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Intramolecular Diels Alder – ROM – RCM Approach Towards the Synthesis of Triquinanes and Magnesium Mediated Carbometallation-Annulation for the Synthesis of Fused Rings
INTRAMOLECULAR DIELS ALDER – ROM – RCM APPROACH TO TOWARDS THE SYNTHESIS OF TRIQUINANES AND MAGNESIUM MEDIATED CARBOMETALLATION-ANNULATION FOR THE SYNTHESIS OF FUSED RINGS

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Abstract

In recent years, there has been a shift in focus in organic synthetic chemistry, steering away from multistep synthesis, leaning towards tandem and one pot reactions. Described herein is a unique, one pot method for the synthesis of linear triquinanes. The strategy involved a one pot intramolecular Diels-Alder – ring opening metathesis – ring closing metathesis sequence to form triquinane 85. Application of the new methodology towards the synthesis of antibiotic $\Delta^{(9,12)}$-capnellene (13) was performed. During our endeavors, the core ring structure 86 was synthesized.

Also described is a second project which involved the synthesis of bicyclic compounds through a new carbometallation-annulation reaction. The reaction was used for the synthesis of dihydrophenanthrene 129 and chiral tricycle 137. Insight into the application to the synthesis of indoles was also investigated.
Acknowledgements

I have had the most incredible and memorable experience in Ottawa. I came here from a little place called Surrey, not knowing anyone and now I’m leaving with an amazing family.

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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ADMP</td>
<td>acyclic diene metathesis polymerization</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>calcd</td>
<td>catalytic</td>
</tr>
<tr>
<td>CM</td>
<td>cross metathesis</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublet</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N'-dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>M⁺</td>
<td>molecular ion</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MS (EI)</td>
<td>mass spectrum by chemical ionization</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Pet ether</td>
<td>petroleum ether</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>PhN(Tf)$_2$</td>
<td>N-phenyltrifluoromethanesulfonimide</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>alkyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>ROM</td>
<td>ring opening metathesis</td>
</tr>
<tr>
<td>ROMP</td>
<td>ring opening metathesis polymerization</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>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (toluenesulfonyl)</td>
</tr>
</tbody>
</table>
1 Introduction – Synthesis of Linear Triquinanes

1.1 Intramolecular Diels-Alder Reaction

The Diels-Alder reaction is undoubtedly one of the most powerful and useful transformations in organic chemistry. Discovered in 1928 by Otto Diels and Kurt Alder,\(^1\) the pericyclic reaction is able to create high molecular complexity from relatively simple precursors. It generates a cyclohexene ring with up to four stereogenic centers and many elegant applications have been reported for the total synthesis of complex natural products.\(^2\) Due to the supra-suprafacial reaction, polarity controlled orientation, and endo/exo selectivity of the diene and dienophile, usually one pair of enantiomers is obtained out of a maximum thirty-two possible isomers.\(^3\) Furthermore, enantioselective [4+2] cycloadditions can be achieved with the use of chiral catalysts, such as Lewis acids\(^4\) and organocatalysts.\(^5\)

The intramolecular version has provided access to diverse polycyclic ring systems which are otherwise difficult to prepare.\(^6\) One can imagine that when both the diene and the dienophile are cyclic, stereoselective preparation of a variety of tricyclic sesquiterpenoids can be achieved (Scheme 1). Depending on the approach of the dienophile to the diene, two compounds can be produced, either the fused or the bridged product. Due to steric constraints the fused ring system is produced more readily. For longer tether lengths, the bridged compound can be formed.

![Scheme 1: Ring systems from the intramolecular Diels-Alder reaction](image)

---

1.2 Cycloaddition of Substituted Cyclopentadiene

The Diels-Alder reaction of cyclopentadiene with a dienophile has been widely used for the formation of bicyclo[2.2.1]heptene compounds. The intramolecular Diels-Alder (IMDA) can therefore incorporate a fused ring on the norbornene skeleton and the type of ring structure depends on the location of the side chain on cyclopentadiene (Scheme 2). It is a well known fact that substituted cyclopentadienes undergo 1,5-sigmatropic hydrogen shifts to give a mixture of three isomers, 1a-1c, and the cycloaddition of each isomer therefore provides a possibility of three products. The initial product from the alkylation of a cyclopentadienyl anion 1a quickly isomerizes to the more stable 1b, and if left for a few days, 1c is also produced to give a mixture of 1b and 1c. It is unlikely that 2c would form since the structure violates Bredt’s rule. If 1a is in sufficient concentration, it has all the electronic and steric requirements to cyclize to form 1a. However this is unlikely since the isomerization of 1a to 1b is faster than the IMDA of 2a. Thus, from a possibility of three products, 2b is the sole product, depending on the tether length of selected.

Scheme 2: Intramolecular Diels-Alder reaction of substituted cyclopentadienes

---

1.2.1 Brieger’s Attempted Synthesis of Longifolene

One of the first examples of the IMDA reaction involved a substituted cyclopentadiene, which was performed by Brieger in 1963 while he unsuccessfully attempted the synthesis of longifolene.⁹ Brieger envisaged the longifolene skeleton coming from the cycloaddition of 3a (Scheme 3). It was hoped that upon heating the mixture of isomers 3a-3c, thermal equilibration would shift towards isomer 3a, which would then cyclize to 4a. Unfortunately, the only product obtained was cycloadduct 4b, which came from isomer 3b.

Based on his results, it was concluded that substituted cyclopentadienes underwent a facile 1,5-sigmatropic hydrogen shift at room temperature, and that isomers 3b and 3c are thermodynamically more stable than 3a.

![Scheme 3: Brieger’s attempt at the longifolene ring structure](image)

---

1.2.2 Fallis' Synthesis of (±)-Cedrene and (±)-Cedrol

With this knowledge in hand, intermediate of type 3b has been used in a variety of natural product syntheses including Fallis’ total synthesis of (±)-cedrene and (±)-cedrol (Scheme 4).\textsuperscript{10} Alkenylcyclopentadiene 5, which was prepared from alkylation of the corresponding tosylate and sodium cyclopentadiene, was heated in a sealed tube in xylene at 155 °C. The cycloaddition proceeded \textit{via} a regioselective \textit{exo} addition to give product 6 in 74\% yield. Subsequent ring expansion and stereoselective methylation of the resulting ketone afforded the racemic synthesis of cedrol (7) and dehydration of 7 gave the racemic product cedrene (8).

\begin{center}
\textbf{Scheme 4:} Fallis' approach to (±)-cedrol and (±)-cedrene
\end{center}

Other examples involving the IMDA reaction as the key step include the synthesis of triquinanes hirsutene\textsuperscript{11} and capnellene.\textsuperscript{12} Through the cleavage of the strained olefin to give the diquinane, further transformations converted the key intermediate to the triquinane.

\textsuperscript{11} Sternbach, D. D.; Ensinger, C. L. \textit{J. Org. Chem.} 1990, 55, 2725
1.3 Polyquinanes and $\Delta^{(9,12)}$-Cappnellene

The growth in research devoted to polyquinane chemistry has steadily increased since the discovery of the first polyquinane, hirsutic acid in 1966. The attention they have garnered in the past four decades is in large part due to their potential biological activity and more significantly, their structural complexity; the main attraction being the challenge that comes in synthesizing the complicated, multicyclic cyclopentanoid ring structure. Triquinanes (9-11) are the most abundant members of the polyquinane family, where linear triquinane 9 has acquired the most attention (Figure 1). The key synthetic difficulty associated with linear triquinanes is the rapid construction of the cis-anti-cis-tricyclo[6.3.0.0$^2$.6]undecane skeletal framework (12) and thus has triggered significant efforts in overcoming this synthetic dilemma. Similar to the history of steroids, triquinanes serve as target molecules to test experimental procedures and develop methodologies. The investigation for an efficient and attractive route to the polyquinane core is a continuing process.

![Figure 1: Triquinane skeletons](image)

One of the more prominent triquinane natural products that has attracted the attention of synthetic organic chemists is $\Delta^{(9,12)}$-cappnellene (13, Figure 2). Natural

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occurring (-)-13 was isolated from the soft coral *Capnella imbricata*, and is believed to be the biogenetic precursor to the more oxygenated members of the capnellane family (14a-14f). These compounds exhibit antibacterial and antitumor activity, similar properties to that of the hirsutane family. Capnellanes are thought to be a chemical defense agent for larvae deposition and microbial growth on coral. The popularity of 13 has lead to an impressive number of total and formal syntheses.

![Capnellane Family](image)

**Figure 2: Capnellane Family**

1.4 Methods Leading to Linear Triquinanes via Diquinanes

There has been an explosion of research and development devoted to the formation of linear triquinanes. Research groups strive to assemble the ring structure with high

---

regio- and stereo-selectivity in the shortest number of steps and attempts to be general enough to apply the methodology to other polyquinane natural products. There are two different views on approaching the triquinane core, the first, starting from a diquinane intermediate that contains appropriate side chains for further annulation to install the third ring. The second view involves generating the tricyclopentanoid framework in a single step. As mentioned above, $\Delta^{(9,12)}$-capnellene (13) has served as an attractive target to test different methodologies.

1.4.1 Sternbach's Approach

Sternbach and coworkers' strategy towards ($\pm$)-hirsutene (22)$^{11}$ involves the generation of the diquinane intermediate via the IMDA reaction of a substituted cyclopentadiene.$^{18}$ The Diels-Alder precursor was prepared, first through condensation of aldehyde 15 and cyclopentadiene to yield fulvene 16 (Scheme 5). The exocyclic double bond, which has Michael accepting character, was easily reduced using lithium aluminum hydride in 93% yield. The crucial IMDA reaction was conducted at 160 °C in refluxing mesitylene to provide tricyclic product 18 in 70% yield. Followed by Jones oxidation of the primary alcohol and ozonolysis of the olefin afforded the key diquinane intermediate 19. Five steps were required to obtain dicarbonyl 20, which then underwent an aldol condensation to form the third ring in triquinane 21. Completion of the synthesis involved hydrogenation of enone 21 over PtO$_2$ and finally a Wittig reaction with methylene ylide to provide ($\pm$)-22 in 93% yield.

Scheme 5: Sternbach's general approach to linear triquinanes via an intramolecular Diels-Alder reaction

This methodology was also applied to the synthesis of angular triquinane sliphinene.18b

1.4.2 Grubbs Approach

Grubbs and Stille also use the IMDA reaction as a key step for their synthesis of capnellene (13, Scheme 6).12 To make this synthetic route even more interesting, they employ a unique ring opening of the Diels-Alder adduct using Tebbe reagent, a titanium based reagent normally used for olefination of carboxyls.19 This reaction sequence started

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with lactone 23 and reduction with DIBAL-H to the corresponding lactol. Horner-Emmons-Wadsworth olefination converted the aldehyde to the α-β unsaturated ketone, however conjugate addition of the alcohol onto enone resulted. It was therefore necessary to treat the compound with LDA and trap the alcohol with p-TsCl to give tosylate 24. Treatment of the tosylate with cyclopentadienyl magnesium chloride provided the substituted cyclopentadiene and heating in benzene, the IMDA reaction gave adduct 25. Tebbe reagent was used to ring open the norbornene compound, resulting in diquinane moiety 26. It then required 7 steps to reduce the vinyl group to the methyl substituent and to convert the enol ether to ketone 27. Ethylidiazoacetate ring expanded the cyclobutane ring to the third cyclopentane ring and decarboxylation with wet DMSO and sodium chloride gave triquinane 28. Lastly, conversion of the carbonyl to the exocyclic olefin using Tebbe reagent completed the racemic synthesis of capnellene (13).

Scheme 6: Grubbs' synthesis of capnellene via an intramolecular Diels-Alder reaction
1.4.3 Shibasaki’s Approach

Another strategy worth mentioning is Shibasaki’s asymmetric Heck reaction.\textsuperscript{20} This was the first catalytic asymmetric synthesis of naturally occurring (-)-13. The reaction sequence started with an intramolecular asymmetric Heck reaction of compound 29 (Scheme 7), between the vinyl triflate and the olefin of cyclopentadiene. Using Pd(OAc)$_2$, (S)-BINAP ligand, and quenching of the reaction with nucleophile 28 provided diquinane 30 in 87\% ee. Five steps were then required to obtain iodide 31, which then underwent radical cyclization to form the third cyclopentane ring. Another five reaction steps were required to complete the enantioselective synthesis of (-)-13. Shibasaki and coworkers have also successfully synthesized $\Delta^{(9,12)}$-capnellene-3\beta,8\beta,10\alpha-triol and $\Delta^{(9,12)}$-capnellene-3\beta,8\beta,10\alpha,14-tetraol using the synthetic route.\textsuperscript{21}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_7.png}
\end{center}

\textbf{Scheme 7:} Shibasaki’s asymmetric synthesis of (-)-capnellene via an asymmetric Heck reaction

As shown, one can approach the synthesis of linear triquinanes through a diquinane intermediate. Although the key steps that lead towards the diquinane are highly creative, each approach requires a large number of additional reaction steps to achieve the triquinane and this can be quite time consuming and inefficient. To circumvent this

problem, a variety of methods have been developed which furnishes the triquinane core in one step from the appropriate starting material.

1.5 Methods Leading to Linear Triquinanes in a Single Step

In recent years, there has been a shift in focus in organic synthetic chemistry, steering away from multistep synthesis, leaning towards tandem and one pot reactions.\textsuperscript{22} Tandem reactions are a series of conversions, combined into one synthetic procedure where the product from the initial reaction is perfectly set up to perform the next reaction. Sequential reactions or one pot procedures involve several transformations that work independently of each other that may require additional reagents, but occur in one reaction vessel. The goal here for both types of procedure is to obtain the highest degree of molecular complexity from relatively simple precursors in just one reaction step.

1.5.1 Curran’s Approach

Curran and co-workers have developed a novel synthetic approach that uses a samarium iodide promoted radical cyclization.\textsuperscript{23} They have impressively shown that radical cyclization can construct five membered rings in a controlled fashion, synthesizing linear triquinanes hirsutene (20),\textsuperscript{2a} hypnophilin,\textsuperscript{2e} and angular triquinane silphioperfolene.\textsuperscript{2d} The general view can be seen in their synthesis of capnellene (13, Scheme 8).\textsuperscript{2a} Key substrate 34 was prepared in eight steps from acetal protected Grignard reagent 33. The radical produced on the tertiary carbon of compound 34, using samarium iodide, reacted with the cyclopentene ring to form the initial diquinane, but the resulting radical quickly underwent a five-exo dig cyclization with the alkyne to furnish 13.

1.5.2 Moore’s Approach

Another inventive approach was conceived by Moore and coworkers where they utilize the well known oxy-cope rearrangement to incorporate complexity in the molecules\(^\text{24}\). Their work was based on additions of vinyl anions to squarate esters, research that was pioneered by Paquette and coworkers\(^\text{25}\). The corresponding bicycle[6.3.0]heptenone was treated with vinyl lithium to give anion \(35\) (Scheme 9). The resulting 1,5-diene and underwent the charge accelerated oxy-cope rearrangement to obtain 5-8 fused ring structure \(36\). Hydrolysis of the silyl enol ether during workup initiated a transannular ring closure to provide substituted linear triquinane \(37\) in one step. Adding functionality to the ring was achieved by altering the substituents on the vinyl piece located at the ring junction of the 5-4 fused ring system as well as changing the substitution pattern on the vinyl lithium that was added to the carbonyl.

\[\text{Scheme 9: Moore’s tandem oxy-cope – transannular ring closure approach to linear triquinanes}\]


1.6 Olefin Metathesis

Carbon-carbon bond forming reactions remain one of the most important transformations in the synthesis of organic compounds. Recently olefin metathesis has become part of the organic chemistry arsenal to do such transformations. Olefin metathesis is essentially the cleavage and the formation of double bonds (Scheme 10).

![Scheme 10: Olefin metathesis](image)

Synthetically useful, high-yielding procedures include ring closing metathesis (RCM) between terminal alkenes of an acyclic diene, cross metathesis (CM), the intermolecular reaction of terminal vinyl groups, and ring opening metathesis (ROM) of strained cyclic alkenes (Scheme 11). Furthermore, traditional methods for synthesizing polymers are acyclic diene metathesis polymerization (ADMP) and ring opening metathesis polymerization (ROMP). Given that the starting material for the RCM and ADMP are the same, the outcome of the reaction can be controlled to some extent by adjusting the dilution of the reaction mixture and product formation is strongly influenced by preexisting conformational constraints in the substrate. This is also the same for preventing or permitting the polymerization step after ROM.

