Development of the 5-exo-dig/Prins Reaction and
Efforts towards the Total Synthesis of (±)-Magellanine

by

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To Sassy, Piku and Bear
Abstract

Gold catalysis has attracted much attention within the chemical community in recent years, and its importance as a synthetic tool has only started to be uncovered. This thesis describes the development of a gold(I) catalyzed transformation and its application to the synthesis of a structurally unique *Lycopodium* alkaloid, Magellanine. Although there have been a few reports on the synthesis of the magellanane core to date, the approach described herein would represent a new and efficient strategy to construct the angularly fused tetracyclic core. The 5-exo-dig/Prins reaction that would be the key step of the synthesis was first developed and studied on a model substrate, enabling the verification of the hypothesis that this transformation could indeed form the A and B rings of Magellanine and be applied to its synthesis. This reaction formed the tricyclic products in good yields and in good exo:endo ratios.

The synthesis of Magellanine was undertaken, but problems of isomerization prevented the synthesis of the desired 5-exo-dig/Prins substrate, which contained the C and D rings of Magellanine with a *cis* relationship at the ring junction. However, an almost identical substrate, save for a *trans* configuration between the C and D rings instead of the *cis* configuration, was prepared and served in further establishing the applicability of this methodology to the synthesis of Magellanine by successfully undergoing the 5-exo-dig/Prins reaction and generating the tetracyclic products.

Studies of the steps following the key transformation were performed on the model substrate, allowing for the evaluation of these steps prior to their use in the synthesis. The results of the studies indicate a possible need to revisit the order in which the steps should be carried out. Promising solutions to the different obstacle encountered during the work are presented, demonstrating how the synthesis of Magellanine through a route featuring the 5-exo-dig/Prins cyclization is attainable.
Abstrait

Depuis les dernières années, la catalyse à l’or attire une attention considérable au sein de la communauté des chimistes, et on commence à peine à découvrir son importance en tant qu’outil synthétique. Dans le présent mémoire sont présentés le développement d’une transformation catalysée à l’or(I) et son application à la synthèse d’un alcaloïde Lycopodium unique sur le plan structural, soit la magellanine. Quoique quelques rapports sur la synthèse du cœur magellanane aient été produits à ce jour, l’approche décrite aux présentes représenterait une toute nouvelle stratégie efficace pour la construction du cœur tétracyclique comportant une fusion angulaire. La réaction 5-exo-dig/Prins, qui serait la principale étape de la synthèse, a d’abord été développé et mis à l’essai sur un substrat modèle, permettant ainsi la vérification de l’hypothèse selon laquelle cette transformation pourrait faciliter la création des anneaux A et B de la magellanine et être appliquée à sa synthèse. Cette réaction a formé des produits tricycliques en bons rendements tout en affichant de bons ratios exo:endo.

La synthèse de la magellanine a été entreprise, mais certains problèmes d’isomérisation ont nui à la synthèse du substrat 5-exo-dig/Prins recherché, lequel comprenait les anneaux C et D de la magellanine ayant une relation cis à la jonction des anneaux. Cependant, un substrat pratiquement identique, à l’exception d’une configuration trans entre les anneaux C et D à la place de la configuration cis, a été préparé et a servi à établir davantage l’applicabilité de cette méthode à la synthèse de la magellanine, et ce, en subissant la transformation 5-exo-dig/Prins et en produisant les produits tétracycliques.

Des études des étapes suivant la transformation principale ont été menées sur le substrat modèle, ce qui a permis l’évaluation de ces étapes avant de les utiliser dans la synthèse. Selon les résultats des études, il sera peut-être nécessaire d’examiner de nouveau l’ordre selon lequel il faudrait exécuter les étapes. Des solutions prometteuses aux différents obstacles rencontrés pendant les travaux sont présentées, démontrant la façon dont il est possible d’entreprendre la synthèse de la magellanine par la cyclisation 5-exo-dig/Prins.
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Oh, and there was a guy...
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1. Introduction

Magellanine and Related Alkaloids

Synthetic organic chemists have found attractive and structurally diverse targets in the alkaloids from the club mosses of the genus *Lycopodium*. These compounds possess polycyclic frameworks decorated with various functional groups. Magellanine (1.1), Magellaninone (1.2) and Paniculatine (1.3) are three Lycopodium alkaloids of the Fawcettimine class which were isolated from the species *Lycopodium paniculatum*¹ and *Lycopodium magellanicum*² by Castillo and coworkers in the mid nineteen-seventies. These alkaloids possess an unusual, angularly fused 6-5-5-6 tetracyclic core and 5 or 6 contiguous stereocentres, one of which is a quaternary carbon centre. Magellanine and Magellaninone differ only in the oxidation state at the C5 position. The compact arrangement and uniqueness of the magellanane skeleton has made these alkaloids an attractive and challenging target for synthetic organic chemists. Several creative and distinct strategies have been used to reach this goal.

*Figure 1.1 Structure of Magellanine, Magellaninone and Paniculatine*

Overman *et al.* first reported an elegant enantioselective total synthesis of Magellanine and Magellaninone in 1993.³ Their strategy was centred around a Prins-Pinacol cyclization (Scheme 1.1). When subjected to Lewis-acidic conditions, dienyl acetal 1.4 underwent Prins cyclization from the convex face of the fused biscyclopentene followed by Pinacol rearrangement to tetracycle 1.6. This paramount step sets the quaternary carbon centre with the desired stereochemistry and completes the magellanane skeleton. In the same year, a racemic synthesis of these two alkaloids was completed by the group of Paquette⁴ through a three-fold annulation of cyclopentenone, which included a Michael-Michael addition for the formation of the A ring (Scheme 1.2).
Scheme 1.1 Key Prins-Pinacol rearrangement of Overman’s approach

Scheme 1.2 Paquette’s consecutive Michael additions

Liao and Yen developed a concise racemic synthesis of Magellanine\(^5\) with a prominent Diels-Alder of masked \(\sigma\)-benzoquinone and oxa-di-\(\pi\)-methane rearrangement (Scheme 1.3). The region- and stereochemical control of the Diels-Alder reaction sets four of the six contiguous stereogenic centres at the beginning of the synthesis.

Scheme 1.3 Liao and Yen’s masked Diels-Alder and oxa-di-\(\pi\)-methane rearrangement sequence
Ishizaki, Takahashi and coworkers published their formal synthesis of racemic Magellanine\textsuperscript{6} which made use of a stereoselective Ireland-Claisen rearrangement. It also featured an intramolecular Pauson-Khand reaction of exocyclic enyne \textbf{1.17} for the formation of the B and C rings (Scheme 1.4).

