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SYNTHESIS OF CYCLOHEPTA[DE]NAPHTHALENES VIA NICHOLAS REACTIONS. THE FIRST TOTAL SYNTHESIS OF MICROSTEGIOL, A REARRANGED ABIETANE

by

Rafiq Ali Taj

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
2011
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Synthesis of Cyclohepta[de]naphthalenes via Nicholas Reactions. The First Total Synthesis of Microstegiol, a Rearranged Abietane

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Declaration of Co-Authorship / Previous Publication

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The thesis also incorporates the outcomes of a research undertaken under supervision of Professor James Green. The collaboration is covered in Chapter 2, 3 and 4 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 advice when needed.

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ABSTRACT

The Nicholas reaction is one of the important organometallic transformations in organic chemistry. The facile synthesis of its precursors, complexation of alkyne with the Co$_2$(CO)$_6$ unit, and straightforward demetallation after the completion of the reaction has made this reaction a tool of first choice for the synthetic chemist. Due to its versatile applications in organic syntheses, Nicholas reaction chemistry was considered to be well suited to the preparation of a cyclohepta[de]naphthalenes. Natural products such as microstegiol, oxomicrostegiol, salvibretol and oxosalvibretol are important examples of compounds possessing cyclohepta[de]naphthalene carbon skeleton, and to date, no synthesis of any of these compounds appears in the literature.

In a model study for the synthesis of cyclohepta[de]naphthalenes, the reactivity pattern of propargyldicobalt cations with derivatives of naphthalene-2,7-diol, such as 2,7-dimethoxy- and dibenzylxynaphthalene, were investigated under conventional Nicholas reaction conditions. Predominantly C-1 monocondensation and 1,6-dicondensation reaction products were formed, while in selected instances C-3 monocondensation or 1,8-dicondensation products were favoured.
The mono- and dicondensation Nicholas reaction products were employed to synthesize cyclohepta[de]naphthalenes via ring closing metathesis and Friedel Crafts reactions. The application of Nicholas reaction chemistry of a selectively protected 2,7-naphthalenediol in the synthesis of the natural product (±)-microstegiol was investigated. The differentially protected 2,7-naphthalenediol allowed the selective replacement of one of oxygen functions by a methyl group, and facile deprotection of other oxygen function allowed tautomerization to a cyclohepta[de]naphthalene-1-one upon seven membered ring closure in most cases. Ultimately the total synthesis of (±)-microstegiol was accomplished in 15 steps with 7.2% overall yield from 2,7-dihydroxynaphthalene.
\[
\begin{align*}
\text{R}^3 \text{R}^4 = \text{OMe or Me} \\
\text{OR}^2 = \text{OMe or O} \\
\text{R}^3 = \text{H}_2 \text{ Me}_2 \text{ or =O}
\end{align*}
\]
DEDICATION

I dedicate this thesis to my parents, for their love and my wife, for her endless cooperation, support and encouragement throughout my studies.
ACKNOWLEDGMENTS

First of all I would like to give thanks to my supervisor, Dr. James Green for accepting me as his student, his constant guidance in class and lab, patience and support throughout my graduate studies. Personally I feel it is difficult to thank him in few sentences. It is promised that his encouragement, sound advice and good company will always be remembered and appreciated.

I would like to thank to my graduate committee members, Dr. Stephen Loeb and Dr. Holger Eichhorn for their help and support. I also would like to thank to Mike Fuerth and Dr. Matthew Revington for their help in NMR spectroscopy.

I would like to thank to all past and present members of Green group, especially Dr. Ahmed Mohamed and Dr. Sheida Amiralaei for their encouragement, kindness and support.
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LIST OF ABBREVIATIONS

Å  angstrom
Ac  acetate
Bn  benzyl
bpy  2,2'-bipyridine
br  broad
brsm  based on the recovered starting material
BSA  N,O-bis(trimethylsilyl)acetamide
BTMSA  bis(trimethylsilyl) acetylene
Bu  butyl
Bu₂BOTf  dibutyl[[(trifluoromethyl)sulfonyl]oxy]borane
BuLi  butyllithium
CAN  ceric ammonium nitrate
CDCl₃  deuterated chloroform
d  doublet
de  diastereomeric excess
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DIAPHOSXs</td>
<td>P-chirogenic diaminophosphine oxides</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1′-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dppm</td>
<td>1,1-bis(diphenylphosphino)methane</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplet</td>
</tr>
<tr>
<td>Equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>LiTMP</td>
<td>lithium 2,2,6,6-tetramethylpiperidide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m/e</td>
<td>ratio of mass to electron charge</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Mo(CO)$_6$</td>
<td>molybdenum hexacarbonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>MSA</td>
<td>molybdate sulfuric acid</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>P(OPh)$_3$</td>
<td>triphenyl phosphite</td>
</tr>
<tr>
<td>PBu$_3$</td>
<td>tributyl phosphine</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>tris(dibenzylideneacetone)dipalladium</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPh$_3$</td>
<td>triphenyl phosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
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<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAHS</td>
<td>tetrabutylammonium hydrogen sulfate</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>tmeda</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (4-toluenesulfonyl)</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield shift from a standard</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

1.1. Nicholas Reaction

The Nicholas reaction is an important organic transformation which employs a propargyl alcohol derivative 1 that has been complexed with octacarbonyldicobalt Co$_2$(CO)$_8$, to give complex 2. A stabilized propargylic cation 3 is generated on treatment of compound 2 with a protic or Lewis acid. Commonly used acids are BF$_3$-OEt$_2$, SnCl$_4$, Bu$_2$BOTf, AgBF$_4$, HF-SbF$_5$ and HBF$_4$-OEt$_2$. These propargylic cations, on treatment with a variety of nucleophiles, give complexed product 4. After the removal of Co$_2$(CO)$_6$ moiety by oxidation, substituted alkyne product 5 is obtained (Scheme 1.1).

![Scheme 1.1](image)

Scheme 1.1. Generation of stabilized dicobalt propargylic carbocation and Nicholas reaction.

This reaction was first described in the literature in 1972 when Nicholas and Pettit$^2$ reported the dehydration of dicobalt hexacarbonyl complexed propargyl alcohol 6 to give 1,3-enyne complex 7, by using an appropriate acid in the absence of a nucleophile. They discovered that there is an equilibrium established between the
complexes of the propargyl alcohol and 1,3-enzyme in the presence of an acid, which allowed them to postulate the existence of stable intermediate 3 in this reaction. This intermediate was the propargyl-Co$_2$(CO)$_6$ cation, which was confirmed by reacting with a variety of carbon based nucleophiles to get product 4 (Scheme 1.2).

![Scheme 1.2. First Nicholas reaction.](image)

These alkyne-Co$_2$(CO)$_6$ complexes can be prepared in a variety of solvents, such as dichloromethane, diethyl ether, heptane, and ethyl acetate, and exist as reddish brown solids or oils that can be purified by chromatography (silica or alumina). They are stable enough that they can be stored at reduced temperature for long periods of time and can be characterized spectroscopically.

The leaving group in Nicholas reactions may be an alcohol, ether (cyclic or acyclic), ester or halide. In the case of enyne-Co$_2$(CO)$_6$ complexes, electrophiles can be used for cation generation. These carbocations are very stable because of the delocalization of the positive charge onto the Co$_2$(CO)$_6$ moiety. The stability of these carbocations is comparable to that of the well-known stable cation, triphenylmethyl.
cation (trityl cation, \( \text{Ph}_3\text{C}^+ \)). This is demonstrated from the \( pK_{R^+} \) value of propargyl carbocation complexes, which is \(-6.8\) to \(-7.4\) \(^4\) (\(-5.5\) in an alternative reference \(^5\)), while for the trityl cation it is \(-6.6\).\(^6\) The electron density distribution of propargyl cation complexes can be studied spectroscopically by comparing the spectra of the cationic species and the parent alcohol complex. For the cation complexes, IR absorption frequencies for the CO ligands are increased by the order of 40-60 cm\(^{-1}\) as compared to that of the neutral complex. Similarly, \(^1\)H NMR and \(^{13}\)C NMR spectra show less of a deshielding effect for the alkyl groups \( \alpha \)- to the newly formed carbocation than expected for the presence of most cations, which supports the delocalization concept of the cation.

The regiochemistry of reactions of these cations is very specific. Nucleophiles exclusively attack at the propargylic position. Usually the nucleophile is present at the time of the \textit{in situ} generation of the cation. Enyne formation is possible by the elimination of \( \text{H}^+ \) from the complexed cation, but this transformation normally doesn’t happen in the presence an appropriate nucleophile.

These propargyldicobalt hexacarbonyl cations can be attacked by a wide variety of nucleophiles. Oxygen based nucleophiles include alcohols and water to give alkoxy and hydroxy groups, respectively.\(^7\) Nucleophiles containing nitrogen include amines, sulfonamides and (rarely) acetonitrile. A broad range of carbon based nucleophiles include electron rich aromatics, ketones, allylsilanes, allylstannanes, allylboranes, and allylborinates.\(^8\) Ketones are less reactive as nucleophiles towards propargyl dicobalt hexacarbonyl cations; they are only successful when present in large concentration and react through their enol forms. Carbonyl derivatives having large concentrations of their enol forms, such as enol silanes, enol boranes and enamines, are considered to be very
trustworthy nucleophiles. Hydrides such as NaCNBH$_3$ can also be used as nucleophiles to reduce the propargyl cations.

In 1987, Schreiber$^{10}$ proposed a model for the structure of propargyldicobalt hexacarbonyl cation complexes, on the basis of variable temperature NMR spectroscopic studies of these species. According to this model, the propargylic carbon slightly bends towards one of the two cobalt atoms. It is fluxional by two processes, an antarafacial migration and a suprafacial migration of the formal cationic carbon between the two cobalt atoms. The antarafacial migration is the lower energy phenomenon, which causes enantiomerization, while the suprafacial migration is a higher energy process which leads to syn/anti isomerization (Figure 1.1).

![Figure 1.1. Fluxional processes in the propargyldicobalt cation (published with the permission of the author)](image-url)
After the Schreiber proposal concerning the structure of propargyldicobalt hexacarbonyl cation was reported, several attempts were made to confirm this structure through X-ray crystallography. Unfortunately, simple versions of these carbocations are not stable enough to perform X-ray crystallography, but in 1998 the Melikyan group successfully obtained the first X-ray crystal structure of a cation stabilized by two alkyne-Co$_2$(CO)$_6$ groups and with BF$_4^-$ as a counterion (8, Figure 1.2).

![Figure 1.2](image-url)  

**Figure 1.2.** Crystal structure of a cation stabilized by two alkyne-Co$_2$(CO)$_6$ units.

1.2. **Decomplexation of Dicobalt Hexacarbonyl Alkyne Complexes**

After the Nicholas reaction is complete, the main issue is the removal of the Co$_2$(CO)$_6$ unit. There are many methods which have been used for this decomplexation. Mainly they are oxidative or reductive methods.
There are three common methods for oxidative removal of the Co$_2$(CO)$_6$ unit from alkynes.

1. Ceric ammonium nitrate (CAN) [(NH$_4$)$_2$Ce(NO$_3$)$_6$];$^{12}$
2. Molecular iodine (I$_2$);$^{13}$
3. Triethyl/methylamine N-oxide (Et$_3$NO).$^{14}$

For the decomplexation of the alkyne, ceric ammonium nitrate (CAN) and molecular iodine (I$_2$) are the most popular oxidizing reagents. Decomplexation by molecular iodine is considered to be the most efficient method (Scheme 1.3).

![Scheme 1.3. Decomplexation of dicobalt hexacarbonyl alkyne complexes by CAN and I$_2$.](image)

The decomplexation of alkyne dicobalt hexacarbonyl complexes by CAN sometimes give an unusual anhydride product. This anomalous behavior of CAN has been observed in both acyclic$^{15}$ and cyclic$^{16-17}$ alkyne dicobalt hexacarbonyl complexes. This oxidative decomplexation happens by using excess of CAN. It has been suggested that this anhydride formation is associated with the insertion of CO into each metal-carbon bond. The removal of the Co$_2$(CO)$_6$ unit could also be done oxidatively by using
trimethylamine N-oxide. It works fine at room temperature and organic solvents (Scheme 1.4).

Scheme 1.4. Anhydride formation by ceric ammonium nitrate and decomplexation with Me₃NO.

Reductive decomplexation is associated with the removal of Co₂(CO)₆ unit from alkyne dicobalt hexacarbonyl complexes to form alkenes rather than alkynes. This transformation has been accomplished on both acyclic and cyclic alkyne dicobalt hexacarbonyl complexes. In the case of cyclic alkyne dicobalt hexacarbonyl complexes, reductive decomplexation is often employed to reduce the angle strain. There are many reagents being employed for this purpose; some of these are:

1. Tributyltin hydride, Bu₃SnH;¹⁸
2. Triethylsilane (Et₃SiH) with bistrimethylsilyl acetylene (BTMSA);¹⁹
3. Sodium hypophosphite (NaPO₂H₂·H₂O);²⁰
4. High pressure H₂/Rh (Rh/C or Wilkinson’s catalyst);²¹
5. Birch reduction.²²

Tributyltin hydride (Bu₃SnH) is very common reagent for reductive decomplexation of both endo- and exocyclic alkyne dicobalt hexacarbonyl complexes to give olefin products. The Isobe group reported that tributyltin hydride completely tolerates free OH groups and works efficiently for terminal and disubstituted alkynes. It gives cis-olefin products in case of disubstituted alkyne complexes. Endocyclic alkyne dicobalt hexacarbonyl complexes give cis-alkenes without migration of the double bond at 65 °C (Scheme 1.5).

\[
\text{(OC)}_6\text{Co}_2\text{OCTBDPS} \xrightarrow{n-\text{Bu}_3\text{SnH (10-20 equiv)}} \xrightarrow{\text{C}_6\text{H}_{10} 65 ^\circ\text{C}, 60\%} \text{OTBDPS}
\]

\[
\text{THPO}\text{Co}_2(\text{CO})_6\text{OH} \xrightarrow{n-\text{Bu}_3\text{SnH (10-20 equiv)}} \xrightarrow{\text{C}_6\text{H}_{10} 65 ^\circ\text{C}, 64\%} \text{THPOOH}
\]

Scheme 1.5. Reductive decomplexation with tri(n-)butyltin hydride.

The Isobe group also developed the hydrosilative reductive decomplexation of dicobalt hexacarbonyl complexes by using triethyl- or triphenylsilanes to give vinylsilanes.¹⁹ The products are exclusively all in cis-form. The main drawback of this reaction is the formation of side products such as O-silylation and olefin-isomerization. The Isobe group worked on this problem and concluded that Co₂(CO)₆ species, removed in this reaction is responsible for the olefin isomerization and O-silylation. To avoid this
problem, Isobe group used bis(trimethylsilyl) acetylene (BTMSA) as a scavenger for the 
Co₂(CO)$_6$ species (Scheme 1.6).

Scheme 1.6. Reductive decomplexation by triethylsilane.

The Isobe group has done considerable further work on the reductive
decomplexation of acetylene dicobalt hexacarbonyl complexes. In 2002, they reported
sodium hypophosphite monohydrate as a safe, effective and economical reagent for the
decomplexation of Nicholas reaction products.$^{30}$ This is a good substitute of well known
toxic and expensive reducing agent, tri(n)-butyltin hydride. They used this reagent on a
variety of heterocyclic alkyne-Co₂(CO)$_6$ complexes ranging from 7-9 membered ring
sizes. There was no issue of olefin migration and even a free OH survived during the
reaction. Sodium hypophosphite has been used for reductive decomplexation of cyclic
ethers but its effectiveness against all carbon cyclic alkyne dicobalt hexacarbonyl
complexes has not been reported yet. (Scheme 1.7)

Scheme 1.7. Reductive decomplexation by sodium hypophosphite monohydrate.
Isobe has removed the Co$_2$(CO)$_6$ moiety from heterocyclic alkyne complexes of ring sizes ranging from 7-10 members by using hydrogenation under a high pressure of H$_2$. This decomplexation was accomplished by treating the complexes with 5 mol% of Rh/C as a catalyst under 100-150 kg/cm$^2$ H$_2$ atmosphere at 60 °C for 5h to give 52-86% product yields, without double bond migration (Scheme 1.8).

**Scheme 1.8.** Reductive decomplexation by hydrogenation under high pressure.

Tanino and his co-worker used the Birch reduction to remove the Co$_2$(CO)$_6$ moiety from cyclic alkynes reductively to give corresponding alkenes during the synthesis of natural product ingenol (Scheme 1.9).^21

**Scheme 1.9.** Reductive decomplexation by Birch conditions.

1.3. α, β-Unsaturated γ-Carbonyl Cation Equivalents
The majority of the organic reactions are polar in character, which means that some reactants are nucleophilic (electron donor), and some are electrophilic (electron acceptor) in character. This polarity is due to the presence of the heteroatoms, particularly in nitrogen and oxygen containing functional groups. These functional groups are responsible for the existence of an alternating donor/acceptor reactivity pattern in a carbon chain, which can be extended as far as conjugated unsaturation is also present. This reactivity pattern often limits readily prepared compounds to 1,3- and 1,5- (odd number of carbon atoms between the functional groups) di-heteroatom substituted synthetic products, while 1,2- and 1,4-disubstituted synthetic products are more difficult to prepare (Figure 1.3).

![Figure 1.3](image-url)

**Figure 1.3.** 1,2- and 1,4- vs 1,3- and 1,5-disubstituted products.

Nevertheless, there are many natural products having 1,2- and 1,4- and 1-6-disubstituted patterns such as jervine\(^23\), (+)-phyllantidine\(^24\), velloziolide\(^25\), and gibberellic acid\(^26\) (Figure 1.4).
The question then arises, how these bifunctional compounds can be generated. In 1967, Seebach and Corey put forward a new concept in synthetic chemistry that these types of compounds can be generated by reversing the polarity of the functional groups. This technique is known as umpolung synthesis. "Umpolung" is a German word which means reversed polarity (Figure 1.5).

Figure 1.4. Umpolung examples.

Figure 1.5. Normal vs Umpolung reactivity.
In umpolung synthesis polarity in the functional group changes in some way. This polarity change may be extended through carbon skeleton to make the α- and γ- carbons electron deficient or β-carbons nucleophilic. This section will focus on how γ- carbonyl cations, and especially α,β-unsaturated γ- carbonyl cations can be generated. There are a few methods that are already in use to generate the γ- carbonyl cations equivalents such as:

1. Ring opening reactions of carbonyl-substituted cyclopropanes;
2. By way of π-allylmolybdenum complexes;
3. By way of π-allylpalladium complexes;
4. By way of iron tetracarbonyl complexes with π-allyl cations;
5. By way of the Nicholas reactions.

1.3.1. Ring Opening Reactions of Carbonyl-Substituted Cyclopropanes

Cyclopropane is extensively being used in synthetic chemistry to prepare a variety of target molecules. This is the smallest member of the cycloalkane family. Its importance in synthetic chemistry is due to the strain in its cyclic structure. The ring strain is usually attributed for the instability and reactivity of small ring compounds. The strain in this ring system can be understood by studying its structure deeply. Cyclopropane (C₃H₆) is a three carbon ring system in which each carbon is formally sp³ hybridized which means that every carbon is tetrahedral and ideally should have 109.5° angle. In cyclopropane the C-C-C angle is 60°. This causes the angle strain in cyclopropane. Another type of strain that arises due to the bond arrangement is torsion strain, which exists because all bonds are not ideally staggered. Since cyclopropane has a
planar structure, because all the C-C and C-H bonds are eclipsed. The total estimated ring strain in cyclopropane is 27.4 kcal/mol (Figure 1.6).28

**Figure 1.6.** Structure of cyclopropane.

In modern synthetic chemistry, cyclopropanes have become an important tool for chemists to synthesize a wide range of organic compounds due to their exceptional reactivity. Their chemical reactivity ranges from electrophilic to nucleophilic. A variety of dipolar reagents such as esters, aldehydes29, imines30, nitrones31, nitriles32, and others, react with cyclopropanes to give five- and six-membered heterocycles. Cyclopropanes with electron withdrawing groups (EWG) react with a variety of nucleophiles as homo-Michael acceptors in ring opening reactions33 (Figure 1.7).

![Diagram of cyclopropane reaction](image)

**EWG = Electron withdrawing group, CO₂R, C(O)R, CN, etc.**

**Figure 1.7.** General reaction of cyclopropane.
In these cases, the activated cyclopropanes are attacked by nucleophiles at the \( \gamma \)-carbon. This was originally introduced by Bone and Perkin.\(^{34}\) They used diethyl malonate 9 as a nucleophile to attack the \( \gamma \)-carbon of highly substituted cyclopropane 10 (no substitution at \( \gamma \)-carbon) in the presence of sodium ethoxide to give tetraester product 11, which eventually suffered a cyclization-decarboxylation to afford cyclic ketone 12 in ca. 50 % yield (Scheme 1.10).

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_{2}\text{Et} \\
\text{EtO}_2\text{C} & \quad \text{CO}_{2}\text{Et} \\
\text{EtO}_2\text{C} & \quad \text{CO}_{2}\text{Et} \\
\text{EtO}_2\text{C} & \quad \text{CO}_{2}\text{Et} \\
\text{EtO}_2\text{C} & \quad \text{CO}_{2}\text{Et}
\end{align*}
\]

\[9 \quad 10 \quad \text{NaOEt} \quad 11 \quad 12\]

**Scheme 1.10.** 1,5-version of ring opening of cyclopropane.

Linstead and co-worker\(^{35}\) extended the Bone and Perkin work by using a vinyl substituted (at the \( \gamma \)-carbon) version of the same substrate 13 to study the regiochemical outcome of this reaction. The major final cyclic product 14 of this reaction with diethyl malonate was of the same type as before, through a 1,5-(\( \gamma \)-) mode of ring opening. They detected a minor product 15, through a 1,7-mode of ring opening (Scheme 1.11). This reaction demonstrates that the ring opening of cyclopropane is favored such as to proceed as if the formal positive charge resides on the more substituted carbon (the \( \gamma \)-carbon).
Scheme 1.11. 1,5- vs 1,7- ring opening of cyclopropane.

Recently, the Charette group reported that enantioenriched, 1-nitrocyclopropane-carboxylates rings can be opened by aromatic alcohols\(^{36}\) in the presence of Cs\(_2\)CO\(_3\) base to afford aryl ether products in good yields (53-84\%), with complete inversion of configuration at the chiral centre. This ring opening tolerates a variety of groups on the phenol and the cyclopropane. Both electron donating (R = o-OMe (78\% yield)) and electron withdrawing groups (R = p-CF\(_3\) (84\%)) give good yields (Scheme 1.12).

Scheme 1.12. Ring opening of enantioenriched cyclopropanes by phenols.
During the same period, the Charette group also reported the Lewis acid catalyzed ring opening of enantioenriched cyclopropanes amine nucleophiles. The reaction proceeds at room temperature, with complete inversion of stereochemistry at reacting site of the cyclopropane (Scheme 1.13).

![Scheme 1.13. Ring opening of enantioenriched cyclopropanes by amines.](image)

The nucleophilic ring opening of electron deficient diactivated cyclopropanes has been reported frequently in literature, but ring opening of mono-activated cyclopropanes has seen less attention. Recently, Movassagh and co-worker reported the one pot nucleophilic ring opening of mono-activated cyclopropanes under very mild conditions with arylselenolates in the presence of a Zn/AlCl₃ system, in moderate to excellent yields (48-90%). The diaryl diselenide 18 was reductively cleaved by using Zn/AlCl₃ system to give zinc selenolate 19. The selenolates are weak bases, but they are powerful soft nucleophiles because of the presence of the highly polarizable selenium atom. The Zn selenolate reacts with mono-activated cyclopropanes 20 (X = COMe, COOH, CN, COOPh, CHO) to afford γ-arylselenenyl ketones, acids, nitriles and aldehydes (21) respectively (Scheme 1.14).
cyclopropane and for the Conia-ene ring closing. This issue was solved by selecting Zn(NTf₂)₂ as Lewis acid, as it can act efficiently in both transformations (Scheme 1.15).


Recently, the Kerr group⁴¹ reported the ring opening of 1,1-cyclopropanediesters 20 by 2-alkynylindole 21, followed by the Conia-ene ring closing, to afford a one step synthesis of tetrahydrocarbazoles 22 in dichloroethane in good to excellent yields (63-88%). Usually, Lewis acids of a different nature are required for the ring opening of the cyclopropane and for the Conia-ene ring closing. This issue was solved by selecting Zn(NTf₂)₂ as Lewis acid, as it can act efficiently in both transformations (Scheme 1.15).

Scheme 1.15. Ring opening of cyclopropanes by indoles.
1.3.2. By Way of $\pi$-Allylmolybdenum Complexes

Cationic transition metal $\pi$-complexes of allyl ligands bearing electron withdrawing groups may be considered to act as stabilized $\gamma$-carbonyl cation equivalents. Most commonly, these are $\pi$-allylmolybdenum, -palladium or -iron complexes. These complexes have a high profile in synthetic chemistry because of their enhanced reactivity relative to the non metallated compounds towards a wide range of nucleophiles to form carbon-carbon and carbon-heteroatom bonds.

Trost discussed the regioselectivity of nucleophilic attack issue in the case of $\gamma$-acetoxy-$\alpha,\beta$-unsaturated esters 23 complexed with Mo(CO)$_5$. In order to check the role of steric and electronic effects on the regioselectivity of reaction of $\pi$-allylmolybdenum complexes, dimethyl malonate and dimethyl methylmalonate 24 were used in the presence of an appropriate base. It was observed in both cases that in the presence of the electron withdrawing group (ester), $\gamma$-alkylation totally dominated to give 25 and there was no sign of $\alpha$-alkylation. In case of dimethyl methylmalonate, the alkylation at the $\gamma$-position was fast and efficient (60% in 2 h) as compared to dimethyl malonate (33% and 66% brsm in 4 h)$^{42}$. This confirms that regioselectivity mainly depends on electronic factors (Scheme 1.16).

\[
\begin{align*}
\text{OAc} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{O} \\
\text{OMe} & \quad \text{R} \\
\text{MeO} & \quad \text{O} \\
\text{OMe} & \quad \text{R}
\end{align*}
\]

BSA = (O,N-bis(trimethylsilyl)acetamide)

\[\text{R} = \text{H} \quad 33\% (66\% \text{ brsm}) \text{ in } 4 \text{ h} \]
\[\text{R} = \text{CH}_3 \quad 60\% \text{ in } 2 \text{ h}\]

Scheme 1.16. $\gamma$-Carbocation equivalents by $\pi$-allylmolybdenum complexes.
The Liebeskind group has had a long-standing interest in using enantiomerically pure complexes of molybdenum for the asymmetric construction of a large variety of organic compounds, especially for the total synthesis of natural products.\textsuperscript{43} They used neutral TpMo(CO)\textsubscript{2}(\eta\textsuperscript{3}-pyranyl) and TpMo(CO)\textsubscript{2}(\eta\textsuperscript{3}-pyridinyl) complexes as versatile enantiomerically pure scaffolds for the asymmetric synthesis of bicyclic organic compounds (Tp = hydridotris(pyrazolyl)borate). These neutral complexes react efficiently with strong acids and electrophiles, but are quite stable against mild acids and electrophiles. In the early work, they synthesized the Chinese herbal medicine, (±)-Bao Gong Teng, from the racemic version of TpMo(CO)\textsubscript{2}(\eta\textsuperscript{3}-pyridinyl) complex 26, where γ-carbocation chemistry was employed. The Mukaiyama-Michael reaction of pyridinyl complex with methyl vinyl ketone (27), gave product 28 in 90% yields. The intramolecular “1,5-Michael reaction” of 27 gave an internal oxo-\eta\textsuperscript{3}-allylmolybdenum complex 29 in 97% yield and with 40:1 exo-endo diastereoselectivity, by the attack of an internal enolate on γ-carbon of this complex.\textsuperscript{44} Oxidative demetallation was done cleanly by ceric ammonium nitrate (CAN) in good to excellent yield (Scheme 1.17).
Scheme 1.17. Neutral TpMo(CO)$_2$(η$^3$-pyridinyl) complexes.