Olefin metathesis is a completely reversible reaction, hence there must be a driving force to push the equilibrium in the appropriate direction. In the case of RCM, CM and the polymerization reactions the equilibrium can be driven by the removal of byproduct ethylene from the reaction mixture. Thus, these reactions are entropically favoured. On the other hand, ROM is energetically favoured and the loss of ring strain pushes the reaction forward.

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1.6.1 Alkylidene Based Olefin Metathesis Catalysts

Part of the reason for its belated application is due to the fact that initial catalysts possessed strong Lewis-acidic character and therefore showed poor activity in the presence of polar functional groups. As a result, applications of olefin metathesis were restricted to the production of nonfunctionalized polymers. Another drawback was its instability in air and water. The popularity of this reaction arose during the development of molybdenum (38) and ruthenium (39, 40) alkylidene based catalysts (Figure 3).

![Figure 3: First generation Schrock and Grubb catalysts](image)

Schrock’s molybdenum catalyst 38 was one of the first catalysts to be widely used. The most impressive feature of 38 is its high activity, which allows it to react with both terminal and internal olefins and to ROMP low strain monomers. It also has the
ability to ring close sterically demanding and electron poor substrates. Despite its remarkable utility and potential applications, synthetic organic chemists did not embrace it immediately. Unfortunately, molybdenum catalysts are extremely sensitive to oxygen and water, therefore difficult to handle and an inconvenience to use. As well, they have poor functional group tolerability, unable to react in the presence of common substituents such as aldehydes and alcohols.

Grubbs ruthenium based catalyst, 39 and 40 were a real breakthrough. Although it doesn’t have the high activity of the molybdenum catalyst, the tolerance toward an array of functional groups and the ease of handling due to reasonable stability against oxygen, water and minor impurities in the solvents makes them extremely practical tools and explains their unrivaled popularity.

The general accepted mechanism of metathesis reactions, the Chauvin mechanism, involves the interconversion of an olefin and a metal alkylidene, as seen in Scheme 12, the general RCM reaction after one catalytic cycle. The first step in the mechanism is a dissociative pathway, starting with a loss of phosphine to go from a 16e⁻ species to the reactive 14e⁻ intermediate. The process generates a metallacyclobutane which then undergoes a series of [2+2] cycloadditions and cycloreversions, while generating ethylene during the cycle.

Scheme 12: Proposed mechanism of ring closing metathesis
1.6.2 Second Generation Olefin Metathesis Catalysts

Continuing research in this area has seen more improvement in catalyst activity and stability. A second generation of ruthenium catalysts has been developed which contains the stable Fischer carbene, the N-hetercyclic carbene (Figure 4). With its increased basicity and increase steric environment as compared to phosphine ligand PCy3, these catalysts have a greater lifetime and reactivity.

![Catalyst Structures](image)

*Figure 4: Grubbs 2nd generation catalysts*

Now, these ruthenium based complexes such as 41 and 42 have similar activity to the molybdennum complexes while still maintaining the high functional group tolerance and air and moisture stability of 40. Grubbs 2nd generation catalysts are able to react with electron deficient and sterically hindered olefins.

It was originally thought that increased reactivity of the 2nd generation was due to increased rate of the phosphine dissociation, however after extensive kinetic studies,27 it was discovered that this is not the case and that 1st generation Grubbs catalyst 40 dissociates at a faster rate than 41. This also means that the backwards reaction, phosphine association (k⁻¹), is also faster. For 41, the coordination of the olefin (k²) is so much faster than k⁻¹, this accounts for the increased activity (Scheme 13).

![Kinetic Scheme](image)

*Scheme 13: Dissociative mechanism*

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The development of Grubbs 2\textsuperscript{nd} generation has exploded and has led to an extreme number of applications. It still has some limitations mainly CM of directly functionlized olefins, such as acrylonitrile.\textsuperscript{28} Despite this restriction it has been involved in key steps for the synthesis of medium rings and macrocyclic molecules. There are also examples of enantioselective RCM, where chirality is induced from a chiral $N$-heterocyclic carbene ligand.\textsuperscript{29}

1.6.3 Third Generation Olefin Metathesis Catalysts

Very recently, a group of 3\textsuperscript{rd} generation ruthenium based catalysts has been developed that are all phosphine free (Figure 5). Complex 43a developed by Hoveyda and coworkers utilize an $i$-propoxy group on the phenylcarbene unit which stabilizes the complex during its resting state.\textsuperscript{30} It readily opens up a coordination site in the presence of the substrate. Grela and coworkers synthesized the bromo (43b) and the nitro (43c) analogues.\textsuperscript{31} Although complex 43b was in general less reactive than 43a, nitro derivative 43c showed great promise in that it was able to undergo CM of directly functionlized olefins including acrylonitrile. Blechert and Wakamatsu have shown that binol- or biphenyl based styrene ligands on their complexes (44 and 45) were more reactive than 43a and Grubbs 2\textsuperscript{nd} generation catalyst (41). Grubbs developed the bispyridine ruthenium catalyst 46,\textsuperscript{28} and Chang and co-workers have applied this catalyst for CM of conjugated enynes.\textsuperscript{32}

1.6.4 Tandem Olefin Metathesis

Tandem reactions are very attractive in the sense that it can build high molecular complexity rapidly from relatively simple starting substrates. One of the first examples of tandem olefin metathesis was reported by Grubbs and co-workers where they synthesized fused bicyclo[n, m, 0] ring systems through a RCM/RCM of dienynes (Scheme 14).\textsuperscript{33} The acetylene (47) positioned between the two olefins, acts as an olefin metathesis relay and generates five, six and seven membered rings (48).

\[ \text{Scheme 14: RCM/RCM of dienynes} \]

It has also shown that combining the energetically favoured ROM and the entropically favoured RCM can be a very useful method for the construction of complex ring systems.\textsuperscript{34} The ROM-CM combination\textsuperscript{35} has also been reported and even the ROM-RCM-CM sequence is feasible.\textsuperscript{36}


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1.7 Research Objectives

The main objective for the project is to develop a one pot procedure towards the linear triquinane core.

1.7.1 Retrosynthesis

Inspired by the work of Grubbs and Stille, and of Fallis\textsuperscript{37}, our synthetic strategy involves an IMDA reaction of cyclopentadiene and the dienophile tethered by a three-carbon chain (51, Scheme 15). Our desired precursor would contain an activated dienophile, making the Diels-Alder reaction more facile. As well, the dienophile would be part of a 1,4-diene moiety. Ideally, once the cycloaddition occurs to give adduct 50 the allyl group would be in the endo position, necessary for the tandem ROM-RCM sequence. The overall plan would furnish the tricyclo(6.3.0.0\textsuperscript{2,6})undecane skeleton (49).

![Scheme 15: Retrosynthetic plan for the synthesis of the linear triquinane skeleton](image)

Our approach is a one pot procedure (IMDA – ROM – RCM) that assembles the triquinane core from readily accessible precursors, the requisite cis-anti-cis ring junction is set in the Diels-Alder reaction and the final product contains double bonds which can be easily derivatized for further functionalization. Once our synthetic strategy is validated, we would apply the methodology towards the total synthesis of $\Delta^{(9,12)}$-capnellene (13).

\textsuperscript{36} Arjona, O.; Csáky, Á. G.; Murcia, M. C.; Plumet, J. \textit{Tetrahedron Lett.} 2000, 41, 9777.
1.7.2 Intramolecular Diels-Alder

The rationale behind our approach begins with the selectivity in the IMDA reaction, where literature precedence predicts the selective formation of tricycle 50b (Scheme 16). Due to 1,5-sigmatropic hydrogen shift, alkylation of cyclopentadienyl anion will yield a mixture of three isomers 52a-52c, where only 52b will cyclize to yield the desired product. The cycloaddition of 52c is unlikely as the product formed from this reaction violates Bredt’s rule. If 52a is in sufficient concentration, it has all the electronic and steric requirements to cyclize to form 50a, but this is unlikely since in order for this to occur, the Diels-Alder reaction of 50a must be faster than the isomerization to 52b, which is not known to occur. Thus, from a possibility of three products, only one is formed, 50b.

Scheme 16: Predicted outcome of intramolecular Diels-Alder
1.7.3 Tandem Ring Opening Metathesis – Ring Closing Metathesis

The rationale for the next part of our strategy, the tandem ROM-RCM reaction, is based on numerous examples of diquinane formation through this protocol. Norbornene compounds are common substrates for ROM because of the strained olefin it contains and has been employed in tandem ROM-RCM sequences. Hagiwara and co-workers have shown that with an allyl group on norbornene structure can produce diquinanes very effectively (Scheme 17).\textsuperscript{34b} Starting materials 53 and 55 were prepared by Diels-Alder reactions of cyclopentadiene with the corresponding \( \alpha,\beta \)-unsaturated carbonyls, followed by addition of vinylmagnesium bromide. Treatment with 1\textsuperscript{st} generation Grubbs catalyst (40), in an atmosphere of ethylene at room temperature, effectively performs the tandem reaction giving diquinanes 54 and 56. Reaction yields ranged from 50-81%.

\begin{center}
\begin{align*}
\text{53} & \xlongequal{40, \text{CH}_2\text{Cl}_2, \text{ethylene, rt}} \text{54} \\
\text{55} & \xlongequal{40, \text{CH}_2\text{Cl}_2, \text{ethylene, rt}} \text{56}
\end{align*}
\end{center}

\textbf{Scheme 17:} Synthesis of diquinanes via tandem ROM-RCM

To further validate our strategy, Aubé and co-workers used the tandem sequence to synthesize their Schmidt rearrangement precursor which was the key step for the total synthesis of 251F (61, Scheme 18).\textsuperscript{38} Treatment of 58 with catalyst 40 in methylene chloride saturated with ethylene afforded the bicyclic enone 59 in 93% yield. Further functional group manipulations, including the intramolecular Schmidt rearrangement of 60, completed the synthesis of 61.

Scheme 18: Aubé synthesis of diquinane intermediate 59 via tandem ROM-RCM

With this theory and background, our attempt to the linear triquinane core was pursued. The next section discusses the results obtained from our approach.
2 Results and Discussion – One Pot Intramolecular Diels-Alder – Ring Opening Metathesis – Ring Closing Metathesis Approach to Linear Triquinanes

2.1 Attempts at the synthesis of a cyclopentadiene with an activated dienophile

With a plan in place, our first synthetic target was compound 50.

![Figure 7: Precursor required for the tandem ROM-RCM](image)

Grubbs and Stille investigated extensively on cyclopentadiene compounds tethered to an \( \alpha,\beta \)-unsaturated ester dienophile as Diels-Alder precursors. When the tether length was either three or four carbon units long, the major product obtained was adduct 63 (Scheme 19). This reaction occurred smoothly under very mild conditions, either at room temperature in benzene in the presence of catalytic hydroquinone, or Lewis acid catalyzed with diethyl aluminum chloride at \(-15\ ^\circ\text{C}\).

![Scheme 19: IMDA of \( \alpha,\beta \)-unsaturated ester](image)

Our plan to synthesize 50, described in Scheme 20, required the substituted cyclopentadiene 64 which could be prepared from the addition of a cyclopentadienyl anion to alkyl bromide 65. The addition of the necessary allyl group would be installed after the cycloaddition reaction. It is necessary for the tandem olefin metathesis sequence.
Although this was not the one pot IMDA-ROM-RCM we were envisioning, it was good starting point and a good model study for the investigations of this approach.

![Scheme 20: Retrosynthetic plan for the synthesis of 50](image)

The synthesis of the required side chain started with ring opening of tetrahydrofuran (66) using boron tribromide and quenching with MeOH giving bromo alcohol 67 in 73% yield.\(^\text{39}\) Oxidation of the primary alcohol to aldehyde 68 occurred smoothly with pyridinium dichromate (PDC) in quantitative yield. Kulkarni and coworkers reported a one pot procedure where PDC was added immediately after 67 was formed. However, it was found that better yields were observed when each reaction was performed separately.

Generation of the desired alkyl bromide was accomplished using the Horner-Wadsworth-Emmons reaction. Phosphonate 69 and sodium hydride converted the aldehyde to enone 70 in 48% yield.\(^\text{40}\)

![Scheme 21: Synthesis of α-β unsaturated ester](image)


With the necessary α-β unsaturated ester in hand, the next task was to alkylate cyclopentadiene using reaction conditions employed by Grubbs and Stille. Following literature procedure, cyclopentadiene was treated with methyl magnesium chloride and to this solution was added alkyl bromide 70. Monitoring the reaction by TLC, starting material was still present after two days of stirring at room temperature. Addition of excess cyclopentadiene and base pushed the reaction to completion and upon purification of the reaction mixture an unknown product was formed in 80% yield. $^1$H and $^{13}$C NMR data suggested that the product formed was bicyclic compound 72 (Scheme 22).

Grubbs and Stille as well as Sternbach$^{41}$ observed this type of product during their initial investigations. The proposed formation of bicyclic product 72 involves the S$_2$ displacement of the bromide with cyclopentadienyl magnesium chloride to give desired substituted cyclopentadiene 64 as an intermediate (Scheme 23). However, in the presence of base, the cyclopentadiene moiety gets deprotonated again and the substrate undergoes a 1,4-conjugate addition to yield the observed product. They suggested that cyclopentadienyl sodium and lithium favored the intramolecular Michael reaction and that using cyclopentadienyl magnesium chloride or bromide circumvented this issue. However, this was not the case for us.

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Scheme 23: Proposed reaction sequence for the formation of bicycle 12

Based on the proposed mechanism, we knew the desired product was forming as an intermediate. The reaction was repeated with MeMgCl, this time using 1.1 equivalence. With this, 35% of 72 was obtained (Entry 1), while the remaining mass balance was starting material (45%).

As outlined in Table 1, our investigations began at varying the base and changing the nature of the metal counterion. It was thought by using a harder counterion, as lithium or sodium, the cyclopentadienyl anion would in turn become a harder nucleophile and thus slow the rate of the 1,4-conjugate addition. Grubbs and Stille stated that sodium and lithium counterions favoured the intramolecular Michael reaction, yet we decided to try butyl lithium (Entry 2) and sodium hydride (Entry 3). As reported, these bases afforded bicycle 72 in 45% and 47% yield respectively. No trace of the desired product was observed.
Table 1: Conditions tested the attempted formation of substituted cyclopentadiene

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Base</th>
<th>pKa</th>
<th>Temp</th>
<th>Yield* 72 (%)</th>
<th>Yield 64 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Br</td>
<td>MeMgCl</td>
<td>48</td>
<td>rt</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Br</td>
<td>BuLi</td>
<td>55</td>
<td>rt</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>Br</td>
<td>NaH</td>
<td>35</td>
<td>rt</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>I</td>
<td>EtMgCl</td>
<td>50</td>
<td>rt</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>Br</td>
<td>EtMgCl</td>
<td>50</td>
<td>rt</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>Br</td>
<td>EtMgCl</td>
<td>50</td>
<td>0 °C</td>
<td>38</td>
<td>0</td>
</tr>
</tbody>
</table>

*Starting material was recovered in all cases

It was considered that using a better leaving group would increase the tendency for the leaving group to undergo displacement. Therefore, the bromide was converted to the iodide. Alkyl iodide 70a was easily prepared from bromide 70, using sodium iodide in refluxing acetone giving the desired alkyl chain in quantitative yields (Scheme 24).42 Testing the iodide and using ethylmagnesium chloride as base unfortunately had no effect on the reaction, giving the bicyclic product 72 in 40% yield (Entry 4).

![Scheme 24: Synthesis of alkyl iodide 14]

Another attempt at synthesizing the substituted cyclopentadiene containing an activated dienophile involved increasing the steric bulk around the alkene by employing a

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t-buty1 ester functionality. The α-β-unsaturated t-buty1 ester 75 was synthesized from aldehyde 68 and treating it with phophonium 74 and sodium hydride in 48% yield (Scheme 25). Again, this substrate had no effect on the reaction. With ethylmagnesium chloride as base, product 72a was formed in 40% yield (Entry 5).

![Scheme 25: Synthesis of α-β unsaturated t-buty1 ester alkyl bromide](image.png)

Perhaps the temperature of the reaction was too high, thus making the Michael reaction feasible. However, performing the reaction at 0 °C provided only the bicyclic compound as well (Entry 6).

2.2 The synthesis of a cyclopentadiene with an unactivated dienophile

Disappointed by our initial results, we decided to abandon this route and concentrate on the synthesis of compound 75.