\textit{Scheme 1.4 Ireland-Claisen and Pauson-Khand steps in the Ishizaki and Takahashi synthesis}

Mukai \textit{et al.} reported in 2007 an enantioselective synthesis of Magellanine, Magellaninone and Paniculatine\textsuperscript{7}, also based on some intramolecular Pauson-Khand methodology. In their case, however, the reaction was used in one instance to form the A and B rings and in another to form the C ring and another five membered carbocycle which would subsequently be converted to the piperidine D ring.

There have been other reports in the literature of approaches to the magellanane core\textsuperscript{8, 9}. In the most recent one, presented by Sarpong and Murphy, the core is constructed in an enantioselective fashion with the use of a palladium-mediated direct methoxypyridine functionalization (Scheme 1.6). This example of C-C bond formation to complete the strained tetracyclic core demonstrates well the power of this method. Without the need for prefunctionalization, C-H activation and functionalization has become a highly efficient tool for organic synthesis and has been the focus of many methodologies developed in the last decade.
Scheme 1.5 Two Pauson-Khand reactions of Mukai’s strategy

\[
\text{TBSO}_2 - \text{OTBS} \xrightarrow{\text{Co}_2(\text{CO})_8, \text{Me}_2\text{S}, \text{DCE, 45 °C}} \text{TBSO}_2 - \text{OTBS} \xrightarrow{3 \text{ steps}} \text{SEMO} - \text{TMS}
\]

Scheme 1.6 Sarpong and Murphy’s direct methoxypyridine functionalization

\[
\text{MeO} - \text{OMe} \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol%), DavePhos (30 mol%), K}_2\text{CO}_3, \text{DMF, 100 °C, 20 h}} \text{MeO} - \text{OMe}
\]

From this point onwards, only the term Magellanine will be used and it should be understood that the synthesis of Magellaninone ensues from the synthesis of Magellanine.

Research Goals and Thesis Overview

We have envisioned a unique approach to the synthesis of Magellanine which reflects the recent interest of our group and of the chemical community in gold catalysis. The aim of the research
presented in this thesis was to explore and develop the key transformation which grants us access to the magellanane framework, and to demonstrate the applicability of this methodology in a synthesis. Chapter 2 will begin with an introduction to gold and its reactivity, as well as to the roles that gold catalysis has played in organic synthesis. Relevant precedent will also be covered and this will include some of the developments made to date in this field by our research group. Following this will be an overview of the development of the specific methodology to be applied in the synthesis which was accomplished with the use of a model substrate. Once the accessibility of the Magellanine core was verified, the model substrate was carried on to probe subsequent steps of the synthesis. This will be covered later in chapter 3, following a discussion of the early stages of the synthesis. In the final section, we will take a look at possible future directions of this research, including potential solutions to encountered problems and alternative approaches, as well as general conclusions which are derived from this work.
2. Gold Catalyzed Organic Transformations

Homogeneous Gold Catalysis in Organic Synthesis

Homogeneous gold catalysis has attracted considerable attention from the chemical community in the last decade. For a long time, gold was believed to be more or less unreactive, but recently gold has been shown to be useful in catalyzing an impressive array of chemical transformations. Increasing attention came about when the potential of gold chemistry became apparent, as gold also possesses several advantages over other metals used in organo-catalysis. In comparison to metals like platinum and rhodium, gold is less expensive and has greater availability. Furthermore, reactions catalyzed by gold generally proceed quite rapidly (within a matter of minutes) and under incredibly mild reaction conditions. Typically, these reactions will occur at room temperature, are not sensitive to air and are tolerant of or even benefit from the presence of water or alcohols. Enthusiasm for gold has not only driven chemists to explore its reactivity through methodology studies, but has also led to gold catalysis becoming an important synthetic tool.\textsuperscript{10} Diverse structures can be put together in a more direct fashion, and frameworks which might be difficult to access by other means are now attainable.

The unique reactivity of gold stems from relativistic effects: an expanded 5d orbital and a contracted 6s orbital result in increased \( \pi \)-acidity and increased backdonation capacity.\textsuperscript{11} One of the outcomes, in terms of reactivity, is that gold is a soft Lewis acid with a high affinity for \( \pi \) systems, especially alkynes. Therefore, gold is most commonly used to activate these \( \pi \) systems towards nucleophilic attack. A general mechanism of this fundamental reactivity is shown in Scheme 2.1. The catalyst used is often a cationic gold species, 2.1, where the electrophilicity of the gold is increased. These catalysts, which can be formed prior to the reaction or generated \textit{in situ}, achieve high turnover numbers and are neither water nor air sensitive and are thus easily handled and stored.\textsuperscript{12} Activation of the alkyne is followed by nucleophilic attack in a trans manner. Protodeauration of the vinyl gold intermediate 2.3 provides the addition product 2.4 and regenerates the catalyst. The proton for this step can come from the nucleophile if it was carrying a hydrogen or must be obtained otherwise from an external source.
Among other transformations, heteroatom nucleophiles are often used for the hydroalkoxylation and hydroamination of alkynes or allenes. A recent total synthesis of Bryostatin 16 by the Trost group features a gold catalyzed hydroalkoxylation of an alkyne (Scheme 2.2). This example demonstrates well the impressive tolerance and chemoselectivity of gold. This key transformation is carried out late in the synthesis on a substrate possessing various functionalities, and the alkyne is selectively activated in the presence of several other unsaturated components. The importance of the gold catalyst is further accentuated by the fact that this degree of selectivity could not be achieved with palladium catalysts.

Various carbon nucleophiles have been used to form new carbon-carbon bonds. These are most commonly electron rich arenes for the hydroarylation of alkynes and allenes, olefins in the cycloisomerization of enynes, and enol-type nucleophiles, often seen in carbocyclizations. This
Addition of Carbon Nucleophiles to C-C Triple Bonds for the Generation of Fused Carbocycles

An important class of enol-type carbon nucleophiles are 1,3-dicarbonyl compounds. In 2004, Toste and co-workers reported a gold(I) catalyzed Conia-Ene reaction of β-keto esters with terminal alkynes (Scheme 2.3). They also showed that with the alkyne positioned one carbon closer to the dicarbonyl portion, these compounds underwent a gold(I) catalyzed 5-endo-dig carbocyclization (Scheme 2.4). These transformations were applied to a wide range of substrates and proceeded with low catalyst loadings to give the cyclized products, many of which were fused carbocycle products, in high yields. Cyclization of these kinds of substrates in a 6-exo-dig fashion proved difficult with the standard gold(I) phosphine cationic complexes, but a novel triethynylphosphine-gold complex developed by Sawamura et al. which provided a holey catalytic environment showed markedly higher reactivity in this pathway (Scheme 2.5).