1.3.3. By Way of π-Allylpalladium Complexes

Similarly, π-allylpalladium complexes are being used extensively for the formation of carbon-carbon or carbon-heteroatom bonds to give neutral products after demetallation.$^{44}$ According to the general concept, attack of nucleophiles on the η$^3$-allylpalladium complexes occur mainly in two distinct ways. Hard nucleophiles, derived from conjugate acids (pK$_a$ > 25), attack on the metal. On the other hand, soft nucleophiles (pK$_a$ < 25), attack on π-allyl unit from the face opposite to the transition metal.$^{45a}$ The main issue of this reaction for γ-carbonyl cation purposes is its regioselectivity. Delbecq and co-workers$^{45}$ reported their work on the predicted regioselectivity of this reaction on the basis of density functional calculations. According to their findings, both steric and electronic effects control the direction of nucleophilic attack (C-1 or C-3) on the η$^3$-
allylpalladium complexes 30 (Scheme 1.18). In order to check the role of steric and electronic effects towards the regioselectivity, several substituted examples were investigated. If \( R^1 = H \), and \( R^2 = CH_3 \) (30, monosubstituted), nucleophiles were predicted to attack mainly on the less substituted carbon to give product 31, while if both \( R^1 \) and \( R^2 = CH_3 \) (disubstituted), nucleophiles were predicted mainly to react at the more substituted carbon to give product 32. If \( R^1 = H \), and \( R^2 = OCH_3 \) (monosubstituted and strongly donating), substitution at the carbon bearing the methoxy group to give product 32 as the only product was predicted. It was also noticed that solvent effect plays an important role in the regioselectivity in these reactions. Two of the most frequently used solvents (THF and DMSO) were employed in these reactions. In the monosubstituted case (\( R^1 = H \), and \( R^2 = OCH_3 \)), the change of solvent did not make any difference to afford 100% regioselectivity in favor of the substituted carbon. In disubstituted case (\( R^1 \) and \( R^2 = CH_3 \)), the change to the more polar solvent gave regioselectivity that was still in favor of the substituted carbon, but to a lesser extent than the earlier case (80% in THF and 70% in DMSO). This trend was totally inverted in case of \( R^1 = H \), and \( R^2 = CH_3 \), as the regioselectivity was in favor of unsubstituted carbon (93% in THF and 59% in DMSO).

![Scheme 1.18](image-url)  
**Scheme 1.18.** Regioselectivity of \( \eta^3 \)-allylpalladium complexes based on substituents.
While both steric and electronic effects are involved in controlling the regioselectivity in palladium-catalyzed allylic alkylation, steric effects are often dominant. However, when there is an electron-withdrawing group on one of the termini of the allylic system, nucleophiles usually attack away from this group. In order to confirm the electronic effect on the regioselectivity of nucleophilic attack on the allylic system, Moreno-Mañas and co-workers selected an allylic substrate with groups of almost the same steric, but different electronic properties on each terminus (phenyl groups, one with a p-nitro and other with a p–OMe group, 33a and 33b).\textsuperscript{46} It was observed that when 33a or 33b (1 equiv) treated with sodium salt of triacetic acid lactone 34 (2.5 equiv), a mixture of allylated pyrones 35a and 35b (ratio 93:7) was obtained in an isolated yield more than 80%. These results show that nucleophile attack on $\pi$-allylpalladium complexes occurs predominantly at the terminus away from the electron withdrawing group (Scheme 1.19).

Scheme 1.19. Electronic effects on the regioselectivity of nucleophilic attack on the allylpalladiums.
When similar reactions were performed between 33a or 33b with sodium salt of acetylacetone 36, exclusively substitution was observed on the π-allylpalladium complexes at the terminus away from the electron withdrawing group to afford a mixture of 37a (minor) and 37b (major). Compound 37a was frequently detected as a minor product in which a double bond isomerization had occurred. Compound 37b was detected as a mixture of E and Z (E > Z) isomers (Scheme 1.20).

![Chemical structure of 37a and 37b]

**Scheme 1.20.** Electronic effects on the regioselectivity of nucleophilic attack on the allyl palladiums.

The Carretero group has reported the overriding contribution of electronic effects over the steric factors. Allyl carbonates having a phenylsulfonyl group (38) on one terminus and groups of various size (Me, n-Hex, or i-Pr) on the other were treated with diethyl malonate in the presence of Pd$_2$(dba)$_3$ and dppe as ligand; γ-substituted products 39 were obtained exclusively despite of the size of the group R (Scheme 1.21).
Scheme 1.21. The overriding of electronic effects over steric ones.

This regioselectivity problem does not restrict itself only to the terminal carbons (C-1 and C-3) of the η^3^-allylpalladium complex, as instances of alkylation at the central carbon (C-2) have also been reported. From the initial reports, it was generally assumed that only less stabilized carbon nucleophiles (pK_a 20-30) gave attack on the central carbon of the η^3^-allylpalladium complex. The Bäckvall group, however, reported the same regioselective C-2 attack with more stabilized carbon nucleophiles (pK_a 14-15), such as diethyl methylmalonate, under certain conditions. These results confirmed that the nucleophile is not the only determining factor in reaction regioselectivity. They selected η^3^-allylpalladium complex 40 as a substrate, and subjected it to reaction with diethyl methylmalonate nucleophile (2-2.5 equiv) in the presence of different ligands (2-6 equiv). Two different products were obtained. The ratio between the products 41 and 42 was strongly under the influence the choice of the ligands. The doubly alkylated product 41 was obtained as a major product when strong σ-donor nitrogen ligands such as L = bpy or tmeda were used, while monalkylated product 42 was produced as a major product when π-acceptor phosphorus ligands such as L = PPh_3, PBU_3, P(OPh)_3, dppf, dppe, or dppb were used (Scheme 1.22).
Scheme 1.22. Regioselectivity of η³-allylpalladium attack based on ligands.

The Hamada group has synthesized dihydroquinolinones, important intermediates for the synthesis of a large variety of natural products containing the dihydroquinoline core, by using palladium catalyzed reactions of γ-acetoxy-α,β-unsaturated carbonyl compounds. In this two step synthesis, 2-aminobenzaldehyde 43 used in the Pd-catalyzed allylic amination of γ-acetoxy-α,β-unsaturated esters 44 gave compounds 45 through γ-attack. The compounds 45 served as potential substrates for Stetter reactions to give dihydroquinolinones 46, on treatment with 10-20 mol % of thiazolium salt 47. The same product could be obtained by using a one-pot, sequential, multi-catalytic process. The process worked well with many types of electron withdrawing groups (esters, nitriles) in the γ-acetoxy-α,β-unsaturated carbonyl compounds (Scheme 1.23).
Scheme 1.23. π-Allylpalladium complexes as γ-carbonyl cation equivalents to form hydroquinolinones.

γ-Substituted-(azido or alkylated)-α,β-unsaturated nitriles or esters are highly attractive targets for synthetic chemists because of their diversity of functional groups. These compounds are usually obtained from α-alkoxy or α-carbonate-β,γ-unsaturated nitriles, attractive precursors for γ-carbocation equivalents, through palladium catalyzed allylic substitution reactions. A variety of nucleophiles have been employed, such as carbon (malonate), nitrogen (amine and azide), oxygen (tin alkoxide) and sulfur based ones. Tsuji and co-workers reported the palladium catalyzed regiospecific substitution reaction on α-alkoxy-β,γ-unsaturated nitriles 48 with malonate ion via a 1,3-transposition reaction, to afford γ-substituted nitriles (49). This approach was further extended to a variety of nucleophiles on the same substrate by the Keinan group (Scheme 1.24).
The Tsuji group further extended the scope of these palladium catalyzed reactions to \( \alpha \)-carbonate-\( \beta \)-,\( \gamma \)-unsaturated nitriles (50) with \( \beta \)-keto esters 51\textsuperscript{53} to afford regioselectively \( \gamma \)-substituted-\( \alpha \),\( \beta \)-unsaturated nitriles (52) in an excellent yield, as a mixture of E/Z (4:1) stereoisomers (Scheme 1.25).

\[
\text{Scheme 1.25. Palladium catalyzed alkylation of allylic carbonate with } \beta \text{-keto ester.}
\]

Murahashi and co-workers reported the palladium catalyzed \( \gamma \)-azidation of \( \alpha \)-acetoxy-\( \beta \),\( \gamma \)-unsaturated nitriles and esters 53\textsuperscript{54} In all cases exclusively \( \gamma \)-substituted products 54 were formed. This work was further extended to \( \alpha \)-carbonate nitriles to give the same type of results (Scheme 1.26).

\[
\text{Scheme 1.26. Palladium catalyzed azidation of alkoxy allyl esters and nitriles.}
\]
Palladium catalyzed allylic alkylation is an important tool for synthetic chemists to form enantiomerically enriched products by using chiral, enantiomerically enriched substrates. Both hetero- and carbon atom based nucleophiles have been used in these enantioselective reactions. The carbon based nucleophiles may be either symmetrically or unsymmetrically substituted at the reacting center. Symmetrical substituted C-nucleophiles give products with only one stereogenic center, while unsymmetrical C-nucleophiles result in the formation of diastereomeric mixtures. The stereochemistry at the carbon undergoing substitution is particularly exciting, with the observance of net retention (double inversion) of configuration. The first inversion occurs by the backside displacement of the leaving group from the olefin-palladium complex in order to make the allylpalladium. The second inversion results by the nucleophilic attack on the face of the allyl complex opposite to the palladium.

Ether linkages at stereogenic carbons are structurally very important. They are present in many natural products. The Lee group used a variety of oxygen nucleophiles, such as primary and secondary (cyclic and acyclic) alcohols (54, 55) to get ether products with complete retention of configuration at the reacting centre. The addition of these nucleophiles to η³-allylpalladium complexes was very challenging, because of the reactivity mismatch between hard alkoxide anions and soft allylpalladium electrophiles. This issue was solved by using Et₂Zn, as the source of the base and the counterion. This decreased the basicity of nucleophile and kept the nucleophilic strength sufficient for η³-allylpalladium complexes. The authors referred it as a “zinc effect”. The yields were better for primary alcohols than for secondary alcohols. Specifically, etherification of γ-acetoxy-α,β-unsaturated ester 56 with 54 resulted in 57 (51%), and with 55 resulted in a
yield of 58 (57%) that could be improved (86%) by increasing the amount (2.2 equiv) of nucleophile (Scheme 1.27).

Scheme 1.27. Etherification at γ-carbon of γ-acetoxy-α,β-unsaturated esters.

Asymmetric synthesis is one of the most advanced branches of organic chemistry, being used particularly to synthesize biologically important molecules in enantiomerically pure form. Metal-catalyzed asymmetric allylic alkylation has many advantages. The asymmetric allylic alkylation (AAA) is being used extensively for the conversion of achiral, prochiral or chiral racemic materials into enantiomerically pure products. The chiral elements can be set into the nucleophile, electrophile or the catalyst. The metal catalyzed allylic alkylation is a multistep reaction, providing many opportunities for the enantiodiscrimination.57

The Hamada group used ester substituted π-allylpalladium complexes as γ-carbonyl cation equivalents to synthesize compounds with all-carbon quaternary stereocenters (59) during the study of Pd-catalyzed asymmetric allylic alkylation of γ-acetoxy-α,β-unsaturated carbonyl compounds 60 with prochiral cyclic β-keto esters 61 as nucleophiles.58 For this purpose, pentavalent chiral phosphine oxides 62 were used as
preligands (P-chirogenic diaminophosphine oxides (DIAPHOSXs)). These preligands were converted \textit{in situ} into trivalent activated siloxyphosphines through tautomerism by using N,O-bis(trimethylsilyl)acetamide (BSA) and Zn(OAc)$_2$ additives. There was no sign of conjugate addition of the nucleophile to the substrate. In the absence of any additive, there was no sign of product. The maximum yield (99\%) and the highest ee occurred when $R^1 =$ ethyl, $R^2 =$ t-Bu and $n = 1$. Lower yields (74 \%) were obtained in case of a smaller ring sized \(\beta\)-keto esters ($n = 0$). Poor ee’s (68 \%) were observed for larger ring sized \(\beta\)-keto esters ($n = 3$) (Scheme 1.28).

\textbf{Scheme 1.28.} \(\pi\)-Allylpalladium complexes as \(\gamma\)-carbonyl cation equivalents to give all-carbon stereocenters.
1.3.4. By Way of Iron Tetracarbonyl Complexes of $\pi$-Allyl cations

$\pi$-Allyl complexes of iron tetracarbonyl are recognized as versatile allylating agents in synthetic chemistry. Their cationic versions are considered as stabilized carbocation equivalents and are highly reactive towards a wide variety of soft nucleophiles. The regioselectivity of nucleophilic addition reactions to these cationic tetracarbonyl ($\eta^3$-allyl) iron complexes has been investigated by many research groups.\(^{59}\) Exclusive $\gamma$-regioselectivity has been observed in the presence of electron withdrawing functional groups such as $\text{CO}_2\text{R}$, $\text{COR}$, $\text{CONR}_2$, $\text{SO}_2\text{Ph}$, etc., at C-1 of the allyl. Although palladium $\eta^3$-allyl complexes are considered to be more reliable reagents, only strong nucleophiles such as the anions derived from malonates and $\beta$-keto esters are sufficiently reactive. On the contrary, iron $\eta^3$-allyl complexes are more flexible towards nucleophiles, and react successfully with silyl enol ethers, silyl ketene acetals, N-stannyl enamines, allylsilanes, allylstannanes, electron-rich arenes, amines, $\beta$-dicarbonyl compounds and zinc cyanocuprates.\(^{60}\)

Green and co-workers employed iron tetracarbonyl complexes of $\alpha,\beta$-unsaturated-$\gamma$-acetoxy esters \(^{63}\) or $\gamma$-benzyloxy ketones \(^{64}\) to afford 1,6-dicarbonyl compounds \(^{65, 66}\) on treatment with various nucleophiles in the presence of Lewis acids. The acetoxy leaving group was replaced with benzyloxy group in \(^{67}\) to avoid the chances of oxidative addition to Fe(0). A variety of Lewis acids were employed in these reactions but boron trifluoride-etherate was proved to be more efficient in most of the cases. There was no issue of regioselectivity, as exclusive $\gamma$-substitution occurred with no trace of $\alpha$-attack, but the transformation occurs with poor simple diastereoselectivity. Retention of double bond configuration for the enone was observed by using suitable Lewis acids. In
E-disubstituted cases, boron trifluoride-etherate was successful, but for Z-disubstituted ones ZrCl₄ was proved to be more efficient (Z/E = 97/3). This retention of configuration of the double bond demonstrates the geometric stability of η⁳-allyl tetracarbonyliron cations; this is a feature not seen in allylpalladiums. The decomplexation of the η²-alkeneiron addition products was done in situ by using trimethylamine N-oxide, to give all-carbon products 65 and 66 (Scheme 1.29).

Scheme 1.29. Nucleophilic substitution of tetracarbonyliron complexes of γ-acetoxy-α,β-unsaturated esters and γ-benzylxyloxy-α,β-unsaturated ketones.

The Enders group has focused their work on enantiomerically enriched version of electron withdrawing group-substituted cationic iron allyl complexes. In particular, enantiomerically enriched (E)-(4S)-benzylxyopent-2-enoic methyl ester ((S)-67) (ee > 95%) gave highly pure 4-amino-enoates (S)-68 (ee = 95-98%) as a single (E)-isomers in fair to good yields (52-91%) through the formation of 1-methoxycarbonyl-3-methylallyltetracarbonyliron complex (ee > 95%), followed by the attack of various
nitrogen nucleophiles. This reaction was done with complete transfer of chirality and overall retention at the γ-site. The retention was a result of a double inversion, the first inversion occurred during the complex formation, and the second during the attack of nucleophiles (Scheme 1.30).

Scheme 1.30. Nucleophilic substitution of tetracarbonyliron allyl complexes with nitrogen nucleophiles.

The Enders group later employed the enantiomerically pure (ee = 85-99%) γ-substituted-α,β-unsaturated esters 69 in Fe(CO)₄-mediated one-pot syntheses to afford optically active tetrahydrofurans and tetrahydropyrans (70). After optimization of the reaction conditions such as solvent, temperature and added bases, a number of different cyclic ethers with ester or sulfone electron withdrawing groups could be formed in poor to fair yields (30-50%). Nearly complete chirality transfer with net retention (double inversion) of configuration occurred at the allylic carbon center (Scheme 1.31).

Scheme 1.31. The Fe(CO)₄-mediated one-pot synthesis of optically active tetrahydrofurans and tetrahydropyrans.
The Enders group also reported the synthesis of highly diastereo- and enantiomerically enriched alkoxy carbonyl-substituted $\eta^3$-tetracarbonyliron allyl cations 72 by means of an auxiliary (8-phenylmenthyl) controlled complexation of diastereo- or enantiopure starting materials 71 of (E)-configuration.\(^{65}\) The complexation of the alkene induced by the 8-phenylmenthyl ester was done with moderate diastereomeric excess, but the exact location of the Fe(CO)$_4$-fragment could not be determined with certainty. These complexes 72 were subjected towards nucleophilic addition reactions by various achiral silyl enol ethers or silyl ketene acetal 73 to give 1,6-dicarbonyl products 74 with near complete overall retention (double inversion) at allylic centre, meaning high diastereomeric excess for the menthyl ester and high enantiomeric purity for methyl ester. Yields were variable (25-98%) (Scheme 1.32).

**Scheme 1.32.** Synthesis of highly diastereo- and enantiomerically enriched $\eta^3$-tetracarbonyliron allyl cations.

Although the γ-carbonyl cation equivalents based on tetracarbonyliron allyl complexes have seen limited use in synthesis, Green and co-workers have reported the synthesis of quaternary carbon centers from iron allyl cations that can be further used to form spirocyclic compounds.\(^{66}\) These quaternary centers were synthesized by reacting the
ester-substituted allyltetracarbonyliron cations 75 with cycloalkylidene-type silyl enol ethers, silyl ketene acetics, and β-ketoesters (76) to give 1,6-dicarbonyl compounds 77 after the in situ decomplexation with Me₂NO. Dieckmann and acyloin cyclization reactions were then employed to convert these quaternary center containing products into spirocyclic [4.5], [5.5], and [5.6] ring systems. The condensation products were obtained from silyl ketene acetics with fair to good yields (37-74%). Consistently slightly better yields were obtained with γ-unsubstituted cases as compared to γ-substituted ones (Scheme 1.33).

Scheme 1.33. Formation of quaternary centers via iron allyl cations.

Although appreciable progress has been made in the synthetic chemistry of γ-carbonyl cation equivalents by using ring opening reactions of electron withdrawing group substituted cyclopropanes and by employing π-allyl complexes of transition metals such as molybdenum, palladium, and iron, there is still significant room for improvement in these methodologies. Activated cyclopropanes are considered to be an indispensable tool for synthetic chemists to form a variety of natural products especially through ring
expansion techniques. Application of cyclopropanes in synthetic chemistry has some limitations. Generally, gem-disubstituted highly electron deficient cyclopropanes are used. Most of the ring opening reactions are done under harsh reaction conditions such as reflux and high pressure. Usually, strong nucleophiles are utilized in these reactions. Ring opening reactions of monosubstituted cyclopropanes have been addressed in literature only sparingly.

The γ-substituted α,β-unsaturated carbonyl complexes of molybdenum have been used for more than the last three decades, but they still have not achieved a significant place in literature. They have regiochemical issues, as both α- and γ-condensations have been reported even for unsymmetrical ester substituted complexes. Usually, they are restricted to reaction with reactive external nucleophiles (anions of malonic esters) or internal nucleophiles.

Among all the π-allyl transition metal complexes, palladium complexes are used most extensively. The electrophilicity of η³-carbonyl complexes of palladium is such that reactive nucleophiles, such as anions of malonic esters, β-keto esters, and heteroatom nucleophiles are needed for reaction. These substitution reactions happen with the complete retention of double bond configuration for E-isomers and with inversion for Z-isomers.

The electron withdrawing group substituted η³-tetracarbonyliron cation complexes are considered to be excellent species for obtaining exclusive γ-attack by nucleophiles. Their reaction conditions are a significant issue of this methodology, since usually the complexation reactions are run under a CO atmosphere and since the η²-
alkene iron complexes are relatively unstable, not surviving on silica. For this reason, these complexes are demetallated in situ.

1.3.5. By Way of the Nicholas Reactions

After the thorough study of all these methodologies, it is observed that the literature is still deprived of such a γ-carbonyl cation species that can be generated easily, is highly stabilized, is reactive with even weak nucleophiles, and whose metal-complexed products are stable enough for chromatography. The Green group has employed Nicholas reactions to afford various synthetic targets for more than a decade. The chemistry of the Nicholas reaction has already been discussed in Section 1.1, where the generation of propargyl carbocation was described. The $pK_R^+$ values of these carbocations reveals their stability, which is due to the presence of the $\text{Co}_2(\text{CO})_6$-moeity. The chemistry of propargyl cation-dicobalt hexacarbonyl complexes with electron withdrawing group substitution has been investigated only rarely. The $pK_R^+$ data demonstrates that there is no appreciable change in the ability to form these cations in the presence of various substituents at the carbonium ion center (Figure. 1.8). As a result, it was expected that the generation of these cations will be possible even in the presence of electron withdrawing group at the remote end. This means that the Nicholas reaction should be a good source of γ-carbocation equivalents.
Figure 1.8. The pK$_R^+$ values for carbocations.

The highly electrophilic nature of these carbocations is evident from Mayr’s table, which explains their ability to react with a variety of even weak nucleophiles, which are usually inactive in a variety of the previously discussed analogous reactions. In Mayr’s table various electrophiles and nucleophiles are arranged on the basis of their electrophilicity (E) and nucleophilicity (N) values, respectively. From these values the possibility of the reaction can be predicted. The rule of thumb is that electrophiles will react at room temperature with those nucleophiles which are located at the same level or below in the table (N + E ≥ -5), but will not react those nucleophiles which are located above. This table gives a good chance for quick look comparison of reactivity among various electrophiles and nucleophiles, and demonstrates that dicobalt hexacarbonyl propargyl carbocations are 10$^{11}$ times more reactive as electrophiles, as compared to PPh$_3$ ligated allylpalladium complexes (Figure 1.9).
Figure 1.9. Mayr’s table (a combination of the electrophilicity and the nucleophilicity scale, published with the permission of the author).
Green and co-workers initially reported the silver-mediated Nicholas reactions of hexacarboxyldicobalt complexes of γ-chloroalkynones and γ-chloroalkyanoates 78 with silyl enol ethers or silyl ketene acetals 79 to give 1,6-dicarbonyl complexes 80 in fair to good yields (51-82 %). The complexes with γ-alkyl substitution underwent Nicholas reaction with a variety of silyl enol ethers to give diastereomeric mixtures of the products. In particular, propiophenone trimethylsilyl enol ether gave good levels of syn diastereoselectivity (syn/anti dr = 8.7-15 : 1), whereas reactions with trimethylsiloxy cyclohexene were only slightly diastereoselective, favouring the anti diastereomer (syn/anti dr = 1 : 1.3-2.1) (Scheme 1.34).

\[
\begin{align*}
\text{Scheme 1.34. Propargyl chlorides as sources for cobalt stabilized γ-carbonyl cations.}
\end{align*}
\]

The Green group extended the application of these types of Nicholas reactions towards the synthesis of cycloheptynedicobalt hexacarbonyl complexes. The hexacarboxyldicobalt complexes of γ-chloroalkynones or –alkyanoates were replaced with γ-methoxy substituted complexes to avoid the stability problems arising from using the chloro-substituted complexes. The use of BF₃·OEt₂ as the Lewis acid of first choice often resulted in low reactivity, especially in case of hexacarboxyldicobalt complexes of
alkynoates. This issue could be solved by switching to Bu$_2$BOTf as Lewis acid. The Bu$_2$BOTf mediated reactions of allyldimetals (stannylsilanes) were employed with $\gamma$-methoxyalkynoate or -alkynone hexacarbonyldicobalt complexes to give tethered allylsilane complexes. In particular, $\gamma$-methoxyalkynoate 81 reacted with silylstannane 82 to give 83 as the main product, in good yield (83%). The carbonyl function of this product was reduced by using DIBAL-H and subsequently converted in situ into acetate 84 under standard conditions of acetylation. The complex 84 was subsequently converted into cycloheptyne complex 85a contaminated with 85b (46%, 87:13, respectively) along with fluorocycloheptyne 86 (44%), when exposed to boron trifluoride-etherate. In the case of stannylsilanes, the Nicholas reaction with cobalt complex 87 gave product 88 contaminated with a small amount of another regioisomer (89) (Scheme 1.35).

Scheme 1.35. Cycloheptyne–cobalt complexes via allylation of stabilized $\gamma$-carbonyl cations.
Green and co-workers performed a series of Nicholas reactions between γ-methoxyalkynoate complexes 90 and a variety of electron rich arenes 91 to give products 92 in good to excellent yields. After having a fair collection of results, it may be concluded that there is no issue of regiochemistry in these systems and the only γ-substitution is possible (Scheme 1.36).

Scheme 1.36. Nicholas reaction with arenes as nucleophiles.

1.3.5.1 Electrophilic Mono- and Disubstitution Reactions of 2,7-Dimethoxynaphthalene

As it will be discussed in subsequent sections, the research area of focus in this thesis is the synthesis of cyclohepta[de]naphthalenes. From a literature survey, it was revealed that the natural products such as microstegiol or salvibretol have the cyclohepta[de]naphthalene structure. The electrophilic substitution pattern of Nicholas reactions on arenes such as benzene has been investigated, but the pattern of reactivity on naphthalenes is unknown. We deem that this is important for the synthesis of these structures. For this purpose, it is necessary to have background knowledge about the regiochemistry of electrophilic substitution reactions of these substrates against a variety of electrophiles. Specifically, 2,7-dimethoxynaphthalene has been used by many groups.
in reaction with different electrophiles to give a variety of mono- and dicondensation products. The dicondensation results are more diverse (C-1,8, C-1,6, C-1,3 and C-3,6) relative to those for monocondensation (C-1 and C-3).

Yasupat and co-worker utilized a number of electron rich naphthalenes (including 2,7-dimethoxynaphthalene) to synthesize tri- and tetrahydroxy derivatives of naphthalenes. In particular, nitration of 2,7-dimethoxynaphthalene 93 was accomplished by its treatment with a mixture of nitric acid and glacial acetic acid at room temperature, to give 1-nitro-2,7-dimethoxynaphthalene 94 (R\textsuperscript{1} = NO\textsubscript{2}) and 1,8-dinitro-2,7-dimethyoxynaphthalene 95 (R\textsuperscript{1} = R\textsuperscript{2} = NO\textsubscript{2}) with limited and excess amounts of nitric acid, respectively. The yields were not reported specifically for 2,7-dimethoxynaphthalene, but in the case of 2,6-dimethoxynaphthalene they were almost quantitative (Scheme 1.37).

\textbf{Scheme 1.37.} Mono and dicondensation of 2,7-dimethoxynaphthalene.

Similar results were reported by Richer and co-worker. In the case of mono condensation, all reaction products were C-1 substituted including 1-nitro, 1-chloro, and 1-bromo-2,7-dimethoxynaphthalenes. In the case of dicondensation, 1,8-disubstitution
was obtained for nitration and chlorination (\(95, R^1 = R^2 = \text{NO}_2 \text{ or Cl}\)), while 1,6-disubstitution (\(96, R^1 = R^2 = \text{Br}\)) occurred for incorporation of the relatively larger bromine atoms in 2,7-dimethoxynaphthalene. This result suggests that the first bromination occurs at the C-1 position, while the second bromine is incorporated at C-6, probably because of steric effects (Scheme 1.37).

During the course of the synthesis of 1,3,4,9-tetramethoxyphenalenyl systems having symmetrical disubstitution patterns by Haddon’s group, 2,7-dimethoxynaphthalene was selected as starting material.\(^{74}\) Reaction with ethyl malonyl chloride under Friedel-Crafts conditions afforded a product with condensation at C-1 (\(94, R^1 = \text{EtCOOCCH}_2\text{CO}\)) in good yield (75%, Scheme 1.37).

Mizutani’s group reported the Vilsmeier-Haack formylation of 93 to give compound 94 (\(R^1 = \text{CHO}, 83\%\)) by treating it with the mixture of N-methylformanilide and POCl\(_3\) in 1,2-dichloroethane.\(^{75}\) The same transformation has also been reported with DMF to afford the product with slight change in yield (78%).\(^{76}\) Formylation of aromatic compounds (i.e, 2,7-dimethoxynaphthalene) also occurs at the more electron rich C-1 position via a free radical method, employing manganese (III) acetate and malonic acid (\(94, R^1 = \text{CHO}, 59\%, \text{Scheme 1.37}\)).\(^{77}\)

Posner and co-worker have employed various derivatives of dihydroartemisinin (DHA) in their research. The fluoro derivative of DHA (97) was subjected to boron trifluoride mediated Friedel-Crafts alkylation with various aromatic and heteroaromatic nucleophiles.\(^{78}\) In particular, this DHA (97) reacted with 2,7-dimethoxynaphthalene 93 in the presence of boron trifluoride-etherate to give product 98.
with alkylation at C-3 in good yield (80%). The alkylation at C-3 might be because of the steric hindrance of this bulky group. (Scheme 1.38)

Scheme 1.38. Alkylation at C-3 of 2,7-dimethoxynaphthalene.

