m, 1H); \textsuperscript{13}C NMR (75 MHz, DMSO-\textit{d}_6) \(\delta\) 169.1, 166.8, 152.3, 150.9, 143.8, 142.4, 141.1, 134.7, 129.1, 129.0, 128.4, 124.8, 124.6, 109.0, 62.1, 61.0, 56.4, 52.8, 48.9, 26.0, 23.2, 22.2; HRMS \textit{m/e} for C\textsubscript{22}H\textsubscript{25}NO\textsubscript{6} calcd 399.1682, found 399.1675.
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