Scheme 2.3 Gold(I) catalyzed Conia-Ene of acetylenic β-keto esters

Scheme 2.4 Gold(I) catalyzed 5-endo-dig carbocyclization of acetylenic dicarbonyl compounds
Silyl enol ethers are frozen enol equivalents which have proven more practical than 1,3-dicarbonyl compounds as the presence of a second carbonyl functionality is not required. In 2006, the Toste group reported the gold(I) catalyzed 5-exo-, 5-endo- and 6-exo-dig cyclizations of silyl enol ether substrates, prepared by 1,4-addition of alkynyl chains onto enones.\textsuperscript{17} In the same report, they further demonstrated the use of a gold(I) catalyzed 5-endo-dig cyclization onto an appended iodoalkyne in the total synthesis of (+)-Lycopladine A. An important feature of this short synthetic sequence is the difference in gold and palladium reactivity which is used to advantage in the consecutive gold and palladium catalyzed steps (Scheme 2.6). The gold performs the 5-endo-dig cyclization and ignores the alkynyl iodide bond of \textbf{2.14} and the vinyl iodide bond of \textbf{2.15}. With the iodide conveniently already in place, oxidative insertion of
palladium proceeds in the following step. The same principle was applied by the Toste group to the
synthesis of (+)-Fawcettimine in the following year (Scheme 2.7). In both syntheses, the quaternary
carbon centre was formed in the gold(I) catalyzed carbocyclization. In 2007, Lee and Lee expanded the
list of examples of [3+2] and [4+2] type products resulting from 1,4-addition and 5-exo- and 6-exo-dig
gold(I) catalyzed processes (Scheme 2.8).

Scheme 2.7 Gold and palladium catalyzed steps in the synthesis of (+)-Fawcettimine

![Scheme 2.7](image)

Scheme 2.8 Examples of 5-exo- and 6-exo-dig cyclizations presented by Lee and Lee

![Scheme 2.8](image)

In the instances shown so far, the number of carbons separating the nucleophilic enol carbon and the
alkyne and substituents on the substrate determined which pathway was followed (5-exo-, 5-endo- or
6-exo-dig). From non-terminal acetylenic β-keto esters, Sawamura and co-workers reported in 2008 the
formation of both 5-exo- and 6-endodig products in varying ratios, but typically favouring the 5-exo-dig
product (Scheme 2.9). Barriault and co-workers showed in 2009 that the 6-endodig product could be
formed exclusively over the 5-exo-dig product in the strained acetylenic silyl enol ether systems which
gave rise to various carbon-bridged medium-sized rings (Scheme 2.10). These mild reaction conditions using phosphino gold(I) catalysts are capable of generating bicyclo[n.3.1]alkenones possessing quaternary carbons at the bridge junctions. This highly efficient method of accessing these complex frameworks can be applied to the synthesis of numerous naturally occurring PPAPs (polyprenylated acylphloroglucinols) such as Hyperforin (2.6), Gasrsubellin A, Papuaforin A and Penostatin F. In similar systems, Sawamura’s group showed that gold(I) complexes with their holey triethynylphosphine ligand (shown in Scheme 2.5) gave superior yields of 7-exo-dig cyclization (Scheme 2.11). The products generated with this method, which also proceeds with substrates varying in ring size, can be applied to the synthesis of natural terpenoids like (+)-Sanadaol (2.31), Salvigenolide and Cynaropicrin.

Scheme 2.9 Gold(I) catalyzed formation of 5-exo- and 6-endodig products (see Scheme 2.5 for ligand structure)

Scheme 2.10 Construction of bicyclo[n.3.1]alkenone frameworks

Scheme 2.11 7-exo-dig carbocyclization using Sawamura’s triethynylphosphine-gold complex (ligand structure in Scheme 2.5)
Barriault and co-workers recently reported 5-\textit{exo-dig} and 6-\textit{endo-dig} carbocyclizations for the formation of fused carbocyclic products.\textsuperscript{24} They showed that both the 5-\textit{exo-} and 6-\textit{endo-dig} products can be generated from the same precursor in a selective manner, depending on the gold(I) catalyst used. It was found that steric and electronic factors of the ligands were dictating the regioselectivity of the reaction. The gold(I) complex with the \textit{N}-heterocycliccarbene ligand (L\textsubscript{1}) was shown to favour the 5-\textit{exo-dig} pathway, whereas the cationic complex with the tetramethyl XPhos ligand (L\textsubscript{2}) showed the highest selectivity for the 6-\textit{endo-dig} pathway.

Organic chemists now have a multitude of methodologies at their disposal for the construction of carbocycles with control over the placement of the double bond. The carbocycles attainable using these gold(I) catalyzed processes range in size and can be part of various structures such as fused rings and bridged structures. Some of these methodologies have been shown to proceed in crowded environments and in systems of high complexity, but to date there have been few examples in synthesis demonstrating the power of these transformations.

\textbf{A New Opportunity for Gold(I) Catalysis in Organic Synthesis}

We came across an opportunity for the development of new methodology and a synthetic application of a gold(I) catalyzed transformation while studying the systems presented for the selective 5-\textit{exo-} and 6-\textit{endo-dig} cyclizations. Products of type 2.38 were being observed when substrates possessing an alkene substituent at the alkyne terminus were subjected to the conditions used to generate 5-\textit{exo} products (Scheme 2.13). These were the result of a Prins reaction following the initial 5-\textit{exo-dig} cyclization.
We envisioned that a substrate such as 2.39 could provide access to the magellanane core via gold(I) catalyzed cyclization and subsequent Prins cyclization, hoping that selectivity for the 5-exo-dig pathway could also be achieved in this type of system. From this sequence, we would also be left with fitting synthetic handles to complete the synthesis of Magellanine.

The feasibility of the application of this methodology to the synthesis of Magellanine would first be verified with a model substrate (2.41).
Development of Methodology

The synthesis of model substrate 2.41 began with the ozonation of cyclohexene to the corresponding dialdehyde which underwent piperidine and acetic acid catalyzed condensation to afford the α,β-unsaturated aldehyde 2.42 (Scheme 2.15). A formal 1,4-addition of the malonate chain 2.44 through the use of dimethyl sulfide and the trapping of the enolate with triisopropylsilyl triflate provided the desired model substrate 2.41 in an E:Z ratio of 11:1.

Scheme 2.15 Synthesis of model substrate 2.41

The malonate chain was synthesized by first propargylating diethyl malonate (Scheme 2.16). Careful distillation allowed for removal of excess malonate and provided a mixture composed primarily of the monoalkylated product 2.44 and some dialkylated malonate. The mixture was then subjected to the Sonogashira reaction conditions with an excess of reagents.