![Scheme 26: Precursor required for the tandem ROM-RCM](image.png)

Described in Scheme 27 is our retrosynthetic plan to tricyclic compound 75. It would be prepared from a thermal [4+2] cycloaddition of substituted cyclopentadiene 76. Side chain 77 would contain a 1,4-diene where upon cycloaddition, the allyl group would directly be incorporated in the endo position for the tandem olefin metathesis sequence. Substituted cyclopentadiene 76 would be prepared by alkylation of the appropriate side chain with cyclopentadiene.
Scheme 27: Retrosynthetic plan for the synthesis of olefin metathesis precursor 75

We initially tried to prepare the desired alkyl chain via carbometallation of an alkyne with DIBAL-H (Scheme 28).²³ Hydroalumination of 4-pentyn-1-ol (78) with DIBAL-H and quenching of the aluminum intermediate with allyl bromide did not provide the desired 1,4-diene. Instead, the intermediate quenched by a proton was recovered in quantitative yields (79).

Scheme 28: Hydroalumination of 4-pentyn-1-ol

A thorough scan of reaction conditions would have probably led to the desired product, but and a literature procedure was found where a Claisen rearrangement was employed.²⁴ Using the protocol, the synthesis of 1,4-diene 79 was easily prepared by a Johnson orthoester Claisen rearrangement of commercially available 1,5-hexadien-3-ol (78) with catalytic propionic acid in refluxing triethylorthocacetate in 93% yield (Scheme 29). The ester functionality was cleanly reduced to the corresponding alcohol 80 with lithium aluminum hydride (LiAlH₄) and subsequent tosylation with p-toluenesulfonyl chloride afforded desired side chain 81 in 79% yield.

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Scheme 29: Synthesis of unactivated dienophile

With the 1,4-diene in hand, the next task was the alkylation of cyclopentadiene. As predicted, the addition occurred smoothly. Treating cyclopentadiene with sodium hydride, the addition of the alkyl chain to give 84 occurred in quantitative yield (Scheme 30). At equilibrium, the mixture of 84a and 84b was found to be in approximately a 0.8:1.0 ratio.

Ethylmagnesium bromide can also be used as base to deprotonate cyclopentadiene. Refluxing a solution of ethylmagnesium bromide and cyclopentadiene to form the nucleophile, then adding tosylate 83 provided 84, albeit in lower yields (60-70%). Though, cleaner material is obtained with this approach.

Scheme 30: Alkylation of cyclopentadiene

We were now able to attempt the one pot IMDA-ROM-RCM reaction sequence. Based on previous experience, we felt the most efficient way to conduct the Diels-Alder was to use the microwave.45

The key step was carried out in toluene at 200 °C at 200 psi for three hours (Scheme 31). Upon completion of the reaction, the vessel was removed from the microwave, purged with argon and Grubbs 2nd generation catalyst (5 mol% based on

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starting material) was added to the vessel. The reaction stirred under an atmosphere of argon for 3 hours. Monitoring the reaction by TLC was difficult since the Rf value of the starting material and product were the same. However, the reaction was allowed to stir for 3 hours and after purification, the desired triquinane core 85 was synthesized. The highest yield obtained for the reaction was 43% yield. 1H NMR showed no trace of starting material.

![Scheme 31: Synthesis of triquinane core](image)

Structure 75 was isolated to elucidate the structure by NMR spectroscopy. COSY and HMQC experiments confirmed the regiochemistry of the cycloaddition. The COSY experiment exhibited long range coupling between H6 and H5 that is attributed to the W conformation between these two protons (Figure 8). The W coupling proposes that the cycloaddition proceeded via a regioselective exo addition.

![Figure 8: Long range W coupling](image)

COSY and HMQC experiments were also performed on the triquinane 85. NMR spectra further confirmed the regiochemistry of the tandem olefin metathesis sequence and NOESY experiments confirmed the cis-anti-cis ring junction (Figure 9). From the spectrum, it was seen that H5 correlates with H1, H6, H10 and H4 correlates with H6, H9. We also that H1 correlates with H6, H5 and H3 sees H9.
Although the one pot reaction has yet to be optimized, we felt it was appropriate to apply the methodology to the total synthesis of capnellene.

2.3 Towards the synthesis of (+)-Capnellene

Our synthesis of capnellene (13) was slightly modified from our original route in that we wanted to incorporate the gem-dimethyl groups directly on the triquinane core. Our retrosynthetic plan is outlined in Scheme 32, where we started from the corresponding substituted cyclopentadiene. The alkyl substituent would contain the gem-dimethyl group in the 3 position and the one pot IMDA-ROM-RCM would yield the capnellene core 86. Subsequent functional group manipulations, mainly the reduction of the vinyl group to the methyl group, would provide the total synthesis of 13.
Scheme 32: Retrosynthetic plan to capnellene

Our original synthesis commenced with the Claisen rearrangement, however we wanted to incorporate the gem-dimethyl groups at this step. The required allylic alcohol was not commercially available, therefore the preparation involved the addition of allylmagnesium bromide to 3-methyl-2-butenal (89) to give 6-methyl-1,5-hexadien-4-ol (90) in 83% yield (Scheme 33).\(^\text{46}\)

Scheme 33: Synthesis of Claisen rearrangement precursor

Heating of alcohol 90 in refluxing triethyl orthoacetate in the presence of catalytic phenol overnight afforded the \(\gamma,\delta\)-unsaturated ester in 65% yield (Scheme 34).\(^\text{47}\) We found that a weaker acid was necessary to achieve the highest yield. Normally propionic acid is used for this variant of the Claisen rearrangement, but we only obtained poor yields with the protocol. Reduction of ester 91 with LiAlH\(_4\) to primary alcohol 92 was accomplished in 87% yield and subsequent treatment with \(p\)-toluenesulfonyl chloride gave tosylate 93 in 93% yield. Treating cyclopentadiene with sodium hydride, the addition of the alkyl chain supplied 88 in 80% yield and at equilibrium, the mixture of 84a and 84b was found to be in approximately a 0.8:1.0 ratio.


With the substituted cyclopentadiene in hand, we were now ready to perform the one pot IMDA-ROM-RCM strategy (Scheme 35). The Diels-Alder reaction was performed in the microwave, at 200 °C in toluene and upon completion Grubbs’s 2nd Generation catalyst was added to the reaction vessel. Stirring at room temperature for three hours we did obtain the desired triquinane core however in a very low 15% yield.

In order to try and figure out what was going wrong, we decided to look at each step individually to determine which part of the sequence was causing problems.\(^{48}\) Examining the IMDA reaction first, we varied the temperature of the reaction (Table 2). Repeating the microwave conditions, 200 °C at 200 psi afforded the tricyclic structure in 31% yield (Entry 1). Refluxing the reaction in toluene provide us with no reaction even

\(^{48}\) A portion of the work was performed by summer student Nicole Stogaitis
after three days (Entry 2). The sealed tube reaction, at 200 °C in toluene, provided the cycloaddition adduct in a low 20% yield after three days. Starting material was recovered in 10% and rest was decomposition (Entry 3). Returning to microwave conditions, we increased the reaction pressure to 300 psi and switched the solvent to benzene, and after four hours the desired product was made in 35% yield (Entry 4). Increasing the temperature and pressure to 260 °C and 400 psi had a negative effect on the reaction as was performing the reaction in toluene (Entry 5 and 6). Higher temperature seems to promote decomposition of the starting material or product. Heating in benzene at 210 °C and 310 psi gave an improved yield of 45% (Entry 7). We repeated the reaction with the unsubstituted version (R = H), and similar yields were obtained (Entry 8).

Table 2: Intramolecular Diels-Alder reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Temp (°C)</th>
<th>psi</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Toluene</td>
<td>μν</td>
<td>200</td>
<td>200</td>
<td>3 h</td>
<td>31%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Toluene</td>
<td>Reflux</td>
<td>110</td>
<td>-</td>
<td>3 d</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Toluene</td>
<td>Sealed tube</td>
<td>200</td>
<td>-</td>
<td>3 d</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Benzene</td>
<td>μν</td>
<td>200</td>
<td>300</td>
<td>4 h</td>
<td>35%</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Benzene</td>
<td>μν</td>
<td>260</td>
<td>400</td>
<td>2.5 h</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Toluene</td>
<td>μν</td>
<td>210</td>
<td>310</td>
<td>2 h</td>
<td>20%</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>Benzene</td>
<td>μν</td>
<td>210</td>
<td>310</td>
<td>1.5 h</td>
<td>45%</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>Benzene</td>
<td>μν</td>
<td>210</td>
<td>310</td>
<td>1.5 h</td>
<td>46%</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>DCE</td>
<td>μν</td>
<td>210</td>
<td>310</td>
<td>1.5 h</td>
<td>44%</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>DMF</td>
<td>μν</td>
<td>210</td>
<td>310</td>
<td>1.5 h</td>
<td>49%</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>Chlorobenzene</td>
<td>μν</td>
<td>210</td>
<td>310</td>
<td>1.5 h</td>
<td>80%</td>
</tr>
</tbody>
</table>

More polar solvents to increase the microwave absorption were then investigated. Dichloroethane and DMF provided similar yields to that of benzene, 44% and 49%
respectively (Entry 9 and 10). Lastly, chlorobenzene was used which offered the highest yields (80%, Entry 11).

COSY and HMQC experiments of compound 87 confirmed the regiochemistry of the cycloaddition. As in the unsubstituted analogue, the COSY experiment exhibited long range coupling between H₆ and H₅ that is attributed to the W conformation between these two protons (Figure 10).

![Figure 10: Long range W coupling of 87](image)

Turning our attention to the olefin metathesis portion of the reaction sequence, both 1st generation Grubbs catalyst and 2nd generation Grubbs catalyst was examined. Performing the tandem ROM-RCM of 87 to 86 in an atmosphere of argon, 1st generation catalyst clearly showed to be superior, increasing the yield from 70% for 2nd generation (Entry 3) to 82% (Entry 1). It was then thought to perform the tandem olefin metathesis reaction in an ethylene atmosphere. Ethylene helps initiate the ROM step and is known to breakdown any intermediates that are stuck in the catalytic cycle. Repeating the same reactions, this time in benzene saturated with ethylene, reactions with both catalysts showed an improvement (Entry 2 and 4). Employing 1st generation Grubbs catalyst converted 87 to triquinane 86 in quantitative yields (Entry 2).

---

Table 3: Conditions for tandem ROM-RCM

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Generation</td>
<td>Argon</td>
<td>3 h</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Generation</td>
<td>Ethylene</td>
<td>1 h</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Generation</td>
<td>Argon</td>
<td>3 h</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Generation</td>
<td>Ethylene</td>
<td>1.5 h</td>
<td>75-92</td>
</tr>
</tbody>
</table>

COSY and HMQC experiments were also performed on triquinane 86. The cis-anti-cis ring junction was confirmed from the NOESY spectrum (Figure 11).

<table>
<thead>
<tr>
<th>Proton</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₃</td>
<td>H₄, H₆, H₁</td>
</tr>
<tr>
<td>H₄,</td>
<td>H₃, H₉, H₈, H₁₀</td>
</tr>
<tr>
<td>H₁₀</td>
<td>H₁₀', H₄, H₉</td>
</tr>
<tr>
<td>H₁₀'</td>
<td>H₅, H₁₀, H₄</td>
</tr>
<tr>
<td>H₈</td>
<td>H₆'</td>
</tr>
<tr>
<td>H₆</td>
<td>H₃, H₆, H₁₃</td>
</tr>
<tr>
<td>H₅</td>
<td>H₉', H₁₀', H₁₁</td>
</tr>
</tbody>
</table>

Figure 11: Important NOESY correlations of 86
With the optimized conditions the one pot IMDA-ROM-RCM was repeated for the unsubstituted version and the triquinane core was achieved in an improved 65% yield (Scheme 36).

**Scheme 36**: One pot IMDA-ROM-RCM with optimized conditions
3 Introduction – Magnesium-Mediated Carbometallation of Propargyl Alcohols

3.1 Carbometallation

The carbometallation reaction has been of great interest since the first reported example by Bähr and Ziegler in 1967.\textsuperscript{50} It was not until the last decade has research been largely devoted to this area. Carbometallation involves adding an organometallic reagent across an unsaturated carbon-carbon bond to form a new organometallic species. This can in turn react with a variety of electrophiles to give the desired product. A wide range of metals have been examined including zinc, aluminum, boron, tin, and reactions with an array of unsaturated acceptors have been reported and reviewed.\textsuperscript{51} Alkynes containing a propargyl or homopropargyl oxygen are the most widely studied where the oxygen is usually a free hydroxyl group or protected as an ether.

Organomagnesium compounds are versatile reagents for carbon-carbon bond formation. While they do not generally add across non-functionalized triple bonds, allyl magnesium halides have been reported to react easily with propargyl alcohols (Scheme 37).\textsuperscript{52}

![Scheme 37: Magnesium mediatated carbometallation of propargyl alcohols](image-url)

---

Note: Portions of the section are taken from the following theses: Forgione, P. PhD (Chemistry) 2001; Penwell, A. J. M.Sc. (Chemistry) 2003; Tessier, P. M.Sc. (Chemistry) 2003.


The addition of organomagnesium compounds to the propargyl alcohol is a regiocontrolled *anti*-carbometallation and the reaction is thought to precede *via* magnesium chelate intermediate 95 (or a closely related species). The use of other Grignard reagents were attempted with little success resulting in low yields. It was found that an addition of copper iodide circumvented this problem and the improvement is thought to be due to transmetallation with the magnesium to form a softer nucleophile.

3.2 Magnesium-Mediated Carbometallation in Synthesis

Motivated by their interest in the synthesis of taxoids and the development of tether controlled intramolecular reactions, the Fallis research group has developed several procedures for the magnesium mediated carbometallation of propargyl alcohols (Scheme 38). Chelate intermediate 98 has reacted with a variety of electrophiles to generate a large library of diverse compounds. The reaction has been used to prepare substituted furans (99)\(^{53}\) and stereodefined enediynes (100).\(^{54}\) Vinyl magnesium chloride as the Grignard reagent dienediols (101), and halodienes (102, 103) can easily be obtained.\(^{55}\)

---


Scheme 38: Magnesium-mediated carbometallation of propargyl alcohols

A desirable aspect of this reaction is that switching the substituents on the propargyl alcohol and the Grignard reagent can change the substitution pattern.

The versatility of this procedure has been shown in the synthesis of complex compounds. Along with the examples presented above, one can synthesize substituted furanones, such as in the short synthesis of the Merck anti-inflammatory drug Vioxx® (107, Scheme 39). Carbometallation of phenylpropargyl alcohol (104) with 4-thioanisylmagnesium chloride and quenching chelate 105 with carbon dioxide provided furanone 106. Oxidation of the thiol to the sulfoxide with m-CPBA gave 107, in a total of two steps.
Scheme 39: Synthesis of Vioxx® via magnesium-mediated carbometallation

A dienediol of type 101 was used as the key intermediate towards the synthesis of the taxane AB ring system. The key steps in the synthesis are carbometallation to prepare the dienediol and a diastereoselective, Lewis acid catalyzed Diels-Alder reaction to form the 6-8 fused ring system (Scheme 40). Addition of vinyl magnesium chloride to methyl propargyl alcohol (108) and quenching the reaction with aldehyde 110 afforded diol 111 in 71% yield. A protection/deprotection sequence, then a series of oxidation procedures furnished Diels-Alder precursor 113 in high yields. In the presence of diethylaluminum chloride, the diastereoselective, Lewis acid catalyzed Diels-Alder reaction completed the taxane AB ring system (114) in a total of eight steps and 22% overall yield.

Scheme 40: Synthesis of taxane AB ring system via magnesium-mediated carbometallation

Recently, it was shown that formation of the magnesium chelate intermediate followed by a palladium cross coupling with an aryl iodide provided a facile route to new tetrasubstituted alkene analogues. This new method was applied to the total synthesis of (Z)-tamoxifen, a selective estrogen receptor modulator (Scheme 41).\(^{57}\) Alkynol 115 was easily prepared through Sonogashira coupling of propargyl alcohol and the corresponding aryl iodide. Carbometallation of phenylmagnesium chloride, transmetallation of magnesium chelate 116 with palladium (0), followed by palladium catalyzed cross coupling reaction with iodobenzene produced the desired analogue 117. Conversion of the primary alcohol to the ethyl substituents afforded the stereoselective synthesis of (Z)-tamoxifen 118.