Haynes and co-workers reported a different regioisomer (C-1) of the same type of product. They used α- and β-benzoate derivatives of 97 (99) and treated with 2,7-dimethoxynaphthalene 93 with boron trifluoride-etherate or tin(IV) chloride (SnCl₄) to give alkylation at C-1 (100) rather than C-3, in good yield (74%). The ¹H NMR data given by both groups is almost identical, and in our view it supports the structure 100. It means that both groups synthesized the identical product but the analysis of ¹H NMR given by Posner was likely wrong. It is noteworthy how this bulky group can substitute at the C-1 position (Scheme 1.39).

Scheme 1.39. Alkylation at C-1 of 2,7-dimethoxynaphthalene.
Yonezawa and co-workers have done a significant amount of work on the structural analysis of various substitution regioisomers of 2,7-dimethoxynaphthalene. A variety of para substituted benzoic acids and benzoyl chlorides were treated with 2,7-dimethoxynaphthalene under Friedel-Crafts acylation conditions to get C-1 substitution in most of the cases. In general, acid chloride based Friedel-Crafts reactions gave C-1 substitution in all cases studied, while the carboxylic acid based Friedel-Crafts reactions gave C-3 condensations, except in the most electron deficient case (R = NO₂), where C-1 condensation was obtained (Scheme 1.40).

**Scheme 1.40.** C-1 and C-3 condensation through Friedel-Crafts acylation.

A similar diversity in regiochemical outcome for 2,7-dimethoxynaphthalene is not restricted to classical electrophilic aromatic substitution only. A variety of electrophiles can be introduced through lithiation chemistry. A number of research groups have
reported this type of work. Rebek’s group synthesized 3,6-dimethyl-2,7-dimethoxynaphthalene 104 (R³ = R⁴ = CH₃) by treating 2,7-dimethoxynaphthalene 93 with TMEDA/n-BuLi (5 equiv each) to give dilithiation at positions 3 and 6 of the starting material. The dilithiated product was treated in situ with dimethyl sulfate to afford the dimethylated product. Zagotto and co-workers synthesized 2,7-dimethoxynaphthalene-3,6-dicarboxylic acid dimethyl ester 104 (R³ = R⁴ = COOCH₃) by dilithiation of 2,7-dimethoxynaphthalene under slightly different lithiation conditions (n-BuLi, Et₂O) followed by the treatment with CO₂ and MSA (molybdate sulfuric acid)/methanol at reflux. Conversely, Kuhnert’s group synthesized 1,6-diformyl-2,7-dimethoxynaphthalene 103 (R¹ = R³ = CHO) in modest yield (44%) along with small amount of 3,6-diformyl-2,7-dimethoxynaphthalene 104 (R³ = R⁴ = CHO, 10%) by refluxing the 93 solution in Et₂O with n-BuLi (3equiv)/TMEDA followed by the treatment with DMF (Scheme 1.41).

![Scheme 1.41. Mono and dicondensation of 2,7-dimethoxynaphthalene through lithiation.](image)

**1.4. Synthesis of Cyclohepta[de]naphthalenes**

The cyclohepta[de]naphthalenes are a class of seven membered-ring compounds, having a four carbon tether between C-1 and C-8 of a naphthalene ring. This cyclohepta[de]naphthalene structure has been seen in number of biologically active natural products such as microstegiol, oxomicrostegiol, salvibretol and
oxosalvibretol. Surprisingly, these natural products have not been reported as synthetic targets before. The construction of the carbon framework of cyclohepta[de]naphthalenes has been accomplished by various chemical ways, such as by sequential Friedel-Crafts acylation of succinic anhydride, by [2+2] cycloaddition/ring expansion reactions of cyclopenta[de]naphthalenes, by malonate alkylation, by reductive carbonyl coupling reactions, by o-xyylene Diels-Alder cycloaddition, and by Claisen rearrangement/olefin metathesis.

In 1932, Fieser and co-worker reported the intermolecular Friedel-Crafts acylations of succinic anhydride onacenaphthene (105) to afford 106. Further intramolecular Friedel-Crafts acylation of 106 resulted the ring closure at the peri position of acenaphthene to give the unusual seven-membered dione 107 rather than the expected six-membered ring structure (Scheme 1.42). The authors suggested that this unusual result was due to the presence of the acenaphthene dimethylene bridge. This statement was further supported when compound 108 was subjected to the same conditions (Friedel-Crafts acylation), and gave no product, due to the absence of activation of the dimethylene bridge. Tsunetsugu’s group reported similar results on aceanthrylene instead of acenaphthene.  

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Scheme 1.42. Synthesis of cyclohepta[de]naphthalene from acenaphthene.

The Boekelheide group reported the synthesis of pleiadiene, (cyclohepta-[de]naphthalene) from acenaphthene (105). The pleiadiene synthesis started with oxidation of acenaphthene to give 1,8-naphthlic anhydride 109 by literature methods. The anhydride was reduced by using LiAlH₄ to afford 1,8-naphthalenedimethanol (110), which further chlorinated to 1,8-bis(chloromethyl)naphthalene (111). The tetraester derivative of cyclohepta[de]naphthalene (112) was afforded by the malonate type alkylation of 111, which eventually was converted into pleiadiene 113 (Scheme 1.43).
Scheme 1.43. Boekelheide's approach towards the synthesis of pleiadiene.

Shields and co-workers synthesized pleiadiene and its derivatives through a photochemical 2+2 cycloaddition of maleic anhydride to acenaphthylene \( \text{114} \) in halogenated solvents.\(^{93} \) The cyclobutane photoadduct formed (\( \text{115} \)) was converted into cyclobutene \( \text{116} \) by oxidative bisdecarboxylation. The cyclohepta[de]naphthalene, (pleiadiene \( \text{113} \)) was then formed from the cyclobutene by isomerization (Scheme 1.44).
Scheme 1.44. Shields’ synthesis of pleiadiene.

Smith’s group reported the synthesis of derivatives of cyclohepta[de]naphthalene by using cycloaddition and ring expansion techniques.\(^{94}\) Acenaphthylene 114 was treated with dichloroketene, generated from zinc and trichloroacetyl bromide, to give directly chlorine-free ketone cycloaddition product 118. The cycloheptenone 119 was prepared from 118 through ring expansion under acidic conditions. Tsunetsugu’s group reported the synthesis of another derivative of cyclohepta[de]naphthalene, dione 120 (62% yield), by the hydrolysis of 117 with silver acetate in acetic acid.\(^{95}\) In their case, the dichloroketene adduct was obtained by treating acenaphthylene with dichloroacetyl chloride-triethylamine (Scheme 1.45).\(^{96}\)

The synthesis of a dihydrocyclohepta[de]naphthalene from naphthalene 2,7-diol (121) was reported by Kotha and Chattopadhyay groups by using Claisen rearrangement and ring closing metathesis (RCM) techniques. The O-allylation of naphthalene-2,7-diol was accomplished by using allyl bromide and K$_2$CO$_3$ in the presence of small amount of tetrabutylammonium hydrogen sulfate (TBAHS) to give 122 (75% yield). The Claisen rearrangement of 122 gave a mixture of products, but one-pot Claisen rearrangement and protection with acetyl groups afforded 1,8-diallyl product 123 in good yield (79% yield). Ring closing metathesis of 123 afforded dihydrocyclohepta-[de]naphthalene 124 (96% yield) by employing the Grubbs 1 catalyst (5 mol%, Scheme 1.46).
Scheme 1.46. Synthesis of a cyclohepta[de]napthalene using Claisen rearrangement.

1.5. Microstegiol and its Derivatives

Microstegiol, a rearranged abietane, has been extracted more than once from various plant species of the genus *salvia* such as *salvia microstegia*, *salvia hypargeia*, *salvia verticillata*, etc. Microstegiol (125)\(^{98}\) has been isolated along with other abietanes (6-hydroxysalvinolone, 7-hydroxytaxodione) and rearranged abietanes such as salvibretol (126), \(^{98c}\) oxomicrostegiol (127), \(^{99}\) oxosalvibretol (128)\(^{98c,m}\) containing the cyclohepta[de]napthalene nucleus (Figure 1.10). The *salvia* plants have been used as folk medicines against various diseases. Their crude extracts have shown antibacterial, antifungal, anticancer, antituberculosis, antiplasmodial and antidiabetic biological
activities. In particular, these extracts were found to be active against cultured human cancer cells such as breast cancer, prostate cancer, lung cancer, and colon cancer. Microstegiol itself has shown activity against the P388 lymphocytic leukemia cell line.

Figure 1.10. Rearranged abietanes.

Kuo and co-workers proposed the biosynthesis of 3-oxomicrostegiol from 3-oxosapapthoquinone through an aldol condensation via enol formation (Scheme 1.47).

Scheme 1.47. Proposed biosynthesis of 3-oxomicrostegiol from 3-oxosapapthoquinone.
Recently, the Rodriguez group has reported the biosynthesis of a bioactive microstegiol derivative, 2β-(4-hydroxy) benzoyloxy microstegiol 129, by a stereoselective rearrangement of an abietane diterpenoid (parvifloron D). Parvifloron D was isolated from *plectranthus ecklonii* along with several other compounds. This proposed rearrangement was apparently accomplished through sequence of chemical transformations including a methyl group migration, a retro-Friedel-Crafts alkylation, and a Friedel Crafts alkylation (Scheme 1.48).

*Scheme 1.48. Bio*synthesis of 2β-(4-hydroxy)benzoyloxy microstegiol 129 from parvifloron D.

Even though these rearranged abietanes (125-129) have been proved to be biologically active natural products against various diseases, none of them ever have been selected as synthetic targets by any research group. The lower level of synthetic attention might be because of their unusual structures. At most, some research groups have reported the synthesis of the cyclohepta[de]naphthalene framework by a variety of synthetic ways (see Section 1.4). The Green group has had a long-standing interest in the
synthesis of seven-membered ring systems by using Nicholas reaction chemistry. In the lab, such chemistry has been developed to incorporate various nucleophiles, including electron rich arenes, at the site γ- to electron withdrawing groups in an umpolung manner. These rearranged abietanes, especially microstegiol, have been selected as synthetic targets for application of this chemistry. As all these natural products have seven membered ring structure on [de] face of a naphthalene nucleus, a number of Nicholas reactions between electron rich naphthalenes (2,7-dimethoxy- or dibenzylxynaphthalenes) and a variety of propargyl alcohol-Co2(CO)6 complexes or their derivatives required investigation to determine the regiochemical outcome of these reactions. The feasibility of the utilization of these Nicholas reaction products towards the generation of seven membered ring structures across the [de] face of naphthalene are to be explored. As all these natural products exist as dehydrotetralone structures, the factors which support the predominance of keto- over enol tautomers of oxygenated cyclohepta[de]naphthalenes also require investigation.
RESULTS AND DISCUSSION

2. MONO- AND DICONDENSATION NICHOLAS REACTIONS ON 2,7-DIMETHOXYNAPHTHALENE

The rearranged abietanes, specifically microstegiol and salvibretol, were targeted due to their potential biological activities and more importantly, due to the fact that the chemistry being employed in the Green group is apparently completely suited for the synthesis of these natural products. In order to synthesize cyclohepta[de]naphthalenes, the reactivity pattern of propargyldicobalt cations with derivatives of naphthalene-2,7-diol, such as 2,7-dimethoxy- and 2,7-dibenzyloxynaphthalenes, were investigated under conventional Nicholas reaction conditions. A number of substituted propargyl alcohol–or propargyl ether dicobalt hexacarbonyl complexes were treated mainly with 2,7-dimethoxynaphthalene in the presence of Lewis acids to afford a variety of mono and dicondensation Nicholas reaction products.

Most of the Nicholas reaction precursors (132) were prepared from commercially available starting materials (131), except 132b and 132d. Compound 131d, trimethylsilylated propargyl alcohol, was synthesized from commercially available propargyl alcohol. Silylation was readily accomplished by the literature method by using trimethylsilyl chloride (TMSCl) to afford 130 in excellent yield (87%). Compounds 130 was cleanly converted into its acetate 131d (90% yield) by using conventional conditions. Compound 131b, methyl 4-methoxybutyronoate, was prepared from propargyl alcohol.
Propargyl methyl ether was synthesized from the alcohol by using a literature method. Finally, the compound 131b was synthesized (71% yield) from the propargyl methyl ether by employing the method used by Jung with some adaptations, such as treating propargyl methyl ether with MeLi followed by the addition of methyl chloroformate (Scheme 2.1).

Scheme 2.1. Synthesis of Nicholas reaction precursors.

The complexation of compounds 131a-f was readily accomplished by adding an excess of Co₂(CO)₈ to their solutions in CH₂Cl₂ to afford 132a-f (77-96% yields, Scheme 2.2)

Scheme 2.2. Complexation of 131a-f with Co₂(CO)₈.
2.1. Monocondensation

For monocondensation reactions, 2,7-dimethoxynaphthalene and 2,7-dibenzylxynaphthalene were selected as readily available electron rich arene nucleophiles to react with approximately equimolar amounts of propargyl alcohol or propargyl ether complexes 132a-f (1.1 equiv) in the presence of BF$_3$-OEt$_2$ (3 equiv) to give monocondensation products 133 and 134 in variable yields (Scheme 2.3, Table 2.1). Most of the monocondensation reactions occurred with complete conversion and without significant contamination from dicondensation products. After a series of monocondensation reactions between 93 or 135 and 132a-f, it was concluded that variable yields and different regioisomeric products (C-1 and C-3) resulted from the influence of various substituents on the propargyl complexes. The monocondensation Nicholas reaction between 93 and all propargyl complexes with no substitution at propargylic carbon 132a-d afforded only C-1 substitution 133a-d, in good yields (Entries 1–4, Scheme 1.34). The presence of a variety groups on the remote site of starting propargyl complexes did not disturb the regiochemistry of the monocondensation products. Both propargyl alcohols and ethers proved to be as equally efficient Nicholas reaction precursors. The products with excellent yields (133a, 93% and 133d, 97%) were obtained for the cases when there was no substitution (132a) or substitution with a SiMe$_3$ group (132d) at the remote end of propargyl complex, respectively. In the cases of an electron withdrawing group or an alkyl group at the remote end of propargyl complexes, the reaction resulted in monocondensation products with good yields (133b, 88% and 133c, 84%, respectively). Substitution at the propargylic site with a comparatively small
group, such as a methyl group (132e), still afforded the C-1 substitution product (133e, 66%) successfully, but with a noticeably lower yield.

A different regioisomeric product (C-3 condensation) was obtained when 93 was reacted with 132f, affording 134f (51%). This less common C-3 condensation was likely due to the steric effect of the bulky phenyl group present on the propargylic site.

Scheme 2.3. Monocondensation Nicholas reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>132</th>
<th>133 (yield, %)</th>
<th>134 (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132a</td>
<td>133a (93)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>132b</td>
<td>133b (88)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>132c</td>
<td>133c (84)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>132d</td>
<td>133d (97)</td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>132f</td>
<td></td>
<td>134f (51)</td>
</tr>
</tbody>
</table>

Table 2.1. Monocondensation Nicholas reactions.

The Nicholas reaction of 2,7-dibenzyloxy-9-naphthalene 135 with ester substituted complex 132b occurred in a similar fashion. Once again, the C-1 monocondensation
product predominated (136, 71%) while a small amount of 1,8-dicondensation product (137, 13%) was also isolated (Scheme 2.4).

Scheme 2.4. Mono and dicondensation products with 2,7-dibenzylxynapthalene.

In summary, it is clear that for the monocondensation reactions of propargyldicobalt complexes, C-1 products were obtained in majority of the cases, except for 134f (C-3 condensation), when a bulky phenyl group was present at the propargylic site.

2.2. Dicondensation

Nicholas reactions on 2,7-methoxynaphthalene (93) could be extended to disubstitution by increasing the amount of propargyl alcohol/ether-Co$_2$(CO)$_6$ complexes 132a–f to 2.2 equiv in the presence of Lewis acids, to afford 1,8-disubstitution (138) and 1,6-disubstitution (139) products (Scheme 2.5, Table 2.2). The regiochemical disposition of these dicondensation products was again under the influence of the structure of the Nicholas reaction precursor complexes 132a-f. The 1,8-disubstitution product was obtained exclusively only (138b, 86%) when there was substitution by an electron withdrawing group at the remote end of propargyldicobalt cation precursor (132b). In the case of the unsubstituted propargyldicobalt cation precursor 132a, the Nicholas reaction afforded 1,8-disubstituted product 138a predominantly (63%) along with small amount of the regioisomeric 1,6-product (139a, 9%). On the other hand, in the case of propargyldicobalt cation precursors substituted with remote methyl (132c) or
trimethylsilyl (TMS) groups (132d), the first substitution took place at the C-1 position, while the second substitution occurred at C-6 (139c, 86%, and 139d, 40%). No 1,8-disubstitution products could be detected. In case of the TMS substituted propargyldicobalt complex, the second condensation was incomplete even when allowing the reaction mixture to warm to room temperature, a significant amount of monocondensation product 133d (59%) was also isolated.

Scheme 2.5. Dicondensation Nicholas reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>132</th>
<th>138 (yield, %)</th>
<th>139 (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132a</td>
<td>138a (63)</td>
<td>139a (9)</td>
</tr>
<tr>
<td>2</td>
<td>132b</td>
<td>138b (86)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>132c</td>
<td></td>
<td>139c (86)</td>
</tr>
<tr>
<td>4</td>
<td>132d</td>
<td></td>
<td>139d (40)</td>
</tr>
</tbody>
</table>

*a In addition, 59% of 133d was isolated.

Table 2.2. Dicondensation Nicholas reactions.

In the above cases, mono- and dicondensation Nicholas reactions were carried out in a one-pot fashion, meaning that only one type of propargyldicobalt complex was treated directly with 93 or 135. In order to confirm the patterns of regiochemistry and to
expand the possible substitution patterns, selected monocondensation products were subjected to a second Nicholas reaction with a different propargyl alcohol complex. In the case of 133a, subjecting the compound to a BF₃-OEt₂ mediated Nicholas reaction with butyn-2-ol dicyclobalt complex 132e gave a second condensation at C-6, to afford 140 (72%). When C-3 substituted monocondensation product 134f was treated with unsubstituted propargyldicobalt complex 132a and BF₃-OEt₂, the second condensation occurred at the “C-1” position (actually the C-5 position in 134f) to afford 141 (50%) (Scheme 2.6).

Scheme 2.6. Second Nicholas reactions on monocondensation starting materials.

All these compounds with a variety of substitution patterns on the naphthalene ring could be distinguished easily by careful study of their ¹H NMR spectra. In the case of a C-1 condensation product, it is clearly confirmed by the presence of one doublet with a small coupling constant (d, J = 2.0–2.5 Hz, H, C-8), three doublets (d, H, C-3, d, H, C-4, d, H, C-5) and one doublet of doublets (dd, H, C-6) in the aromatic region of the ¹H NMR spectrum, while in the case of C-3 condensation products, two singlets (s, H, C-1, s, H,
C-4), one doublet (d, H, C-5) one small J doublet (d, J = 2.5 Hz, H, C-8) and one doublet of doublets (dd, H, C-6) were present. Similarly, the dicondensation products (C-1/C-8 and C-1/C-6) could be distinguished by their $^1$H NMR spectra. In the case of C-1/C-8 dicondensation products, simple $^1$H NMR spectra were obtained, showing only two doublets (d, 1H each for C-3, C-4, C-5, and C-6) for symmetrical compounds in the aromatic region, while in the case of C-1/C-6 dicondensation products, four resonances were present, two singlets (s, H, C-5, and s, H, C-8) and two doublets (d, H, C-3 and d, H, C-4). Dicondensation products (both C-1/C-6 and C-1/C-8) could also be distinguished by the presence of AB quartets for the –CH$_2$ groups, with large coupling constants, due to restricted rotation.

In summary, a consistent pattern of reactivity of 2,7-dimethoxynaphthalene with a variety of propargydicobalt complexes was observed in Lewis acid mediated Nicholas reactions. Propargydicobalt complexes without substitution or with substitution of an electron withdrawing group at the remote end afforded C-1 monocondensation and C-1/C-8 disubstitution products. In the cases when the propargyl cations possessed remote alkynyl substitutions other than electron withdrawing groups, the first substitution occurred at C-1 while the second occurred at C-6. Propargyl complexes with substitution at the propargylic position afforded different products for monocondensation. For moderate sized groups, the first substitution happened at the C-1 position, while for relatively larger groups monocondensation occurred at the C-3 position. This trend is not restricted to Nicholas reactions only, it has been observed in a variety of other reactions (see Section 1.4).
3. SYNTHESIS OF CYCLOHEPTA[DE]NAPHTHALENES

3.1. Attempts to Synthesize Cycloheptyne[de]naphthalene-Co$_2$(CO)$_6$ Complexes

The Green group has had a long standing interest in the synthesis of arene-fused seven membered rings by using Nicholas reaction chemistry.$^{104}$ For example, a BF$_3$-OEt$_2$ mediated intramolecular electrophilic aromatic substitution on indole nucleus 142 afforded an accidental synthesis of an unstable tetracyclic indole complex 143.$^{105}$ Similarly, Djurdjevic and Green reported the synthesis of a variety of cycloheptyne-Co$_2$(CO)$_6$ complexes 144 incorporating a number of electron rich biaryls, via intramolecular Nicholas reactions 145, during the course of the synthesis of allocolchicines (Scheme 3.1).$^{106}$

As a result, the initial attempts at cyclohepta[de]naphthalene synthesis were based on the possibility of a double Nicholas reaction between 2,7-dimethoxynaphthalene (93) and 1,4-dimethoxybutyne-Co₂(CO)₆ complex to give a cycloheptyne[de]naphthalene-Co₂(CO)₆ complex. This one-pot synthesis of cycloheptyne[de]naphthalene-Co₂(CO)₆ complex was attempted by reacting equimolar amounts of 2,7-dimethoxynaphthalene (93) and 1,4-dimethoxybutyne-Co₂(CO)₆ complex in the presence of excess BF₃·OEt₂. This attempt never ended with any evidence of cyclization product; rather monocondensation product 146 was clearly visible in the ¹H NMR spectrum of the crude reaction product (Scheme 3.2).

Scheme 3.2. Attempted one-pot synthesis of cycloheptyne[de]naphthalene-Co₂(CO)₆ complex.

After the unsuccessful attempt to afford a one-pot synthesis of a cycloheptyne[de]naphthalene-Co₂(CO)₆ complex, monocondensation Nicholas reaction product 133b was selected as a starting material to get a cyclized compound. The ester function of 133b was easily reduced to alcohol 147 by using diisobutylaluminum hydride (DIBAL–H) in Et₂O. The Lewis acid (BF₃·OEt₂) mediated intramolecular electrophilic aromatic substitution of primary alcohol complex 147 never finished with a cyclic product; rather starting material was recovered with some decomposition. Having thought that an OH group was not a sufficiently good leaving group, another substrate was prepared. The ester function of 133b was converted into acetate group by sequential
reduction of the ester into an alcohol followed by acetyl protection to give 148. The acetyl protected version of 147 (148) also completely restricted cyclization under BF₃-OEt₂ mediated cyclization conditions (Scheme 3.3).

Scheme 3.3. Unsuccessful attempts to synthesize cycloheptyne[de]naphthalene-Co₂(CO)₆ complex.

After the failure of all attempts towards the cobalt mediated cycloheptyne[de]-naphthalene synthesis, the decomplexed Nicholas reaction products were employed to afford the cyclohepta[de]naphthalenes. From the series of mono- and dicondensation Nicholas reactions between 2,7-dioxygenated naphthalene and a variety of propargyldicobalt complexes, a clear understanding has been developed about the substitution patterns of 2,7-dioxygenated naphthalene. On the basis of this understanding, three different approaches were developed for the construction of the
cyclohepta[de]naphthalene ring system by using various mono- and dicondensation Nicholas reaction products as potential precursors for ring synthesis such as:

1. Cyclohepta[de]naphthalene synthesis via ring closing metathesis (RCM);
2. Cyclohepta[de]naphthalene synthesis via ring closing by Friedel-Crafts alkylation;
3. Cyclohepta[de]naphthalene synthesis via ring closing by Friedel-Crafts acylation.

3.2. Cyclohepta[de]naphthalene Synthesis via Ring Closing Metathesis (RCM)

The first cyclohepta[de]naphthalene synthesis was targeted through ring closing metathesis. For this purpose, the disubstitution Nicholas reaction product 138a was selected as a potential precursor for this approach, as it was one of the few cases where naphthalene 1,8-disubstitution was obtained. This approach began with the decomplexation of 138a. It has already been discussed in Section 1.2 that the first choice as a decomplexation reagent is iodine (I₂), as in most of the cases it gives good to excellent yields. Specifically in this case, iodine did not work. It resulted the complete decomposition of the substrate. The use of trimethylamine N-oxide (Me₃NO) was also not successful. It gave poor yield for decomplexation. Finally, the decomplexation of 138a was accomplished by using ceric ammonium nitrate [(NH₄)₂Ce(NO₃)₆] in acetone at very low-temperature (-78 °C), to afford diyne 149 (57%) with incomplete conversion of starting material (89%, based on recovered starting material (brsm)). Semi hydrogenation of decomplexed diyne 149 was done in the presence of the Lindlar catalyst (Pd/CaCO₃/Pb(OAc)₂) to give diallylated naphthalene 150 (89%, 98% brsm).

Finally, this diene was treated with Grubbs 1st generation catalyst (5 mol %) to afford 2,7-
dihydrocyclohepta[de]naphthalene 151 in good yield (85%) through ring closing metathesis (RCM, Scheme 3.4). While this project was moving successfully towards the synthesis of the tricyclic product, Kotha and Chattopadhyay groups reported the synthesis of 2,7-diacetoxydihydrocyclohepta[de]naphthalene 124 by using Claisen rearrangement and ring closing metathesis (see Scheme 1.46 and Scheme 3.4). 97


3.3 Cyclohepta[de]naphthalene Synthesis via Ring Closing by Friedel-Crafts Alkylation

The dipropargylation of the 2,7-dioxygenated naphthalene and ring closing metathesis afforded a symmetrical cyclohepta[de]naphthalene, but provided limited opportunities for further synthetic activities towards unsymmetrical systems, in order to target any natural product possessing this type of carbon skeleton. After a short
investigation, a monocondensation product (133b) was selected as starting material to explore further extension of this synthetic work towards the synthesis of cyclohepta[de]naphthalenes. The removal of the Co\(_2\)(CO)\(_6\) unit from 133b was readily accomplished by using iodine in THF at room temperature, to afford 152 in excellent yield (98%). Catalytic hydrogenation of the triple bond of 152 was sluggish on Pd/C, but replacing Pd/C with Rh/C allowed the reduction of the alkyne function to occur cleanly at room temperature in methanol, to afford alkanoate 153 in excellent yield (99%). The addition of excess of MeLi (7 equiv) to a solution of 153 in Et\(_2\)O resulted in attack on the ester function to afford tertiary alcohol 154 as the only product in good yield (90%). A reduction in the amount of methyllithium (3 equiv) employed for this reaction resulted in a lower yield of the 3\(^{\circ}\) alcohol product (61% yield) along with a noticeable amount of ketone 155 (25% yield). Finally, a solution of tertiary alcohol 154 in dichloromethane was treated with H\(_2\)SO\(_4\), to afford 7,7-dimethyltetrahydrocyclohepta[de]naphthalene 156 in good yield (70%), contaminated with small amount of elimination product 157 (8%) (Scheme 3.5).
Scheme 3.5. Synthesis of a cyclohepta[de]naphthalene via ring closing by Friedel-Crafts alkylation.

The complete separation of compounds 156 and 157 was unsuccessful chromatographically. After employing various solvent systems, hexane : CH₂Cl₂ (4:1) resulted in relatively good separation. Repeated thin layer chromatography (TLC) attempts resulted in the separation of 156, to a complete enough degree for characterization. The attempt to cyclize compound 154 in an excess of BF₃-OEt₂ resulted in the elimination product only. A couple of attempts were made to convert elimination product into cyclic product 156. The exposure of solution of 157 in CH₂Cl₂ to H₂SO₄ or CF₃COOH did not result in the isolation of 156; rather starting material was recovered with some decomposition (Scheme 3.6).
Scheme 3.6. Attempts to cyclize the elimination product.