Scheme 2.16 Synthesis of malonate chain 2.44

The reaction conditions developed for the cyclization of substrate 2.35 consisted in the addition of the gold(I) catalyst to the starting material in acetone and stirring at room temperature for 5 minutes. We subjected 2.41-E to these conditions using the NHC catalyst (2.45) which favoured the exo pathway in
the 2.35 system and also various phosphino gold catalysts in order to evaluate the selectivity in this system (Figure 2.2). The cationic complexes presented in Figure 2.2 can easily be obtained by mixing the corresponding commercially available gold(I) chlorides with the appropriate silver salt in acetonitrile at room temperature. In all cases, we observed the formation of 3 major products in varying ratios (Table 2.1).

Figure 2.2 Au(I) catalysts

![Catalyst Diagrams]

Table 2.1 Cyclization of 2.41-E with various gold(I) catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>5-exo (2.49, 2.50)</th>
<th>6-endo (2.51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHC (2.45)</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>JohnPhos (2.46)</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>XPhos (2.47)</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeXPhos (2.48)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture.

<sup>b</sup> Incomplete conversion after standard reaction time of 5 minutes, ratio of starting material:exo:endo is 15:3:1.

Incomplete conversion after overnight reaction, ratio of starting material:exo:endo is 5:5:1.
Two of the products formed (2.49, 2.50) are the result of the 5-exo-dig cyclization followed by the Prins cyclization. The proposed mechanism for their formation is the stepwise process shown in Scheme 2.17. The alkyne undergoes nucleophilic attack from the silyl enol ether upon activation by the gold(I) catalyst. The resulting oxonium is attacked by the double bond in a Prins fashion, generating carbocationic intermediate 2.54. This intermediate can undergo elimination and protodeauration to give 2.50. Intermediate 2.54 can also isomerize to carbocationic intermediate 2.55, which can eliminate and protodeaurate to product 2.49. Product 2.51 is the result of the 6-endo-dig cyclization followed by the Prins cyclization, elimination and protodeauration (Scheme 2.18). It can be said that both the initial cyclization and the Prins reaction readily happen for both pathways, as products resulting from hydrolysis of the silyl enol ether and from only 5-exo-dig or 6-endo-dig cyclization (and hydrolysis of the oxonium upon work-up) were not observed. Suppression of the second cyclization and isolation of the aldehyde occurred with a substrate possessing large steric bulk on the alkene, a result which supports the proposed two-step mechanism. This substrate will be presented in the scope section of the document. Echavarren and co-workers reported an analogous intramolecular [4+2] of arylalkynes or 1,3-enynes with alkenes.25 Through mechanistic and computational studies they determined that a stepwise attack on the alkyne followed by a Friedel-Crafts-type reaction was taking place (Scheme 2.18). They also proposed the formation of a gold carbene from the initial attack on the alkyne, prior to stabilized carbocation formation and attack from the aromatic ring. The formation of a gold carbene has not been determined in our case. Products resulting from the hydration of the alkyne, a common side reaction in gold catalysis especially with esters in proximity to the alkyne, were not observed either.

The 2.41-E system clearly displays a preference for the 5-exo-dig pathway: the use of the NHC catalyst 2.45 resulted in mostly 5-exo-dig products as was expected; however, the phosphine catalysts also favoured 5-exo-dig products. These phosphine catalysts exhibited a preference for the 6-endo-dig pathway in the 2.35 systems, albeit MeXPhos (2.48), which had given the highest 6-endo-dig ratio for those systems, gave the lowest exo:endo ratio in the case of substrate 2.14-E.

For all entries presented in Table 2.1, a new bottle of acetone was used and the starting material underwent complete conversion in under 5 minutes except in the case of MeXPhos (2.48). When an older bottle of acetone with a slightly elevated water content was used, reactions with the XPhos (2.47) and MeXPhos (2.48) catalysts progressed, however at a very decreased rate, resulting in the incomplete conversion of the starting material even after extensive periods of time (over 1 week). We decided to
Scheme 2.17 Proposed mechanism for the 5-exo-dig/Prins cyclization

Scheme 2.18 Proposed mechanism for the 6-endo-dig/Prins cyclization
continue our studies with the NHC (2.45) and JohnPhos (2.46) catalysts. These catalysts showed the highest exo selectivities and displayed favourable reaction conditions, as reaction times with these catalysts did not suffer from the presence of water. In fact, the use of distilled acetone or the addition of 5 equivalents of water did not have a significant impact on product ratios. The addition of large amounts of water (ratios of acetone:water up to 10:1) resulted in an increase in the exo:endo product ratio, but these values were no greater than those offered by running the reaction in toluene (toluene was found to be the best solvent of the solvent screen, results are presented at a later point). The addition of such amounts of water to toluene also resulted in increased exo selectivity, but this was countered by the incomplete conversion of the starting material after prolonged reaction times. We still observed greater exo selectivity in toluene with smaller amounts of water present, and under very dry reaction conditions, exo:endo ratios dropped to 5:1 with the NHC catalyst (2.45). In general, reactions run in toluene showed a high sensitivity to the amount of water present, especially with the NHC catalyst (2.45). We know that the amount of water present in the reaction can potentially have a large impact on the reaction: an external source of proton is necessary for protodeauration, and we have seen in other systems that too much water can suppress the Prins reaction. Determination of the optimal amount of water was not pursued in this case in the interest of time and due to the relatively small gain, as the undesired endo product is already formed in minimal amounts and the Prins reaction readily happens.

Substrate 2.41-Z reacts at a much slower rate under these conditions and undergoes virtually no conversion. There was no detectable conversion of the Z isomer after 24 hours and minimal traces of
product by $^1$H NMR after 6 days. We did observe the reaction of the $Z$ isomer of \textbf{2.41} with NHC (\textbf{2.45}) in wet dichloromethane overnight to give primarily a product which resembles the products obtained from \textbf{2.41-E}, but its structure was not determined. Isomerization of the $Z$ isomer to the $E$ isomer using heat or acid was unsuccessful, and thus, in a synthetic context, once the mixture is subjected to the reaction conditions, the unreacted $Z$ isomer is removed at a later step.

We proceeded with a solvent screen with the NHC (\textbf{2.45}) and JohnPhos (\textbf{2.46}) catalysts (Table 2.2). Most reactions proceeded in short periods of time (minutes, hours in methanol and benzene), however reactions in acetonitrile and hexanes took several days. This is believed to be the result of poor solubility of the catalyst in these solvents. A sample of known composition of \textbf{2.49}, \textbf{2.50} and \textbf{2.51} was subjected to the reaction conditions in hexanes to verify that the elevated \textit{exo:endo} ratio was not a result of decomposition of the \textit{endo} product, and it was found that there was no decomposition in the same amount of time that the original experiment was run. From the reactions usually complete in shorter periods of time, we observed that product ratios did not change whether the reaction was stopped shortly after completion or several hours or even days after completion. In accordance with this, the ratios do not change when resubmitting a crude mixture to the reaction conditions. Stirring overnight in chloroform or with silica gel also has no effect on the product ratios.