3.3 Carbometallation of Vinyl Propargyl Alcohols

Further probing the scope of the methodology founded a new annulation procedure to attach functionalized benzene rings to cyclic ketones. The strategy involved carbometallation of a vinylpropargyl alcohol (121) with vinylv magnesium chloride. Six-$\pi$-electrocyclic ring closure of the resulting triene (123), followed by oxidation generated the functionalized benzaldehyde (Scheme 42). The vinylpropargyl alcohol can be obtained from the related vinyl triflate 119, derived from an appropriate cyclic ketone, which was then coupled through a Sonogashira reaction with propargyl alcohol to give 121. A desirable aspect of the method is that various functional groups can be attained depending on the electrophile used to quench magnesium chelate 122.
Scheme 42: Carbometallation of vinylpropargyl alcohols with vinylmagnesium chloride

Of considerable interest were chiral bicyclic ketones due to their high potential for chiral asymmetric transformations. Norcamphor, camphor, nopinone and bicyclo[3.2.1]octan-2-one were chosen as substrates for this investigation. The vinylpropargyl alcohols were prepared via the general protocol: conversion of the corresponding ketone to the triflate using lithiumdiisopropyl amide (LDA) and trapping of the enolate with N-phenyltrifluoromethanesulfonamide58 (PhN(Tf)2). The triflate underwent Sonogashira palladium coupling, with propargyl alcohol to give the desired vinylpropargyl alcohols 126, 127, 128, and 129 (Table 4).

Carbometallation of the alkynols with vinylmagnesium chloride and subsequent quenching with a proton worked well with the chiral compounds. A pleasant surprise was that the trienes generated 126 and 127, cyclized under the reaction conditions (Entry 1 and 2). The diene was formed in one pot from the vinyl propargyl alcohol. However, the more conformationally mobile ring systems, trienes generated from alkynols 128 and 129, did not cyclize and only trienes 132 and 133 were isolated (Entry 3 and 4).

Table 4: Carbometallation of bicyclic vinyl propargyl alcohols

\[
\begin{align*}
1. & \quad \text{MgCl} \\
& \quad \text{Cyclohexane, reflux} \\
2. & \quad \text{NH}_4\text{Cl, rt}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargyl Alcohol</th>
<th>Triene/Cyclized Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Propargyl Alcohol 126" /></td>
<td><img src="image2" alt="Triene/Cyclized Product 130" /></td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Propargyl Alcohol 127" /></td>
<td><img src="image4" alt="Triene/Cyclized Product 131" /></td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Propargyl Alcohol 128" /></td>
<td><img src="image6" alt="Triene/Cyclized Product 132" /></td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Propargyl Alcohol 129" /></td>
<td><img src="image8" alt="Triene/Cyclized Product 133" /></td>
<td>64</td>
</tr>
</tbody>
</table>

The cyclization of triene 133 was attempted in refluxing toluene; however, only starting material was obtained. The protection of the allylic alcohol as the methyl ether using sodium hydride and methyl iodide, was necessary to induce cyclization at 150 °C in a sealed tube (Scheme 43).
3.4 Research Objectives

We were very close to completing the project and publishing the results. However, one question we wanted to answer before submitting the paper was whether reaction conditions could be found to allow for the tandem carbometallation-cyclization for the bicycle[3.1.1] based vinylpropargyl alcohol 128 (Scheme 44). If this could occur, this would make our general approach an attractive multi-component reaction.

Given that electrocyclic ring closures are thermal reactions, the logical step was to increase the reaction temperatures for the carbometallation reaction.

It was also felt that another example could be synthesized to further demonstrate the novelty of carbometallation-annulation strategy. The target molecule dihydrophenanthrene 138 was to be synthesized (Figure 12).
This is an attractive target since its core structure is part of a variety of natural products such as antibiotics pradimicin A and benanomicin A.\textsuperscript{59} Also, the dihydrophenanthrene core is exhibited in discotic liquid crystals.\textsuperscript{60}

### 3.5 Retrosynthesis

The approach to the molecule comes from the established route developed in our lab (Scheme 45). Dihydrophenanthrene 138 would originate from carbometallation of vinyl propargyl alcohol 140 and vinyl magnesium chloride followed by cyclization of the resulting triene 139. Alkynol 140 would be prepared from tetralone (141).

![Scheme 45: Retrosynthetic plan to dihydrophenanthrene 138](image)

The next section discusses the results obtained from the cyclization of alcohol 128 and the synthesis of 138.


\textsuperscript{60} Foster, E. J.; Babuin, J.; Nguyen, N.; Williams, V.E. Chem. Comm. 2004, 18, 2052.
4 Results and Discussion – Magnesium-Mediated Carbometallation – Aryl Annulation Protocol for the Synthesis of Fused Rings

4.1 Tandem carbometalltion-annulation of nopinone based vinyl propargyl alcohol

The plan was commenced by performing the carbometallation reaction of propargyl alcohol 128 in toluene. Alcohol 128 was prepared from the corresponding triflate 142 by palladium coupling with propargyl alcohol in 95% yield. We predicted that the carbometallation reaction would proceed smoothly to the desired cyclohexadiene 137, or perhaps triene 132. Under the initial reaction conditions, vinylmagnesium chloride (3 eq.) and cyclohexane, only the triene was recovered. Our initial attempt at switching to the higher boiling solvent toluene resulted in mysterious results. Obtaining an unknown product, preliminary characterization suggested cyclohexadiene 143 was obtained (Scheme 46). Compound 143 would have resulted from the olefin isomerization of the initially formed cyclohexadiene after thermal cyclization. However examination of the $^{13}$C NMR spectrum suggested that 143 was not the compound isolated due to the absence a CH signal.

![Scheme 46: Formation of originally suggested cyclohexadiene 143](image)

Initial characterization did not provide sufficient information for structure determination so it was subjected to oxidative conditions in hopes to obtain more insight. Upon treatment of compound “143” with MnO$_2$, $^1$H NMR showed a distinct doublet in the region of a typical aldehyde. This suggested that the aldehyde proton was coupling to one $\alpha$-hydrogen, signifying that an $\alpha,\beta$-unsaturated carbonyl moiety was present. Based on this evidence it was concluded that reduction of propargyl alcohol 128 to allylic alcohol 144 had occurred during the carbometallation step and oxidation gave aldehyde.
145 (Scheme 47). This also explains the missing CH₂ peak, unfortunately the vinyl group did not add across the alkyne.

Scheme 47: Oxidation of allylic alcohol

The geometry of the allylic alcohol is a trans orientation, due to the two olefin protons having a coupling constant of 15.6 Hz. In an nOe difference experiment, irradiation of alkene proton H₂ generated an nOe at proton H₃ (Figure 13). Furthermore, irradiation of proton H₁ generated an nOe at bridgehead proton H₄. These interactions confirmed the trans orientation of the allylic alcohol.

Figure 13: nOe interactions of 144

The attempts to add the vinyl piece across the propargyl alcohol are shown in Table 5. Adding MgCl₂ to the mixture has shown to improve reactions yields for carbometallation. It is proposed that the salt prevents aggregate formation from the Grignard reagent. However, the presence of the additive did not improve the reaction and only allylic alcohol 144 was obtained in 40% yield. It was also observed in our lab that reagents purchased from Fluka were superior than sources from other companies. Unfortunately, changing the source from Aldrich to Fluka, running the reaction in toluene or cyclohexane gave only the reduced product (Entry 4 and 5). Finally, a bottle from
Acros was obtained and in cyclohexane, to our excitement, the desired triene (132) was formed in 77% (Entry 6).

**Table 5: Cyclization of [3.1.1] bicycle**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Source</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield 144 (%)</th>
<th>Yield 132 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aldrich</td>
<td>Toluene</td>
<td>-</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Aldrich</td>
<td>Cyclohexane</td>
<td>-</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Aldrich</td>
<td>Toluene</td>
<td>MgCl₂</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Fluka</td>
<td>Toluene</td>
<td>MgCl₂</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Fluka</td>
<td>Cyclohexane</td>
<td>MgCl₂, CuI</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Acros</td>
<td>Cyclohexane</td>
<td>-</td>
<td>0</td>
<td>77</td>
</tr>
</tbody>
</table>

With these results, the reaction was performed again, this time using Acros Organics and toluene as solvent (Scheme 48). Refluxing the mixture overnight did not provide the predicted products, triene 132 or cyclohexadiene 137. Interestingly, instead the fully aromatized product 137 was obtained. Once electrocyclization occurred, the diene oxidized in the presence of air. This was favorable as now we were able to obtain the final, functionalized aromatic ring from the vinylpropargyl alcohol in one pot.
4.2 Hydromagnesiation of the Propargyl Alcohol

We are still in the process of trying to explain the reduction of propargyl alcohol 128 to the allylic alcohol 144. A hydride source must be present in the bottle of vinylmagnesium chloride purchased from Aldrich Chemicals and Fluka Chemicals. However, where the hydride originates from, we cannot determine. Calling customer service at Aldrich Chemicals, we were informed that both bottles of vinylmagnesium chloride contain no stabilizers and certificate of analysis states that no impurities are present.

All that we can state is that due to the \textit{trans} geometry of the allylic alcohol, the addition of the hydride is possibly a regiocontrolled, \textit{anti}-hydromagnesiation. The intermediate is most likely magnesium chelate 147, a similar intermediate to that of the carbometallation reactions (Figure 14). Hydroalumination of propargyl alcohols with LiAlH$_4$ are also considered to involve intermediates like 148 to furnish the \textit{trans} alkene.

\textbf{Figure 14:} Proposed intermediate for hydromagnesiation hydralumination of propargyl alcohols
4.3 Synthesis of Dihydrophenanthrene 129

The first step towards 138 started with treating tetralone (141) with LDA and trapping the resulting enolate with PhN(Tf)2 to furnish triflate 149 in 82% yield (Scheme 49). Sonogashira palladium coupling reaction of the triflate with propargyl alcohol gave alcohol 140 in 53%. Carbometallation with vinylmagnesium chloride (Acros Organics) and quenching the reaction with saturated aqueous ammonium chloride provided triene 139 in 77% yield. Heating the triene directly in toluene was attempted; however, only decomposition of the compound was observed. It was necessary to methylate the alcohol with sodium hydride and methyl iodide. Refluxing methyl ether 150 in toluene gave cyclohexadiene 151 in 76% yield. To complete the synthesis, aromatization with MnO2 provided the desire dihydrophenanthrene 138 in 48% yield.

\[
\text{LDA, PhN(Tf)2} \rightarrow \text{141} \xrightarrow{-78^\circ \text{C}, 82\%} \text{149} \xrightarrow{\text{PdCl}_2(PPh_3)_2 (5 \text{ mol\%}), \text{CuI} (10 \text{ mol\%})} \xrightarrow{\text{THF}:\text{NET}_3 (1:1), \text{reflux}, 16 \text{ h}, 53\%} \]

\[
\text{140} \xrightarrow{1. \xrightarrow{\text{MgCl}}, \text{Cyclohexane}, 2. \text{NH}_4\text{Cl, rt, 77\%}} \text{139} \xrightarrow{\text{KOH}, \text{MeI}, \text{THF, rt, 3 h, 87\%}} \text{150} \xrightarrow{\text{Toluene, reflux, 16h, 76\%}} \text{151} \xrightarrow{\text{MnO}_2, \text{toluene, reflux, 5h, 48\%}} \text{138}
\]

Scheme 49: Synthesis of 138

---

5 Conclusions and Future Work

5.1 Synthesis of Linear Triquinanes

Studies towards the synthesis of linear triquinanes were described. Triquinane core 85 was synthesized via a novel one pot IMDA-ROM-RCM approach from substituted cyclopentadiene 76. This was a one pot reaction that assembled the triquinane core with the requisite cis-anti-cis ring junction. Also, the IMDA reaction utilized microwave accelerated conditions for improved yields.

Pleased with our initial success, this approach was applied to the synthesis of natural product capnellene (13). Triquinane core 86 was successfully built albeit in low yields. Fortunately, optimization of the IMDA microwave conditions, using chlorobenzene as solvent, improved the yields for this step. It was also found that the tandem ROM-RCM sequence worked best with Grubbs 1st generation catalyst under an atmosphere of ethylene. The combination of the two optimized reaction conditions provided the unsubstituted triquinane core 85 in 65% yield.

The one pot reaction to the capnellene core must be repeated with the optimized reaction conditions. Once this is prepared, the completion of the total synthesis of 13 is envisioned first with allylic oxidation of the olefin with selenium oxide to give enone 152 (Scheme 50). However, it must be aware that a tertiary alcohol may form from this reaction. Reduction of the enone using lithium/ammonia gives carbonyl 153. The terminal alkene would then be converted to the aldehyde through ozonolysis and then reduction of the resulting aldehyde with sodium borohydride or a milder reducing agent, would provide alcohol 154. Lastly, Wittig olefination would give exo cyclic compound 155, mesylation of the remaining alcohol, followed by reduction with LiAlH4 should provide us with the total synthesis of capnellene (13).
5.2 Magnesium-Mediated Carbometallation – Annulation Protocol

A carbometallation-annulation protocol was applied towards the nopinone based propargyl alcohol 128 to give the functionalized aromatic compound 146 in one pot. Through the investigations we found that the quality of the Grignard reagent is essential for the efficiency of the reaction. In our case, some sources of reagents caused reduction of the propargyl alcohol to allylic alcohol 144. An explanation for the reduction is not known. Perhaps deuterium studies can be performed to determine the mechanism of the reaction.

With the completion of the last project, a spin off project could be the synthesis of the indoles through the carbometallation-annulation protocol. Speckamp and coworkers have done palladium catalyzed couplings on pyrrolidinone system 157 including Stille couplings, Sonogashira couplings and CO insertions.\(^{62}\)

The plan for the synthesis of indoles would start with the conversion to triflate 157 from 156 with LDA and Comin's reagent\(^6\) (Scheme 51). Sonogashira coupling with propargyl alcohol would give vinylpropargyl alcohol 158. The next step is to add vinyl magnesium chloride across propargyl alcohol 158 and quench the chelate 159 with a variety of electrophiles. Heating the resulting compound should induce electrocyclization to provide cyclic product 160. Subsequent oxidation and deprotection would furnish the desired substituted indole 161.

Scheme 51: Proposed synthesis of substituted indoles

5.3 Claims to Original Research

1. Developed an efficient route to linear triquinane core 85 through a one pot intramolecular Diels-Alder – ring opening metathesis – ring closing metathesis sequence.

2. Applied the new methodology towards the synthesis to the core structure of capnellene (86).

3. Prepared substrates through the carbometallation-annulation protocol, including a one pot synthesis of chiral compound 137.

4. Completed the basic studies required for the successful application of the carbometallation protocol for indole syntheses.

6 Experimental

General Experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in flame-dried glassware using dry solvents. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Dichloromethane, dimethyl formamide, benzene, toluene and triethylamine were distilled from calcium hydride. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. All starting material was purchased from Aldrich Chemical Company, all transition metal catalysts were purchased from Strem Chemical, Inc. and all were used without purification unless otherwise stated.

Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F254 (E. Merck). TLC spots were visualized under ultraviolet light or developed by heating the plate after treatment with potassium permanganate, phosphomolybdic acid or ninhydrin stains. Room temperature corresponds to 21 °C. Anhydrous magnesium sulfate (MgSO4) was used to dry solutions in organic solvents. Excess solvents were removed in vacuo at pressures obtained by a water or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with VWR Silica Gel 60 (230-400 mesh). Petroleum ether refers to a mixture of hydrocarbons with boiling range of 30-60 °C.

The base n-butyllithium (n-BuLi) was titrated by dissolving diphenyl acetic acid (180 mg, 0.848 mmol) in THF (5 mL). The solution was cooled to 0 °C and n-BuLi was added dropwise until a yellow colour persisted.

Grignard reagents were titrated by dissolving diphenyl ditelluride (100 mg, 0.244 mmol) in THF (5 mL). Grignard reagent was added dropwise until a yellow colour persisted.

Microwave reactions were performed in a CEM Model ESP-1500 Plus oven equipped with a pressure monitoring device and an EST-300 Plus fiber optic temperature
probe. All reactions were heated in a quartz tube and when non-polar solvents were employed, such as benzene and toluene, a carboflon™ was added.

Infrared (IR) spectra were obtained as neat films in a sodium chloride cell. All IR spectra were recorded on an ABB Bomem MB Series Fourier transform infrared spectrometer (FTIR). $^1$H NMR (300 or 500 MHz) and $^{13}$C NMR (75 or 125 MHz) were run on Bruker AMX300 spectrometer, Bruker AMX500 spectrometer or Varian INOVA500 spectrometer. Chemical shifts are reported downfield from tetramethylsilane ($\delta$ scale) in ppm. $^1$H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants (Hz), and integration. Low resolution mass spectroscopy (MS), using either electron impact (EI) or chemical ionization (CI), was performed on a V. G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV (for EI). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV. Melting points were determined with a Thomas–Hoover Unit melting point apparatus and uncorrected.