### 3.4 Cyclohepta[de]naphthalene Synthesis via Ring Closing by Friedel-Crafts Acylation

The synthesis of gem-dimethylcyclohepta[de]naphthalene 156 was appreciable progress towards the target. Most of the natural products having cyclohepta[de]naphthalene skeleton, possess gem-dimethyl group on the cycloheptane ring. Nevertheless, it has been found that all the natural products possessing this type of carbon skeleton exist as dehydrotetralones (i.e., keto tautomers of naphthols). It is not trivial to selectively deprotect one of the two methoxy groups from 156 to get a tetralone structure. To get around this issue, commercially available 2-acetoxy-7-methoxynaphthalene 158 was easily prepared by treating 7-methoxy-2-naphthol with acetic anhydride. This naphthalene derivative was expected to not only provide the opportunity to get a tetralone structure, but the unequal electron density on the two aromatic rings was expected to facilitate the selective substitution on the more electron
rich ring. The BF$_3$-OEt$_2$ mediated Nicholas reaction of 158 with 132b was somewhat sluggish as compared to 2,7-dimethoxynaphthalene, but ultimately afforded the product of substitution ortho to methoxy function in an excellent yield over 6 h (159, 88%). The superiority of Bu$_2$BOTf over BF$_3$-OEt$_2$ has been demonstrated many times in our group while employing Nicholas reactions on substrates possessing Lewis basic groups.$^{70,71}$ The same reaction was rapidly (0.5 h) accomplished by using a substoichiometric amount of Bu$_2$BOTf (0.7 equiv), to afford the product 159 in a similar yield (90%). The decomplexation of 159 was straightforward by using iodine in THF to give alkynoate 160 in excellent yield (93%). The reduction of alkyne function was very sluggish with Rh/C. This alkynoate was completely unreactive in ethyl acetate even in the presence of Pd/C. Ultimately, catalytic hydrogenation of 160 in methanol was done over Pd/C cleanly to afford 161 in excellent yield (93%). The treatment of the alkanoate 161 with K$_2$CO$_3$ in methanol at reflux slowly accomplished the hydrolysis of both the methyl ester and acetate functions to afford 162 (76% yield). After the complete failure of ring closure of 162 on subjecting with a number of acidic conditions such as trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA), a noticeable amount of ring closure was observed when 162 was exposed to polyphosphoric acid (PPA) at room temperature. Eventually, after optimization of the reaction conditions, it was found that exposure of 162 solution in CH$_2$Cl$_2$ to PPA at reflux slowly accomplished the ring closure to afford 163 in good yield (80%, Scheme 3.7).
Scheme 3.7. Synthesis of a cyclohepta[de]naphthalene via ring closing by Friedel-Crafts acylation.

Spectroscopic evidence confirmed the existence of 163 entirely as the phenolic tautomter. All the four aromatic protons (\(^1\)H NMR \(\delta\) 7.71 (d, J = 8.9, 1H), 7.63 (d, J = 8.8, 1H), 7.12 (d, J = 8.8, 1H), 6.93 (d, J = 8.9, 1H,) in the \(^1\)H NMR spectrum and IR \(\nu_{\text{max}}\) 3009 cm\(^{-1}\) for the phenolic O-H entirely support the structure 163.\(^{108}\) Indeed, conjugation between the aromatic system and the ketone entirely supports the existence of this compound as its phenolic tautomer. Various literature examples such as 1-hydroxy-7,12-pleiadenedione (164, Figure 3.1)\(^{109}\) and 1-hydroxy-8,9-dihydrocyclohepta[de]-
naphthalene-7,10-dione (165, Figure 3.1) provide additional support for the existence of this type of structure. This enolic-phenolic tautomer 163 possessing keto group in the cycloheptane ring is a potential precursor to afford compounds similar to salvibretol (126).

**Figure 3.1.** Literature examples to support structure 163.

The necessity of having the demanding dehydrotetralone tautomer has already been expressed. Both PM5 (E\text{rel} = -6.84 kcal/mol) and DFT (E\text{rel} = -3.87 kcal/mol) calculations (B88-PW9 functional, dzvp basis set) on 163 and related structures suggest that 167 without a ketone function in the cycloheptane unit will strongly favor the keto tautomer (dehydrotetralone, Figure 3.2).

**Figure 3.2.** PM5 and DFT calculations supporting the keto tautomer.
After having the PM5 and DFT calculation results in hand, it was important to determine if the existence of 1-hydroxycyclohepta[de]naphthalene entirely into its keto form (cyclohepta[de]naphthalene-1(7H)-one) was truly feasible. Consequently, decomplexed and reduced ester 161 was subjected to reaction with methyllithium (3 equiv) to afford tertiary alcohol naphthol 167 in a good yield (70%). Subsequently, a rapid ring closure occurred to afford 168 (70%) exclusively as keto tautomer, when only one drop of H₂SO₄ was added into the solution of 167 in CH₂Cl₂ at 0 °C. NMR spectroscopic results confirmed the complete absence of the enol tautomer of 168. The spectroscopic evidence includes the ¹H NMR resonances at δ 7.13 (d, J = 8.4, 1H), 6.79 (d, J = 8.4, 1H) for the aromatic protons and δ 7.29 (d, J = 9.7, 1H), 5.97 (d, J = 9.7, 1H) for olefinic protons, and the presence of an α-proton on the 3° carbon at δ 3.63 ppm (singlet), supporting the structure 168. Furthermore, the absence of an O–H peak in IR spectrum and the presence of ketonic carbon peak in the ¹³C NMR spectrum at 203.2 ppm provided additional logical proof to support the existence of 168 in its keto tautomeric form. The existence of this keto tautomer at the cost of a loss of aromaticity in one of the naphthalene rings could be rationalized by the angle strain present in the enolic form. Compound 168 has a close resemblance with the framework of rearranged abietanes such as microstegiol 125 and its derivatives 127 and 129 (Scheme 3.8).

3.5 Utilization of 2,7-dibenzyl oxynaphthalene Towards the Synthesis of Cyclohepta[de]naphthalene

The carbon framework of compound 168 is apparently closer to natural products, microstegiol, oxomicrostegiol, salvibretol and oxosalvibretol. In all these natural products there is a methyl group instead of the methoxy function and an isopropyl group at the C-3 position. After a brief investigation, 2,7-dibenzyl oxynaphthalene was selected as a potential starting material to synthesize cyclohepta[de]naphthalene compounds. The benzyl groups are not only sufficient to make a naphthalene sufficiently electron rich for Nicholas reactions, but can be easily removed to regenerate the hydroxy functions. One of the hydroxy functions could be converted into the methyl group that is a key step in the synthesis of these natural products.

The viability of 2,7-dibenzyl oxynaphthalene towards the Nicholas reaction has already been demonstrated (compound 136 (70% yield)). The decomplexation of
compound 136 was done cleanly with iodine in THF without any issue, to give compound 169 (90% yield). The reduction of the triple bond and removal of the benzyl function as one-pot reaction was problematic over Pd/C under a hydrogen atmosphere, but compound 169 was easily reduced over Rh/C to give compound 170 (83% yield). The ester function was rapidly converted into a tertiary alcohol by adding excess MeLi (7 equiv) to the solution of compound 170 in Et₂O to afford compound 171 in excellent yield (92%). It was expected that in a manner similar to the transformation of compound 154 to 156 (Scheme 3.5), compound 171 would cyclize to give cyclohepta[de]naphthalene. The exposure of compound 171 to H₂SO₄, however never resulted in a cyclization (Scheme 3.9).
Scheme 3.9. Attempt to synthesize cyclohepta[de]naphthalene from 2,7-dibenzylidoxynaphthalene.

In an alternate attempt to afford cyclohepta[de]naphthalene from the monocondensation Nicholas reaction product 136, compound 171 was debenzylated over Pd/C in EtOAc to afford an excellent yield of compound 172 (96%). The addition of one
drop of H₂SO₄ to a solution of compound 172 in CH₂Cl₂ also failed to give a cyclohepta[de]naphthalene structure, but rather the tertiary alcohol cyclized with one of the naphthalenediol hydroxy functions to afford compound 173 (85% yield, Scheme 3.10).

Scheme 3.10. Synthesis of a naphtho fused oxepane 173.

In summary, after the unsuccessful attempts of getting a cobalt mediated cyclohept[de]ynenaphthalene synthesis, the decomplexed Nicholas reaction products were employed to afford cyclohepta[de]naphthalenes. Nicholas reaction mono and dicondensation products were used to afford cyclohepta[de]naphthalene structures through various chemical techniques such as ring closing metathesis and Friedel Crafts alkylation and acylation.
4. MICROSTEGIOL

4.1. Model Study of Microstegiol

After the successful synthesis of methoxydimethyl cyclohepta[de]naphthalenone 168, a close analog to microstegiol and its derivatives, and failed attempt to get the cyclohepta[de]naphthalene structure from 136, it was decided to focus on microstegiol as our primary synthetic target. If we carefully compare the structure of 168 and any of the naturally occurring cyclohepta[de]naphthalenes, a clear lacking of a methyl group in place of the methoxy function, and the absence of an isopropyl group at C-3 (α-carbon) is evident in 168, relative to the carbon skeleton of microstegiol (Figure 4.1). For this purpose it was decided to revise the whole synthetic scheme.

![Figure 4.1](image)

**Figure 4.1.** Structural comparison between 168 and microstegiol.

4.1.1 Selective Protection of 2,7-Dihydroxynaphthalene

In order to install the methyl group (at C-2 position in the starting material or C-6 in cyclohepta[de]naphthalene) and to attain the rearranged abietane structure, it was decided to begin with more appropriate starting material that can fulfill these challenges. After a brief investigation, 2,7-dihydroxynaphthalene was selected as staring material. Selectively protecting 2,7-dihydroxynaphthalene with benzyl (Bn) and acetyl (Ac) groups not only provided sufficient electron density in the naphthalene ring for the Nicholas
reaction with a γ-carbonyl cation equivalent, but also provided the system with a groups that could be selectively removed at many stages, to install the methyl group. Indeed, 7-benzyloxy-2-naphthol is commercial available; nevertheless it was synthesized in the lab from 2,7-dihydroxynaphthalene with a slight change to the literature method.111 The solution of 2,7-dihydroxynaphthalene in DMF was refluxed for 4 h in the presence of benzyl chloride (1.1 equiv) and K₂CO₃ (1.5 equiv) to afford the 7-benzyloxy-2-naphthol 174 (40% yield, literature yield 46% as the sole product) along with some 2,7-dibenzoyloxynaphthalene as a side-product 135 (20% yield). The rapid synthesis of compound 175 was accomplished in excellent yield (95%) by treating the solution of 7-benzyloxy-2-naphthol in CH₂Cl₂ with acetic anhydride in the presence of an excess of triethylamine (Scheme 4.1).

![Scheme 4.1. Selective protection of 2,7-dihydroxynaphthalene.](image)

**4.1.2. Nicholas Reaction between Selectively Protected Naphthalenediols and 132b, and the Synthesis of Precursor to Methylation**

Compound 175 was expected to react with 132b selectively on the more electron rich ring at ortho to benzyloxy group. Once again a very sluggish Nicholas reaction
between 175 and 132b was noticed in the presence of BF$_3$-OEt$_2$ (3 equiv) to afford 176 (24 h, 0 °C, 45%, 66% brsm), but a substoichiometric amount of Bu$_2$BOTf (0.7 equiv) was sufficient to convert 175 rapidly into 176 in excellent yield (1.5 h, 0 °C, 90%, Scheme 4.2). Removal of the Co$_2$(CO)$_6$ unit was done cleanly with iodine in THF, to give an excellent yield of 177 (90%). It was first attempted to accomplish both the reduction of the triple bond and the removal of the benzyl group in one pot fashion, by using well-known conditions of Pd/C and H$_2$. Unfortunately, these conditions resulted in a complex reaction mixture containing the product in an unacceptable yield. Catalytic hydrogenation on Rh/C cleanly reduced the triple bond of 177 without affecting the benzyl group in ethyl acetate to give 178 in excellent yield (92%). The benzyl group then was slowly removed through catalytic hydrogenolysis by treating the solution of 178 in ethyl acetate with H$_2$, Pd/C, to give phenolic acetate 179 in excellent yield (96%). The phenol group of 179 was readily converted into its triflate 180 in excellent yield (96%) in the presence of trifluoromethanesulfonic anhydride (Tf$_2$O) and pyridine.
Scheme 4.2. Nicholas reaction and triflation.

4.1.3. Incorporation of the Methyl Group

In order to incorporate the methyl group, a variety of catalysts, ligands and methyl organometallic reagents were tried. No product was formed in some of the cases and poor yields of the product in other cases. In the first attempt, a solution of the triflated derivative 180 in 1,4-dioxane was treated with trimethylboroxine (TMB) in the presence of tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄). After 4 h at reflux, there was no sign of a reaction product. In the end, the starting material was completely recovered from reaction mixture. In the second attempt, the methodology was changed completely.
This time, a solution of 180 in DMF was treated with tetramethyltin (Me₄Sn) in the presence Pd(PPh₃)₂Cl₂ and LiCl. This afforded methylated and deacylated product 181 in a poor yield (35%); a small amount of dihydroxynaphthalene side product 182 (11%) was also formed under these conditions (Scheme 4.3).

**Scheme 4.3. Attempts to incorporate the methyl group.**

After having these poor results, it was decided to use the well-known methylaluminium reagent DABAL-Me₃ (DABCO-(AlMe₃)₂), an adduct of 1,4-diazabicyclo[2.2.2]octane (DABCO) and trimethylaluminium. DABAL-Me₃ was freshly prepared in the lab by the simple mixing of DABCO with slightly more than double the amount of highly pyrophoric trimethylaluminium. Significant care was required in this preparation, as a small amount of unreacted AlMe₃ could cause the whole material to catch fire (Scheme 4.4).
Scheme 4.4. Preparation of DABAL-Me₃.

In the third attempt, compound 180 was completely unreactive on the treatment with DABAL-Me₃ in Pd₂(dba)₃/XPhos catalyzed reaction. After 4 h at reflux, only starting material was recovered from the reaction mixture (Scheme 4.5).¹¹⁵

Scheme 4.5. Attempts to incorporate the methyl group.

In the fourth attempt, the methyl incorporation was rapidly accomplished by simply replacing the XPhos ligand with Cy-JohnPhos, to afford 183 in good yield (84%) and small amount of deacetylated product 181 (7%). After optimization of the reaction, it was found that 1.5 mol% of Pd₂(dba)₃ and 3 mol% of Cy-JohnPhos were sufficient to complete this reaction in 1 h reflux, to give 183 in excellent yield (Scheme 4.6).¹¹⁵

Scheme 4.6. Incorporation of the methyl group.
4.1.4. Accomplishment of the Cyclohepta[de]naphthalene and Hydroxylation

Both of these methylnaphthalenes (181 and 183) were potential precursors for tertiary alcohols synthesis. Compound 183 afforded tertiary alcohol 184 in excellent yield (94%) on treatment with excess of methyllithium, while 181 converted into 184 in good yield (70%) under the same set of conditions (same number of equiv. of MeLi). A solution of 184 in CH₂Cl₂ then was subjected to one drop of H₂SO₄ at room temperature, which afforded a rapid cyclization to yield the cyclohepta[de]naphthalenone 185 in excellent yield (87%, Scheme 4.7).

Scheme 4.7. Formation of the cyclohepta[de]naphthalenone.
The incorporation of a hydroxy group at the 3° carbon α to the ketone function was accomplished by exposing the solution of cyclohepta[de]naphthalenone 185 in DMF to open air in the presence of sodium hydride (NaH) at 0 °C (Scheme 4.8). The α-hydroxy ketone product 186 (42% yield) was obtained along with the relatively unstable α-hydroxylated epoxide 187 (31% yield). A small amount of another product with ring expansion 188 (9% yield) was obtained. In order to check the relationship between the orientation of the hydroxy group and epoxide group in 187, its 1H NOESY spectrum was studied. The irradiation of the methyl peaks (0.84 ppm and 1.03 ppm) showed cross peaks between the 0.84 ppm (methyl) and 4.37 ppm (hydroxy) resonances, while cross peaks between 1.03 ppm (methyl) and both the 3.95 and 4.21 ppm (epoxide CH) resonances were observed. This spectral data supported the cis-relationship between OH and epoxy groups.

Scheme 4.8. Incorporation of the hydroxy group.
4.1.5. Attempts Towards Incorporation of the Isopropyl Group

If the structure of cyclohepta[de]naphthalenone 185 is compared to microstegiol 125, it is apparent that compound 185 lacks only the isopropyl group of the natural product. Therefore, to complete a microstegiol synthesis, the first choice was to extend the current materials onward and to try to install an isopropyl group on compound 185 or 186. In order to employ Suzuki–Miyaura coupling to install the isopropyl group, halogenation at the proper position was needed. The exposure of 185 in carbon tetrachloride (CCl₄) in the presence of pyridine and iodine resulted complete decomposition of the starting material. The treatment of compound 185 with N-bromosuccinimide (NBS) or bromine resulted no reaction at all, and starting material was collected from the reaction mixture. Compound 168 was also resulted completely unreactive against the same reagents (Br₂, CH₂Cl₂, Scheme 4.9).

![Scheme 4.9. Attempts to install a halogen group.](image-url)
After the failure of an incorporation of halogen group on cyclohepta[de]naphthalenone 185, it was decided to attempt halogenation on appropriate precursor to 185, such as 181 or 184. The exposure of 184 in CH₂Cl₂ resulted complete decomposition of the material, while bromination of 181 was accomplished cleanly in 1.5 h in dichloromethane to afford 189 in good yield (70%). Careful study of the ¹H NMR spectrum of 189 demonstrated that bromination had occurred at the C-3 rather than the intended C-6 position. Resolution enhancement of ¹H NMR clarified the picture that bromination had occurred at the C-3 position close to methyl group. This could be further confirmed by comparing its ¹H NMR with its close relative compound having substitution at C-6 position. In case of substitution at C-6, it was expected to have two singlets and two doublets in ¹H NMR. The ¹H NMR peaks in the aromatic region for compound 189 (substitution at C-3) were entirely different from the compound with C-6 substitution. The presence of one singlet, two doublet of doublets and one doublet (¹H NMR δ 7.90 (s, 1H), 7.63 (dd, J = 8.8, 3.3 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.8, 2.2 Hz, 1H)) confirmed the structure of 189 (Scheme 4.10).

Indeed, this brominated product 189 would not able to lead to the synthesis of the natural product microstegiol (125). It was decided to work with this compound to attain two main advantages. First, at least it will provide a plausible test pathway for the installation of the isopropyl group that will eventually help to synthesize the natural product. Secondly, this is not out of question that synthesized final product from 189, closely resembling to microstegiol, but having isopropyl group at the wrong position, might be biologically more active even than microstegiol itself. With this thinking, brominated naphthol 189 was exposed to Suzuki–Miyaura coupling conditions to incorporate the isopropenyl group. This gave isopropenynaphthol product 190 with low yield (48%). In another attempt, the hydroxyl group of brominated naphthol 189 was protected with a benzyl group by treating 189 with benzyl bromide and potassium carbonate at reflux in acetone for 4 h to give (191) in good yield (83%). This benzyloxy brominated naphthalene 191 was heated to reflux with isopropenylboronic acid pinacol ester for 10 h in the presence of Pd(PPh$_3$)$_4$ in 1,2-dimethoxyethane (DME), to afford
isopropenyl product 192 in excellent yield (90%). While the benzyl group nicely supported the Suzuki–Miyaura coupling reaction to give excellent yields, it has been demonstrated many times in our lab that the cycloheptane ring closure adjacent to a benzyloxy function is not readily done. Therefore, hydrogenolysis of the benzyl group and concomitant reduction of the isopropenyl group were accomplished in a one-pot fashion over Pd/C under H₂, to afford isopropynaphthol 193 in good yield (80%, Scheme 4.11).

Scheme 4.11. Incorporation of the isopropyl group.
Compound 193 was treated with an excess of MeLi in diethyl ether to afford tertiary alcohol naphthol 194 (85%). The ring closure of the tertiary alcohol was accomplished rapidly by H₂SO₄ in dichloromethane to give 3-isopropylcyclohepta[de]naphthalenone 195 (90%). Finally, hydroxylation was also accomplished uneventfully by exposing tricyclic compound 195 in DMF to air in the presence of NaH, to give 196 (Scheme 4.12).


4.2. Synthesis of Microstegiol

After the successful incorporation of a methyl group at the C-6 position and incorporation of a hydroxy group α- to the ketone function in conjunction with synthesis of cyclohepta[de]naphthalenones in model studies, the synthesis of microstegiol could now be targeted. The apparent challenge remaining in the synthesis of microstegiol was the incorporation of the isopropyl group.
4.2.1 Incorporation of Isopropyl Group

After the complete failure of installing the isopropyl group at the proper position at any later stage during the model studies of cyclohepta[de]naphthalenone synthesis, it was decided to incorporate the isopropyl group at a very early stage. For this purpose benzyloxynaphthalene diethyl carbamate 197 was prepared from compound 174 via literature methods. Compound 197 was intended to be a suitable precursor for ortholithiation. It was expected that the treatment of 197 in THF with LiTMP followed by the addition of isopropyl bromide or chloride will result in the incorporation of isopropyl group at C-3. In our hand, this reaction never afforded the intended product; rather the amide function was removed to give 7-benzyloxy-2-naphthol 174. Similar results were obtained by the treatment of 197 with n-BuLi followed by the addition of either acetone or acetyl chloride (Scheme 4.13).

Scheme 4.13. Attempts towards isopropyl incorporation.
After the failure of incorporation of isopropyl group through ortho lithiation chemistry, it was decided to employ the Suzuki–Miyaura reaction. For this purpose, bromination of 2,7-dihydroxynaphthalene was done by using a literature method.\textsuperscript{119} 2,7-Dihydroxynaphthalene was treated with bromine (2 equiv) in dichloromethane to afford a mixture of 1,3-, 1,6-dibromo and 1,3,6-tribromo-2,7-dihydroxynaphthalenes. Generally, in the literature only 1,3- and 1,6-dibromo-2,7-dihydroxynaphthalene have been reported and 1,3,6-tribromo-2,7-dihydroxynaphthalene has rarely been identified.\textsuperscript{118} These brominated naphthols were reduced by tin in acetic acid to afford a mixture of 3,6-dibromo-2,7-dihydroxynaphthalene \textsuperscript{198} and (predominantly) 3-bromo-2,7-dihydroxynaphthalene \textsuperscript{199}. From experimentation with this reduction, it was revealed that only the bromine at positions C-1 and C-8 could be reduced under normal reduction conditions. The removal of 3,6-dibromo-2,7-dihydroxynaphthalene from the mixture was the real challenge. All the chromatographic techniques with a variety of solvent systems completely failed. In the end, 3-bromo-2,7-dihydroxynaphthalene (\textsuperscript{199}, 86\%) was completely separated from the mixture by the recrystallization from toluene (Scheme 4.14).

Further extending the Diederich protocol, one of the hydroxy groups of 3-bromo-2,7-dihydroxynaphthalene (199) was protected with a methoxymethyl (MOM) group by treating its solution in acetonitrile (CH₃CN) with methoxymethyl chloride (MOMCl) in the presence of triethylamine (Et₃N) as a base, to afford 200 with selective C-2 alcohol protection in slightly better yield (57%) than the literature report (50%). Protection of the remaining OH with a benzyl group afforded 201 in excellent yield (92%). The removal of the MOM group was done under acidic conditions to afford 202 in excellent yield (96%). The free OH of 202 then was readily protected with an acetyl group by conventional conditions, to afford 203 in excellent yield (96%, Scheme 4.15).
Scheme 4.15. Synthesis of brominated selectively protected naphthalene.

In a manner similar to compound 175, in compound 203 it was necessary for Nicholas reaction to have one of the two aromatic rings more electron rich (the non-brominated one) than the other. For this purpose, an attempt was made to obtain the required selectively protected 3-bromo-2,7-dihydroxynaphthalene 203 in the minimum number of steps. It was first attempted to protect C-2 alcohol by an acetyl group, but the reaction gave C-7 protection (204). On the other hand, treatment of 199 with benzyl chloride/bromide resulted in the protection of the C-2 alcohol (205), rather than the C-7 alcohol. Both of these selective protections went entirely in an inverted way (Scheme 4.16).
Scheme 4.16. Failed attempts to approach compound 203.

The isopropyl group incorporation continued with the Suzuki-Miyaura coupling of 203 with isopropenylboronic acid pinacol ester under conventional conditions to afford isopropenyl incorporated product 206 in good yield (80%). The coupling was followed by the reduction of the alkene over Rh/C, to afford 207 in excellent yield (92%, Scheme 4.17).

Scheme 4.17. Incorporation of the isopropyl group on a differentially protected 3-bromo-2,7-dihydroxynaphthalene 203.
4.2.2 Nicholas Reaction and Synthesis of Cyclohepta[de]naphthalenone

Compound 207, with benzyloxy and acetoxy groups on the naphthalene ring, have distinctly different levels of electron density in each arene ring. As a result, the BF$_3$–OEt$_2$ (3 equiv) mediated Nicholas reaction between compounds 207 and 132b at 0 °C resulted in the electrophilic substitution on the more activated ring, ortho to benzyloxy group, to afford 208 in excellent yield (89%). There was no sign of a polyalkylated product. It could be recalled, in the model study, that the BF$_3$–OEt$_2$ mediated Nicholas reaction did not work well for 175 (without the isopropyl group), and switching to Bu$_2$BOTf afforded an excellent yield of the product. Removal of Co$_2$(CO)$_6$ unit was accomplished rapidly with I$_2$ in THF to afford an excellent yield of 209 (87%). After the incorporation of the four carbon electrophile, removal of benzyl group and reduction of triple bond were targeted. Once again, the logical treatment of the solution of 209 in ethyl acetate with H$_2$ over Pd/C was attempted to induce both hydrogenation of the triple bond and hydrogenolysis of the benzyloxy group in one pot to afford 210. This time, the process worked nicely to give a good yield of the product (84%). It is noteworthy to mention that this attempt for compound 177 failed to give a clean reaction (Scheme 4.18).
Scheme 4.18. Nicholas reaction, decomplexation and reduction.

The naphthol function of 210 was rapidly transformed into its triflate 211 (83%) by treating it with trifluoromethanesulfonic anhydride (Tf₂O) in the presence of pyridine. By using the optimized conditions employed in model studies for the incorporation of methyl group, a solution of triflated compound 211 in THF was heated to reflux with DABAL-Me₃ in the presence of catalytic amounts of Pd₂(dba)₃ (1.5 mol%) and Cy- JohnPhos (3 mol%); this afforded the compound 212 in excellent yield (91%) in one hour. In order to get the appropriate cyclization precursor, the ester functional group of compound 212 was converted into a tertiary alcohol by treating it with excess methyllithium, to afford an excellent yield (92%) of 213. The ¹H NMR (especially the aromatic region) of compounds 212 and 213 not only confirm the substitution of isopropyl group at C-6 position but also support the structure of compound 189 with substitution at C-3 position. In a manner similar to the synthesis of various cyclohepta[de]naphthalenones, such as 168, 185 and 195, addition of one drop of H₂SO₄
into a solution of 213 in CH₂Cl₂ resulted the ring closure, along with the tautomerization of the naphthol function to afford compound 214 (81%, Scheme 4.19).

4.2.3. Incorporation of Hydroxyl Function/Accomplishment of the Total Synthesis of (±)-Microstegiol

The first total synthesis of (±)-microstegiol was only one step away, namely incorporation of a hydroxy function α- to the keto group of compound 214. A similar set of conditions used in the model study for the synthesis of cyclohepta[de]naphthalenones (186 and 196) was employed. To a solution of compound 214 in DMF, NaH was added and the reaction mixture was exposed to an oxygen atmosphere, resulting in clean hydroxylation to give (±)-microstegiol 215 (63%) without any identifiable side product (Scheme 4.20). The spectroscopic data of product 215 was entirely identical to that of natural product isolated from plant *salvia microstegia*.

![Scheme 4.20. Incorporation of the hydroxy function.](image)

4.2.4. Attempts to Synthesize Enantiomerically Pure Microstegiol

After the successful synthesis of (±)-microstegiol, different ways were explored to get the enantiomerically pure natural product. None of the attempts resulted in the formation of the enantiomerically pure product. In the first attempt, a solution of compound 214 in DMF at room temperature was treated with nitrosobenzene (1 mol%) and (S)-proline (20 mol%), followed by the treatment with CuSO₄ in methanol. This resulted in no new product at room temperature. Heating the reaction mixture at reflux
mainly resulted ring opening of the seven membered ring to afford 216, along with a trace amount of 215, which was racemic by HPLC analysis. A change of the solvent (CHCl₃) did not make any difference in the reaction outcome (Scheme 4.21).

Scheme 4.21. Attempt to synthesize enantiomerically pure microstegiol by way of nitrosobenzene/(S)-proline.