The \textit{exo} products are still favoured in all cases and we were encouraged to see that the selectivity for these could be increased. With both NHC (\textbf{2.45}) and JohnPhos (\textbf{2.46}), we observed good \textit{exo:endo} ratio in toluene and we also observed good ratios in methanol using JohnPhos (\textbf{2.46}). Toluene seemed to be the best choice since the reaction is complete in under 5 minutes, whereas in methanol the reaction takes a few hours. It is also interesting to note the decreased selectivity for the \textit{exo} products in the chlorinated solvents for NHC (\textbf{2.45}) as well as JohnPhos (\textbf{2.46}). With reaction conditions which were repeated, a slight variation in the ratios of \textbf{2.49} to \textbf{2.50} could be observed; however, their sum and therefore the ratio of \textit{exo} to \textit{endo} products remained the same. The cause for these observations was not further investigated since both \textit{exo} products, as will be discussed later in the document, can be used in the synthesis. Lowering or raising of the temperatures at which reactions were run had little to no impact on product ratios. Cooling dramatically slowed reaction rates and it seems that the majority of conversion took place upon warming to room temperature for both NHC (\textbf{2.45}) and JohnPhos (\textbf{2.46}) in acetone. Heating (50 °C in toluene) prior to the addition of the NHC catalyst (\textbf{2.45}) had no effect on product ratios.
Table 2.2 Solvent screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>5-exo (2.49, 2.50)</th>
<th>6-endo (2.51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHC (2.45)</td>
<td>Acetone</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>NHC (2.45)</td>
<td>Toluene</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>NHC (2.45)</td>
<td>CH$_2$Cl$_2$</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>NHC (2.45)</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>NHC (2.45)</td>
<td>MeOH</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>NHC (2.45)</td>
<td>EtOAc</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>NHC (2.45)</td>
<td>PhH</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>NHC (2.45)</td>
<td>MeCN</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>NHC (2.45)</td>
<td>Hexanes</td>
<td>&gt;20</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>JohnPhos (2.46)</td>
<td>Acetone</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>JohnPhos (2.46)</td>
<td>Toluene</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>JohnPhos (2.46)</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>JohnPhos (2.46)</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>JohnPhos (2.46)</td>
<td>MeOH</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>JohnPhos (2.46)</td>
<td>PhH</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>JohnPhos (2.46)</td>
<td>MeCN</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR of the crude reaction mixture.
Yields were obtained following the solvent screen for the original reaction conditions in acetone and in the solvents which presented the best exo:endo ratios in reasonable reaction times (Table 2.3). Upon completion, the solvent was evaporated and the crude mixture was placed on a column of silica, and fractions containing any of the three major products 2.49, 2.50 and 2.51 were combined to afford the

**Table 2.3 Yields for the 5-exo-dig/Prins cyclization**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Isolated Yield for Mixture (%)</th>
<th>Calculated Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 mol% NHC (2.45), Acetone, rt</td>
<td>92</td>
<td>80, 12</td>
</tr>
<tr>
<td>2</td>
<td>2.5 mol% NHC (2.45), Toluene, rt</td>
<td>95</td>
<td>88, 7</td>
</tr>
<tr>
<td>3</td>
<td>2.5 mol% NHC (2.45), PhH, rt</td>
<td>92</td>
<td>82, 10</td>
</tr>
<tr>
<td>4</td>
<td>2.5 mol% NHC (2.45), MeCN, rt</td>
<td>91</td>
<td>80, 11</td>
</tr>
<tr>
<td>5</td>
<td>2.5 mol% JohnPhos (2.46),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetone, rt</td>
<td>96</td>
<td>80, 16</td>
</tr>
<tr>
<td>6</td>
<td>2.5 mol% JohnPhos (2.46),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toluene, rt</td>
<td>97</td>
<td>90, 7</td>
</tr>
<tr>
<td>7</td>
<td>2.5 mol% JohnPhos (2.46),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PhH, rt</td>
<td>89</td>
<td>83, 6</td>
</tr>
<tr>
<td>8</td>
<td>2.5 mol% JohnPhos (2.46),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MeCN, rt</td>
<td>92</td>
<td>79, 13</td>
</tr>
<tr>
<td>9</td>
<td>2.5 mol% JohnPhos (2.46),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MeOH, rt</td>
<td>84</td>
<td>77, 7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR of the isolated mixture.
isolated mixture. All reactions proceeded in good yields, with NHC (2.45) and JohnPhos (2.46) in toluene showing the best results. The TBS silyl enol ether substrate also cyclized to give the corresponding cyclized products in similar ratios and slightly lower yields (Table 2.4). We believe the low \textit{exo:endo} ratio with the NHC (2.45) catalyst to be a result of dry reaction conditions. The same ratio was obtained for substrate 2.68 under the same dry conditions. No aldehyde products could be detected by crude NMR and the \textit{Z} isomer of the starting material was still present in the crude mixture, as was the case for 2.41-\textit{Z}. The three products obtained were characterized as a mixture of inseparable isomers.

\textbf{Table 2.4 Cyclization of TBS silyl enol ether substrate 2.68-E}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Isolated Yield for Mixture (%)</th>
<th>Calculated Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 mol% NHC (2.45), Toluene, rt</td>
<td>86</td>
<td>72</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>2.5 mol% JohnPhos (2.46), Toluene, rt</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

* Determined by $^1$H NMR of the isolated mixture.

\textbf{Scope}

As a part of methodology studies of the gold(I) catalyzed 5-\textit{exo-dig}/Prins cyclization, we began an evaluation of the reaction scope. We were interested in the difference in reactivity that may arise when the alkene moiety attached to the alkyne is altered, as in substrates 2.73 and 2.74. These were synthesized through a formal 1,4-addition of the alkylated malonate 2.43 onto enal 2.42, followed by
Sonogashira coupling of \(2.72-E\) with vinyl bromide to obtain \(2.73-E\), and β-bromostyrene for \(2.74-E\) (Scheme 2.20).