Compounds were named using ACD/I-Lab Web service (ACD/IUPAC Name 6.04).
4-Bromobutan-1-ol (67)

The compound was prepared according to the procedure described in Ref. 39. Tetrahydrofuran (5.62 mL, 69.3 mmol) was added dropwise to a solution of BBr₃ (2.18 mL, 23.1 mmol) in CH₂Cl₂ (30 mL) at 0 °C. The mixture was heated at reflux and stirred for 1.5 h. The reaction was cooled to rt, quenched with MeOH and heated at reflux for an additional 1 h. Removal of methyl borate and methanol in vacuo provided pure bromoalcohol 67 as an orange oil (7.74 g, 73%).

¹H NMR (300 MHz, CDCl₃) δ 3.67 (t, J = 6.3 Hz, 2H), 3.43 (t, J = 6.6 Hz, 2H), 1.99-1.89 (m, 3H), 1.74-1.64 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 62.3, 34.0, 31.4, 29.5; HRMS (EI) m/z calcd for C₄H₇BrO (M⁺ - 18) 133.9731, found 133.9725. ¹H NMR and ¹³C NMR spectra of this sample were in good agreement with that reported for this compound⁶₄

4-Bromobutanal (68)

The compound was prepared according to the procedure described in Ref. 40. PDC (1.86 g, 4.94 mmol) was added to a solution of alcohol 67 (500 mg, 3.29 mmol) in CH₂Cl₂ (5 mL). The reaction stirred at rt for 2 h. The mixture was filtered through a pad of silica gel, washing with Et₂O. The filtrate was concentrated. Chromatography (pet ether/Et₂O, 3:1) afforded 68 as a yellow oil (520 mg, 100%). Aldehyde 68 was carried to the next reaction immediately after purification.

¹H NMR (300 MHz, CDCl₃) δ 9.77 (s, 1H), 3.42 (t, J = 3.9 Hz, 2H), 2.63 (t, J = 4.2 Hz, 2H), 2.14 (quintet, J = 4.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 200.8, 42.3, 32.8, 25.1; HRMS (EI) m/z calcd for C₄H₇BrO (M⁺) 149.9968, found 149.9613. ¹H NMR and ¹³C

NMR spectra of this sample were in good agreement with that reported for this compound. \(^{40}\)

**Ethyl-(2E)-6-bromohex-2-enoate (70)**

![Chemical Structure](image)

The compound was prepared according to the procedure described in Ref. 40. Triethyl phosphonoacetate (3.10 mL, 15.6 mmol) was added to a suspension of sodium hydride (375 mg, 15.6 mmol) in THF (25 mL). The milky white solution stirred at rt until gas evolution ceased. A solution of 68 (2.13 g, 14.2 mmol) in THF (25 mL) was added to the mixture and the reaction stirred for 3 h. Diluted mixture with H₂O and the aqueous phase was extracted with CH₂Cl₂ (3x). Combined CH₂Cl₂ extracts were washed with H₂O (3x), brine, dried and concentrate. Chromatography (pet ether/Et₂O, 3:1) afforded 70 as a yellow oil (1.42 g, 45%).

\(^1\)H NMR (300 MHz, CDCl₃) δ 6.88 (ddd, \(J = 15.6, 7.0, 7.0\) Hz, 1H), 5.85 (ddd, \(J = 14.1, 1.5, 1.5\) Hz, 1H), 4.16 (q, \(J = 7.1\) Hz, 2H), 3.54 (t, \(J = 6.5\) Hz, 2H), 2.35 (q, \(J = 7.1\) Hz, 2H), 1.99 (quintet, \(J = 7.0\) Hz, 2H), 1.26 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (75 MHz, CDCl₃) δ 166.8, 147.1, 122.9, 60.7, 33.0, 31.1, 30.8, 14.6; HRMS (EI) m/z calcld for C₉H₁₃BrO₂ (M⁺) 220.0098, found 220.0094. \(^1\)H NMR and \(^13\)C NMR spectra of this sample were in good agreement with that reported for this compound. \(^{40}\)

**Ethyl-4,5,6,7-tetrahydro-3aH-inden-4-ylacetate (72)**

![Chemical Structure](image)
Ethylmagnesium bromide (1.09 mL, 1.09 mmol, 1 M in THF) was added to a solution of freshly distilled cyclopentadiene (81.8 μL, 0.994 mmol) in THF (2 mL) at 0 °C. The solution was heated at reflux for 4 h. The reaction was cooled to 0 °C and to this was added a solution of 70 (200 mg, 0.904 mmol) in THF (2 mL). After 2 h of stirring at rt the reaction was diluted with with Et₂O. The organic phase was washed with HCl (10% aq, 3x), NaHCO₃ (sat. aq, 3x), brine, dried and concentrated. Chromatography (petroleum ether/Et₂O, 19:1) afforded 72 as a colorless oil (74 mg, 40%). Starting material was also recovered (54 mg, 54%).

¹H NMR (300 MHz, CDCl₃) δ 6.38-6.17 (m, 3H), 4.09 (qd, J = 7.2, 2.1 Hz, 2H), 3.20-3.10 (m, 1H), 2.88 (d, J = 1.5 Hz, 2H), 2.63 (q, 9.0 Hz, 1H), 2.06-1.71 (m, 5H), 1.63-1.50 (m, 1H), 1.20 (t, 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.6, 151.3, 132.5, 131.3, 126.4, 60.6, 51.1, 46.1, 42.3, 34.1, 30.8, 25.0, 14.6; IR (neat) ν = 2957, 2873, 1729 cm⁻¹; MS (EI) m/z (relative intensity) 206 (M⁺, 50), 177 (6), 132 (100), 91 (23), 69 (23); HRMS (EI) m/z calcd for C₁₃H₁₈O₂ (M⁺) 206.1306, found 206.1290.

**Ethyl-(2E)-6-iodohex-2-enoate (70a)**

![Ethyl-(2E)-6-iodohex-2-enoate (70a)](image)

The compound was prepared according to the procedure described in Ref. 42. A mixture of 70 (500 mg, 2.26 mmol), sodium iodide (1.01 g, 6.78 mmol) and acetone (5mL) was heated at reflux and stirred for 3 h. The heterogeneous mixture was filtered through a pad a silica gel, washing with Et₂O. Concentration of the filtrate afforded 70a as a clear oil (540 mg, 89%).

¹H NMR (300 MHz, CDCl₃) δ 6.86 (ddd, J = 15.6, 7.0, 7.0 Hz, 1H), 5.85 (ddd, J = 15.6, 1.5, 1.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H), 2.31 (q, J = 7.2 Hz, 2H), 1.95 (quintet, J = 6.9 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.8, 146.9, 122.9, 60.7, 33.1, 31.8, 14.6, 5.9; HRMS (EI) m/z calcd for C₈H₁₃IO₂
(M⁺) 267.9960, found 267.9956. ¹H NMR and ¹³C NMR spectra of this sample were in good agreement with that reported for this compound.⁴²

**tert-Butyl-(2E)-6-iodohex-2-enoate (70b)**

![Structural formula of tert-Butyl-(2E)-6-iodohex-2-enoate (70b)]

(1-Butoxycarbonylmethyl)triphenylphosphonium bromide (1.5 g, 3.28 mmol) was added to a suspension of sodium hydride (78 mg, 3.28 mmol) in THF (5 mL). The milky white solution stirred at rt until gas evolution ceased and then heated to reflux for 45 min. The reaction cooled to rt and a solution of aldehyde 68 (492 mg, 3.28 mmol) in THF (5 mL) was added and the reaction continued to stir for an additional 16 h. Diluted mixture with H₂O and the aqueous phase was extracted with Et₂O (3x). Combined Et₂O extracts were washed with H₂O (3x), brine, dried and concentrate. Chromatography (pet ether/Et₂O, 3:1) afforded 70b as yellow oil (390 mg, 48%).

¹H NMR (300 MHz, CDCl₃) δ 6.77 (ddd, J = 15.6, 7.0, 7.0 Hz, 1H), 5.77 (ddd, J = 15.6, 1.5, 1.5 Hz, 1H), 3.38 (t, J = 6.6 Hz, 2H), 2.32 (q, J = 7.2 Hz, 2H), 1.98 (quintet, J = 6.6 Hz, 2H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 145.8, 124.6, 80.6, 33.1, 31.2, 30.6, 28.5; IR (neat) ν = 2981, 1712, 1652, 1159 cm⁻¹; MS (EI) m/z (relative intensity) 192 (M⁺-57, 10), 177 (31), 57 (100);

**tert-Butyl-4,5,6,7-tetrahydro-3aH-inden-4-ylacetate (72a, Table 1, Entry 5)**

![Structural formula of tert-Butyl-4,5,6,7-tetrahydro-3aH-inden-4-ylacetate (72a)]

Ethylmagnesium bromide (1.18 mL, 1.18 mmol, 1 M in THF) was added to a solution of freshly distilled cyclopentadiene (0.097 mL, 1.18 mmol) in THF (3 mL) at 0 °C. The
solution was heated to reflux for 4 h. The reaction was cooled to 0 °C and to this was added a solution of 70b (270 mg, 1.08 mmol) in THF (3 mL). After 2 h of stirring at rt the reaction was diluted with with Et₂O. The organic phase was washed with HCl (10% aq, 3x), NaHCO₃ (sat. aq, 3x), brine, dried and concentrated. Chromatography (petroleum ether/Et₂O, 19:1) afforded 72a as a colorless oil (101 mg, 40%). Starting material was also recovered (136 mg, 51%).

1H NMR (300 MHz, CDCl₃) δ 6.40-6.18 (m, 3H), 3.11-3.16 (m, 1H), 2.8 (d, J = 1.4 Hz, 2H), 2.53 (q, J = 5.4 Hz, 1H), 2.02-1.94 (m, 2H), 1.86-1.82 (m, 1H), 1.75-1.69 (m, 2H), 1.59-1.53 (m, 1H), 1.39 (s, 9H); 13C NMR (75 MHz, CDCl₃) δ 175.5, 151.3, 132.1, 130.8, 126.0, 79.9, 51.9, 45.8, 41.8, 33.8, 30.3, 28.1, 24.7; IR (neat) ν = 3501, 3071, 2953, 1652 cm⁻¹; MS (EI) m/z (relative intensity) 177 (M⁺-53, 45), 132 (100), 91 (21), 69 (23);

**Ethyl-(4E)-octa-4,7-dienoate (81)**

![Ethyl-(4E)-octa-4,7-dienoate (81)](image)

The compound was prepared according to the procedure described in Ref. 44a. A solution of 1,5-hexadien-3-ol (2 mL, 17.9 mmol) and propionic acid (80 μL, 1.07 mmol) in triethyl orthoacetate (22.9 ml, 125 mmol) was heated to 145 °C under conditions for distillative removal of ethanol. When distillation of ethanol was complete (ca 3 h), the reaction was cooled to rt and diluted with Et₂O. The organic phase was washed with HCl (10% aq, 3x), NaHCO₃ (sat. aq, 3x), brine, dried and concentrated. Chromatography (pet ether/Et₂O, 19:1) afforded 81 as a colorless oil (2.38 g, 93%).

1H NMR (300 MHz, CDCl₃) δ 5.78 (ddt, J = 17.1, 10.2, 6.3 Hz, 1H), 5.52-5.39 (m, 2H), 5.03-4.93 (m, 2H), 4.10 (q, J = 7.1 Hz, 2H), 2.73-2.69 (m, 2H), 2.36-2.28 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl₃) δ 173.6, 137.4, 129.7, 129.3, 115.4, 60.6, 37.0, 34.6, 28.3, 14.6; IR (neat) ν = 2980, 1737 cm⁻¹; MS (EI) m/z (relative intensity) 168 (M⁺, 13), 123 (11), 94 (34), 80 (100); HRMS (EI) m/z calcd for C₁₀H₁₆O₂ (M⁺) 168.1150,
found 168.1171. ^1^H NMR and ^13^C NMR spectra of this sample were in good agreement with that reported for this compound.\(^{44a}\)

**(4E)-Octa-4,7-dien-1-ol (82)**

\[
\text{\includegraphics[width=0.7\textwidth]{82.png}}
\]

The compound was prepared according to the procedure described in Ref. 44a. A solution of ester 81 (1 g, 5.94 mmol) in dry THF (10 mL) was added dropwise to a suspension of LiAlH\(_4\) (450 mg, 11.9 mmol) in dry THF (20 mL) at rt. After 30 min, \(\text{H}_2\text{O}\) was added dropwise until mixture turned white. HCl (10% aq) was added until the solution turned clear. Et\(_2\)O extracts (3x) were combined and washed with \(\text{H}_2\text{O}\) and brine, dried and concentrated. Chromatography (pet ether/Et\(_2\)O, 3:1) afforded 82 as a colorless oil (690 mg, 92%).

\(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.79 (ddt, \(J = 17.1, 10.2, 6.6\) Hz, 1H), 5.46-5.42 (m, 2H), 5.03-4.92 (m, 2H), 3.62 (t, \(J = 6.6\) Hz, 2H), 2.73-2.70 (m, 2H), 2.11-2.05 (m, 2H), 1.62 (quintet, \(J = 6.9\) Hz, 2H), 1.50 (bs, 1H); \(^13^C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 137.6, 131.2, 128.8, 115.3, 62.9, 37.1, 32.7, 29.2; IR (neat) \(\nu = 3352, 2929, 912\) cm\(^{-1}\); too unstable for MS. \(^1^H\) NMR and \(^13^C\) NMR spectra of this sample were in good agreement with that reported for this compound.\(^{44}\)

**(4E)-Octa-4,7-dien-1-yl-4-methylbenzenesulfonate (83)**

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\]

Triethylamine (1.78 mL, 12.78 mmol), \(p\)-toluenesulfonyl chloride (1.63 g, 8.53 mmol) and DMAP (26 mg, 0.213 mmol) were added to a solution of alcohol 82 (538 mg, 4.26 mmol) in CH\(_2\)Cl\(_2\) (20 mL). The mixture stirred at rt for 24 h. The reaction was washed
with HCl (10%aq, 3x), H₂O, brine, dried and concentrated. Chromatography (pet ether/Et₂O, 19:1 or pure CH₂Cl₂) afforded 83 as a colorless oil (948 mg, 79%).

¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.73 (ddt, J = 16.7, 10.4, 6.4 Hz, 1H), 5.38-5.22 (m, 2H), 4.99-4.92 (m, 2H), 3.99 (t, J = 6.4 Hz, 2H), 2.67-2.63 (m, 2H), 2.42 (s, 3H), 2.04-1.98 (m, 2H), 1.68 (quintet, J = 6.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 145.0, 137.3, 133.5, 130.2, 129.7, 129.6, 128.3, 115.4, 70.2, 36.9, 28.8, 28.5, 22.1; IR (neat) ν = 3076, 2925, 1362, 1177 cm⁻¹; too unstable for MS.

1-((4E)-Octa-4,7-dien-1-yl)cyclopenta-1,3-diene
and 2-((4E)-Octa-4,7-dien-1-yl)cyclopenta-1,3-diene (84)

**Procedure A:** Sodium hydride (51.4 mg, 2.14 mmol) was added to a solution of freshly distilled cyclopentadiene (0.176 mL, 2.14 mmol) in THF (5 mL) at 0 °C. Bubbling started due to hydrogen gas evolution and the solution turned red due to the formation of cyclopentadienylsodium. Once bubbling ceased, tosylate 83 (300 mg, 1.07 mmol) in THF (5 mL) was added via cannula. The reaction slowly warmed to rt and stirred for 6 h. Diluted with HCl (10%aq) and the aqueous phase was extracted with pet ether (3x). Combined pet ether extracts (3x) were washed with H₂O, brine, dried and concentrated. Chromatography (pure pet ether) afforded 84 as a colorless oil (186 mg, 99%).