Attempts were made to employ Davis oxaziridines for enantioselective OH incorporation. In one attempt a solution of 214 in THF was added dropwise to a solution of KHMDS in THF at -78°C, followed by the slow addition of (1R)-(-)-(10-camphor-sulfonyl)oxaziridine. After stirring the reaction mixture for 1 h, the same racemic product 215 resulted. Utilization of another enantiomerically pure oxaziridine ((1R)-(-)(8,8-dichloro-10-camphorsulfonyl)oxaziridine) in a similar procedure did not make any difference, only affording racemic 215 (47%). The enantiomeric excess (ee) of the product 215 was determined by high performance liquid chromatography (HPLC) (Scheme 4.22).
Scheme 4.22. Attempts to synthesize enantiomerically pure microstegiol by way of oxaziridines.
5. SUMMARY

The substitution pattern of mono- and disubstitution of Nicholas reactions on various versions of protected 2,7-dihydroxynaphthalenes and the utilization of the selected condensation products towards the synthesis of cyclohepta[de]-naphthalenes have been investigated. In monocondensation Nicholas reactions, in most of the cases, C-1 condensations were obtained for alkyne-Co$_2$(CO)$_6$ complexes having no substitution or substitution with a smaller group (CH$_3$) at the propargylic position and C-3 condensation product afforded for the complex having a phenyl group at the propargylic position. In dicondensation Nicholas reactions, C-1, C-8 and C-1, C-6 dicondensation products were obtained. The alkyne-Co$_2$(CO)$_6$ complexes having no substitution or substitution with an electron withdrawing group afforded C-1, C-8 dicondensation products while for the rest of the complexes C-1, C-6 dicondensation products were obtained. Selected C-1 monocondensation and C-1, C-8 dicondensation products were potential starting materials for the synthesis of cyclohepta[de]naphthalenes. The seven membered ring structures have been developed through ring closing metathesis (RCM) from a C-1, C-8 dicondensation product and through Friedel-Crafts alkylation and acylation techniques by the use of selected C-1 monocondensation products.

A dichotomy in the ring closure was observed for tertiary alcohol and carboxylic acid functions in cyclization onto a 2-naphthol. The tertiary alcohols (168, 185, 195, and 214) afforded the keto-tautomeric dehydrotetralone structures, while the Friedel-Crafts acylation reaction of the carboxylic acid (163) gave exclusively the enol-naphthol tautomer. The replacement of the oxygen based group at C-7 with a methyl group was very challenging. After using a variety of methyl reagents and ligands in the presence of
Pd$_2$(dba)$_3$, DABAL-Me$_3$ and Cy-JohnPhos were proved to be the suitable reagents for this transformation.

After having prepared cyclohepta[de]naphthalene 186, the installation of an isopropyl group was the only feature needed to accomplish the synthesis of microstegiol. All attempts at isopropyl group installation on 186 were unsuccessful. It was decided to install the isopropyl group at an early stage of the synthetic scheme. The bromination of 2,7-dihydroxynaphthalene was accomplished at the C-3 position and eventually was converted into an isopropyl group through a Suzuki coupling reaction and reduction of the isopropenyl group. Following construction of cyclohepta[de]naphthalene via steps worked out earlier, hydroxylation at the α-position was done readily to afford racemic microstegiol. While attempts at preparing the enantiomerically pure material were not successful, this presents the first total synthesis of microstegiol.

In this synthetic work, three different 2,7-dioxygenated naphthalenes (2,7-dimethoxynaphthalene, 7-methoxy-2-naphthol and 2,7-dihydroxynaphthalene) were used to afford a variety of cyclohepta[de]naphthalenes. Dihydrocyclohepta[de]naphthalene (151) and gem-dimethyl cyclohepta[de]naphthalene (156) were synthesized from 2,7-dimethoxynaphthalene. The enol-tautomeric cyclohepta[de]naphthalene (163) and gem-dimethyl cyclohepta[de]naphthalene dehydrotetralone (keto-tautomer, 168) structures were prepared from 7-methoxy-2-naphthol. The natural product microstegiol and its isomeric product (196) with isopropyl group at the C-6 position were synthesized from 2,7-dihydroxynaphthalene (Scheme 5.1.).
Scheme 5.1. Summary of the synthesis of a variety of cyclohepta[de]naphthalenes.

In summary, the Nicholas reaction-based γ-carbonyl cation chemistry on 2,7-dioxygenated naphthalene led to the synthesis of the carbon framework of the natural product, (±)-microstegiol (129). The incorporation of methyl group in place of C-7 oxygen-based function and the installation of hydroxy and isopropyl groups on the carbons vicinal to the keto function were the key steps in the total synthesis of (±)-microstegiol, which was accomplished in 15 steps with a 7.2% overall yield from 2,7-dihydroxynaphthalene.
6. FUTURE WORK

After accomplishing the synthesis of the natural product, (±)-microstegiol, the foremost extension of this research work is the synthesis of enantiomerically pure microstegiol (216, Scheme 6.01). The enantioselective incorporation of hydroxy function needs more exploration, as the most commonly used reagents such as Davis oxaziridines and (S)-proline/nitroso benzene have resulted in the racemic product (Scheme 4.21 and 4.22).

Scheme 6.1. Asymmetric synthesis of microstegiol.

Enzyme based enantioselective α-hydroxy ketone synthesis is very common. Various micro-organisms are used to provide the required enzyme for this type of compound, such as bacillus megaterium\(^ {122}\) (to provide a cytochrome P450 BM-3, capable of efficient and highly enantioselective hydroxylation at the alpha position of certain carboxylic ester and peptide groups), burkholderia cepacia\(^ {123}\) (source of a lipase), and rhizopus oryzae (source of a lipase, good for hydrolysis of a variety of ketones both linear and cyclic). The Demir group has reported the rhizopus oryzae mediated enantioselective hydrolysis of α-acetoxy aryl and alkyl ketones to afford α-hydroxy ketones.\(^ {124}\) In order to apply this technique on compound 214 or 215, the racemic product 215 could be easily converted into its acetate by using the conventional conditions, or compound 214 could be directly oxidized into the α-acetoxy ketone (216) by the use of manganese (III) acetate.
(Scheme 6.02). The treatment of \( \alpha \)-acetoxketine \( \text{(216)} \) with \textit{rhizopus orzae} in the presence of 10% \( \text{CaCO}_3 \) would be expected to selectively hydrolyze only one enantiomer to afford a mixture of enantiomerically enriched hydroxy ketone \( \text{(S)-215} \) and unhydrolyzed acetate \( \text{(R)-215} \). The \( \alpha \)-hydroxy ketone could easily be separated from the mixture by flash chromatography. However, the kinetic resolution process can only give maximum theoretical yield 50%, because most of the time the other enantiomer is unimportant.

![Scheme 6.2](image)

**Scheme 6.2.** Enzyme based synthesis of enantioselective \( \alpha \)-hydroxy ketone by kinetic resolution.

Another important analog of microstegiol is salvibretol \( \text{(130)} \). Salvibretol could also be synthesized from an appropriate compound of the synthetic scheme for microstegiol such as compound \( \text{212} \). The hydrolysis of ester group of compound \( \text{212} \) could be easily done by treating with \( \text{K}_2\text{CO}_3 \) on reflux to give compound \( \text{217} \). The treatment of \( \text{217} \) solution in \( \text{CH}_2\text{Cl}_2 \) with polyphosphoric acid (PPA) on reflux could afford cyclization product \( \text{218} \) (similar chemistry has been discussed in Scheme 3.7). It is
highly expected that this compound will be stable in its enol form, as DFT calculations support this enol structure (see Figure 3.1). The addition NaH into the solution of 218 in THF followed by the addition of MeI would afford compound 219. In literature, there is precedent for C-alkylation in related systems. During the synthesis of 219, a variety of solvents and corresponding appropriate bases would be employed to get C-alkylation. There is precedent in other diones to suggest that the treatment of the diketone compound 219 with methylmagnesium bromide (CH₃MgBr) will only attack the non-conjugated ketone (not the α,β-unsaturated ketone) to afford the natural product, (±)-salvibretol 130 (Scheme 6.03).

Scheme 6.3. The synthesis of salvibretol 130.
EXPERIMENTAL

All the solvents, such as tetrahydrofuran, diethyl ether, dichloromethane, and toluene were used after passing through a solvent purification system. Methanol, ethyl acetate and chromatographic solvents were used without passing through solvent purification system. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. The temperature -78 °C refers to a bath containing a mixture of dry ice (CO$_2$(s)) and acetone, while 0 °C to a bath containing ice.

In a conventional workup, the reaction was quenched with a saturated aqueous ammonium chloride solution, followed by the extraction with organic solvents. The organic solution was dried over anhydrous magnesium sulphate, followed by the filtration. The volatiles were evaporated under reduced pressure to give the crude product.

Flash column chromatography was performed by using silica gel 60 (230-400 mesh) obtained from Silicycle chemical division. Analytical thin layer chromatography (TLC) was performed over silica gel 60 F$_{254}$ sheets. The preparative thin layer chromatography was carried out over Silicylic silica gel GF-254 plates.

NMR spectra were recorded on Bruker Advance 300 or 500 MHz for $^1$H and 75 or 125 MHz for $^{13}$C in CDCl$_3$ unless otherwise stated. Chemical shifts are given in ppm, while coupling constants (J) are in Hz. Mass spectra of all the new compounds were recorded on a Varian 3800/1200L GS/MS in direct probe mode using electron impact (EI) at 20 eV. High-resolution mass spectra were run by time-of-flight mass spectroscopy at 70 eV at the McMaster Regional Center for Mass Spectrometry. Infrared (IR) spectra were recorded by using KBr plates on a Bruker Vector 22 FT-IR spectrophotometer.
General procedure for complexation

To a solution of alkyne compound in anhydrous diethyl ether at 0 °C was added an excess of dicobalt octacarbonyl (Co$_2$(CO)$_{8}$) in one portion. The reaction mixture was stirred for 1-3 h before filtration through Celite®. The solvent was removed under reduced pressure to afford crude compound. Flash chromatography afforded pure compound as a reddish brown viscous oil or solid.

**Hexacarbonyl[µ-η$^4$-(prop-2-yn-1-ol)]dicobalt (132a)**

![Chemical structure of 132a]

Compound 132a was prepared in 96% yield as a reddish brown solid by a literature method.$^{127}$

**Hexacarbonyl [µ-η$^4$-(methyl 4-methoxy-2-butynoate)]dicobalt (132b)**

![Chemical structure of 132b]

Compound 132b was prepared in 80% yield as a reddish brown viscous oil by a literature method. $^{103}$
Hexacarbonyl[μ-η⁴-(but-2-yn-1-ol)]dicobalt (132c)

Compound 132c was prepared in 77% yield as a reddish brown solid by a literature method.¹²⁸

Hexacarbonyl[μ-η⁴-(3-(trimethylsilyl)prop-2-yn-1-ol)]dicobalt (132d)

Compound 132d was prepared in 85% yield as a reddish brown solid by a literature method.⁶⁸b

Hexacarbonyl[μ-η⁴-(but-3-yn-2-ol)]dicobalt (132e)

Compound 132e was prepared in 81% yield as a reddish brown solid by a literature method.¹²⁹
Hexacarbonyl[µ-η⁴-(1-phenylprop-2-yn-1-ol)]dicobalt (132f)

Compound 132f was prepared in 79% yield as a reddish brown solid by a literature method. ¹²⁷

Hexacarbonyl[µ-η⁴-(2,7-dimethoxy-1-(prop-2-ynyl)naphthalene)]dicobalt (133a)

Method 1

To a solution of 2,7-dimethoxynaphthalene 93 (0.050 g, 0.27 mmol) in CH₂Cl₂ (15 mL) was added propargyl alcohol complex 132a (0.100 g, 0.292 mmol). BF₃·OEt₂ (101 µL, 0.797 mmol) was added dropwise at 0 °C. After 3h of continuous stirring, NH₄Cl(aq) was added and the mixture was subjected to a conventional extractive workup (CH₂Cl₂). The volatiles were evaporated under reduced pressure to afford the crude product. The residue was subjected to flash chromatography (50:1 petroleum ether: Et₂O) to give, 133a
Hexacarbonyl[µ-η^4-(2,7-dimethoxy-1-(3-carbomethoxyprop-2-vinyl) naphthalene)]
dicobalt (133b)

Subjecting 93 (0.210 g, 1.12 mmol), 132b (0.508 g, 1.23 mmol) and BF₃·OEt₂ (425 µL, 3.35 mmol) to Method 1 to give product 133b (0.560 g, 88% yield) following flash chromatography (5:1 petroleum ether: Et₂O) as red brown solid. 133b: IR (KBr) ν_max 3003, 2951, 2097, 2063, 2028, 1708; ¹H NMR δ 7.72 (d, J = 8.9, 1H), 7.68 (d, J = 8.9, 1H), 7.18 (d, J = 2.3, 1H), 7.10 (d, J = 8.9, 1H), 7.02 (dd, J = 8.9, 2.3, 1H), 4.64 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.53 (s, 3H); ¹³C NMR 198.4, 170.7, 158.5, 154.7, 133.9, 130.2, 128.8, 124.4, 119.1, 116.2, 109.3, 101.1, 99.4, 79.3, 55.2, 54.9, 52.4, 29.1; MS m/e for C_{21}H_{14}Co₂O₈ calcd (M⁺-2CO) 455.9454, found 455.9441.

(0.127 g, 93% yield). 133a: IR (KBr) ν_max 3003, 2960, 2090, 2055 cm⁻¹; ¹H NMR δ 7.71 (d, J = 8.9, 1H), 7.70 (d, J = 8.9, 1H), 7.22 (d, J = 2.4, 1H), 7.10 (d, J = 8.9, 1H), 7.04 (dd, J = 8.9, 2.4, 1H), 5.95 (s, 1H), 4.60 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H); ¹³C NMR 199.9, 158.4, 154.7, 133.9, 130.2, 128.6, 124.6, 120.1, 116.1, 109.7, 101.6, 96.1, 73.5, 55.4, 55.1, 29.5; MS 484 (M⁺-CO), 456 (M⁺-2CO), 428 (M⁺-3CO), 372 (M⁺-5CO); HRMS m/e for C_{21}H_{14}Co₂O₈ calcd (M⁺-2CO) 455.9454, found 455.9441.
**Hexacarbonyl[µ-η^4-(2,7-dimethoxy-1-(but-2-ynyl)naphthalene)]dicobalt (133c)**

Subjecting 93 (0.0960 g, 0.511 mmol), 132c (0.200 g, 0.562 mmol) and BF₃·OEt₂ (196 µL, 1.55 mmol) to **Method 1** gave product 133c (0.225 g, 84% yield) following flash chromatography (100:1 Petroleum ether: Et₂O) as red brown solid. 133c: IR (KBr) \( \nu_{\text{max}} \) 2941, 2086, 2044, 2015, 1629 cm\(^{-1}\); \(^1\)H NMR \( \delta = 7.73 \) (d, \( J = 9.0, 1H \)), 7.71 (d, \( J = 9.0, 1H \)), 7.26 (d, \( J = 2.2, 1H \)), 7.12 (d, \( J = 8.9, 1H \)), 7.03 (dd, \( J = 8.9, 2.2, 1H \)), 4.61 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 2.42 (s, 3H); \(^{13}\)C NMR 200.1, 158.4, 154.6, 133.8, 130.2, 128.5, 124.5, 119.6, 116.1, 109.5, 101.6, 98.1, 94.2, 55.3, 55.0, 29.5, 21.0; MS m/e 442 (M\(^+\) -3CO), 414 (M\(^+\) -4CO), 386 (M\(^+\) -5CO), 358 (M\(^+\) -6CO); HRMS m/e for C\(_{22}\)H\(_{16}\)Co\(_{2}\)O\(_8\) calcd (M\(^+\) -CO) 497.9560, found 497.9583.
Hexacarbonyl[µ-η⁴-(2,7-dimethoxy-1-(3-trimethylsilylprop-2-ynyl) naphthalene)] dicobalt (133d)

Subjecting 93 (0.0433 g, 0.230 mmol), 132d (0.1092 g, 0.2640 mmol) and BF₃·OEt₂ (87 µL, 0.69 mmol) to Method 1 gave product 133d (0.1308 g, 97% yield) following flash chromatography (50:1 Petroleum ether: Et₂O) as red brown solid. 133d: IR (KBr) \( \nu_{\text{max}} \) 2959, 2083, 2042, 2013, 1629 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.73 (d, \( J = 8.8 \), 1H), 7.72 (d, \( J = 8.8 \), 1H), 7.26 (d, \( J = 2.3 \), 1H), 7.12 (d, \( J = 8.9 \), 1H), 7.05 (dd, \( J = 8.9, 2.3 \), 1H), 4.72 (br s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 0.06 (s, 9H); \(^{13}\)C NMR 200.6, 158.7, 154.8, 134.0, 130.3, 128.7, 124.8, 120.0, 115.8, 110.6, 109.8, 102.5, 79.3, 55.3, 55.2, 30.6, 0.3; MS m/e 556 (M⁺ -CO), 528 (M⁺ -2CO), 500 (M⁺ -3CO), 444 (M⁺ -5CO); HRMS for C\(_{24}\)H\(_{22}\)Co\(_2\)O\(_8\)Si calcd. (M⁺ -3CO) 499.9900, found 499.9898.
Hexacarbonyl[µ-η⁴-(2,7-dimethoxy-1-(1-methylprop-2-ynyl)-naphthalene)]dicobalt (133e)

Subjecting 93 (0.0498 g, 0.264 mmol), 132e (0.0880 g, 0.247 mmol) and BF₃·OEt₂ (105 µL, 0.829 mmol) to Method 1 gave product 133e (0.0920 g, 66% yield) following flash chromatography (40:1 Petroleum ether: Et₂O) as a red brown solid. 133e: IR (KBr) νmax 3039, 2957, 2098, 2031, 1706 cm⁻¹; ¹H NMR (58:42 mixture of rotamers) δ 7.66-7.70 (m, 2H, both rotamers), 7.60 (d, J = 2.3, 1H minor), 7.35 (d, J = 1.9, 1H major), 7.10 (d, J = 8.9, 1H, minor), 7.08 (d, J = 8.8, 1H, major), 7.03 (dd, J = 8.8, 2.3, 1H, major), 7.02 (dd, J = 8.9, 1.9, 1H minor), 6.09 (s, 1H, both), 5.65 (q, J = 7.5, 1H, minor), 5.04 (q, J = 6.9, 1H, major), 3.99 (s, 3H, minor), 3.97 (s, 3H, major), 3.96 (s, 3H, minor), 3.93 (s, 3H, major), 1.89 (d, J = 6.9, 3H, major), 1.88 (d, J = 7.5, 3H, minor); ¹³C NMR 200.3, 199.9, 158.7, 157.1, 156.3, 154.1, 133.5, 133.3, 130.6, 130.4, 128.9, 128.8, 125.4, 125.4, 124.9, 124.7, 124.4, 116.1, 115.5, 111.0, 110.3, 104.6, 102.4, 101.8, 101.0, 74.1, 72.6, 56.1, 55.3, 55.2, 55.0, 37.7, 35.3, 22.4, 21.5; MS m/e 498 (M⁺-CO), 470 (M⁺-2CO), 442 (M⁺-3CO), 414 (M⁺-4CO), 386 (M⁺-5CO); HRMS m/e for C₂₂H₁₆O₈ calc. (M⁺-2CO) 469.9611, found 469.9608.
Hexacarbonyl[µ-η^4-(2,7-dimethoxy-3-(1-phenylprop-2-ynyl)-naphthalene)]dicobalt (133f)

Subjecting 93 (0.0560 g, 0.298 mmol), 132f (0.1500 g, 0.3588 mmol) and BF_3OEt_2 (113 µL, 0.892 mmol) to **Method 1** gave product 133f (0.0900 g, 51% yield) following flash chromatography (10:1 Petroleum ether: Et_2O) as a red brown solid. 133f: IR (KBr) \( \nu_{\text{max}} \) 2922, 2089, 2050, 2014, 1632 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.78 (s, 1H), 7.62 (d, \( J = 8.9 \), 1H), 7.48 (d, \( J = 7.3 \), 2H), 7.26 (m, 2H), 7.18 (t, \( J = 7.3 \), 1H), 7.02 (obscred d, \( J = 2.5 \), 1H), 7.01 (s, 1H), 6.98 (dd, \( J = 8.9 \), 2.5, 1H), 6.46 (s, 1H), 6.01 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H); \(^{13}\)C NMR 199.5, 158.1, 155.5, 144.2, 134.9, 131.4, 129.1, 128.4, 127.9, 126.9, 123.8, 116.2, 105.0, 104.8, 100.5, 74.1, 55.4, 55.2, 48.7; MS m/e 532 (M^+ -2CO), 476 (M^+ -4CO), 448 (M^+ -5CO), 420 (M^+ -6CO); HRMS m/e for C_{27}H_{18}Co_2O_8 calcd. (M^+ -4CO) 475.9869, found 475.9853.
Hexacarbonyl[µ-η⁴-(2,7-dibenzylxylo-1-(3-carboxethoxyprop-2-ynyl) naphthalene)] dicobalt (136) and Dodecacarbonyl[µ-η⁴-(2,7-dibenzylxylo-1,8-di(3-carboxethoxyprop-2-ynyl) naphthalene)]tetracobalt (137)

Subjecting 2,7-dibenzylxynaphthalene (135) (0.754 g, 2.21 mmol), 132b (1.009 g, 2.437 mmol) and BF₃·OEt₂ (842 µL, 6.64 mmol) to Method 1 gave products, in order of elution 136 (1.133 g, 71% yield) as a red brown solid, and 137 (0.3210 g, 13%), following flash chromatography (5:1 Petroleum ether: Et₂O) as a red brown viscous oil. 136: IR (KBr) υmax 3039, 2957, 2098, 2031, 1706 cm⁻¹; ¹H NMR δ 7.81 (dd, J = 8.9, 2.4, 2H), 7.66 (d, J = 7.1, 2H), 7.62 (d, J = 7.1, 2H), 7.45-7.59 (m, 7H), 7.28 (dd, J = 8.7, 1.9, 1H), 7.26 (d, J = 8.8, 1H), 5.39 (s, 2H), 5.33 (s, 2H), 4.81 (br s, 2H), 3.56 (s, 3H); ¹³C NMR 198.3, 170.5, 157.7, 154.1, 137.0, 134.0, 130.2, 128.8, 128.5, 127.9, 127.6, 127.5, 127.4, 127.3, 124.8, 120.0, 116.5, 111.5, 103.1, 99.0, 79.6, 70.7, 69.6, 52.4, 29.5; MS m/e 610 (M⁺-4CO), 554 (M⁺-6CO); HRMS for C₃₃H₂₄Co₂O₁₀ calcd. (M⁺-6CO) 554.0339, found 554.0354.
137: IR (KBr) \( \nu_{\text{max}} \) 2951, 2097, 2063, 2030, 1709 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.67 (d, \( J = 8.9\), 2H), 7.51 (d, \( J = 7.3\), 4H), 7.40 (apparent t, \( J = 7.3\), 4H), 7.33 (t, \( J = 7.1\), 2H), 7.16 (d, \( J = 8.9\), 2H), 5.35 (d, \( J = 16.7\), 2H), 5.30 (1/2 ABquartet, \( J = 12.2\), 2H), 5.22 (1/2 ABquartet, \( J = 12.2\), 2H), 4.82 (d, \( J = 16.6\), 2H), 3.36 (s, 6H); \(^{13}\)C NMR 198.2, 170.4, 155.6, 137.0, 132.2, 130.8, 128.5, 127.9, 127.2, 126.8, 121.4, 112.0, 99.6, 80.2, 71.0, 52.3, 31.0; MS m/e; Anal. Calcd for C\(_{46}H_{28}Co_4O_8\): C, 50.02, H, 2.56. Found: C, 49.87, H, 2.52.

**Dodecacarbonyl[µ-η\(^4\)-(2,7-dimethoxy-1,8-di(prop-2-ynyl)naphthalene)]tetracobalt**

(138a) and **Dodecacarbonyl[µ-η\(^4\)-(2,7-dimethoxy-1,6-di(prop-2-ynyl)naphthalene)]tetracobalt** (139a)
Method 2

To a solution of 2,7-dimethoxynaphthalene 93 (0.100 g, 0.531 mmol) in CH₂Cl₂ (10 mL) was added propargyl alcohol complex 132a (0.393 g, 1.149 mmol) followed by dropwise addition of Lewis acid BF₃·OEt₂ (202 µL, 1.59 mmol) at 0 °C. After 3h of continuous stirring, NH₄Cl(aq) was added and the mixture was subjected to a conventional extractive workup. The residue was purified by flash chromatography (10:1 Petroleum ether:Et₂O) to give, in order of elution, 139a (0.040 g, 9% yield), and 138a (0.280 g, 63% yield) as a red brown solid.

138a: IR (KBr) νmax 2917, 2090, 2051, 2021 cm⁻¹; ¹H NMR δ 7.70 (d, J = 8.9, 2H), 7.12 (d, J = 8.9, 2H), 5.83 (s, 2H), 5.22 (d, J = 16.4, 2H), 4.50 (d, J = 16.4, 2H), 3.99 (s, 6H); ¹³C NMR 199.6, 156.1, 131.9, 130.7, 126.5, 121.3, 110.1, 97.5, 73.8, 55.9, 30.6; MS m/e 808 (M⁺-CO), 780 (M⁺-2CO), 752 (M⁺-3CO), 724(M⁺-4CO), 696(M⁺-5CO), 668(M⁺-6CO), 640(M⁺-7CO), 612(M⁺-8CO); HRMS m/e for C₃₀H₁₆Co₄O₁₄ calcd. (M⁺-CO) 807.7917, found 807.7904.