**Scheme 2.20 Preparation of substrates for scope evaluation**

The use of intermediate \(2.72\) allows for efficient access to many substrates varying in alkyne substitution. Certain complications did arise with this approach; however, these problems can be avoided by the implementation of simple solutions. The first issue is the presence of residual silanol from the addition step during the Sonogashira coupling which significantly decreases the yield of this reaction. The TIPS silanol is fairly difficult to remove by flash chromatography; it was therefore removed by distillation after chromatography of the crude mixture delivered a mixture of desired silyl enol ether \(2.72-E\) with the silanol. The distillation was carried out in a Kugelrohr apparatus, where the sample was heated at 110 °C under vacuum (<1 Torr) for up to 30 minutes. This method consistently reduced the silanol content to minimal amounts, if not completely, with no loss or degradation of the product. Removal of the silanol prior to the coupling resulted in a jump from a 6% yield to a 53% yield in the same set of conditions. The second obstacle was the considerably lower yield of the Sonogashira coupling on the substrate \(2.72\) in comparison with substrate \(2.43\), which was of 53% compared to 89% when using vinyl bromide as the coupling partner. This is a minor issue as it is only relevant to methodology studies and does not have the big impact that it might have if it concerned a step in a synthesis. Nevertheless, the waste of compound \(2.72\) would ideally be kept to a minimum and the same amount of material would produce more substrates and in the end would save on time and costs. The pre-catalyst Pd(\(\eta^3\)-1-PhC\(3\)H\(4\))(\(\eta^5\)-C\(5\)H\(5\)),
PhC₃H₄)(η⁵-C₅H₅) (2.75, Figure 2.3), reported by Baird and co-workers, is highly active and reacts rapidly with mono- and bidentate tertiary phosphine ligands (triphenyl phosphine in our case) to generate the palladium(0) species which catalyzes cross-coupling reactions.²⁶ Compound 2.75 is readily synthesized and is easy to handle and store. It was found that the use of 2.75 with triphenylphosphine in the Sonogashira couplings raised the yields by at least 20 percentage points in comparison with Pd(PPh₃)₄ and PdCl₂(PPh₃)₂ for reactions with vinyl bromide and by 16 percentage points in comparison with PdCl₂(PPh₃)₂ for reactions with β-bromo styrene.

Figure 2.3 Pd(η³-1-PhC₃H₄)(η⁵-C₅H₅)

Substrates 2.73-E and 2.74-E were subjected to both the NHC (2.45) and JohnPhos (2.46) catalysts in toluene, conditions which had given very similar results for the model substrate 2.41. Silyl enol ether 2.73-E furnished primarily tricyclic product 2.76 upon treatment with the gold(I) catalysts, a result of 5-exo-dig and Prins cyclization (Table 2.5). Product 2.76 was obtained in good yields; however, this result was not reproducible. The starting material was consumed in all cases and, typically, the crude NMR showed product 2.76 with a mixture of other products, which did not include aldehydes, in minor amounts. In some cases, another product formed in appreciable amounts but it was not isolated. We were able to obtain X-ray crystallographic data of 2.76. The crystal structure (Figure 2.4) confirmed that the gold(I) catalyzed transformation, which forms the crucial quaternary carbon centre, affords the correct configuration for the application to the synthesis of Magellanine.

Under the same reaction conditions, substrate 2.74-E gave the 5-exo-dig products 2.77 and 2.78, where 2.77 underwent the Prins cyclization and 2.78 did not (Table 2.6). We assumed that the formation of compound 2.78 in significant amounts with this substrate is due to the steric bulk present at the terminal carbon of the alkene which is not present in substrates 2.41 and 2.73-E. Repeating the experiments also gave the products in varying yields, but again, starting material was consumed in all cases. JohnPhos (2.46) generally gave 2.77 in higher yields and produced much less of the aldehyde 2.78. The cause for the inconsistencies in these reactions has not been determined and requires further
investigation. One possibility is the presence of residual metals in the starting material from the previous Sonogashira coupling, another is the amount of water present; we saw with the model substrate 2.41-E that for reactions run in toluene, small variations in water content affected the ratio of products obtained.

Table 2.5 Gold(I)catalyzed reaction of 2.73-E

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au(I) catalyst</th>
<th>Yield (2.76, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHC (2.45)</td>
<td>52-80</td>
</tr>
<tr>
<td>2</td>
<td>JohnPhos (2.46)</td>
<td>62-73</td>
</tr>
</tbody>
</table>

Table 2.6 Gold(I) catalyzed reaction of 2.74-E

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au(I) catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHC (2.45)</td>
<td>70-73</td>
</tr>
<tr>
<td>2</td>
<td>JohnPhos (2.46)</td>
<td>70-94</td>
</tr>
</tbody>
</table>
Figure 2.4 Crystal structure of 2.76
3. Progress Towards the Total Synthesis of Magellanine

Retrosynthetic Analysis

As previously mentioned, we envisioned in our route key intermediate 3.5 to undergo the 5-exo-dig/Prins cyclization, completing the Magellanine skeleton. The steps following the central transformation would involve removal of the silyl group, oxidation, and isomerization and hydrogenation of the appropriate double bonds. The final sequence to reach our target would require conversion of the ester groups to the alcohol, and deprotection and methylation of the nitrogen. As for the synthesis of compound 3.5, we would perform the formal 1,4-addition of malonate chain 2.44 onto the α,β-unsaturated aldehyde 3.4. In order to access 3.4, we decided that we would utilize a diastereoselective intramolecular Diels-Alder catalyzed by indium(III) triflate developed by Taguchi et al. This route was attractive because the necessary cis configuration of the rings would be established exclusively. Following the reduction of the lactam 3.3 to a secondary amine and protection, we anticipated that, similarly to the model substrate, oxidative cleavage of the double bond and aldol condensation would afford 3.4. A common strategy to reach the Diels-Alder precursor 3.2 is through the condensation of acryloyl chloride with hexadienyl amine 3.1, which itself is derived from ethyl sorbate.

Scheme 3.1 Retrosynthetic analysis
Accessing the 5-exo-dig/Prins precursor

The synthesis of Magellanine via the proposed Diels-Alder route first required the synthesis of the Diels-Alder substrate (Scheme 3.2). It began with the deconjugation of commercially available ethyl sorbate to give ester \(3.8\), which is subsequently reduced. The resulting alcohol \(3.9\) is tosylated and converted to azide \(3.11\) by nucleophilic displacement using sodium azide. This azide is then reduced to afford hexadienyl amine \(3.1\). The four steps prior to the reduction of the azide were carried out in succession without purification. Amine \(3.1\) was purified by careful distillation and was then condensed with acryloyl chloride, which itself was obtained by refluxing acrylic acid and thionyl chloride overnight and distilling the crude mixture.

Scheme 3.2 Synthesis of the intramolecular Diels-Alder precursor

With amide \(3.2\) in hand, we then proceeded with the intramolecular Diels-Alder reaction. Treating \(3.2\) with indium(III) triflate in water and isopropanol at 50 °C overnight yielded solely the endo product in a 71% yield. Attempts at scaling up this reaction to greater than 2 g of starting amide \(3.2\) were unsuccessful and resulted in significantly decreased yields. The lactam obtained from the Diels-Alder reaction was reduced to the corresponding amine which was then tosylated to give intermediate \(3.13\) (Scheme 3.3).