**Procedure B:** Ethylmagnesium bromide (5.25 mL, 1 M in THF, 5.25 mmol) was added to a solution of freshly distilled cyclopentadiene (0.432 mL, 5.25 mmol) in THF (5 mL) at 0 °C. The solution was heated at reflux for 4 h. The solution was cooled to 0 °C and to this was added a solution of tosylate 83 (500 mg, 1.75 mmol) in THF (5 mL). The reaction stirred at rt for 16 h. Diluted with HCl (10%aq) and the aqueous phase was extracted with pet ether (3x). Combined pet ether extracts (3x) were washed with H₂O,
brine, dried and concentrated. Chromatography (pure pet ether) afforded 84 as a colorless oil (186 mg, 99%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.43-5.98 (m, 3H), 5.87-5.74 (m, 1H), 5.50-5.36 (m, 2H), 5.03-4.94 (m, 2H), 2.92 (bs, 1H), 2.85 (bs, 1H), 2.72-2.70 (m, 2H), 2.41-2.31 (m, 2H), 2.03-2.01 (m, 2H), 1.65-1.52 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 150.2, 147.4, 137.8, 135.1, 134.0, 132.8, 131.8, 131.7, 130.8, 128.34, 128.29, 126.7, 126.3, 115.1, 43.6, 41.6, 37.1, 32.7, 32.6, 30.5, 29.8, 29.7, 28.9; IR (neat) $\nu$ = 2929, 1432, 972 cm$^{-1}$; MS (EI) $m/z$ (relative intensity) 174 (M$^+$, 8), 119 (10), 80 (100), 67 (12), 41 (12); HRMS calcd for C$_{13}$H$_{18}$ (M$^+$) 174.1408, found 174.1400.

7-Allyl-1,2,3,6,7,7a-hexahydro-3a,6-methanoindene (75)

A microwave quartz vessel was charged with substituted cyclopentadiene 84 (100 mg, 0.572 mmol), chlorobenzene (5 mL) and a carboflon$^\text{TM}$. The solution was degassed with argon for 15 min. The microwave apparatus was quickly assembled and the reaction was heated at 210 °C and 310 psi for 2 h. The solution was directly loaded onto the chromatographic column. Purification using pure pet ether afforded 75 as a clear oil (80 mg, 80%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.16 (d, $J$ = 5.6 Hz, 1H), 5.92 (dd, $J$ = 5.6, 2.9 Hz, 1H), 5.77 (ddt, $J$ = 17.1, 10.3, 6.7 Hz, 1H), 4.96-4.89 (m, 2H), 2.77 (bs, 1H), 1.97-1.77 (m, 7H), 1.66-1.61 (m, 1H), 1.38 (d, $J$ = 8.1 Hz, 1H), 1.30-1.22 (m, 1H), 1.21 (d, $J$ = 8.1 Hz, 1H), 1.12-1.07 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 141.7, 138.5, 132.6, 114.4, 63.5, 53.0, 52.0, 49.0, 47.2, 39.2, 31.5, 27.1, 27.0; IR (neat) $\nu$ = 2951, 2906, 2864 cm$^{-1}$; MS (EI) $m/z$ (relative intensity) 174 (M$^+$, 35), 159 (14), 145 (16), 133 (28), 119 (23), 92 (100), 80 (72), 97 (21); HRMS calcd for C$_{13}$H$_{18}$ (M$^+$) 174.1408, found 174.1411.
7a-Vinyl-2,3,3a,3b,4,6a,7,7a-octahydro-1H-cyclopenta[a]pentalene (85)

**Procedure A:** A microwave quartz vessel was charged with substituted cyclopentadiene 84 (100 mg, 0.572 mmol), chlorobenzene (5 mL) and a carboflon™. The solution was degassed with argon for 15 min. The microwave apparatus was quickly assembled and the reaction was heated at 210 °C and 310 psi for 2 h. The quartz vessel was removed from the apparatus, placed with a septum and the solution was degassed with argon for 10 min. The solution was then purged with ethylene for another 10 min. While maintaining an ethylene atmosphere, Grubbs 1st generation catalyst (24.3 mg, 0.0286 mmol) was added. After being stirred at rt for 2 h under ethylene atmosphere the reaction was quenched with DMSO (0.100 mL). The mixture was concentrated *in vacuo* and chromatography (pure pet ether) afforded 85 as a clear oil (65 mg, 65%).

**Procedure B:** A solution of Diels-Alder adduct 75 (50.0 mg, 0.287 mmol) in benzene (5 mL) was degassed with argon for 15 min. The solution was purged with ethylene for another 10 min. While maintaining the ethylene atmosphere, Grubbs 1st generation catalyst was added (12.2 mg, 0.0144 mmol) and after being stirred at rt for 2 h under ethylene atmosphere the reaction was quenched with DMSO (0.050 mL). The mixture was concentrated *in vacuo* and chromatography (pure pet ether) afforded 85 as a clear oil (49.5 mg, 99%).

$^1$H NMR (500 MHz, CDCl₃) δ 5.87 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.61-5.49 (m, 2H), 4.87 (dd, $J = 17.4$, 1.4 Hz, 1H), 4.80 (dd, $J = 10.6$, 1.4 Hz, 1H), 3.19-3.14 (m, 1H), 2.55-2.49 (m, 1H), 2.33-2.29 (m, 1H) 2.16-2.11 (m, 1H), 1.90 (dd, $J = 13.0$, 8.5 Hz, 1H), 1.82-1.59 (m, 6H), 1.58-1.48 (m, 2H); $^{13}$C NMR (125 MHz, CDCl₃) δ 147.3, 135.5, 128.0, 109.0, 58.6, 58.2, 50.8, 49.8, 43.4, 39.4, 36.4, 31.4, 23.9; IR (neat) ν = 2953, 2927, 2856 cm⁻¹; MS (El) $m/z$ (relative intensity) 174 (M⁺, 100), 159 (40), 145 (48), 131 (95), 119 (70),
108 (68), 91 (96), 79 (76), 67 (50); HRMS calcd for C_{13}H_{18} (M^+) 174.1408, found 174.1393.

**6-Methylhepta-1,5-dien-4-ol (90)**

![Chemical Structure](image)

The compound was prepared according to the procedure described in Ref. 46. Allylmagnesium bromide (100 mL, 100 mmol, 1M in Et₂O), via syringe pump was slowly added to a solution of 3-methyl-2-butenal (5.51 mL, 57.1 mmol) in Et₂O (115 mL) at 0 °C. The reaction stirred at rt for 16 h. The grey solution was cooled to 0 °C and slowly quenched with HCl (10% aq, 25 mL) until a white ppt started to form. The aqueous phase was extracted with Et₂O (3x), the combined Et₂O extracts were washed with H₂O, dried and concentrated. Chromatography (pure CH₂Cl₂) afforded 90 as a colorless oil (5.98 g, 83%).

$^1$H NMR (300 MHz, CDCl₃) δ 5.78 (ddt, $J = 17.1, 10.1, 7.1$ Hz, 1H), 5.19-5.06 (m, 3H), 4.37 (dt, $J = 8.6, 6.4$ Hz, 1H), 2.26-2.21 (m, 2H), 1.70 (d, $J = 1.2$ Hz, 3H), 1.66 (d, $J = 1.3$, 3H), 1.08 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl₃) δ 135.8, 134.9, 127.5, 118.2, 68.1, 42.5, 30.1, 26.1, 18.6; MS (EI) m/z (relative intensity) 108 (M⁺-18, 2), 85 (100), 67 (9), 55 (7), 41 (25); HRMS calcd for C₈H₁₂ (M⁺ – 18) 108.0935, found 108.0952. Characterization of this sample was in good agreement with that reported for this compound.⁶⁵

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Ethyl-(4E)-3,3-dimethylocta-4,7-dienoate (91)

![Chemical Structure](image)

The compound was prepared according to the procedure described in Ref. 47. A solution of alcohol 90 (3.00 g, 23.8 mmol) and phenol (111 mg, 1.18 mmol) in triethyl orthoacetate (30.5 ml, 166 mmol) was heated to 145 °C under conditions for distillative removal of ethanol. When distillation of ethanol was complete (ca 24 h), the reaction was cooled to rt and diluted with Et₂O. The organic phase was washed with HCl (10% aq, 3x), NaOH (10% aq, 3x), brine, dried and concentrated. Chromatography (petroleum ether/Et₂O gradient, 19:1 (200 mL), 9:1 (200 mL), 3:1) afforded 91 as a colorless oil (3.03 g, 65%)

¹H NMR (300 MHz, CDCl₃) δ 5.80 (ddt, J = 17.1, 10.1, 6.3 Hz, 1H), 5.50 (dt, J = 14.3, 1.2 Hz, 1H), 5.34 (dt, J = 15.6, 6.3 Hz, 1H), 5.02-4.93 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.72 (tq, J = 6.3, 1.4 Hz, 2H), 2.24 (s, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.10 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 172.2, 140.2, 137.6, 129.6, 124.4, 116.3, 115.2, 60.3, 47.6, 37.0, 35.8, 27.9, 14.7; IR (neat) ν = 2962, 2930, 1735 cm⁻¹; MS (EI) m/z (relative intensity) 196 (M⁺, 11), 162 (11), 129 (15), 109 (95), 108 (100), 93 (64), 81 (28), 67 (46), 55 (21); HRMS calcd for C₁₂H₂₀O₂ (M⁺) 196.1463, found 196.1492.

(4E)-3,3-Dimethylocta-4,7-dien-1-ol (92)

![Chemical Structure](image)

A solution of ester 91 (500 mg, 2.55 mmol) in THF (10 mL) was added dropwise to a suspension of LiAlH₄ (193 mg, 5.09 mmol) in THF (10 mL) at rt. After 30 min, H₂O was added dropwise until mixture turned white. HCl (10% aq) was added until the solution turned colourless. Et₂O extracts (3x) were combined and washed with H₂O and brine,
dried and concentrated. Chromatography (petroleum ether/Et<sub>2</sub>O, 3:1) afforded 92 as a colorless oil (340 mg, 87%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.79 (ddt, J = 17.1, 10.3, 6.4 Hz, 1H), 5.45 (d, J = 15.8 Hz, 1H), 5.34 (dt, J = 9.6, 6.0 Hz, 1H), 5.02-4.95 (m, 2H), 3.62 (t, J = 7.1 Hz, 2H), 2.73 (bt, J = 5.9 Hz, 2H), 1.57 (t, J = 7.1 Hz, 2H), 1.37 (bs, 1H), 0.99 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 141.5, 137.6, 124.5, 115.3, 68.3, 60.6, 45.8, 37.1, 35.3, 28.0; IR (neat) ν = 3345, 2959, 2936, 2899 cm<sup>-1</sup>; too unstable for MS.

**(4E)-3,3-Dimethylocta-4,7-dien-1-yl 4-methylbenzenesulfonate (93)**

![Structural formula of (4E)-3,3-Dimethylocta-4,7-dien-1-yl 4-methylbenzenesulfonate (93)](image)

Triethylamine (5.96 mL, 42.8 mmol), p-toluenesulfonyl chloride (5.44 g, 28.5 mmol) and DMAP (86 mg, 0.710 mmol) were added to a solution of alcohol 92 (2.20 g, 14.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The mixture stirred at rt for 24 h. The reaction was washed with HCl (10% aq, 3x), H<sub>2</sub>O, brine, dried and concentrated. Chromatography (petroleum ether/Et<sub>2</sub>O, 19:1 or pure CH<sub>2</sub>Cl<sub>2</sub>) afforded 93 as a colorless oil (4.07 g, 93%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.75 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.72 (m, 1H), 5.24 (m, 2H), 4.95 (m, 2H), 3.98 (t, J = 7.4 Hz, 2H), 2.66 (m, 2H), 2.42 (s, 3H), 1.63 (t, J = 7.4 Hz, 2H), 0.93 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 145.0, 139.8, 137.5, 133.5, 130.1, 128.2, 125.3, 115.4, 68.7, 41.2, 37.0, 35.2, 27.9, 22.0; IR (neat) ν = 2962, 1363 cm<sup>-1</sup>; too unstable for MS.

**1-((4E)-3,3-Dimethylocta-4,7-dien-1-yl)cyclopenta-1,3-diene**

and **2-((4E)-3,3-Dimethylocta-4,7-dien-1-yl)cyclopenta-1,3-diene (88)**

![Structural formulas of 1-((4E)-3,3-Dimethylocta-4,7-dien-1-yl)cyclopenta-1,3-diene and 2-((4E)-3,3-Dimethylocta-4,7-dien-1-yl)cyclopenta-1,3-diene (88)](image)
**Procedure A:** Sodium hydride (51.4 mg, 2.14 mmol) was added to a solution of freshly distilled cyclopentadiene (0.18 mL, 2.14 mmol) in THF (5 mL) at 0 °C. The solution turned red due to the formation of cyclopentadienyl anion. Once bubbling ceased, tosylate 93 (300 mg, 1.07 mmol) in THF (5 mL) was added via cannula. The reaction slowly warmed to rt and stirred for 1.5 hr. The mixture was extracted with petroleum ether (3x). Petroleum ether extracts (3x) were combined and washed with H₂O and brine, dried and concentrated. Chromatography (petroleum ether) afforded 88 as a colorless oil (186 mg, 99%).

**Procedure B:** Ethylmagnesium bromide (4.86 mL, 1 M in THF, 4.86 mmol) was added to a solution of freshly distilled cyclopentadiene (0.400 mL, 4.86 mmol) in THF (5 mL) at 0 °C. The solution was heated at reflux for 4 h. The solution was cooled to 0 °C and to this was added a solution of tosylate 93 (500 mg, 1.62 mmol) in THF (5 mL). The reaction stirred at rt for 16 h. Diluted with HCl (10% aq) and the aqueous phase was extracted with pet ether (3x). Combined pet ether extracts (3x) were washed with H₂O, brine, dried and concentrated. Chromatography (pure pet ether) afforded 88 as a colorless oil (194 mg, 60%).

¹H NMR (300 MHz, CDCl₃) δ 6.42-5.92 (m, 3H), 5.84 (ddt, J = 17.1, 103, 6.3 Hz, 1H), 5.47-5.27 (m, 2H), 5.04-4.95 (m, 2H), 2.92 (s, 1H) 2.85 (s, 1H), 2.77 (bt, 2H), 2.33-2.22 (m, 2H), 1.53-1.42 (m, 2H), 1.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 151.0, 148.1, 141.6, 141.5, 138.1, 135.3, 134.0, 132.8, 130.7, 126.0, 125.5, 124.1, 115.1, 43.8, 43.1, 42.3, 41.6, 37.2, 36.1, 36.1, 27.7, 26.3, 25.5; IR (neat) ν = 2959, 2917 cm⁻¹; MS (El) m/z (relative intensity) 202 (M⁺, 14), 187 (13), 161 (21), 109 (78), 92 (100), 67 (77), 43 (25); HRMS calcd for C₁₅H₂₂ (M⁺) 202.1721, found 202.1730.

7-Allyl-1,1-dimethyl-1,2,3,6,7,7a-hexahydro-3a,6-methanoindene (87)
A microwave quartz vessel was charged with substituted cyclopentadiene 88 (100 mg, 0.495 mmol), benzene (5 mL) and a carbofalon™. The solution was degassed with argon for 15 min. The microwave apparatus was quickly assembled and the reaction was heated at 210 °C and 310 psi for 2 h. The solution was directly loaded onto the chromatographic column. Purification using pure pet ether afforded 87 as a clear oil (45 mg, 45%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.18 (d, $J = 5.7$ Hz, 1H), 5.90 (dd, $J = 5.7$, 2.8 Hz, 1H), 5.76 (ddt, $J = 17.0$, 10.0, 7.2 Hz, 1H), 4.96-4.89 (m, 2H), 2.75 (bs, 1H), 2.04-1.99 (m, 1H), 1.93-1.87 (m, 1H), 1.81-1.52 (m, 5H), 1.38 (broad dd, 1H), 1.12 (dt, $J = 7.9$, 1.9 Hz, 1H), 0.97 (s, 6H), 0.82 (dd, $J = 5.1$, 2.1 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 142.2, 138.7, 132.3, 114.7, 65.2, 62.6, 50.8, 47.8, 44.3, 42.3, 40.6, 36.5, 32.9, 28.1, 26.8; IR (neat) $\nu$ = 2957, 2864, 908 cm$^{-1}$; MS (EI) m/z (relative intensity) 202 (M$^+$, 16), 187 (20), 161 (17), 109 (26), 92 (100), 67 (24); HRMS calcd for C$_{15}$H$_{22}$ (M$^+$) 202.1712, found 202.1712.