139a: IR (KBr) νmax 2922, 2091, 2048, 2016 cm⁻¹; ¹H NMR δ 7.67 (d, J = 8.5, 1H), 7.57 (s, 1H), 7.19 (s, 1H), 7.08 (d, J = 8.5, 1H), 6.05 (s, 1H), 5.86 (s, 1H), 4.59 (s, 2H), 4.26 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H); ¹³C NMR 199.8, 156.5, 154.4, 133.2, 130.4, 128.2, 127.8, 124.4, 120.0, 110.0, 100.9, 97.9, 96.1, 73.8, 73.4, 55.4, 54.7, 39.3, 29.7 ;
Dodecacarbonyl[μ-η⁴-(2,7-dimethoxy-1,8-di(3-carbomethoxyprop-2-ynyl)naphthalene)]tetracobalt (138b)

Subjecting a solution of 2,7-dimethoxynaphthalene 93 (0.0258 g, 0.137 mmol), propargyl ether complex 132b (0.1314 g, 0.317 mmol) and BF₃·OEt₂ (115 µL, 0.91 mmol) to Method 2 gave product 138b (0.1117 g, 86% yield) following flash chromatography (5:1 Petroleum ether:Et₂O) as a red brown solid. 138b: IR (KBr) \( \nu_{\text{max}} \) 3004, 2950, 2907, 2076, 1710 \( \text{cm}^{-1} \); \(^1\)H NMR \( \delta \) 7.71 (d, J = 9.0, 2H), 7.10 (d, J = 9.0, 2H), 5.19 (d, J = 16.5, 2H), 4.69 (d, J = 16.5, 2H), 3.94 (s, 6H), 3.46 (s, 6H); \(^{13}\)C NMR 198.2, 170.5, 156.0, 132.0, 130.9, 126.3, 120.2, 109.7, 99.8, 80.2, 55.6, 52.3, 30.8; MS m/e 896 (M⁺-2CO), 840 (M⁺-4CO), 784 (M⁺-6CO), 728 (M⁺-8CO), 700 (M⁺-9CO); Anal. Calcd for C₃₄H₂₀Co₄O₁₈: C, 42.88; H, 2.12. Found: C, 43.12, H, 2.10.
Dodecacarbonyl[µ-η4-(2,7-dimethoxy-1,6-di(but-2-ynyl) naphthalene)]tetracobalt

(139c)

Subjecting 93 (0.1000 g, 0.5314 mmol), 132c (0.400 g, 1.12 mmol) and BF₃·OEt₂ (202 µL, 1.59 mmol) to Method 2 gave product 139c (0.3950 g, 86% yield) following flash chromatography (100:1 Petroleum ether: Et₂O) as a red brown solid. 139c: IR (KBr) νₑₓₑₑ 2949, 2085, 2000, 1631 cm⁻¹; ¹H NMR δ 7.71 (d, J = 8.9, 1H), 7.60 (s, 1H), 7.27 (s, 1H), 7.13 (d, J = 8.9, 1H), 4.62 (s, 2H), 4.30 (s, 2H), 4.01 (s, 3H), 3.98 (s, 3H), 2.55 (s, 3H), 2.44 (s, 3H); ¹³C NMR 200.1, 156.6, 154.6, 133.3, 130.4, 128.3, 127.4, 124.4, 119.6, 109.8, 100.7, 99.3, 98.2, 94.3, 55.3, 54.7, 34.8, 29.7, 21.0, 20.4; MS m/e 808 (M⁺-2CO), 780 (M⁺-3CO), 724 (M⁺-5CO), 640 (M⁺-8CO), 612 (M⁺-9CO); HRMS m/e for C₃₂H₂₀Co₄O₁₄, calcd (M⁺-3CO) 779.8334, Found: 7779.8342.
Subjecting 93 (0.050 g, 0.266 mmol), 132d (0.242 g, 0.585 mmol) and BF$_3$-OEt$_2$ (118 µL, 0.931 mmol) to **Method 2**, with the exception that the reaction mixture was additionally warmed to room temperature for 5 h, followed by flash chromatography (50:1 petroleum ether: Et$_2$O) gave products, in order of elution, 139d (0.105 g, 40% yield) as a red brown solid, and 133d (0.091 g, 59% yield). **139d**: IR (KBr) $\nu_{\text{max}}$ 2960, 2089, 2050, 2023, 1632 cm$^{-1}$; $^1$H NMR $\delta$ 7.70 (d, $J = 8.9$, 1H), 7.61 (s, 1H), 7.21 (s, 1H), 7.12 (d, $J = 8.9$, 1H), 4.70 (br s, 2H), 4.38 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 0.25 (s, 9H), 0.12 (s, 9H); $^{13}$C NMR 200.3, 156.6, 154.9, 133.4, 131.1, 128.3, 127.6, 124.5, 119.9, 112.7, 110.6, 110.0, 100.7, 79.4, 79.2, 55.3, 54.6, 34.9, 30.7, 0.5, 0.4; MS m/e 952 (M$^+$ - CO), 924 (M$^+$ -2CO), 896 (M$^+$ -3CO), 840 (M$^+$ -5CO), 784 (M$^+$ -7CO); HRMS (electrospray, negative ion) m/e for C$_{36}$H$_{32}$O$_9$Si$_2$ calcd (M -H$^+$) 978.8580: found 978.8584.
Dodecacarbonyl[µ-η4-(6-(but-3-yn-2-yl)-2,7-dimethoxy-1-(prop-2-ynyl)naphthalene)]tetracobalt (140)

Subjecting 133a (0.0300 g, 0.0585 mmol), 132e (0.0330 g, 0.0926 mmol) and BF3-OEt2 (25 µL, 0.20 mmol) to Method 1 gave product 140 (0.0360 g, 72% yield) following flash chromatography (100:1 Petroleum ether: Et2O) as a red brown solid. 140: IR (KBr) \( \nu_{\text{max}} \) 2935, 2089, 2050, 2018, 1627 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.69 (d, \( J = 8.9 \), 1H), 7.63 (s, 1H), 7.22 (s, 1H), 7.09 (d, \( J = 8.9 \), 1H), 6.02 (s, 1H), 5.90 (s, 1H), 4.80 (q, \( J = 7.1 \), 1H), 4.66 (1/2 ABquartet, \( J = 15.3 \), 1H), 4.57 (1/2 ABquartet, \( J = 15.3 \), 1H), 4.01 (s, 3H), 3.97 (s, 3H), 1.77 (d, \( J = 7.1 \), 3H); \(^{13}\)C NMR 199.9, 156.1, 154.5, 133.0, 132.8, 128.5, 126.8, 124.4, 119.9, 110.0, 105.4, 101.0, 96.2, 74.1, 73.5, 55.5, 54.9, 35.3, 30.0, 22.1; MS m/e 822 (M\(^+\)-CO), 794 (M\(^+\)-2CO), 766 (M\(^+\)-3CO), 738 (M\(^+\)-4CO), 710 (M\(^+\)-5CO), 682 (M\(^+\)-6CO), 654 (M\(^+\)-7CO), 626 (M\(^+\)-8CO), 598 (M\(^+\)-9CO); HRMS m/e for C\(_{31}\)H\(_{18}\)Co\(_4\)O\(_{14}\) calcd. (M\(^+\)-4CO) 737.8228, found 737.8201.
Dodecacarbonyl[μ-η⁴-(2,7-dimethoxy-6-(1-phenylprop-2-ynyl)-1-(prop-2-ynyl) napththalene)]tetracobalt (141)

Subjecting 134f (0.0372 g, 0.0632 mmol), 132a (0.0238 g, 0.0695 mmol) and BF₃-OEt₂ (24 µL, 0.19 mmol) to Method 1 gave product 141 (0.0380 g, 65% yield) following flash chromatography (10:1 Petroleum ether: Et₂O) as a red brown viscous oil. 141: IR (KBr) νmax 2929, 2089, 2049, 1629 cm⁻¹; ¹H NMR δ 7.80 (s, 1H), 7.66 (d, J = 9.0, 1H), 7.51 (d, J = 7.6, 2H), 7.27-7.31 (apparent t, J = 7.6, 2H), 7.21 (t, J = 7.4, 1H), 7.17 (d, J = 1.0, 1H), 7.07 (d, J = 9.0, 1H), 6.46 (s, 1H), 6.05 (s, 1H), 5.88 (s, 1H), 4.60 (1/2 AB quartet, J = 15.4, 1H), 4.52 (1/2 AB quartet, J = 15.4, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ¹³C NMR 199.4, 155.7, 154.5, 144.0, 132.8, 131.4, 128.9, 128.6, 128.4, 126.9, 124.2, 119.8, 110.0, 101.1, 100.4, 96.0, 74.0, 73.5, 55.4, 55.2, 48.5, 29.6; MS m/e 884 (M⁺-CO), 856 (M⁺-2CO), 828 (M⁺-3CO), 800 (M⁺-4CO); HRMS for C₃₆H₂₉Co₄O₁₄, calcd. (M⁺-4CO) 799.8384, found 799.8414.
To a solution of 138a (0.0970 g, 0.116 mmol) in acetone (30 mL) with silica gel (0.600 g) was added ceric ammonium nitrate (0.360 g) at -78°C. The reaction was stirred for 4 h, followed by the addition of H₂O and filtration through Celite®. After a conventional aqueous workup, the mixture was concentrated under reduced pressure. Preparative TLC (10:1 Petroleum ether : Et₂O) afforded, in order of elution, 138a (0.0350 g, 36% recovery), and 149 (0.0175 g, 57%, 89% based on recovered starting material). 149: mp 144-145°C; IR (KBr) νmax 3291, 2932, 2107, 1618 cm⁻¹; ¹H NMR δ 7.72 (d, J = 9.0, 2H), 7.18 (d, J = 9.0, 2H), 4.31 (d, J = 2.6, 4H), 4.03 (s, 6H), 2.16 (t, J = 2.6, 2H); ¹³C NMR 156.7, 133.5, 130.1, 126.2, 117.3, 111.0, 84.7, 69.1, 56.9, 17.3; MS m/e 264 (M⁺); HRMS m/e for C₁₈H₁₆O₂, calcd (M⁺) 264.1150, found 264.1153.

1,8-Diallyl-2,7-dimethoxynaphthalene (150)
To a solution of 149 (0.0200 g, 0.0758 mmol) in 20 mL of a mixture of ethyl acetate: 1-hexene: pyridine (10: 1: 1) was added Lindlar Catalyst (5 mole %) at room temperature. The reaction was stirred under an H₂ atmosphere for 3 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (5:1 Petroleum ether : Et₂O) to give, in order of elution, 150 (0.0180 g, 89%, 98% based on recovered starting material), and 149 (0.0018 g). 150: 93-94 °C(lit. mp 189-194 °C):^130 IR (KBr) ν max 3077, 2934, 1614 cm⁻¹; ^1H NMR δ 7.72 (d, J = 8.9, 2H), 7.18 (d, J = 8.9, 2H), 6.22 (m, 2H), 5.09 (dd J= 10.3, 1.9, 2H), 4.84 (dd, J= 17.3, 1.9, 2H), 3.93 (s, 6H), 3.91 (br s, 4H); ^13C NMR 155.7, 139.0, 134.9, 129.4, 126.3, 120.4, 114.5, 111.0, 56.8, 30.9; MS m/e 268 (M⁺); HRMS m/e for C₁₈H₂₀O₂ calcd (M⁺) 268.1463, found 268.1466.

(Z)-1,6-Dimethoxy-7,10-dihydrocyclohepta[de]naphthalene (151)

![Image of Z)-1,6-Dimethoxy-7,10-dihydrocyclohepta[de]naphthalene](image)

To a solution of 150 (0.0170 g, 0.0634 mmol) in CH₂Cl₂ (2 mL), was added Grubbs’ 1 catalyst (0.0027 g, 5 mole %) at room temperature. After 6 h the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure and the crude product was purified by preparative TLC (100:1 Petroleum ether: Et₂O) to give product 151 (0.0130 g, 85%).151: mp 95-96 °C; IR (KBr) ν max 3033, 2934, 1616 cm⁻¹; ^1H NMR δ 7.58 (d, J = 9.0, 2H), 7.10 (d, J = 9.0, 2H), 6.19 (m, 2H), 4.02 (d, J= 5.6, 4H), 3.92 (s,
6H); $^{13}$C NMR 154.0, 134.8, 130.9, 128.3, 126.8, 120.2, 112.0, 57.3, 24.3; MS m/e 240 (M$^+$), HRMS m/e for C$_{16}$H$_{16}$O$_2$ calcd (M$^+$) 240.1150, found 240.1150.

2,7-Dimethoxy-1-(3-carbomethoxyprop-2-ynyl)naphthalene (152)

![Structure of 152]

Method 3

To a solution of 133b (0.446 g, 0.782 mmol) in THF (50 mL) at room temperature, an excess of iodine (I$_2$) was added. The solution was stirred for 3 h. Following the addition of aqueous sodium bisulfite, the mixture was subjected to a conventional extractive workup (Et$_2$O). Purification by preparative TLC (1:1 Petroleum ether: Et$_2$O) gave 152 (0.218 g, 98% yield). 152: mp 80-81 °C; IR (KBr) $\nu_{max}$ 2956, 2233, 1712, 1628; $^1$H NMR $\delta$ 7.72 (d, J = 9.0, 1H), 7.69 (d, J = 8.9, 1H), 7.22 (d, J = 2.4, 1H), 7.11 (d, J = 9.0, 1H), 7.05 (dd, J = 8.9, 2.4, 1H), 4.11 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.70 (s, 3H); $^{13}$C NMR 158.4, 154.6, 154.0, 133.7, 129.9, 128.9, 124.3, 116.1, 113.6, 110.1, 101.2, 87.7, 71.9, 56.1, 55.0, 52.2, 14.5; MS m/e 284 (M$^+$); Anal. for C$_{17}$H$_{16}$O$_4$ Calcd. C, 71.82; H, 5.67. Found: C, 71.72; H, 5.47.
2,7-Dimethoxy-1-(3-carbomethoxypropyl)naphthalene (153)

To a solution of 152 (0.210 g, 0.739 mmol) in MeOH (20 mL) under H₂ was added Rh/C (excess) at room temperature. The solution was stirred for 6 h with monitoring by TLC. The suspension was filtered and the solvent was removed under reduced pressure. Preparative TLC (2:1 Petroleum ether: Et₂O) to give product 153 (0.211 g, 99% yield).

153: IR (KBr) \( \nu_{\text{max}} \) 2954, 1740, 1628; \(^1\)H NMR \( \delta \) 7.69 (d, \( J = 8.9 \), 1H), 7.66 (d, \( J = 8.9 \), 1H), 7.32 (d, \( J = 2.0 \), 1H), 7.12 (d, \( J = 8.9 \), 1H), 7.03 (dd, \( J = 8.9, 2.0 \), 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.70 (s, 3H), 3.11 (t, \( J = 7.6 \), 2H), 2.44 (t, \( J = 7.1 \), 2H), 2.00 (m, 2H); \(^{13}\)C NMR 174.1, 158.2, 155.0, 134.3, 129.9, 127.4, 124.7, 121.4, 115.7, 110.5, 101.9, 56.1, 55.1, 51.2, 33.5, 24.4, 24.2; MS m/e 288 (M⁺); HRMS m/e for C₁₇H₂₀O₄ calcd (M⁺) 288.1362, found 288.1360.

1-(4-Hydroxy-4-methylpentyl)-2,7-dimethoxynaphthalene (154)
To a solution of 153 (0.114 g, 0.396 mmol) in Et₂O (10 mL) at 0 °C was added MeLi (1.9 mL, 1.5 M, 2.9 mmol). The solution was stirred for 3 h before adding aqueous NH₄Cl and a conventional extractive workup (Et₂O) performed. The volatiles were removed under reduced pressure. Purification by preparative TLC (1:1 Petroleum ether: Et₂O) gave product 154 (0.103 g, 90% yield): mp 45-46 °C. In case when a modest excess of MeLi (3 equiv) was used, the reaction resulted the mixture of 154 (61% yield) and 155 (25% yield). 154: IR (KBr) υ max 3422 br, 2966, 1627 cm⁻¹; ¹H NMR δ 7.70 (d, J = 8.9, 1H), 7.66 (d, J = 8.9, 1H), 7.24 (d, J = 2.3, 1H), 7.13 (d, J = 8.9, 1H), 7.03 (dd, J = 8.9, 2.3, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.07 (t, J = 7.6, 2H), 1.74 (m, 2H), 1.69 (m, 2H), 1.38 (br s, 1H), 1.23 (s, 6H); ¹³C NMR 158.0, 154.8, 134.1, 130.0, 127.1, 124.8, 122.6, 115.5, 110.8, 102.0, 70.9, 56.3, 55.1, 43.8, 29.1, 25.4, 24.4; MS m/e 288 (M⁺), HRMS m/e for C₁₈H₂₄O₃ calcd (M⁺) 288.1725, found 288.1713.

5-(2,7-Dimethoxynaphthalen-1-yl)pentan-2-one (155)

155: IR (KBr) υ max 2937, 1712, 1627 cm⁻¹; ¹H NMR δ 7.68 (d, J = 8.9, 1H), 7.66 (d, J = 8.9, 1H), 7.36 (d, J = 2.4, 1H), 7.12 (d, J = 8.9, 1H), 7.02 (dd, J = 8.9, 2.4, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.05 (t, J = 7.7, 2H), 2.54 (t, J = 6.9, 2H), 2.15 (s, 3H), 1.93 (m, 2H); ¹³C NMR 209.2, 158.2, 154.9, 134.3, 130.0, 127.4, 124.7, 121.8, 115.9, 110.5,
101.9, 56.3, 55.4, 43.1, 30.0, 24.2, 23.2; MS m/e 272 (M⁺).

**1,6-Dimethoxy-7,7-dimethyl-7,8,9,10-tetrahydrocyclohepta[de]-naphthalene (156)**

To a solution of 154 (0.0750 g, 0.260 mmol) in CH₂Cl₂ (10 mL), one drop of H₂SO₄ was added. The solution was refluxed for 24 h. Water was added and a conventional extractive workup performed (CH₂Cl₂). Purification by preparative TLC (4:1 Hexanes:CH₂Cl₂) gave, product 156 (0.0490 g, 70% yield) contaminated with 157 (0.0056 g, 10% yield). 156: mp 101 °C; IR (KBr) $\nu_{\text{max}}$ 2929, 1612 cm⁻¹; ¹H NMR δ 7.54 (d, J = 8.9, 1H), 7.52 (d, J = 8.8, 1H), 7.09 (d, J = 8.9, 1H), 7.06 (d, J = 8.8, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.00 (br m, 2H), 1.95 (m, 2H), 1.69 (m, 2H), 1.52 (s, 6H); ¹³C NMR 158.8, 154.5, 137.6, 131.7, 127.3, 126.9, 125.4, 122.9, 112.1, 111.6, 84.6, 57.4, 56.0, 41.1, 39.4, 25.5, 22.1; MS m/e 270 (M⁺); HRMS m/e for C₁₈H₂₂O₂ calcd (M⁺) 270.1620, found 270.1614.
2,7-Dimethoxy-1-(4-methylpent-3-enyl)naphthalene (157)

157: mp 55-56 °C; IR (KBr) \( \nu_{\text{max}} \) 2926, 1620 cm\(^{-1}\); \( ^1\)H NMR \( \delta \) 7.69 (d, J = 9.4, 1H), 7.66 (d, J = 9.4, 1H), 7.25 (d, J = 2.1, 1H), 7.13 (d, J = 8.7, 1H), 7.02 (dd, J = 8.7, 2.1, 1H), 5.36 (t, J = 7.2, 1H), 3.95 (s, 6H), 3.05 (m, 2H), 2.31 (m, 2H), 1.73 (s, 3H), 1.61 (s, 3H); \( ^{13}\)C NMR 158.1, 155.0, 134.2, 131.8, 130.0, 127.2, 124.8, 124.6, 122.7, 115.7, 110.9, 102.0, 56.5, 55.2, 28.2, 25.7, 25.5, 17.6; HRMS m/e for C\(_{18}\)H\(_{22}\)O\(_2\) calcd (M\(^+\)) 270.1620, found 270.1606.

Hexacarbonyl[\( \mu-\eta^4\)-(7-acetoxy-2-methoxy-1-(3-carboxethoxyprop-2-enyl)naphthalene)]dicobalt (159)

Subjecting 158 (0.249 g, 1.15 mmol), 132b (0.525 g, 1.27 mmol) and BF\(_3\)-OEt\(_2\) (440 \( \mu\)L, 3.50 mmol) to Method 1 to give product 159 (0.609 g, 88% yield) in 6 h, following
flash chromatography (10:1 Petroleum ether: Et₂O) as a red brown viscous oil. The same product was prepared from 158 (0.250 g, 1.16 mmol), 132b (0.527 g, 1.27 mmol) with better yield (0.623 g, 90%) just in 0.5 h when Bu₂BOTf (0.807 mL, 1 M, 0.7 equiv.) was used instead of BF₃OEt₂. 159: IR (KBr) \( \nu_{\text{max}} \) 3004, 2952, 2099, 2063, 2029, 1765, 1709; \(^1\)H NMR \( \delta \) 7.82 (d, \( J = 9.0 \), 1H), 7.81 (d, \( J = 8.8 \), 1H) 7.62 (d, \( J = 2.2 \), 1H), 7.25 (d, \( J = 9.0 \), 1H), 7.11 (dd, \( J = 8.8, 2.2 \), 1H), 4.60 (s, 2H), 3.95 (s, 3H), 3.76 (s, 3H), 2.33 (s, 3H); \(^{13}\)C NMR 198.3, 170.7, 169.6, 155.0, 149.5, 133.4, 130.0, 129.0, 127.0, 120.2, 118.8, 114.3, 112.0, 98.7, 94.1, 55.4, 52.7, 28.4, 21.0; MS m/e 542 (M⁺-2CO), 514 (M⁺-3CO), 486 (M⁺-4CO), 458 (M⁺-5CO), 430 (M⁺-6CO); HRMS m/e for C₂₄H₁₆Co₂O₁₁ calcd (M⁺-3CO) 513.9509, found 513.9511.

7-Acetoxy-2-methoxy-1-(3-carbomethoxyprop-2-ynyl)naphthalene (160)

Subjecting 159 (0.284 g, 0.475 mmol) to Method 3, followed by recrystallization from Et₂O afforded 160 (0.138 g, 93% yield). 160: mp 132-133 °C; IR (KBr) \( \nu_{\text{max}} \) 2917, 2234, 1761, 1712; \(^1\)H NMR \( \delta \) 7.80 (d, \( J = 8.9 \), 1H), 7.78 (d, \( J = 8.9 \), 1H), 7.61 (d, \( J = 1.9 \), 1H), 7.23 (d, \( J = 8.9 \), 1H), 7.14 (dd, \( J = 8.9, 1.9 \), 1H), 4.07 (s, 2H), 3.95 (s, 3H), 3.70 (s, 3H), 2.38 (s, 3H); \(^{13}\)C NMR 169.4, 154.7, 154.0, 149.5, 133.1, 129.9, 129.2, 126.9, 118.8, 114.8, 113.7, 112.7, 87.4, 72.0, 56.3, 52.3, 21.0, 14.6; MS m/e 312 (M⁺); HRMS m/e for
C_{18}H_{16}O_5 \text{ calcd (M}^+\text{) } 312.0998, \text{ found } 312.0991.

**7-Acetoxy-1-(3-carbomethoxypropyl)-2-methoxynaphthalene (161)**

![Chemical structure](image)

To a solution of 160 (0.157 g, 0.503 mmol) in MeOH (15 mL) under H₂ was added Pd/C (excess). The solution was stirred for 12 h, following which the suspension was filtered and the filtrate concentrated under reduced pressure. Preparative TLC (1:1 Petroleum ether: Et₂O) gave 161 (0.148 g, 93% yield) as colorless solid. **161**: mp 125 °C; IR (KBr) ν_{max} 3067, 2950, 1759, 1734; ^1H NMR δ 7.79 (d, J = 8.8, 1H), 7.72 (d, J = 9.0, 1H), 7.65 (d, J = 2.0, 1H), 7.22 (d, J = 9.0, 1H), 7.11 (dd, J = 8.8, 2.0, 1H), 3.92 (s, 3H), 3.68 (s, 3H), 3.09 (t, J = 7.5, 2H), 2.42 (t, J = 7.5, 2H), 2.37 (s, 3H), 1.98 (m, 2H); ^13C NMR 173.9, 169.5, 154.9, 149.1, 133.6, 129.9, 127.6, 127.1, 122.3, 118.4, 114.0, 112.7, 56.1, 51.2, 33.5, 24.7, 24.0, 21.1; MS m/e 316 (M⁺); HRMS m/e for C_{18}H_{20}O_5 calcd (M⁺) 316.1311, found 316.1316.
1-(3-Carboxypropyl)-7-hydroxy-2-methoxynaphthalene (162)

To a solution of 161 (0.117 g, 0.370 mmol) in methanol (20 mL) was added an excess of sodium hydroxide. Following heating to reflux for 18 h, the mixture was acidified (3 M HCl) and a conventional extractive workup performed (Et₂O). Recrystallization from CH₂Cl₂ afforded product 162 (0.0730 g, 76% yield). 162: mp 164-165 °C; IR (KBr) ν_max 3385 br, 2924, 1703, 1626; ¹H NMR (acetone-d₆) δ 7.63 (d, J = 8.8, 1H), 7.62 (d, J = 9.0, 1H), 7.28 (br s, 1H), 7.11 (d, J = 9.0, 1H), 6.93 (dd, J = 8.8, 2.1, 1H), 3.87 (s, 3H), 2.99 (t, J = 7.7, 2H), 2.35 (m, 2H), 1.85 (m, 2H); ¹³C NMR (acetone-d₆) 174.5, 156.0, 155.1, 134.8, 130.2, 127.7, 124.5, 120.7, 115.7, 110.3, 104.8, 55.8, 33.3, 24.8, 24.1; MS m/e 260 (M⁺); HRMS m/e for C₁₆H₁₆O₄ calcd (M⁺) 260.1049, found 260.1045.
6-Hydroxy-1-methoxy-9,10-dihydrocyclohepta[de]naphthalen-7(8H)-one (163)

A solution of polyphosphoric acid (PPA, ca. 0.1 g, excess) and 162 (0.100 g, 0.385 mmol) in CH₂Cl₂ (20 mL) was heated to reflux for 36 h. Water was added and the mixture was subjected to a conventional extractive workup (CH₂Cl₂). Preparative TLC (2:1 Petroleum ether: Et₂O) gave 163 (0.075 g, 80% yield). 163: mp 90 °C; IR (KBr) \( \nu_{\text{max}} \) 3009, 2970, 1616 cm⁻¹; \(^1\)H NMR \( \delta \) 12.73 (s, 1H), 7.71 (d, J = 8.9, 1H), 7.63 (d, J = 8.8, 1H), 7.12 (d, J = 8.8, 1H), 6.93 (d, J = 8.9, 1H), 3.95 (s, 3H), 3.01 (t, J = 7.1, 2H), 2.71 (t, J = 7.4, 2H), 2.39 (m, 2H); \(^13\)C NMR 207.4, 162.5, 157.3, 136.2, 135.7, 128.6, 123.2, 122.4, 116.5, 115.2, 110.3, 56.2, 42.3, 29.5, 25.4; MS m/e 242 (M⁺); HRMS for C\(_{15}\)H\(_{14}\)O\(_3\) calcd (M⁺) 242.0943, found 242.0931.

7-Hydroxy-1-(4-hydroxy-4-methylpentyl)-2-methoxynaphthalene (167)
To a solution of 161 (0.1030 g, 0.3259 mmol) in Et₂O at 0 °C was added MeLi (0.76 mL, 1.1 mmol, 1.5 M in Et₂O). After 4 h of stirring, aqueous NH₄Cl was added. After a conventional workup, purification by TLC (1:1 Petroleum ether: Et₂O) gave product 167 (0.0625 g, 70% yield): mp 140 °C; IR (KBr) v_max 3358, 2967 cm⁻¹; ¹H NMR δ 8.10 (br s, 1H), 7.65 (d, J = 8.8, 1H), 7.61 (d, J = 8.9, 1H), 7.33 (d, J = 2.2, 1H), 7.08 (d, J = 8.9, 1H), 7.01 (dd, J = 8.8, 2.2, 1 H), 3.91 (s, 3H), 2.95 (br t, J = 7.0, 2H), 2.60 (br s, 1H), 1.65 (m, 4H), 1.21 (s, 6H); ¹³C NMR 154.6, 154.5, 134.4, 130.3, 127.3, 124.5, 122.1, 115.6, 110.7, 105.3, 72.0, 56.4, 43.5, 29.0, 25.4, 24.3; MS m/e 274 (M⁺); HRMS m/e for C₁₇H₂₂O₃ calcd 274.1569, found 274.1574.

6-Methoxy-10,10-dimethyl-8,9,10,10a-tetrahydrocyclohepta-[de]naphthalen-1(7H)-one (168)

![chemical structure](image)

To a solution of 167 (0.0625 g, 0.228 mmol) in CH₂Cl₂ (10 mL) was added one drop of H₂SO₄ at 0 °C. After 0.5 h of stirring, a conventional extractive workup (CH₂Cl₂) followed by preparative TLC (10:1 Petroleum ether: Et₂O) afforded 168 (0.0410 g, 70% yield). 168: mp 85-87 °C; IR (KBr) v_max 2934, 1653, 1615 cm⁻¹; ¹H NMR δ 7.29 (d, J = 9.7, 1H), 7.13 (d, J = 8.4, 1H), 6.79 (d, J = 8.4, 1H), 5.97 (d, J = 9.7, 1H), 3.84 (s, 3H), 3.63 (s, 1H), 3.36 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.51 (m, 1H), 1.38 (m, 1H), 1.27 (m, 1H), 1.17 (s, 3H), 0.66 (s, 3H); ¹³C NMR 203.2, 157.7, 145.5, 140.8, 129.4, 127.9,
124.4, 123.5, 108.9, 58.3, 55.7, 43.2, 37.0, 27.5, 24.3, 21.5, 20.2; MS m/e 256 (M+); HRMS m/e for C_{17}H_{20}O_{2} calcd 256.1463, found 256.1457.

**Methyl 4-(2,7-bis(benzyloxy)naphthalen-1-yl)but-2-yanoate (169)**

Subjecting \textbf{136} (0.989 g, 1.368 mmol) to \textbf{Method 3} gave the crude reaction product, which upon recrystallization from methanol gave product \textbf{169} (0.537 g, 90% yield). \textbf{169}: mp 102-103 °C; IR (KBr) \( \nu_{\text{max}} \) 3033, 2233, 1717, 1710, 1627 cm\(^{-1}\); \( ^1\text{H} \) NMR \( \delta \) 7.71 (d, J = 9.0, 1H), 7.05 (d, J = 9.0, 1H), 7.54-7.34 (m, 10 H), 7.33 (d, J = 2.5, 1H), 7.16 (d, J = 9.0, 1H), 7.13 (dd, J = 8.5, 2.5, 1H), 5.24 (s, 4H), 4.11 (s, 2H), 3.7 (s, 3H); \( ^{13}\text{C} \) NMR 157.7, 153.9, 136.9, 136.8, 133.7, 130.0, 128.9, 128.4, 127.8, 127.5, 127.2, 124.7, 116.7, 114.7, 112.0, 103.2, 87.6, 72.2, 71.1, 70.0, 52.3, 14.9; MS m/e 436 (M+); HRMS m/e for C_{29}H_{24}O_{4} calcd. 436.1672, found 436.1675.
Methyl 4-(2,7-bis(benzyloxy)naphthalen-1-yl)butanoate (170)

To a solution of 169 (0.181 g, 0.4146 mmol) in ethyl acetate was added Rh/C. The reaction mixture was stirred for 4 h under a hydrogen atmosphere. The suspension was filtered and the volatiles were evaporated under reduced pressure to give the crude reaction product. After preparative TLC (1:1 Petroleum ether: Et2O), product 170 (0.150 g, 83% yield) was obtained as a viscous oil. 170: IR (KBr) $\nu_{\text{max}}$ 2958, 1742, 1628 cm$^{-1}$; $^1$H NMR $\delta$ 7.72 (d, $J = 9.0$, 1H), 7.65 (d, $J = 9.0$, 1H), 7.56-7.35 (m, 11H), 7.16 (d, $J = 9.0$, 1H), 7.14 (dd, $J = 9.0$, 2.5, 1H) 5.30 (s, 2H), 5.20 (s, 2H), 3.70 (s, 3H), 3.23 (t, $J = 7.5$, 2H), 2.50 (t, $J = 7.5$, 2H), 2.00 (m, 2H); $^{13}$C NMR 173.9, 157.3, 154.1, 137.5, 137.1, 134.2, 130.0, 128.8, 128.4, 127.8, 127.7, 127.5, 127.4, 127.1, 124.9, 122.2, 116.3, 112.0, 103.6, 70.9, 69.9, 51.2, 33.6, 29.2, 24.4; MS m/e 440 (M$^+$); HRMS m/e for C$_{29}$H$_{28}$O$_4$ calcd. 440.1988, found 440.1973.