From this point, we intended to reach enal \(3.15\) via the same steps as those used to access the model substrate \(2.41\) (Scheme 3.4). Ozonolysis of \(3.13\) provided the desired dialdehyde product as a mixture. Seeing as this compound was unstable to purification, we looked to obtain this product by other means. We were enthusiastic to see that the Lemieux-Johnson conditions afforded dialdehyde \(3.14\) cleanly and
in good to excellent yields. Always present was a minimal amount of the *trans* isomer, in a *cis* to *trans* ratio ranging from 7:1 to 14:1. The first attempt at the aldol condensation was with catalytic piperidine and acetic acid in refluxing benzene with a Dean-Stark. These conditions resulted only in condensation to the product whose rings are fused in a *trans* configuration. NOE experiments showed no correlation between the protons at the ring junctions. Not wanting to rely on the absence of a signal, the configuration of the product was verified by isomerizing *cis* dialdehyde 3.14 under mildly basic conditions for several days, and then submitting the mixture, composed of the *trans* isomer primarily and some remaining *cis* isomer, to aldol condensation conditions (Scheme 3.5). The major product obtained from this sequence was indeed enal 3.16. This also confirmed that the *trans* product 3.16 was not the consequence of a *trans* dialdehyde starting material but that the isomerization was occurring under the reaction conditions.

**Scheme 3.4 Lemieux-Johnson and aldol condensation**

**Scheme 3.5 Isomerization of dialdehyde 3.14 and aldol condensation**
Dialdehyde 3.14 was subjected to several other aldol condensation or addition conditions. These include condensation conditions reported by Parsons and coworkers in their work on structures of the Maytansinoids (Table 3.1, entry 1)\(^{28}\), and by Corey and coworkers as part of their synthetic sequence to Gibberillic acid (Table 3.1, entry 2)\(^{29}\). In both cases, the formation of a single enal product was achieved from the dialdehyde precursor. These dialdehydes resembled ours in that they were derived from a cyclohexene structure and bore a stereocentre \(\alpha\) to one of the aldehydes. Although the selective formation of 3.19 and 3.21 may have been a result of the system’s bias, Corey and Snyder showed that a system’s bias could be overcome with the right set of conditions, as exemplified by the regioselective aldol condensation of dialdehyde 3.22 to either the 6-5 fused ring structure 3.23 or 3.24.\(^{30}\) Therefore, the conditions showing the best selectivity (Table 3.1, entries 3 and 4) as well as some showing moderate selectivity (Table 3.1, entries 5 and 6) for either regioisomer were also tried. Under all of these conditions, however, only the enal of \(\text{trans}\) configuration 3.16, complex mixtures or degradation were observed. Although products 3.19 and 3.21 possessed a 6-5 fused ring structure, the stereocentres \(\alpha\) to their aldehydes in their dialdehyde precursors were not at the ring junction as it was in our case. We were unsuccessful in our attempts at obtaining the desired product 3.15 using other Lewis acid-weak base conditions, such as \(\text{Bu}_2\text{BOTf}\) with DIPEA (Table 3.1, entry 7), and the mild conditions developed for Horner-Wadsworth-Emmons reactions of base-sensitive aldehydes and phosphonates (Table 3.1, entry 8).\(^{31}\) We had hoped that under Mukaiyama aldol conditions (Table 3.1, entry 9), we would have been able to form the desired enolate selectively, however we again primarily obtained the \(\text{trans}\) enal 3.16. The addition of a drying agent (\(\text{MgSO}_4\)) to reactions which did not call for a drying agent did not have a significant impact on the outcome of the reaction.

\[\text{Scheme 3.6 Aldol condensation in the synthesis of a portion of the Maytansinoids by Parsons}\]
Scheme 3.7 Aldol condensation in Corey’s synthesis of Gibberellic acid

Scheme 3.8 Snyder and Corey’s regioselective aldol condensation of a cholestanone derived dialdehyde

Table 3.1 Aldol conditions
The difficulties encountered with the isomerization from the necessary cis configuration to the trans configuration during the aldol reaction led us to the idea that the trans isomer could perhaps be isomerized to some degree to the cis isomer, by way of kinetic protonation, provided the cis product was favored under kinetic conditions. We first looked at kinetic protonation of the trans enal 3.16 which we already had in hand. We tried the deprotonation of α,β-unsaturated aldehyde 3.16 under kinetic control conditions, using either an excess of LDA or KH at -78 °C, and quenching with a concentrated solution of the hindered alcohol BHT. In both cases, the trans enal 3.16 was recovered, and small amounts of other aldehydes could be observed by crude NMR. When the reactions were quenched with deuterium oxide, new aldehyde peaks were also present, and again in small amounts. However, deuteration at the 4 position was judged to the best of our abilities as not significant; integration of the ring junction hydrogens remained more or less unchanged. These results indicated that under the reaction conditions, the enal was not being deprotonated or did not remain deprotonated. Conditions where the deprotonation of the enal has been confirmed to take place must be established before we can evaluate the success of the kinetic protonation.

Scheme 3.9 Attempts at kinetic protonation of 3.16

We also considered structure 3.27 to be a good candidate for the kinetic protonation because deprotonation at the ring junction would be facilitated by the presence of the amide (Scheme 3.10). This would only be necessary of course if 3.26 also isomerized under the aldol conditions. The resulting compound 3.28 would then be fully reduced and reoxidized to the α,β unsaturated aldehyde. Attempts at obtaining dialdehyde 3.26 from lactam 3.3, however, were unsuccessful. The Lemieux-Johnson conditions seemed to proceed smoothly by TLC, but extraction of the reaction mixture upon completion using various organic solvents yielded little to no product, and the suspected desired product, only observed by TLC, remained in the aqueous phase. Ozonolysis of 3.3 yielded in all attempts a mixture of products, primarily carboxylic acids.
Efforts Towards Intermediate 3.15 by Alternative Approaches

The most direct way to access compound 3.15 from intermediate 3.13 would be by means of oxidative cleavage and aldol condensation, but the ineffectiveness of this route compelled us to look for alternative approaches. We first wanted to explore methods which could bring us to 3.15 from the same intermediate 3.13, whose synthesis had already been established. We came across miscellaneous conditions for the conversion of cyclohexene to cyclopent-1-ene carbaldehyde. These included Cook’s oxidation of cyclohexene with iron phthalocyanine\(^{32}\) and the bismuth sulfate catalyzed oxidation\(^{33}\) reported by Suzuki, Moro-Oka and Ikawa. Under no circumstances was an enal product observed.