3,3-Dimethyl-7a-vinyl-2,3,3a,3b,4,6a,7,7a-octahydro-1H-cyclopenta[a]pentalene (86)

**Procedure A:** A microwave quartz vessel was charged with substituted cyclopentadiene 88 (100 mg, 0.495 mmol), benzene (5 mL) and a carbofalon™. The solution was degassed with argon for 15 min. The microwave apparatus was quickly assembled and the reaction was heated at 210 °C and 310 psi for 2 h. The quartz vessel was removed from the apparatus, placed with a septum and the solution was degassed with argon for 10 min. The solution was then purged with ethylene for another 10 min. While maintaining the ethylene atmosphere, Grubbs 1st generation catalyst (21.0 mg, 0.0248 mmol) was added. After being stirred at rt for 2 h under ethylene atmosphere the reaction was quenched
with DMSO (0.100 mL). The mixture was concentrated in vacuo and chromatography (pure pet ether) afforded 86 as a clear oil (15.1 mg, 15%).

**Procedure B:** A solution of Diels-Alder adduct 87 (50.0 mg, 0.247 mmol) in benzene (5 mL) was degassed with argon for 15 min. The solution was purged with ethylene for another 10 min. While maintaining the ethylene atmosphere, Grubbs 1st generation catalyst was added (10.5 mg, 0.0124 mmol) and after being stirred at rt for 2 h under ethylene atmosphere the reaction was quenched with DMSO (0.050 mL). The mixture was concentrated in vacuo and chromatography (pure pet ether) afforded 86 as a clear oil (49.2 mg, 99%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.00 (dd, J = 17.5, 10.5 Hz, 1H), 5.61-5.52 (m, 1H), 4.90 (dd, J = 17.5, 1.0 Hz, 1H), 4.75 (dd, J = 10.5, 1.5 Hz, 1H), 3.11-3.09 (m, 1H), 2.56-2.53 (m, 2H), 2.14-2.10 (m, 1H), 1.88-1.84 (m, 2H), 1.77 (dd, J = 13.5, 8.0 Hz, 1H), 1.57 (bd, J = 3.3 Hz, 1.53-1.46 (m, 3H), 1.43-1.40 (m, 1H), 1.01 (s, 3H), 0.95 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 150.0, 136.0, 128.7, 107.8, 69.7, 58.5, 52.3, 45.6, 45.1, 41.7, 41.1, 40.0, 36.4, 30.3, 25.8; IR (neat) ν = 2943, 2863, 1467, 900 cm$^{-1}$; MS (EI) m/z (relative intensity) 202 (M$^+$, 10), 187 (100), 161 (6), 148 (33), 105 (22), 91 (22), 79 (16); HRMS calcd for C$_{15}$H$_{22}$ (M$^+$) 202.1721, found 202.1726.

**(1R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl trifluromethanesulfonate (142)**

\[ \text{OSO}_2\text{CF}_3 \]

$n$-Butyllithium (10.9 mL, 2.5 M in hexanes, 27.1 mmol) was added dropwise to a solution of diisopropylamine (3.80 ml, 27.1 mmol) in THF (10 mL) at -78 °C and the solution stirred for 30 min. At -78 °C nopinone (2.5 mL, 18.1 mmol) was added. The solution was warmed to rt and stirred for an additional 40 min. The clear solution cooled to -78 °C again and to this was added a solution of N-phenyltrifluromethanesulfonimide (7.10 g, 27.1 mmol) in THF (20 mL). The reaction was warmed to rt and stirred for 16 h.

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The reaction was quenched with H₂O and the aqueous phase was extracted with Et₂O (3x). The combined organic phases were washed with H₂O (3x), brine, dried and concentrated. Chromatography (pure pet ether) provided 142 as a colourless oil (3.03 g, 62%).

¹H NMR (300 MHz, CDCl₃) δ 5.53-5.50 (m, 1H), 2.54 (dt, J = 9.2, 5.7 Hz, 1H), 2.40-2.22 (m, 2H), 2.15-2.09 (m, 1H). 1.36 (d, J = 9.2 Hz, 1H), 1.32 (s, 3H), 0.91 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 121.0, 116.8, 111.8, 46.6, 40.5, 40.1, 32.1, 28.6, 25.9, 21.2; IR (neat) ν = 2949, 1658, 1414 cm⁻¹; MS (El) m/z (relative intensity) 270 (M⁺, 3), 226 (16), 162 (9), 77 (52), 55 (100); HRMS (EI) m/z calced for C₁₀H₁₃F₃O₂S (M⁺) 270.0537, found 270.0496.

(1R)-3-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)prop-2-yn-1-ol (128)

A round bottom flask equipped with a water condenser was charged with Pd(PPh₃)₂Cl₂ (130 mg, 0.18 mmol), copper(I)iodide (70 mg, 0.37 mmol), triflate 142 (1.00 g g, 3.7 mmol), triethylamine (18.5 mL) and THF (18.5 mL). The yellow mixture was degassed with argon for 15 min. To the mixture was added propargyl alcohol (0.236 mL, 4.1 mmol) and quickly the mixture turned from yellow to orange, to red and then to black. The mixture stirred at refluxed for 16 h. The mixture was filtered through a pad of silica gel washing with Et₂O. The filtrate was concentrate. Chromatography (pet ether/Et₂O, 3:1) afforded propargyl alcohol 128 as a dark yellow oil (619 mg, 95%).

¹H NMR (300 MHz, CDCl₃) δ 5.96 (bs, 1H), 4.37 (s, 2H), 2.38 (dt, J = 9.0, 5.6 Hz, 1H), 2.31 (quintet, J = 3 Hz, 3H), 2.23 (td, J = 5.7, 1.2 Hz, 1H), 2.08 (bs, 1H), 1.67 (s, 1H), 1.26 (s, 3H), 1.20 (d, J = 9.0 Hz, 1H) 0.86 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 131.9,
129.7, 87.3, 86.7, 52.1, 47.3, 40.5, 38.3, 32.4, 31.7, 26.4, 21.4; IR (neat) ν 3607, 2955, 1375 cm⁻¹; MS (EI) m/z (relative intensity) 176 (M⁺, 82), 161 (16), 145 (44), 133 (100), 103 (79), 77 (55); HRMS (El) m/z calc'd for C₁₂H₁₆O (M⁺) 176.1201, found 176.1213.

(1R, 2E)-3-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)prop-2-en-1-ol (144)

Vinylmagnesium chloride (4.12 mL, Aldrich Chemicals batch #02813AB, 1.6 M in THF, 6.60 mmol) was added dropwise to a solution of vinylpropargyl alcohol 128 (363 mg, 2.06 mmol) in toluene (20 mL). The brown reaction mixture stirred at reflux for 16 h. The reaction was quenched with saturated aqueous NH₄Cl (10 mL) at 0°C and the mixture stirred for 10 min. Dichloromethane was added followed by water and the aqueous phase was extracted with dichloromethane (3x). The combined organic phases were washed with H₂O (2x), brine, dried with MgSO₄ and concentrated. Chromatography (petroleum ether/Et₂O, 3:1) afforded 144 as a clear oil (154 mg, 42%).

¹H NMR (300 MHz, CDCl₃) δ 6.22 (d, J = 15.6 Hz, 1H), 5.67 (dt, J = 9.5, 6.1 Hz, 1H), 5.54 (bs, 1H), 4.17 (d, J = 5.9 Hz, 2H), 2.53-2.47 (m, 3H), 2.40 (dt, J = 8.7, 5.7 Hz, 1H), 2.33-2.27 (m, 1H), 2.11-2.09 (m, 1H), 1.30 (s, 3H), 1.11 (d, J = 8.7 Hz, 1H), 0.78 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 146.0, 133.4, 125.2, 124.6, 64.4, 41.6, 41.3, 38.1, 32.3, 31.6, 26.7, 21.2; IR (neat) ν = 3348, 2920 cm⁻¹; MS (EI) m/z (relative intensity) 178 (M⁺, 18), 163 (7), 147 (38), 135 (13), 105 (64), 91 (100), 69 (28), 43 (97); HRMS (El) m/z calc'd for C₁₂H₁₆O (M⁺) 178.1357, found 178.1350.

(1R, 2E)-3-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)acrylaldehyde (145)
Manganese (II) oxide (742 mg, 8.52 mmol) was added to a solution of allylic alcohol 144 (152 mg, 0.852 mmol) in toluene (10 mL). The black mixture stirred at reflux for 16 h. The mixture was filtered through a pad of silica washing with Et<sub>2</sub>O. The filtrate was concentrated. Chromatography (pet ether/Et<sub>2</sub>O, 19:1) afforded 145 as a yellow oil (142 mg, 95%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.55 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 15.6 Hz, 1H), 6.17 (bs, 1H), 6.01 (dd, J = 15.6, 7.8 Hz, 2.57-2.51 (m, 1H), 2.49-2.44 (m, 3H), 2.17-2.13 (m, 1H), 1.56 (s, 1H), 1.32 (s, 3H), 1.32 (d, J = 9 Hz, 1H), 0.75 (s, 3H);<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 194.7, 153.7, 146.6, 137.3, 125.9, 41.7, 40.8, 38.2, 33.4, 31.5, 26.4, 21.2; IR (neat) ν = 2949, 2821, 1682, 1612cm<sup>-1</sup>; MS (GCMS) m/z (relative intensity) 176 (M<sup>+</sup>, 7), 133 (73), 105 (100), 91 (72), 77 (52).

(1R)-(2,2-Dimethyl-1,2,3,4-tetrahydro-1,3-methanonaphthalen-7-yl)methanol (146)

Vinylmagnesium chloride (2.6 mL, Acros Organics, 15% wt in THF, 4.34 mmol) was added dropwise to a solution of 145 (191 mg, 1.08 mmol) in toluene (13 mL). The brown reaction mixture stirred at reflux for 16 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) at 0°C and the mixture stirred for 10 min. Dichloromethane was added followed by water and the aqueous phase was extracted with dichloromethane.
The combined organic phases were washed with H₂O (2x), brine, dried with MgSO₄ and concentrated. Chromatography (petroleum ether/Et₂O, 3:1) afforded 146 as a clear oil (115 mg, 53%). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.11-7.07 (m, 2H), 6.90 (s, 1H), 4.60 (s, 2H), 2.94 (bs, 2H), 2.71 (t, 5.5 Hz, 1H), 2.60 (dt, 9.3, 5.9 Hz, 1H), 2.25 (m, 1H), 1.35 (s, 3H), 1.23 (bs, 1H), 1.21 (d, 9.3 Hz, 1H), 0.61 (s, 3H); \(^1\)C NMR (125 MHz, CDCl₃) δ 147.1, 137.3, 134.4, 127.8, 124.7, 124.5, 62.4, 47.7, 40.4, 39.0, 32.6, 31.8, 26.0, 21.2; IR (neat) ν = 3336, 2980, 2916, 2867 cm⁻¹; MS (EI) m/z 202.1 (M⁺, 8), 159 (14), 129 (100), 115 (7); HRMS calcd for C₁₄H₁₈O (M⁺) 202.1356, found 202.1353.

3,4-Dihydropinaphthalen-1-yl trifluoromethanesulfonate (149)

![Chemical Structure](image)

The compound was prepared according to the procedure described in Ref. 69. n-Butyllithium (7.42 mL, 2.3 M, 16.7 mmol) was added dropwise to a solution of diisopropylamine (2.18 mL, 16.7 mmol) in THF (5 mL) at -78 °C and the solution stirred for 30 min. At -78 °C was added tetralone (2.02 mL, 15.2 mmol). The solution warmed to rt and stirred for an additional 30 min. The clear solution cooled to -78 °C again and to this was added a solution of N-phenyltrifluoromethanesulfonimide (5.7 g, 16.0 mmol) in THF (10 mL). The reaction was warmed to rt and stirred for 3 h. The reaction was quenched with H₂O and the aqueous phase was extracted with Et₂O (3x). The combined organic phases were washed with H₂O (3x), brine, dried and concentrated. Chromatography (pet ether) provided 149 as a colourless oil (3.29 g, 78%).

\(^1\)H NMR (500 MHz, CDCl₃) δ 7.37-7.35 (m, 1H), 7.27-7.25 (m, 2H), 7.18-7.17 (m, 1H), 6.02 (t, J = 4.8 Hz, 1H), 2.86 (t, J = 8.0 Hz, 2H), 2.52-2.48 (m, 2H); \(^1\)C NMR (125 MHz, CDCl₃) δ 146.4, 136.2, 129.1, 128.6, 127.7, 126.9, 122.4, 121.2, 119.9, 117.7, 26.8, 22.3. \(^1\)H NMR and \(^1\)C NMR spectra of this sample were in good agreement with that reported for this compound.\(^6\)
3-(3,4-Dihyronaphthalen-1-yl)prop-2-yn-1-ol (140)

A round bottom flask equipped with a water condenser was charged with Pd(PPh₃)₂Cl₂ (414 mg, 0.591 mmol), copper(I)iodide (225 mg, 1.18 mmol), triflate 149 (3.29 g, 11.8 mmol), triethylamine (25 mL) and THF (25 mL). The yellow mixture was degassed with argon for 15 min. To the mixture was added propargyl alcohol (0.755 mL, 13.0 mmol) and quickly the mixture turned from yellow to orange, then to red and then to black. The mixture stirred at refluxed for 16 h. The mixture was filtered through a pad of silica gel washing with Et₂O. The filtrate was concentrate. Chromatography (pet ether/Et₂O, 3:1) afforded propargyl alcohol 140 as a dark yellow oil (1.71 g, 79%).

¹H NMR (500 MHz, CDCl₃) δ 7.59 (d, J = 7.5 Hz, 1H), 7.23 (td, J = 7.4, 0.8 Hz, 1H), 7.18 (td, J = 7.4, 1.4 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 6.47 (t, J = 4.8 Hz, 1H), 4.52 (s, 2H), 2.78 (t, J = 7.9 Hz, 2H), 2.75 (bs, 1H), 2.38-2.34 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 135.8, 134.8, 132.3, 127.6, 127.2, 126.5, 124.8, 121.1, 88.1, 83.3, 51.3, 26.9, 23.4; IR (neat) ν = 3359, 2935, 2830, 1487 cm⁻¹; MS (EI) m/z (relative intensity) 184 (M⁺,100), 152 (63), 141 (52), 115 (41); HRMS (EI) m/z calcd for C₁₃H₁₂O (M⁺) 184.0888, found 184.0832.
2-(3,4-Dihyronaphthalen-1-ylmethylene)but-3-en-1-ol (139)

Vinylmagnesium chloride (2.45 mL, Acros Organics, 15% wt in THF, 4.12 mmol) was added to a solution of 140 (190 mg, 1.03 mmol) in toluene (5 mL) at rt. A water condenser was quickly placed on the round bottom flask and the dark brown solution was stirred at reflux for 16 h. The solution was cooled to 0 °C and the reaction was quenched with saturated aqueous NH₄Cl (10 mL) and the yellow solution stirred for 30 min at rt. Dilution with H₂O and the aqueous phase was extracted with EtOAc (3x). The combined organic extracts were washed with H₂O (3x), dried and concentrated. Flash chromatography (pet ether/Et₂O, 3:1) afforded 139 as a yellow oil (168 mg, 77%).

¹H NMR (500 MHz, CDCl₃) δ 7.17 (s, 4H), 6.73 (ddd, J = 18.0, 11.3, 0.9 Hz, 1H), 6.49 (s, 1H), 5.98 (td, J = 4.7, 1.6 Hz, 1H) 5.39 (dt, J = 18.0, 0.9 Hz, 1H), 5.13 (dt, J = 11.3, 1.4 Hz, 1H), 4.48 (d, J = 1.1 Hz, 2H), 2.80 (t, J = 7.7 Hz, 2H), 2.42 – 2.37 (m, 2H) 2.20 (bs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 135.9, 134.6, 133.4, 132.9, 129.8, 128.2, 127.4, 127.1, 126.4, 124.2, 114.2, 64.0, 27.8, 23.2; IR (neat) ν = 3606, 3448, 3054, 2987, 2306, 1422 cm⁻¹; MS (EI) m/z (relative intensity) 212 (M⁺, 55), 181 (100), 165 (53), 141 (35), 128 (26); HRMS (EI) m/z calcd for C₁₅H₁₆O (M⁺) 212.1201, found 212.1199.

4-[2-(Methoxymethyl)buta-1,3-dien-1-yl]-1,2-dihydonaphthalene (150)
triene 139 (160 mg, 0.754 mmol) and methyl iodide (0.24 mL, 3.95 mmol) were added to a suspension of NaH (60 mg, 60% suspension in mineral oil, 1.58 mmol) in THF (20 mL) at rt. The solution stirred at rt for 16 h. Diluted the reaction with H₂O and the aqueous phase was extracted with Et₂O (3x). The combined Et₂O extracts were washed with H₂O (3x), brine, dried and concentrated. Flash chromatography (pet ether/Et₂O, 19:1) afforded methyl ether 150 as a colourless oil (155 mg, 87%).