5-(2,7-Bis(benzyloxy)naphthalen-1-yl)-2-methylpentan-2-ol (171)
To a solution of 170 (0.250 g, 0.568 mmol) in Et₂O (20 mL) was added MeLi (2.65 mL, 1.5 M in Et₂O, 3.97 mmol) at 0 °C. The reaction mixture was stirred for 2 h before quenching with aqueous NH₄Cl. The mixture was subjected to a conventional extractive workup (Et₂O). The volatiles were evaporated under reduced pressure to give a crude product, which was subjected to preparative TLC (1:1 Petroleum ether: Et₂O) to give product 171 (0.230 g, 92%). 171: IR (KBr) \( \nu_{\text{max}} \) 3447, 2965, 1654 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.72 (d, \( J = 8.5 \), 1H), 7.64 (d, \( J = 9.0 \), 1H), 7.53-7.35 (m, 10 H), 7.31 (d, \( J = 2.0 \), 1H), 7.17 (d, \( J = 9.0 \), 1H), 7.13 (dd, \( J = 9.0 \), 2.5, 1H), 5.23 (s, 2H), 5.22 (s, 2H), 3.07 (t, \( J = 7.25 \), 2H), 1.69-1.59 (m, 4H), 1.18 (s, 6H); \(^{13}\)C NMR 157.0, 153.8, 137.4, 136.9, 134.0, 129.9, 128.4, 128.3, 127.7, 127.6, 127.34, 127.27, 126.9, 124.8, 123.0, 116.0, 111.9, 103.5, 70.7, 70.6, 69.8, 43.8, 28.9, 25.5, 24.3; MS m/e 440 (M\(^+\)); HRMS for C\(_{30}\)H\(_{32}\)O\(_3\) calcd. 440.2410, found 440.2381 and for (M\(^+\) - H\(_2\)O) calc. 422.2246, found 422.2252.

1-(4-Hydroxy-4-methylpentyl)naphthalene-2,7-diol (172)

To a solution of 171 (0.113 g, 0.2568 mmol) in ethyl acetate (20 mL) was added Pd/C (excess) under H\(_2\) at room temperature for debenzylolation. After stirring for 10 h, the reaction mixture was filtered and solvents were removed under reduced pressure to give crude product 172, which was purified by preparative TLC (1:2 Petroleum ether: Et₂O) to
give pure 172 (0.064 g, 96%). 172: IR (KBr) $\nu_{\text{max}}$ 3368, 2975, 2930, 1933 cm$^{-1}$; $^1$H NMR (in acetone-d$_6$) $\delta$ 8.47 (s, 1H), 8.33 (s, 1H), 7.63 (d, $J = 8.50$, 1H), 7.50 (d, $J = 9.0$, 1H), 7.25 (d, $J = 2.0$, 1H), 6.95 (d, $J = 8.5$, 1H), 6.91 (dd, $J = 8.75$, 2.2, 1H), 3.35 (s, 1H), 2.96 (t, $J = 7.75$, 2H), 1.72 (m, 2H), 1.61 (m, 2H), 1.16 (s, 6H); $^{13}$C NMR (in acetone-d$_6$) 156.5, 153.2, 136.1, 130.9, 127.8, 124.8, 119.4, 115.8, 115.4, 105.7, 70.8, 44.4, 31.6, 30.3, 26.1, 25.1; MS m/e 260 (M$^+$); HRMS for C$_{16}$H$_{20}$O$_3$ calcd. (M$^+$ - H$_2$O) 242.1307, found 242.1302.

4,4-Dimethyl-1,2,3,4-tetrahydronaphtho[2,1-b]oxepin-10-ol (173)

![Chemical Structure](image)

To a solution of 172 (0.050 g, 0.19 mmol) in CH$_2$Cl$_2$ was added one drop of concentrated H$_2$SO$_4$ at room temperature. The reaction mixture was stirred for 1 h. After conventional aqueous workup (CH$_2$Cl$_2$) and evaporation of the volatiles under reduced pressure, the crude product was subjected to preparative TLC (2:1 Petroleum ether: Et$_2$O) to give 173 (0.040 g, 85% yield). 173: IR (KBr) $\nu_{\text{max}}$ 3239, 1686, 1655 cm$^{-1}$; $^1$H NMR (in acetone-d$_6$) $\delta$ 8.51 (s, 1H), 7.71 (d, $J = 9.0$, 1H), 7.56 (d, $J = 8.7$, 1H), 7.37 (d, $J = 2.4$, 1H), 7.03 (dd, $J = 8.85$, 2.3, 1H), 6.88 (d, $J = 8.7$, 1H), 3.07 (m, 2H), 1.77 (m, 4H), 1.27 (s, 6H); $^{13}$C NMR (in acetone-d$_6$) 156.6, 154.3, 135.1, 131.0, 128.0, 127.6, 127.0, 122.2, 117.1, 106.0, 78.5, 41.2, 28.3, 26.4, 21.5; MS m/e 242 (M$^+$); HRMS for C$_{16}$H$_{18}$O$_2$ calcd 242.1307, found 242.1296.
7-(Benzyloxy)naphthalen-2-ol (174)

![Chemical Structure](image)

Compound **174** was prepared in 40% yield as a pinck solid from 2,7-naphthalenediol by a literature method[^1]. **174**: mp 147 °C (recrystallized from CH$_2$Cl$_2$); literature mp 183 °C (recrystallized from CHCl$_3$).

2-Acetoxy-7-benzyloxynaphthalene (175)

To a solution of 7-benzyloxy-2-naphthol (2.000 g, 7.991 mmol) in CH$_2$Cl$_2$ (50 mL), were added Et$_3$N (2 mL, excess) and acetic anhydride (2 mL, excess). After 1 h of stirring, the mixture was subjected to a conventional extractive workup. Recrystallization from Et$_2$O afforded product **175** (2.1958 g, 94% yield) as a white crystalline solid. **175**: mp 121 °C; IR (KBr) $\nu_{max}$ 2938, 1751 cm$^{-1}$; $^1$H NMR $\delta$ 7.78 (d, J = 8.9, 1H), 7.76 (d, J = 8.9, 1H), 7.49 (d, J = 7.4, 2H), 7.45 (d, J = 2.2, 1H), 7.42 (apparent t, J = 7.5, 2H), 7.36 (t, J = 7.5, 1H), 7.22 (dd, J = 8.8, 2.2, 1H), 7.19 (d, J = 2.2, 1H), 7.10 (dd, J = 9.0, 2.2, 1H), 5.19 (s, 2H), 2.36 (s, 3H); $^{13}$C NMR 169.5, 157.3, 149.0, 136.7, 135.0, 129.3, 129.1, 128.6, 128.0, 127.5, 127.0, 118.8, 118.7, 117.5, 107.1, 70.0, 21.1; MS m/e 292 (M$^+$); HRMS for C$_{19}$H$_{16}$O$_3$ calcd 292.1099, found 292.1097.
Hexacarbonylµ-η⁴-(7-acetoxy-2-benzyloxy-1-(3-carboxethoxyprop-2-vynyl)naphthalene]dicobalt (176)

![Chemical Structure of 176](attachment:image.png)

To a solution of 175 (0.2000 g, 0.6849 mmol) in CH₂Cl₂ (10 mL) was added 132b (0.3120 g, 0.7534 mmol) and Bu₂BOTf (479 µL, 1 M, 0.479 mmol) was added dropwise at 0 °C. After 1 h of continuous stirring, NH₄Cl(aq) was added and the mixture was subjected to a conventional extractive workup. The residue was purified by flash chromatography (2:1 Petroleum ether: Et₂O) to give 176 (0.4150 g, 90% yield) as a red brown solid. 176: IR (KBr) ν max 2953, 2113, 2063, 2031, 1765, 1708 cm⁻¹; ¹H NMR δ 7.80 (d, J = 8.8, 1H), 7.78 (d, J = 9.0, 1H), 7.65 (d, J = 2.1, 1H), 7.46 (d, J = 7.2, 2H), 7.39 (apparent t, J = 7.2, 2H), 7.33 (t, J = 7.2, 1H), 7.31 (d, J = 9.0, 1H), 7.14 (dd, J = 8.8, 2.1, 1H), 5.28 (s, 2H), 4.68 (br s, 2H), 3.64 (s, 3H), 2.34 (s, 3H); ¹³C NMR 198.2, 170.5, 169.5, 154.2, 149.5, 136.8, 133.5, 130.0, 128.9, 128.6, 128.0, 127.34, 127.25, 121.0, 119.0, 114.6, 113.9, 98.3, 78.8, 70.9, 52.6, 28.9, 21.0; MS m/e 618 (M⁺-2CO), 590 (M⁺-3CO), 506 (M⁺-6CO); HRMS m/e for C₃₀H₂₀Co₂O₁₁ calcd (M⁺-2CO) 617.9771, found 617.9735.
7-Acetoxy-2-benzyloxy-1-(3-carbomethoxyprop-2-ynyl)naphthalene (177)

Subjecting 176 (0.3630 g, 0.5385 mmol) to Method 3 gave the crude reaction product, which upon recrystallization in methanol gave product 177 (0.1880 g, 90% yield). 177: mp 144 °C; IR (KBr) υ_{max} 2956, 2234, 1761, 1712 cm^{-1}; ^1H NMR δ 7.79 (d, J = 8.8, 1H), 7.75 (d, J = 9.0, 1H), 7.67 (d, J = 1.5, 1H), 7.49 (d, J = 7.5, 2H), 7.43 (apparent t, J = 7.5, 1H), 7.36 (t, J = 7.5, 1H), 7.26 (d, J = 9.0, 1H), 7.17 (dd, J = 8.8, 1.5, 1H), 5.25 (s, 2H), 4.13 (s, 2H), 3.72 (s, 3H), 2.39 (s, 3H); ^13C NMR 169.5, 154.1, 154.1, 149.6, 136.8, 133.3, 130.1, 129.3, 128.6, 128.1, 127.3, 119.2, 116.0, 114.4, 114.1, 87.4, 72.3, 71.4, 52.4, 21.2, 15.1; MS m/e 388 (M^+); HRMS m/e for C_{24}H_{20}O_{5} calcd. 388.1311, found 388.1298.

7-Acetoxy-2-benzyloxy-1-(3-carbomethoxypropyl)naphthalene (178)

To a solution of 177 (0.2000 g, 0.5154 mmol) in ethyl acetate (20 mL) under H_2 was
added Rh/C (excess) at room temperature. The solution was stirred for 18 h with monitoring by TLC. The suspension was filtered and the solvent was removed under reduced pressure. Preparative TLC (2:1 Petroleum ether: Et₂O) to give product **178** (0.1880 g, 93% yield). **178**: bp 180-185 °C (0.15 torr); IR (KBr) \( \nu_{\text{max}} \) 2956, 1763, 1731 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.81 (d, \( J = 8.8 \), 1H), 7.73 (d, \( J = 2.1 \), 1H), 7.72 (d, \( J = 8.9 \), 1H), 7.50 (d, \( J = 7.4 \), 2H), 7.44 (apparent t, \( J = 7.4 \), 2H), 7.37 (t, \( J = 7.4 \), 1H), 7.29 (d, \( J = 8.9 \), 1H), 7.16 (dd, \( J = 8.8 \), 2.1, 1H), 5.22 (s, 2H), 3.64 (s, 3H), 3.20 (t, \( J = 7.7 \), 2H), 2.46 (t, \( J = 7.4 \), 2H), 2.40 (s, 3H), 2.05 (m, 2H); \(^{13}\)C NMR 173.8, 169.5, 154.0, 149.0, 137.2, 133.6, 129.8, 128.4, 127.7, 127.5, 127.3, 127.0, 123.0, 118.6, 114.2, 114.1, 70.9, 51.2, 33.6, 24.7, 24.3, 21.0; MS m/e 392 (M\(^+\)); HRMS m/e for C\(_{24}\)H\(_{24}\)O\(_5\) calcd. 392.1624, found 392.1610.

**7-Acetoxy-1-(3-carbomethoxypropyl)-2-hydroxynaphthalene (179)**

![Chemical Structure](image)

To a solution of **178** (0.1900 g, 0.4846 mmol) in ethyl acetate (20 mL) under H\(_2\) was added Pd/C (excess) at room temperature. The solution was stirred for 4 h with monitoring by TLC. The suspension was filtered and the solvent was removed under reduced pressure. Preparative TLC (1:1 Petroleum ether: Et₂O) afforded product **179** (0.1400 g, 96% yield). **179**: mp 80-81 °C IR (KBr) \( \nu_{\text{max}} \) 3425 br, 2952, 1759, 1733 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.75 (d, \( J = 8.8 \), 1H), 7.57 (d, \( J = 8.8 \), 1H), 7.56 (d, \( J = 2.3 \), 1H), 7.25 (br s,
1H), 7.07 (d, J = 8.8, 1H), 7.07 (dd, J = 8.8, 2.3, 1H), 3.74 (s, 3H), 3.02 (t, J = 7.8, 2H),
2.43 (t, J = 6.8, 2H), 2.38 (s, 3H), 1.96 (m, 2H); $^{13}$C NMR 175.6, 170.0, 152.5, 149.0,
133.7, 130.0, 127.7, 127.1, 118.3, 118.2, 117.7, 113.7, 51.9, 32.6, 24.3, 23.8, 21.2; Ms
m/e 302 (M$^+$); HRMS m/e for C$_{17}$H$_{18}$O$_5$ calcd. 302.1154, found 302.1141.

**7-Acetoxy-1-(3-carbomethoxypropyl)-2-(trifluoromethylsulfonyloxy) naphthalene**

(180)

![Chemical structure of 7-Acetoxy-1-(3-carbomethoxypropyl)-2-(trifluoromethylsulfonyloxy) naphthalene](image)

To a solution of 179 (0.1700 g, 0.5629 mmol) in CH$_2$Cl$_2$ (20 mL) were added
pyridine (136 µL, 1.69 mmol) and (F$_3$CSO)$_2$O (105 µL, 0.625 mmol) respectively. The
reaction mixture was stirred for 0.5 h. Following conventional extractive workup
(CH$_2$Cl$_2$), preparative TLC (1:1 Petroleum ether: Et$_2$O) gave product 180 (0.2347 g, 96%
yield) as a viscous oil. 180: IR (KBr) $\nu_{\text{max}}$ 2955, 1765, 1738 cm$^{-1}$; $^1$H NMR $\delta$
7.91 (d, J = 8.9, 1H), 7.86 (d, J = 2.1, 1H), 7.80 (d, J = 9.1, 1H), 7.37 (d, J = 9.1, 1H), 7.35
(dd, J = 8.9, 2.1, 1H), 3.72 (s, 3H), 3.17 (m, 2H), 2.48 (t, J = 7.3, 2H), 2.40 (s, 3H), 2.03 (m, 2H);
$^{13}$C NMR 173.4, 169.4, 149.8, 145.5, 113.2, 130.7, 130.3, 129.8, 128.8, 122.2, 119.1,
118.5 (q, J$_{CF}$ = 319.8), 115.9, 51.6, 33.4, 25.6, 24.8, 21.1; MS m/e 434 (M$^+$); HRMS m/e
for C$_{18}$H$_{17}$F$_3$O$_7$S calcd. 434.0647, found 434.0641.
To a solution of Pd$_2$(dba)$_3$ (0.0058 g, 0.0063 mmol) and (2-biphenyl)-dicyclohexylphosphine (0.0045 g, 0.013 mmol) in anhydrous THF (20 mL), were added DABAL-Me$_3$ (0.0987 g, 0.385 mmol, in THF) and 180 (0.1860 g, 0.4281 mmol, in THF (2 mL)) sequentially. After 0.5 h of stirring, dilute HCl (1 M) was added. After conventional extractive workup (Et$_2$O). The residue was subjected to preparative TLC (1:1 Petroleum ether: Et$_2$O), which afforded in order of elution 183 (0.1080 g, 84% yield) and 181 (0.0080 g, 7% yield); 183: colorless crystals, mp 48 °C; IR (KBr) $\nu_{\text{max}}$ 2951, 1769, 1736 cm$^{-1}$; $^1$H NMR $\delta$ 7.81 (d, J = 9.0, 1H), 7.73 (d, J = 2.0, 1H), 7.63 (d, J = 8.5, 1H), 7.29 (d, J = 8.5, 1H), 7.19 (dd, J = 9.0, 2.0, 1H), 3.72 (s, 3H), 3.06 (m, 2H), 2.51 (s, 3H), 2.50 (t, J = 7.0, 2H), 2.39 (s, 3H), 1.96 (m, 2H); $^{13}$C NMR 173.8, 169.8, 148.6, 134.5, 133.9, 132.6, 130.6, 129.9, 129.0, 126.1, 119.7, 114.6, 51.5, 33.9, 28.0, 24.8, 21.2, 20.1; MS m/e 300 (M$^+$); HRMS m/e for C$_{18}$H$_{20}$O$_4$ calcd. 300.1362, found 300.1351.
181: viscous oil; IR (KBr) $\nu_{\text{max}}$ 3395 br, 2953, 1736 cm$^{-1}$; $^1$H NMR $\delta$ 7.70 (d, $J$ = 9.0, 1H), 7.56 (d, $J$ = 8.5, 1H), 7.44 (d, $J$ = 2.3, 1H), 7.14 (d, $J$ = 9.0, 1H), 7.08 (dd, $J$ = 8.5, 2.3, 1H), 3.76 (s, 3H), 3.01 (m, 2H), 2.52 (t, $J$ = 7.0, 2H), 2.47 (s, 3H), 1.95 (m, 2H); $^{13}$C NMR 174.4, 153.9, 133.6, 133.5, 133.1, 130.4, 127.9, 126.8, 126.1, 116.4, 105.9, 51.7, 33.9, 28.2, 24.5, 20.1; MS m/e 258 ($M^+$); HRMS m/e for C$_{16}$H$_{18}$O$_3$ calcd. 258.1256, found 258.1259.

7-Hydroxy-1-(4-hydroxy-4-methylpentyl)-2-methylnaphthalene (184)

![Chemical Structure](image)

To a solution of 183 (0.0380 g, 0.127 mmol) in Et$_2$O at 0 °C was added MeLi (0.59 mL, 1.5 M in Et$_2$O, 0.89 mmol), was added. After 4 h of stirring, aqueous NH$_4$Cl was added. After conventional workup (Et$_2$O) and purification by TLC (1:1 Petroleum ether: Et$_2$O) gave product 184 (0.0306 g, 94% yield). 184: mp 145-146 °C; IR (KBr) $\nu_{\text{max}}$ 3312 br, 2968, 1635 cm$^{-1}$; $^1$H NMR $\delta$ (DMSO-d$_6$) 9.57 (s, 1H), 7.67 (d, $J$ = 8.8, 1H), 7.51 (d, $J$ = 8.3, 1H), 7.25 (d, $J$ = 2.1, 1H), 7.07 (d, $J$ = 8.3, 1H), 6.99 (dd, $J$ = 8.8, 2.1, 1H), 4.09 (s, 1H), 2.87 (m, 2H), 2.41 (s, 3H), 1.57 (m, 4H), 1.08 (s, 6H); $^{13}$C NMR (DMSO-d$_6$) 155.4, 133.7, 133.3, 132.4, 129.8, 126.8, 125.8, 125.5, 116.9, 105.1, 68.7, 44.0, 29.3, 28.8, 24.3, 19.8; MS m/e 258 ($M^+$); HRMS for C$_{17}$H$_{22}$O$_2$ calcd. ($M^+$) 258.1620, found 258.1620.
6,10,10-Trimethyl-8,9,10,10a-tetrahydrocyclohepta[de]naphthalen-1(7H)-one (185)

![Chemical Structure Image]

To a solution of 184 (0.0260 g, 0.101 mmol) in CH₂Cl₂ (10 mL) was added one drop of H₂SO₄. The solution was stirred for 4 h. A conventional extractive workup (CH₂Cl₂) followed by preparative TLC (1:4 hexanes: CH₂Cl₂) afforded product 185 (0.0210 g, 87% yield). 185: mp 73-74 °C; IR (KBr) νmax 2955, 1654 cm⁻¹; ¹H NMR δ 7.33 (d, J = 9.8, 1H), 7.11 (1/2 AB quartet, J = 7.7, 1H), 7.08 (1/2 AB quartet, J = 7.7, 1H), 6.05 (d, J = 9.8, 1H), 3.66 (s, 1H), 2.99 (m, 1H), 2.70 (m, 1H), 2.36 (s, 3H), 1.90 (m, 1H), 1.55 (m, 1H), 1.32 (m, 1H), 1.21 (s, 3H), 1.19 (m, 1H), 0.67 (s, 3H); ¹³C NMR 203.6, 145.7, 138.9, 136.9, 128.9, 128.1, 126.6, 125.9, 58.2, 42.3, 37.4, 29.7, 26.8, 25.6, 24.9, 20.4, 19.9; MS m/e 240 (M⁺); HRMS m/e for C₁₇H₂₀O calcd. 240.1514, found 240.1518.
10a-Hydroxy-6,10,10-trimethyl-8,9,10,10a-tetrahydrocyclohepta-[de]naphthalen-1(7H)-one (186)

(2R*,3R*,10aS*)-10a-Hydroxy-6,10,10-trimethyl-8,9,10,10a-tetrahydrocyclohepta [de]naphthalen-1(7H)-one 2,3-oxide (187)

2,2,6-Trimethyl-2,3,4,5-tetrahydronaphtho[1,8-bc]oxocin-11-ol (188)

To a solution of 185 (0.0200 g, 0.0833 mmol) in dry DMF (3 mL), was added NaH (0.0024 g, 0.10 mmol). After the reaction mixture stirring for 3 h in open air, it was subjected to conventional extractive workup (Et₂O). Preparative TLC (1:1 hexanes: CH₂Cl₂) gave, in order of elution, products 186 (0.0090 g, 42% yield), 187 (0.0070 g, 31% yield) and 188 (0.0020 g, 9% yield). 186: mp 102 °C; IR (KBr) νmax 3450, 2959, 1657 cm⁻¹; ¹H NMR δ 7.29 (d, J = 9.8, 1H), 7.10 (d, J = 7.6, 1H), 6.95 (d, J = 7.6, 1H), 6.20 (d, J = 9.8, 1H), 4.40 (s, 1H), 3.64 (m, 1H), 2.79 (m, 1H), 2.34 (s, 3H), 2.33 (m, 1H), 1.83 (m, 1H), 1.45 (m, 1H), 1.29 (m, 1H), 0.82 (s, 6H); ¹³C NMR 205.6, 148.0, 143.5, 140.4, 138.8, 130.2, 128.8, 127.3, 123.1, 84.4, 42.4, 39.0, 27.9, 26.8, 23.2, 22.0, 21.5; MS m/e 256 (M⁺); HRMS m/e for C₁₇H₂₀O₂ calcd. 256.1463, found 256.1473.
187: mp 110-111 °C; IR (KBr) ν_max 3456, 2924, 1698 cm^{-1}; $^1$H NMR δ 7.15 (1/2 AB quartet, J = 7.7, 1H), 7.11 (1/2 AB quartet, J = 7.7, 1H), 4.37 (s, 1H), 4.21 (d, J = 4.2, 1H), 3.95 (d, J = 4.2, 1H), 3.46 (dd, J = 14.3, 14.3, 1H), 2.87 (dd, J = 14.3, 5.9, 1H), 2.49 (m, 1H), 2.35 (s, 3H), 1.78 (m, 1H), 1.58 (m, 1H) 1.26 (m, 1H), 1.03 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR 212.1, 143.9, 139.3, 138.3, 130.2, 127.5, 127.2, 85.2, 59.5, 54.4, 43.7, 39.5, 28.7, 27.8, 25.7, 23.4, 21.7; MS m/e 272 (M+); HRMS m/e for C_{17}H_{20}O_{3} calcd. 272.1412, found 272.1404.

188: Visous oil; $^1$H NMR δ 7.50 (d, J = 8.5, 1H), 7.48 (d, J = 8.5, 1H), 7.162 (d, J = 8.5, 1H), 7.119 (d, J = 8.0, 1H), 6.12 (s, 1H), 3.95 (m, 1H), 2.95 (m, 1H), 2.45 (s, 3H), 2.19 (m, 1H), 1.69 (m, 1H), 1.65 (s, 3H), 1.61 (m, 1H), 1.25 (m, 1H), 1.17 (s, 3H); $^{13}$C NMR 148.4, 134.4, 133.6, 131.9, 128.3, 126.7, 126.1, 125.2, 115.1, 85.1, 33.1, 27.4, 26.4, 26.2, 22.8, 19.8, 14.0; MS m/e 298 (M+); HRMS m/e for C_{17}H_{22}O_{2}, calcd (M+) 256.1463, found 256.1454.
Methyl 4-(3-bromo-7-hydroxy-2-methylnaphthalen-1-yl)butanoate (189)

To a solution of 181 (0.060 g, 0.23 mmol) in CH₂Cl₂ (10 mL) was added bromine (18 µL, 0.34 mmol) slowly at room temperature. The reaction mixture was stirred for 1.5 h. After the conventional workup with aqueous NH₄Cl followed by evaporating the volatiles under reduced pressure, a crude product was obtained. After preparative TLC (2:1 Petroleum ether: Et₂O) and recrystallization from CH₂Cl₂, pure product 189 (0.055 g, 70% yield) was afforded. 189: mp 123-125 °C; IR (KBr) νmax 3381, 2951, 1735 cm⁻¹; ¹H NMR δ 7.91 (s, 1H), 7.61 (d, J = 9.0, 1H), 7.39 (d, J = 2.5, 1H), 7.08 (dd, J = 8.5, 2.5, 1H), 6.30 (s, 1H), 3.75 (s, 3H), 3.06 (m, 2H), 2.57 (s, 3H), 2.52 (m, 2H), 1.92 (m, 2H); ¹³C NMR 174.6, 154.2, 135.2, 132.8, 132.4, 129.5, 128.5, 121.8, 117.6, 106.2, 51.9, 33.7, 29.3, 24.4, 19.9; MS m/e 336 (M⁺); HRMS m/e for C₁₆H₁₇BrO₃, calcd (M⁺) 336.0361, found 336.0369.

Methyl 4-(7-(benzyloxy)-3-bromo-2-methylnaphthalen-1-yl)butanoate (191)
To a solution of 189 (0.148 g, 0.440 mmol) and K$_2$CO$_3$ (0.091 g, 0.66 mmol) in acetone (20 mL) was added benzyl bromide (63 µL, 0.53 mmol). The reaction mixture was refluxed for 4 h. After the extractive workup with aqueous NH$_4$Cl followed by evaporating the volatiles under reduced pressure, crude product 191 was obtained. The recrystallization from CH$_3$OH afforded pure white crystalline compound 191 (0.153 g, 0.3655 mmol, 83% yield). 191: mp 75-76 °C; IR (KBr) $\nu_{max}$ 2362, 1773, 1735 cm$^{-1}$; $^1$H NMR $\delta$ 7.93 (s, 1H), 7.62 (d, $J = 9.0$, 1H), 7.55-7.35 (m, 6H), 7.21 (dd, $J = 9.0$, 2.0, 1H), 5.28 (s, 2H), 3.75 (s, 3H), 3.08 (m, 2H), 2.59 (s, 3H), 2.48 (apparent t, $J = 7.0$, 2H), 1.89 (m, 2H); $^{13}$C NMR 173.7, 157.1, 137.0, 135.7, 132.8, 132.2, 129.4, 129.1, 128.7, 127.9, 127.5, 122.0, 104.4, 70.1, 51.5, 33.6, 29.4, 24.3, 19.9; MS m/e 426 (M$^+$); HRMS m/e for C$_{23}$H$_{23}$BrO$_3$, calcd (M$^+$) 426.0831, found 426.0833.

**Methyl 4-(7-benzyloxy-2-methyl-3-(prop-1-en-2-yl)naphthalen-1-yl)butanoate (192)**

![Methyl_4-(7-benzyloxy-2-methyl-3-(prop-1-en-2-yl)naphthalen-1-yl)butanoate](image)

To a solution of K$_2$CO$_3$ (0.077 g, 5.9 mmol) in degassed water (2 mL) was added a solution of 191 (0.060 g, 0.14 mmol), isopropenylboronic acid pinacol ester (0.046 g, 0.28 mmol), Pd(PPh$_3$)$_4$ (0.008 g, 0.007 mmol) and LiCl (0.018 g, 0.19 mmol) in
DME (10 mL). The resulting solution was stirred for 10 h at 80 °C before it was diluted with water. The crude product was extracted from aqueous phase with Et₂O. The purification was done with flash chromatography (5:1 Petroleum ether: Et₂O) to afford pure 192 as a viscous liquid (0.049 g, 90% yield). 192: IR (KBr) \( \nu_{\text{max}} \) 2951, 2360, 1736, 1625 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.68 (d, \( J = 9.0 \), 1H), 7.53-7.31 (m, 7H), 7.17, dd, \( J = 8.75, 2.2, 1H \), 5.28 (s, 2H), 5.22 (s, 1H), 4.91 (s, 1H), 3.73 (s, 3H), 3.03 (m, 2H), 2.48 (apparent t, \( J = 7.0, 2H \)), 2.41 (s, 3H), 2.07 (s, 3H), 1.89 (m, 2H); \(^{13}\)C NMR 173.9, 156.7, 147.1, 141.2, 137.3, 134.1, 132.1, 131.2, 129.8, 129.5, 128.5, 127.8, 127.5, 124.8, 117.6, 114.7, 104.3, 70.0, 51.5, 33.9, 28.5, 25.0, 24.3, 16.6; MS m/e 388 (M\(^+\)); HRMS m/e for C\(_{26}\)H\(_{28}\)O\(_3\), calcd (M\(^+\)) 388.2038, found 388.2047.

**Methyl 4-(7-hydroxy-3-isopropyl-2-methylnaphthalen-1-yl)butanoate (193)**

![Chemical Structure](attachment:image.png)

To a solution of 192 (0.040 g, 0.10 mmol) in ethyl acetate (20 mL) was added Pd/C (excess) under H\(_2\) at room temperature for debenzylation and reduction of isopropenyl group. After stirring for 4 h, after filtration and removal of solvents under reduced pressure a crude 193 was obtained, which was purified by preparative TLC (1:1
Petroleum ether: Et₂O) to give 193 as a white solid (0.025 g, 80% yield). 193: mp 165-167 °C; IR (KBr) \( \nu_{\text{max}} \) 3443, 2959, 1773, 1627 cm\(^{-1}\); \(^1\)H NMR (300 MHz) \( \delta \) 7.68 (d, \( J = 9.1 \), 1H), 7.53 (s, 1H), 7.40 (d, \( J = 2.1 \), 1H), 7.05 (dd, \( J = 8.9, 2.4 \), 1H), 6.13 (br s, 1H), 3.75 (s, 3H), 3.28 (m, 1H), 3.05 (m, 2H), 2.54 (apparent t, \( J = 6.9 \), 2H), 2.45 (s, 3H), 1.95 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H); \(^1^3\)C NMR 174.5, 153.4, 143.0, 133.3, 132.5, 131.7, 130.1, 127.8, 121.9, 116.4, 105.8, 51.7, 39.6, 28.8, 24.6, 23.6, 15.0; MS m/e 300 (M\(^+\)); HRMS m/e for C\(_{19}\)H\(_{24}\)O\(_{3}\), calcld (M\(^+\)) 300.1725, found 300.1728.

8-(4-Hydroxy-4-methylpentyl)-6-isopropyl-7-methylnaphthalen-2-ol (194)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

To a solution of 193 (0.015 g, 0.050 mmol) in Et₂O (15 mL) was added MeLi (218 μL, 1.6 M in Et₂O, 0.35 mmol) at 0 °C. The reaction mixture was stirred for 2 h before quenching with aqueous NH₄Cl. The mixture was subjected to conventional extractive workup (Et₂O). The volatiles were evaporated under reduced pressure to give a crude product, which was subjected to preparative TLC (2:1 Petroleum ether: Et₂O) to give product 194 (0.012 g, 80%). 194: mp 162-163 °C (CH₂Cl₂); IR (KBr) \( \nu_{\text{max}} \) 3228, 2959, 1626 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 7.67 (d, \( J = 8.5 \), 1H), 7.51 (s, 1H), 7.35 (m, 1H), 7.04 (dd, \( J = 8.75\), 1H).
2.2 (m, 1H), 3.28 (m, 1H), 3.00 (m, 2H), 2.44 (s, 3H), 1.73 (m, 4H), 1.31 (d, J = 7.0, 6H), 1.25 (s, 6H); $^{13}$C NMR 153.5, 142.9, 134.3, 132.1, 131.6, 130.1, 127.6, 121.6, 116.5, 105.9, 71.7, 43.9, 30.0, 29.7, 29.3, 24.5, 23.6, 15.1; MS m/e 300 (M$^+$); HRMS m/e for C$_{20}$H$_{28}$O$_2$, calcd (M$^+$) 300.2089, found 300.2090.

5-Isopropyl-6,10,10-trimethyl-8,9,10,10a-tetrahydrocyclohepta[de]naphthalen-1(7H)-one (195)

To a solution of 194 (0.010 g, 0.033 mmol) in CH$_2$Cl$_2$ was added one drop of concentrated H$_2$SO$_4$ at room temperature. The reaction mixture was stirred for 1 h. After conventional aqueous workup (CH$_2$Cl$_2$) and evaporation of the volatiles under reduced pressure, the crude product was subjected to preparative TLC (10:1 Petroleum ether: Et$_2$O) to give 195 (0.008 g, 85%) as a solid. IR (KBr) $\nu_{\text{max}}$ 2958, 1757, 1734, 1654 cm$^{-1}$; $^1$H NMR (acetone-d$_6$) $\delta$ 7.48 (d, J = 9.7, 1H), 7.22 (s, 1H), 5.94 (d, J = 9.7, 1H), 3.55 (s, 1H), 3.26 (m, 1H), 3.09 (m, 1H), 2.74 (m, 1H), 2.34 (s, 3H), 1.90 (m, 1H), 1.55 (m, 2H), 1.27 (d, J = 7.0, 3H), 1.20 (d, J = 7.0, 3H), 1.17 (s, 3H), 1.06 (m, 1H), 0.61 (s, 3H); $^{13}$C NMR 203.9, 146.2, 145.6, 138.9, 135.6, 134.3, 127.6, 125.8, 123.4, 57.9, 41.6, 37.5, 29.6, 26.4, 25.9, 25.3, 23.6, 23.1, 19.8, 15.0; MS m/e 282 (M$^+$); HRMS m/e for C$_{20}$H$_{26}$O$_1$, calcd
10a-Hydroxy-5-isopropyl-6,10,10-trimethyl-8,9,10,10a-tetrahydrocyclohepta[de]-
naphthalen-1(7H)-one (196)

To a solution of 195 (0.005, 0.02 mmol) in DMF (10 mL) was added NaH (0.637 g, 0.0265 mmol). The reaction mixture was stirred for 10 h under oxygen. After conventional extractive workup (Et₂O) and evaporation of volatiles under reduced pressure, the crude product was subjected to preparative TLC (5:1 Petroleum ether: Et₂O) to give 196. 196: ¹H NMR 7.28 (d, J = 9.0, 1H), 6.93 (s, 1H), 6.19 (d, J = 9.6, 1H), 4.42 (s, 1H), 3.70 (m, 1H), 3.20 (m, 1H), 2.90 (m, 1H), 2.30 (s, 3H), 1.81 (m, 1H), 1.28 (d, J = 6.9, 3H), 1.29 (s, 3H), 1.16 (d, J = 6.9, 3H), 0.90 (s, 3H), 0.89 (s, 3H); MS m/e 298 (M⁺).
7-(Benzyloxy)naphthalen-2-yl diethylcarbamate (197)

To a solution of NaH (0.132 g, 5.5 mmol) in THF (10 mL) was added a solution of 7-benzyloxy-2-naphthol 174 (0.550 g, 2.20 mmol) in THF (20 mL) dropwise followed by the addition of diethyl carbamyl chloride (371 µL, 2.93 mmol). The mixture was stirred for 12 h at room temperature under nitrogen. After conventional extractive workup (Et₂O) and evaporation of volatiles under reduced pressure, the crude product was subjected to flash chromatography (1:1 EtOAc : Hexane) to give 197 (0.644 g, 84% yield) as a colorless solid. 197: mp 86-88 °C; IR (KBr) νmax 3443, 1716 cm⁻¹; ¹H NMR δ 7.76 (d, J = 8.5, 1H), 7.75 (d, J = 8.5, 1H), 7.50 (d, J = 7.0, 2H), 7.48 (d, J = 2.5, 1H), 7.42 (apparent t, J = 7.5, 2H), 7.36 (t, J = 7.5, 1H), 7.20 (dd, J = 9.0, 2.5, 1H), 7.17 (d, J = 2.0, 1H), 7.15 (dd, J = 9.0, 2.2, 1H), 5.17 (s, 2H), 3.52-3.41 (m, 4H), 1.32-1.23 (m, 6H); ¹³C NMR 157.1, 154.3, 149.8, 136.8, 135.1, 129.2, 128.8, 128.6, 128.0, 127.5, 126.7, 119.2, 118.4, 117.5, 107.0, 70.0, 42.2, 41.9, 14.2, 13.4; MS m/e 349 (M⁺).
3-Bromonaphthalene-2,7-diol (199)

![Chemical Structure of 3-Bromonaphthalene-2,7-diol](image)

Compound 199 was prepared in 86% yield as white crystalline solid by the method of Diederich. 119 199: mp 187-188 °C (toluene); lit. mp 190-191 °C (toluene). 119

6-Bromo-7-(methoxymethoxy)naphthalen-2-ol (200)

![Chemical Structure of 6-Bromo-7-(methoxymethoxy)naphthalen-2-ol](image)

Compound 200 was prepared in 57% yield as a white solid by the method of Diederich. 119 200: mp 106-107 °C (CH₂Cl₂ : Petroleum Ether); lit. mp 107-108 °C. 119

6-(Benzyloxy)-2-bromo-3-(methoxymethoxy)naphthalene (201)

![Chemical Structure of 6-(Benzyloxy)-2-bromo-3-(methoxymethoxy)naphthalene](image)

Compound 201 was prepared in 92% yield as a white solid by the method of Diederich. 119 201: mp 114-115 °C (toluene); lit. mp 114-115 °C (toluene). 119
7-(benzyloxy)-3-bromonaphthalen-2-ol (202)

![Chemical structure of 7-(benzyloxy)-3-bromonaphthalen-2-ol (202)]

Compound 202 was prepared in 96% yield as a white solid by the method of Diederich.\textsuperscript{119} 202: mp 153-154 °C (toluene); lit. mp 153-154 °C (toluene).\textsuperscript{119}

2-Acetoxy-7-benzyloxy-3-bromonaphthalene (203)

![Chemical structure of 2-Acetoxy-7-benzyloxy-3-bromonaphthalene (203)]

Compound 202 was synthesized from 2,7-naphthalenediol by using the Diederich procedure.\textsuperscript{119} To a solution of 202 (1.500 g, 4.573 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) was added Et\textsubscript{3}N (1 mL, excess) and acetic anhydride (1 mL, excess). The reaction mixture was stirred for 0.5 h and then the reaction mixture was concentrated under reduced pressure. Further purification was done by recrystallization from CH\textsubscript{2}Cl\textsubscript{2} and Petroleum Ether (5:1) to give colorless crystalline solid 203 (1.624 g, 96%).\textsuperscript{203} 203: mp 125-126 °C (CH\textsubscript{2}Cl\textsubscript{2}-petroleum ether); IR (KBr) \textit{\nu}_{\text{max}} 2940, 1773, cm\textsuperscript{-1}; \textsuperscript{1}H NMR \delta 8.03 (s, 1H), 7.65 (d, J = 9.0, 1H), 7.52 (d, J = 7.5, 2H), 7.51 (s, 1H), 7.46 (t, J = 7.5, 2H), 7.41 (t, J = 7.5, 1H), 7.25 (dd, J = 9, 2.5, 1H), 7.13 (dd, J = 2.5, 1H), 5.15 (s, 2H), 2.45 (s, 3H); \textsuperscript{13}C NMR
168.7, 157.3, 145.7, 136.3, 133.8, 131.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.4, 120.0, 112.0, 106.6, 69.8, 20.7; MS m/e 370 (M⁺); HRMS m/e for C₁₉H₁₅BrO₃ calcd (M⁺) 370.0205, found 370.0193.

2-Acetoxy-7-benzyloxy-3-(prop-1-en-2-yl)naphthalene (206)

To a solution of K₂CO₃ (0.746 g, 5.41 mmol) in degassed water (3 mL) was added a solution of 203 (0.500 g, 1.35 mmol), isopropenylboronic acid pinacol ester (508 µL, 2.70 mmol), Pd (PPh₃)₄ (0.078 g, 0.067 mmol) and LiCl (0.172 g, 4.05 mmol) in DME (20 mL). The resulting solution was stirred for 12 h at 80 °C before it was diluted with water. The crude product was extracted from aqueous phase with Et₂O. The organic extract was dried over MgSO₄, the solvent was evaporated to get pure product 206 (0.359 g, 80% yield) as a colorless crystalline solid following flash chromatography (5:1 Petroleum ether: Et₂O). 206: Mp 91-92 °C; IR (KBr) νmax 2921, 1762, 1633 cm⁻¹; ¹H NMR δ 7.80 (obscured d, J = 8.9, 1H), 7.79 ( s, 1H), 7.56 (d, J = 7.3, 2H), 7.51 (s, 1H), 7.49 (apparent t, J = 7.6, 2H), 7.43 ( t , J = 7.2, 1H), 7.31 (dd, J = 8.9, 2.5, 1H), 7.23 ( d, J = 2.5, 1H), 5.37 (s, 1H), 5.28  s, 1H), 5.21 (s, 2H), 2.40 (s, 3H), 2.28 (s, 3H); ¹³C NMR 169.3, 157.0, 146.5, 141.6, 136.6, 134.0, 133.1, 129.1, 128.4, 127.8, 127.7, 127.3, 127.0,
To a solution of 206 (0.500 g, 1.51 mmol) in ethyl acetate (25 mL) was added Rh/C (0.0050 g). The reaction was stirred for 2 h under an H₂ atmosphere, with monitoring by TLC. The reaction mixture was filtered and solvents evaporated under reduced pressure to give a colorless solid, which upon crystallization (petroleum ether-Et₂O) gave product 207 as a crystalline solid (0.463 g, 1.386 mmol, 92% yield). 207: mp 91-92°C; IR (KBr) νmax 2963, 1759 cm⁻¹; ¹H NMR δ 7.79 (d, J = 9.0, 1H), 7.77 (s, 1H), 7.55 (d, J = 7.2, 2H), 7.48 (apparent t, J = 7.3, 2H), 7.48 (s, 1H), 7.41 (t, J = 7.3, 1H), 7.28 (dd, J = 9.0, 2.5, 1H), 7.22 (dd, J = 2.5, 1H), 5.21 (s, 2H), 3.21 (septet, J = 6.9, 1H), 2.45 (s, 3H), 1.41 (d, J = 6.9, 6H); ¹³C NMR 169.6, 156.6, 147.5, 137.0, 136.7, 133.2, 128.9, 128.5, 127.9, 127.5, 127.4, 125.2, 118.8, 118.4, 106.5, 69.8, 27.7, 23.0, 20.9; MS m/e 334 (M⁺); HRMS m/e for C₂₂H₂₀O₃, calcd (M⁺) 334.1569, found 334.1563.
Hexacarbonyl[μ-η⁴-(methyl 4-(7-acetoxy-2-(benzyloxy)-6-isopropyl naphthalen-1-yl)but-2-ynoate)]dicobalt (208)

To a solution of 207 (0.600 g, 1.80 mmol) in CH₂Cl₂ (30 mL) was added cobalt complex 132b (0.818 g, 1.98 mmol) and BF₃-OEt₂ (680 µL, 5.39 mmol) at 0 °C. The mixture was stirred for 4 h under nitrogen and then aqueous NH₄Cl was added. After a conventional extractive workup the volatiles were evaporated under reduced pressure to give a reddish brown solid, which was subjected to column chromatography (10:1 Petroleum ether: Et₂O) to give product 208 (1.145 g, 89% yield). 208: IR (KBr) ν max 2964, 2095, 2031, 1759, 1706 cm⁻¹; ¹H NMR δ 7.76 (d, J = 9.0, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 7.48 (d, J = 7.3, 2H), 7.41 (apparent t, J = 7.4, 2H), 7.34 (t, J = 7.3, 1H), 7.30 (d, J = 9.0, 1H), 5.27 (s, 2H), 4.68 (br s, 2H), 3.66 (s, 3H), 3.14 (septet, J = 6.8, 1H), 2.39 (s, 3H), 1.35 (d, J = 6.8, 6H); ¹³C NMR 198.2, 170.5, 169.6, 153.5, 148.1, 137.4, 136.8, 131.7, 128.5, 128.4, 127.83, 127.80, 127.3, 126.1, 120.5, 115.5, 113.4, 98.4, 78.7, 70.7, 52.5, 28.9, 27.6, 23.02, 22.95, 20.8; MS m/e 716 (M⁺); HRMS m/e for C₃₃H₂₆O₁₁Co₂, calcd (M⁺-6CO) 548.0473, found 548.0486.
To a solution of 208 (0.830 g, 1.16 mmol) in THF (50 mL) was added I$_2$ (excess). After 1 h, aqueous sodium bisulfite was added. After conventional extractive workup (Et$_2$O) and removal of volatiles under reduced pressure gave colorless solid which was purified by recrystallization from methanol to give a colorless crystalline solid 209 (0.435 g, 87% yield). 209: mp 92-93 °C; IR (KBr) $\nu_{\text{max}}$ 2962, 2233, 1757, 1712 cm$^{-1}$; $^1$H NMR $\delta$ 7.74 (d, $J = 9.0$, 1H), 7.71 (s, 1H), 7.59 (s, 1H), 7.48 (d, $J = 7.3$, 2H), 7.41 (apparent t, $J = 7.4$, 2H), 7.34 (t, $J = 7.3$, 1H), 7.26 (d, $J = 9.0$, 1H), 5.25 (s, 2H), 4.12 (s, 2H), 3.72 (s, 3H), 3.11 (septet, $J = 6.9$, 1H), 2.43 (s, 3H), 1.33 (d, $J = 6.9$, 6H); $^{13}$C NMR 169.7, 154.1, 153.4, 148.2, 137.6, 136.8, 131.6, 128.9, 128.6, 128.0, 127.3, 127.2, 126.2, 115.5, 115.1, 114.6, 87.6, 72.2, 71.4, 52.4, 27.7, 23.0, 21.0, 15.0; MS m/e 430 (M$^+$); HRMS m/e for C$_{27}$H$_{26}$O$_5$, calcd (M$^+$) 430.1780, found 430.1797.
Methyl 4-(7-acetoxy-2-hydroxy-6-isopropylnaphthalen-1-yl)-butanoate (210)

To a solution of 209 (0.530 g, 1.23 mmol) in ethyl acetate (20 mL) was added excess of Pd/C. The reaction mixture was stirred for 15 h under an H₂ atmosphere. The mixture was filtered and volatiles were evaporated under reduced pressure to give a residue that was further subjected to preparative TLC (1:1 Petroleum ether : Et₂O) to give 210 as a viscous oil (0.356 g, 84% yield). 210: IR (KBr) νmax 3427 br, 2962, 1756, 1735 cm⁻¹; ¹H NMR δ 7.67 (s, 1H), 7.56 (d, J = 8.8, 1H), 7.50 (s, 1H), 7.12 (br s, 1H), 7.05 (d, J = 8.8, 1H), 3.75 (s, 3H), 3.09 (septet, J = 6.8, 1H), 3.00 (t, J = 7.6, 2H), 2.42 (obscured m, 2H), 2.42 (s, 3H), 1.96 (m, 2H), 132 (d, J = 6.8, 6H); ¹³C NMR 175.2, 170.3, 151.5, 147.4, 135.7, 132.0, 127.5, 127.0, 126.0, 118.1, 117.8, 114.7, 51.5, 32.7, 27.4, 24.3, 23.7, 22.9, 20.8; MS m/e 344 (M⁺); HRMS m/e for C₂₀H₂₄O₅, calcd (M⁺) 344.1624, found 344.1622.
Methyl-4-(7-Acetoxy-6-isopropyl-2-(trifluoromethylsulfonyloxy)naphthalen-1-yl)butanoate (211)

To solution of 210 (0.346 g, 1.01 mmol) in CH₂Cl₂ (20 mL) were added (F₃CSO₂)₂O (204 µL, 1.21 mmol) and pyridine (204 µL, 3.02 mmol) at room temperature. The solution was stirred for 0.5 h. After conventional extractive workup (CH₂Cl₂), the volatiles were removed under reduced pressure to give crude product, which was subjected to preparative TLC (5:1 Petroleum ether : Et₂O) to give a viscous oil product 211 (0.396 g, 83% yield). 211: IR (KBr) ν max 2967, 1763, 1739 cm⁻¹; ¹H NMR δ 7.80 (s, 1H), 7.79 (s, 1H), 7.76 (d, J = 9.1, 1H), 7.34 (d, J = 9.1, 1H), 3.71 (s, 3H), 3.12-3.18 (m, 3H), 2.46 (t, J = 7.1, 2H), 2.44 (s, 3H), 2.03 (m, 2H), 1.33 (d, J = 6.9, 6H); ¹³C NMR 173.1, 169.2, 148.4, 144.8, 140.8, 131.3, 131.1, 129.2, 128.3, 126.3, 118.7, 118.4 (d, J_CF = 319 Hz), 116.9, 51.1, 33.1, 27.7, 25.3, 24.7, 22.6, 22.5, 20.6; MS m/e 476 (M⁺); HRMS m/e for C₂₁H₂₃F₃O₇S calcd (M⁺) 476.1117, found 476.1115.
Methyl 4-(7-acetoxy-6-isopropyl-2-methylnaphthalen-1-yl)butanoate (212)

To a solution of 211 (0.390 g, 0.819 mmol) in THF (20 mL) were added Pd$_2$(dba)$_3$ (0.011 g, 0.012 mmol), (2-biphenyl)dicyclohexylphosphine (0.0090 g, 0.026 mmol) and DABAL-Me$_3$ (0.168 g, 0.656 mmol). The reaction mixture was heated to reflux for 1 h, followed by addition of dilute HCl solution. After conventional extractive workup (Et$_2$O) and evaporating the volatile under reduced pressure to give a crude product, which was purified by preparative TLC (5:1 Petroleum ether : Et$_2$O) to give product 212 (0.255 g, 91%) as a viscous oil. 212: IR (KBr) $\nu_{\text{max}}$ 2962, 1760, 1737 cm$^{-1}$; $^1$H NMR $\delta$ 7.75 (s, 1H), 7.72 (s, 1H), 7.63 (d, $J = 8.2$, 1H), 7.28 (d, $J = 8.2$, 1H), 3.74 (s, 3H), 3.16 (septet, $J = 6.9$, 1H), 3.07 (m, 2H), 2.52 (obscured m, 2H), 2.52 (s, 3H), 2.45 (s, 3H), 1.99 (m, 2H), 1.38 (d, $J = 6.5$, 6H); $^{13}$C NMR 173.6, 169.7, 147.2, 137.9, 134.0, 132.7, 131.0, 130.9, 128.8, 125.9, 125.6, 115.7, 51.3, 33.7, 27.8, 27.6, 24.8, 22.9, 20.9, 19.8; MS m/e 342 (M$^+$); HRMS m/e for C$_{21}$H$_{26}$O$_4$, calcd (M$^+$) 342.1831, found 342.1824.
8-(4-Hydroxy-4-methylpentyl)-3-isopropyl-7-methylnaphthalen-2-ol (213)

To a solution of 212 (0.221 g, 0.646 mmol) in Et₂O (20 mL) was added MeLi (3.0 mL, 4.5 mmol, 1.5 M in Et₂O) at 0 °C. The reaction mixture was stirred for 6 h before quenching with aqueous NH₄Cl. The mixture was subjected to conventional extractive workup (Et₂O). The volatiles were evaporated under reduced pressure to give a crude product, which was subjected to preparative TLC (1:1 Petroleum ether : Et₂O) to give product 213 (0.178 g, 92% yield) as a colorless solid. 213: mp 141-142 °C; IR (KBr) νₘₐₓ 3348 br, 2963, 1630 cm⁻¹; ¹H NMR δ 7.61 (s, 1H), 7.54 (d, J = 8.3, 1H), 7.39 (br s, 1H), 7.33 (s, 1H), 7.13 (d, J = 8.3, 1H), 3.41 (septet, J = 6.9, 1H), 2.96 (m, 2H), 2.60 (br s, 1H), 2.46 (s, 3H), 1.73 (m, 4H), 1.37 (d, J = 6.9, 6H), 1.25 (s, 6H); ¹³C NMR 152.8, 135.8, 133.4, 132.0, 131.6, 128.0, 126.4, 125.6, 125.5, 105.8, 72.0, 43.8, 29.3, 29.1, 27.2, 24.4, 22.7, 20.1; MS m/e 300 (M⁺); HRMS m/e for C₂₀H₂₈O₂, calcd (M⁺) 300.2089, found 300.2085.
2-Isopropyl-6,10,10-trimethyl-8,9,10,10a-tetrahydrocyclohepta-[de]naphthalen-1(7H)-one (214)

To a solution of 213 (0.170 g, 0.566 mmol) in CH₂Cl₂ was added one drop of concentrated H₂SO₄ at room temperature. The reaction mixture was stirred for 1 h. After conventional aqueous workup (CH₂Cl₂) and evaporation of the volatiles under reduced pressure, the crude product was subjected to preparative TLC (20:1 Petroleum ether : Et₂O) to give 214 (0.130 g, 81% yield) as a colorless solid. 214: mp 46-47 °C; IR (KBr) \( \nu_{\text{max}} \) 2958, 1655 cm⁻¹; \(^1\)H NMR \( \delta \) 7.06 (m, 3H), 3.66 (s, 1H), 3.04 (apparent septet, \( J = 6.9, 1H \)), 2.96 (m, 1H), 2.67 (m, 1H), 2.34 (s, 3H), 1.87 (m, 1H), 1.49 (m, 1H), 1.36 (m, 1H), 1.25 (m, 1H), 1.17 (s, 3H), 1.16 (d, \( J = 6.9, 3H \)), 1.14 (d, \( J = 6.9, 3H \)), 0.62 (s, 3H); \(^{13}\)C NMR 203.0, 143.0, 138.9, 138.6, 138.2, 135.4, 128.9, 128.7, 126.0, 58.3, 43.2, 37.3, 27.3, 26.4, 25.8, 24.3, 22.0, 21.8, 20.4, 20.3; MS m/e 282 (M⁺); HRMS m/e for C₂₀H₂₆O calcd (M⁺) 282.1948, found 282.1991.
10a-Hydroxy-2-isopropyl-6,10,10-trimethyl-8,9,10,10a-tetrahydrocyclohept[a]naphthalen-1(7H)-one ((±)-Microstegiol) (215)

To a solution of 214 (0.052 g, 0.18 mmol) in DMF (10 mL) was added NaH (0.0067 g, 0.28 mmol). The reaction mixture was stirred for 12 h under oxygen. After conventional extractive workup (Et₂O) and evaporation of volatiles under reduced
pressure, the crude product was subjected to preparative TLC (50:1 Petroleum ether : Et₂O) to give 215 (0.035 g, 64% yield) as a colorless solid: mp 57-58 °C (lit. enantiomerically pure material) mp 69-70 °C); 97a IR (KBr) νₘₐₓ 3443, 2962, 1654 cm⁻¹; ¹H NMR δ 7.07 (d, J = 7.5, 1H), 6.97 (s, 1H), 6.91 (d, J = 8.0, 1H), 4.52 (s, 1H), 3.61 (apparent t, J = 13.1, 1H), 3.00 (apparent septet, J = 6.9, 1H), 2.79 (ddd, J = 14.1, 6.4, 2.3, 1H), 2.37 (m, 1H), 2.33 (s, 3H), 1.82 (m, 1H), 1.47 (m, 1H), 1.29 (m, 1H), 1.21 (d, J = 6.0, 3H), 1.16 (d, J = 6.9, 3H), 0.80 (s, 3H), 0.79 (s, 3H); ¹³C NMR 206.1, 143.3, 141.0, 140.9, 139.3, 137.4, 130.1, 129.0, 126.7, 84.4, 42.9, 39.0, 28.0, 27.0, 26.8, 23.5, 22.1, 21.7, 21.4, 21.1; MS m/e 298 (M⁺); HRMS m/e for C₂₀H₂₆O₂, calcd (M⁺) 298.1933, found 298.1940.
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Acta 1995, 78, 1037.


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<td>Taj, R. A.; Abhayawardhana, A.; Green, J. R. <em>Synlett</em> 2009, 292.</td>
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