¹H NMR (300 MHz, CDCl₃) δ 7.14 (s, 4H), 6.70 (ddd, J = 17.9, 11.4, 0.9 Hz, 1H), 6.41 (s, 1H), 5.98 (td, J = 5.7, 1.5 Hz, 1H), 5.39 (d, J = 17.8 Hz, 1H), 5.10 (dt, J = 11.2, 1.5 Hz, 1H), 2.79 (t, J = 6.7 Hz, 2H), 2.42-2.35 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 136.4, 135.1, 133.9, 133.4, 130.3, 130.2, 127.9, 127.5, 126.8, 124.7, 115.0, 74.4, 58.4, 28.3, 23.6; IR (neat) ν = 3161, 2936, 2865, 2814, 1468 cm⁻¹; MS (EI) m/z (relative intensity) 226 (M⁺, 56), 196 (38), 181 (100), 165 (75), 141 (40), 115 (41); HRMS (EI) m/z calcd for C₁₆H₁₈O (M⁺) 226.13577, found 226.1394.

3-(Methoxymethyl)-1,9,10,10a-tetrahydrophenanthrene (151)

Methyl ether 150 (110 mg, 0.49 mmol) was dissolved in toluene (20 mL) and the solution refluxed for 16 h. Toluene was removed in vacuo and flash chromatography (pet ether/Et₂O, 29:1) afforded cyclohexadiene 151 as a yellow oil (83 mg, 76%).

¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, J = 9.0 Hz, 1H), 7.20-7.10 (m, 3H), 6.65 (d, J = 2.2 Hz, 1H), 5.86-5.90 (m, 1H), 3.99 (q, J = 11.5 Hz, 2H), 3.34 (s, 3H), 2.86-2.77 (m, 2H), 2.68-2.54 (m, 1H), 2.31 (dt, J = 16.8, 6.4 Hz, 1H), 2.11-1.98 (m, 2H), 1.58-1.45 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 138.3, 137.0, 134.8, 133.6, 129.5, 127.4, 126.5, 125.1, 123.7, 117.6, 75.4, 58.1, 36.5, 31.4, 31.0, 30.3; IR (neat) ν = 3155, 2936, 1803,
1377 cm\(^{-1}\); MS (EI) \(m/z\) (relative intensity) 224 (M\(^+\), 75), 193 (65), 179 (100), 165 (54), 152 (23); HRMS (EI) \(m/z\) calcd for C\(_{16}\)H\(_{18}\)O (M\(^+\)) 226.1357, found 226.1352.

**9,10-Dihydrophenanthrene-3-carbaldehyde (138)**

Manganese (II) oxide (115 mg, 1.33 mmol) was added to a solution of 151 (30 mg, 0.133 mmol) in toluene (5 mL) at rt. The mixture stirred at refluxed for 16 h. The mixture was filtered through a pad of silica gel washing with CH\(_2\)Cl\(_2\). The filtrate was concentrated. Chromatography (pet ether/Et\(_2\)O, 19:1) afforded aldehyde 138 as a colourless oil (22 mg, 80%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 10.01 (s, 1H), 8.23 (d, \(J = 1.5\) Hz, 1H), 7.83 (d, \(J = 7.5\) Hz, 1H), 7.72 (dd, \(J = 7.6, 1.6\) Hz, 1H), 7.38 (d, \(J = 7.6\) Hz, 1H), 7.34 (dt, \(J = 7.3, 1.8\) Hz, 1H), 7.28-7.25 (m, 2H), 2.96-2.87 (m, 4H), \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 192.0, 144.4, 139.8, 137.0, 135.5, 135.3, 133.1, 128.8, 128.7, 128.1, 127.1, 124.7, 123.8, 29.3, 28.3; IR (neat) \(\nu\) = 2930, 2835, 1698 cm\(^{-1}\); MS (EI) \(m/z\) (relative intensity) 208 (M\(^+\), 100), 179 (70), 162 (8), 89 (10); HRMS (EI) \(m/z\) calcd for C\(_{15}\)H\(_{12}\)O (M\(^+\)) 226.0888, found 208.0887.
Appendix I
13C with proton decoupling

Current Data Parameters
NAME NW2-112
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date 20041023
Time 19:07
INSTRO a3300
RMSE 5 mm GIP 1/1
RUPROG 200p39
TD 32768
SOLVENT CDCl3
NS 365
DS 0
DM 17065.611 Hz
FDMES 0.548877 Hz
AG 0.9110004 sec
DG 36.49 Hz
DM 27.892 usec
de 6.08 usec
Fe 300.0 K
D1 1.00000000 sec
d12 0.03000000 sec
d12 0.00002000 sec

----------- CHANNEL f1 -----------
NUC1 13C
P1 5.00 usec
P1 5.00 dB
SF01 75.4758653 MHz

----------- CHANNEL f2 -----------
CP/PPAR0 3111165
NUC2 1H
CP/PPAR0 70.00 usec
P2 3.00 dB
P12 13.48 dB
P13 15.63 dB
SF02 300.1241860 MHz

F2 - Processing parameters
SI 155536
SF 75.4777590 MHz
WNC 20
SSB 0
LB 1.00 Hz
GB 0
pc 1.40

1D NMR plot parameters
CX 20.60 cm
cy 12.50 cm
F1P 160.000 ppm
F1 12074.83 Hz
F2P 10.000 ppm
F2 754.66 Hz
PPM/cm 7.500000 ppm/cm
Hz/cm 568.00787 Hz/cm
Current Data Parameters
NAME: NNO2-130
EXPND: 1
PROCEQ: 1

F2 - Acquisition Parameters
Date: 20041201
Time: 17:45
INSTRUM: ev300
PRBHRD: 5 mm GNP 1H/1
PULPROG: zg30
tD: 30720
SOLVENT: CDCl3
NS: 16
gs: 0
SWH: 5081.301 Hz
FIDRES: 0.165407 Hz
PD: 3.0228990 sec
TD: 405.4
DD: 988.400 usec
TE: 6.00 usec
D1: 300.0 K
D2: 1.00000000 sec

************** CHANNEL f1 **************
NUC1: 1H
P1: 10.50 usec
PL1: -3.00 dB
SF01: 300.1319477 MHz

F2 - Processing parameters
SI: 65536
SF: 300.1300000 MHz
MDW: EN
SSS: 0
LB: 0.10 Hz
DG: 0
PC: 1.00

10 NMR plot parameters
CX: 20.00 cm
cy: 3.00 cm
F1P: 10000 ppm
F1: 3001.30 Hz
F2P: 0.000 ppm
F2: 0.00 Hz
APPMCM: 0.50000 ppm/cm
HZCM: 150.06500 Hz/cm
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: File: PROTON

Pulse Sequence: gCOSY
Solvent: CDC13
Temp. 298.15 K
INOVA-500 "inova500"

Relax. delay 1.060 sec
Acq. time 0.150 sec
Width 3417.5 Hz
2D Width 3417.5 Hz
Single scan
256 increments
OBSERVE H1, 500.1739577 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sg. sine bell 0.037 sec
FT size 1024 x 1024
Total time 5 min, 25 sec
1H NMR

Current Data Parameters
NAME      NMO2-115-500
EXPNO     1
PROONO    1

F2 - Acquisition Parameters
Date      2004/01/29
TIME      13:18
INSTRUM   AV500HD
FREQBDY   5 mm T60 85/1H
PULPROG   zg30
TD         99936
SOLVENT   Acetone
NS         1
DS         0
SWM        7440.476 Hz
FI0RES     0.113033 Hz
AQ         4.4040894 sec
RG         203.0
DEW        0.082000 usec
DE          6.00 usec
TE          300.0 K
DI         0.01000000 sec

========== CHANNEL ft ==========
NUC1       1H
F1         14.00 usec
PL1        0.00 dd
SF01       500.1327766 MHz

F2 - Processing parameters
S1         59536
SF         500.1300049 MHz
WDW        EM
SSB        0
LB          0.00 Hz
GB          0
PC          1.00

1D NMR plot parameters
CX         20.00 cm
CY         3.00 cm
F1P        10.000 ppm
F1         5001.30 Hz
F2P        0.000 ppm
F2          0.00 Hz
PPMCM      0.50000 ppm/cm
HzCM        250.06500 Hz/cm
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmsl/vnmrsys/data
Sample directory:

Pulse Sequence: NOESY
Solvent: CDC13
Temp. 26.6 C / 293.1 K
File: NNnougan-ncsly
INOVA-300 "INOVA300"

Relax. delay 1.000 sec
Mixing 2.000 sec
Acq. time 0.137 sec
Width 3732.9 Hz
90 Width 3732.9 Hz
16 repetitions
2 x 150 increments
OBSERVE 1H, 590.1739577 MHz
DATA PROCESSING
Gauss apodization 0.063 sec
F1 DATA PROCESSING
Gauss apodization 0.079 sec
FT size 2048 x 2048
Total time 5 hr, 23 min, 53 sec
13C with proton decoupling

![Carbon-13 NMR spectrum with proton decoupling](image)

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Current Data Parameters
- **NAME**: NMR
- **Experiment**: 0
- **PROCNO**: 1

**F2 - Acquisition Parameters**
- **Gate**: 2048
- **Time**: 17.58
- **INSTN**: 300
- **PROBID**: 5 mm, GMR, 1H/2
- **PULPPROG**: zgpp3b
- **TD**: 32768
- **SOLVENT**: CDCl3
- **MS**: 0
- **WS**: 0
- **SNHR**: 17885.61 Hz
- **FIDRES**: 0.548977 Hz
- **AG**: 0.8190004 sec
- **AG**: 6.61 Hz
- **DW**: 27.800 us
- **DE**: 6.300 us
- **TE**: 300.0 K
- **Di**: 1.000000000 sec
- **d11**: 0.010000000 sec
- **d12**: 0.000000 sec

**--------- CHANNEL f1 ---------**
- **NUC1**: 13C
- **P1**: 5.00 us
- **PL1**: -6.00 dB
- **SF01**: 75.4752653 MHz

**--------- CHANNEL f2 ---------**
- **CPD**: watt16
- **NUC2**: 1H
- **PCD**: 70.00 usec
- **PL2**: -3.00 dB
- **PL12**: 13.48 dB
- **PL13**: 15.63 dB
- **SF02**: 300.13114860 MHz

**F2 - Processing parameters**
- **SI**: 65536
- **SF**: 75.4677190 MHz
- **KOM**: EN
- **SSG**: 0
- **LB**: 1.00 Hz
- **GW**: 0
- **GC**: 1.40

**1D NMR plot parameters**
- **CX**: 20.00 cm
- **CY**: 8.00 cm
- **F1P**: 180.000 ppm
- **F1**: 12584.19 Hz
- **F2P**: -0.00 ppm
- **F2**: -0.00 Hz
- **PPMCH**: 5.00000 ppm/cm
- **HZoM**: 675.20959 Hz/cm
13C with proton decoupling

Current Data Parameters
NAME AM02-143
EXPRES 2
PRONO 1

F2 - Acquisition Parameters
Date 2004/12/08
Time 13.14
INSTUM av300
NMM 5 mm GP1 1H/1
PULPROG zgqg30
TD 32768
SOLVENT CDCl3
NS 307
DS 0
SWM 17895.61 Hz
FIDRES 0.546877 Hz
AQ 0.5110004 sec
RG 3649.1
Dw 27.000 usec
DE 6.000 usec
TE 300.0 K
D1 1.00000000 sec
D11 0.00000000 sec
D12 0.00002000 sec

------------ CHANNEL f1 --------------
NOC1 13C
P1 5.00 usec
P11 6.00 usec
SF1 75.4752993 MHz

------------ CHANNEL f2 --------------
CPDROG waltle
NOC2 in
PC2 7.06 usec
PL2 13.69 dB
PL12 13.86 dB
PL13 15.63 dB
SF2 300.1314966 MHz

F2 - Processing parameters
SI 65536
SF 75.4579195 MHz

MOD EN
LS 1.00 Hz
LG 0.00 Hz
HF 0.45

1D NMR plot parameters
Cx 20.00 cm
CY 8.00 cm
FP1 150.0000 ppm
F1 11320.16 Hz
FP2 0.003 ppm
F2 0.00 Hz
FPKOM 7.550000 ppm/cm
HZOM 566.007793 Hz/cm
Current Data Parameters
NAME   N(Tosyl)-methyl
EXPNO  1
PROCNO 1

F2 - Acquisition Parameters
Date... 000504.17
Time... 15:02
INSTRUM av300
PRBIRD 5 mm QNP 1H/1
PULPROG zg30
TD... 30720
SOLVENT CDCl3
NS... 16
DS... 0
SW... 5081.301 Hz
FIDRES... 0.105407 Hz
AQ... 3.0283980 sec
DG... 256
DW... 98.400 usec
DE... 6.00 usec
TE... 300.0 K
DT... 1.00000000 sec

CHANNEL f1
NUCI... 1H
PP... 10.50 usec
PL1... -3.00 dB
SF01... 300.1318477 MHz

F2 - Processing parameters
SI... 65536
SF... 300.1300000 MHz
WDW... EM
SSG... 0
LB... 0.10 Hz
GB... 0
PC... 1.00

10 NMR plot parameters
CX... 20.00 cm
CY... 10.00 cm
F1P... 10.000 ppm
F1... 3001.30 Hz
F2P... 0.000 ppm
F2... 0.00 Hz
PP2CM... 0.50000 ppm/cm
H2CM... 150.00500 Hz/cm
13C with proton decoupling

Current Data Parameters
NAME MW22-105
EXPRG 2
ACQDGM 1

F2 - Acquisition Parameters
DATE 2004/01/16
TIME 14:23
INSTMR ABRAMS
PROBCH 5 mm 180 88/1H
USFRES 1000/300
SOV 60/250
SOLVENT DMSO
V5 470
V3 0
V2 3000 0.029 Hz
V1 RES 0.008295 Hz
AG 1.0512244 sec
FG 1654
SH 16.000 usec
SE 22.00 usec
S 500.0 K
ST 1.00000000 sec
SF1 0.00000000 sec
SF2 0.00000000 sec

------- CHANNEL 1 -------
V1C1 13C
V1 8.00 usec
P11 0.20 usec
SF1 125 7762649 MHz

------- CHANNEL 2 -------
DPDTH SQD 16
V2C2 1H
PD1Q2 0.00000000 usec
P2 0.20 usec
P12 1.044 usec
P13 1.00 usec
SF2 500 1500000 MHz

F2 - Processing parameters
SL 50702
ST 125 7762649 MHz
ACQ 20
SSB 0
LB 1.00 Hz
SB 0
PC 1.00

1D NMR plot parameters
EX 10.00 cm
FY 10.00 cm
FP 219.264 ppm
F1 2751.47 Hz
FG 1.0288 ppm
FP -2456.86 Hz
PPM 11 9386 30 ppm
H2CM 1561 66150 Hz/cm
13C with proton decoupling

Current Data Parameters

VNAME: NS2-148-600
EXPNO: 0
PROCNO: 1

- Acquisition Parameters
  DATE: 2005-11-02
  TIME: 17:55
  INSTRUMENT: AVS500D1
  OTHER: 5 mm 160 QC/H
  PULSERQ: 90/19/30
  ID: 050530
  SOLVENT: CDCl3
  NS: 3000
  DW: 0
  SW: 20300.028 Hz
  FIDRES: 0.458122 Hz
  AG: 1.091246 sec
  RG: 2000
  DM: 18.850 usec
  DE: 50.00 usec
  TE: 500.0 K
  DT: 1.000000000 usec
  DT1: 0.000000000 sec
  DT2: 0.000000000 sec

--- CHANNEL 1 ---

CH1 13C
L1 10.00 usec
L2 20.00
SFD1 125.77703843 MHz

--- CHANNEL 2 ---

CPROQ2 waitmil
CH1 60.00 usec
L1 14.94 ms
L2 14.94 ms
SFD2 500.132205 MHz

- Processing parameters
  ST: 300.0
  SF: 125.77703843 Hz
  KOM: 2K
  CSB: 0
  CB: 1.00 Hz
  TC: 1.00

- 1D NMR plot parameters
  D1: 20.00
  C1: 100.00 Hz
  F1: 250.000 ppm
  F11: 70.0 Hz
  F2: -638.70 Hz
  SPWM: 11.000 ppm/cm
  4D1: 128.33326 Hz/cm