We began investigating a route which would take us from intermediate 3.13 to the desired enal 3.15 through the lithium bromide-HMPA mediated ring contraction of an epoxyalcohol. The ring contraction of cis-2,3-epoxycyclohexanols to cyclopentene-1-carboxaldehydes was first reported by Magnusson and Thorén\(^{34}\) (Scheme 3.11), following work done by Rickborn and Gerkin\(^{35}\) on the formation of cyclopentane-carboxaldehydes from epoxycyclohexanes using lithium bromide-HMPA. The rearrangement was proposed to proceed through epoxide ring opening by the bromide, which is facilitated by the HMPA-solubilized lithium ion (Scheme 3.12). Intermediate 3.32 then undergoes the ring contraction with expulsion of the bromide, and upon dehydration, produces enal 3.34 essentially as the sole product. To account for this, they proposed that under the kinetically controlled conditions, where polar effects play a major role, compound 3.31 undergoes nearly exclusive nucleophillic attack at carbon 3. The ring contraction then proceeds from the most stable conformation and where the participating components lie in a \textit{trans} coplanar arrangement. With two of their substrates, they observed the formation of isomeric aldehydes in significant amounts and therefore proposed alternative
mechanisms, involving proton shifts or a concerted ring contraction and epoxide opening, for their formation.

Scheme 3.11 Ring contraction of cis-2,3-epoxycyclohexanols to cyclopentene-1-carboxaldehydes

Bergman and Magnusson later reported that the formation of these α,β-unsaturated aldehydes involved many possible transition states, where conformational changes and proton shifts could take place, and that not only isomeric aldehydes, but also isomeric epoxyalcohols and α,β-unsaturated ketones could be generated. They also showed that with other stereo- and regioisomers of the starting epoxyalcohols, enal products could also be predominantly generated, typically one enal isomer being favoured. It would be very difficult to predict, however, in the case of each epoxyalcohol isomer of a different substrate, which transition state would dominate and therefore which epoxyalcohol isomer could produce the desired enal.

We nevertheless undertook this ring contraction and began preparing some of the epoxyalcohol stereo- and regioisomers. Each isomer could be attained from intermediate 3.13. We considered an allylic oxidation followed by epoxidation to be the best methods for accessing regioisomers 3.35. Our attempts at the allylic oxidation of 3.13 using selenium dioxide were unsuccessful; however, we were able to
install an acetoxy group in the allylic position using palladium acetate and copper acetate in acetic acid under an atmosphere of oxygen and in the presence of hydroquinone (Scheme 3.14). Cleavage of the acetate provided allylic alcohol 3.37. With allylic alcohol 3.37 in hand, we proceeded with the epoxidation of the major isomer using m-CPBA, which afforded epoxyalcohol 3.38, where the epoxide and the alcohol have a cis relationship. We then tried subjecting cis-3.38 to the ring contraction conditions of lithium bromide and HMPA in toluene at reflux. Although the starting material was consumed, we only observed the formation of a mixture of products and the presence of an aldehyde was only detected in traces. The minor isomer of 3.37 was not isolated in sufficient quantities to perform the epoxidation and ring contraction experiment.

**Scheme 3.13 2,3-Epoxyalcohol isomers accessible from 3.13 for the possible ring contraction to enal 3.15**

**Scheme 3.14 Formal allylic oxidation of 3.13 and subsequent epoxidation**

**Scheme 3.15 Attempted ring contraction of epoxyalcohol cis-3.38**
We also tried obtaining the other epoxyalcohol regioisomers 3.36 from intermediate 3.13. Our first inclination for the synthesis of these substrates was to perform an epoxide opening to allylic alcohol 3.40, which could then be epoxidized. Treating 3.13 with m-CPBA afforded epoxide 3.39 in a diastereomeric ratio of 4 to 1. These epoxides were subjected to base induced ring opening conditions like LDA or Et₂NH, n-BuLi and t-BuOK in THF at −78 °C, but in all cases, only starting material was recovered. Upon treatment of 3.39 with Et₂NH and n-BuLi in THF from 0 °C to reflux, we saw complete consumption of the starting material; however, only traces of alkene peaks could be observed by crude NMR. We also tried epoxide opening with selenium followed by oxidation and elimination, but the desired allylic alcohol product was not observed. We looked into alternative options to complete this task, such as a 1,3-transposition, a singlet oxygen ene and a hydroxyiodination followed by an elimination, but we did not have the opportunity to explore these courses.

Scheme 3.16 Epoxidation of 3.13 and attempts at ring opening

Proof of Principle

Although we did not believe the configuration at the ring junction to be the correct one for the synthesis of Magellanine, we performed the formal 1,4-addition on enal 3.16 and obtained the precursor 3.41 (Scheme 3.17). This would enable us to verify the applicability of our methodology to the synthesis on a substrate minimally different from the one required. A single diastereomer of compound 3.41 was isolated. The presence of other diastereomers could not be detected by crude NMR nor could any be isolated. The yield was quite low, most likely due to the greater steric hindrance about the β carbon of the enal in comparison with the model enal 2.42, which would especially have an impact with the large propargylated malonate nucleophile used. This is supported by the recovery of much of the starting material (44%). Submitting 3.41 to the gold(I) catalyzed conditions using JohnPhos (2.46) gave a mixture of 3 products whose alkene region of the proton spectrum closely matched that of the mixture of
products 3.42, 3.43 and 3.44 obtained from the model substrate. Although the endo product 3.44 could be observed by NMR, it was present in a quantity too little to allow for characterization, and therefore only the exo products 3.42 and 3.43 were characterized as an inseparable mixture.

Scheme 3.17 Preparation and cyclization of substrate 3.41

The successful cyclization of substrate 3.41 was encouraging: as with the model substrate 2.41-E, the exo products were favoured and the yield was high. This suggests that the protected piperidine ring poses a minimal influence on the outcome of this reaction and that we can therefore expect similar results when the cis fused substrate 3.5 is attained. We hope that the increased exo selectivity seen with the trans fused substrate 3.41 in comparison with the model substrate will also be present with the cis fused substrate 3.5.
Further Exploration with the Model Substrate

With the model substrate, we began exploring the steps following the key gold(I) catalyzed transformation, which would take us to our final goal of Magellanine. The first step following the cyclization of \(2.41-E\) was the removal of the TIPS group. Treating the mixture of products \(2.49\), \(2.50\) and \(2.51\) to TBAF overnight provided the mixture of alcohols \(3.45\), \(3.46\) and \(3.47\). These were then oxidized to the corresponding ketones using the Dess-Martin periodinane (Scheme 3.18). The use of DMP allows for oxidation and isomerization of \(\text{exo}\) product \(3.49\) to \(3.48\) in one step, whereas two separate steps of oxidation (best accomplished using PCC) and isomerisation using acetic acid must be carried out otherwise. We were unsuccessful in our attempts at isomerizing one of the \(\text{exo}\) isomers to the other prior to the oxidation step.

**Scheme 3.18** Deprotection, oxidation and isomerization of the mixture of tricyclic compounds \(2.49, 2.50\) and \(2.51\)
We were disappointed that the oxidation did not result in the α,β-unsaturated ketone that is present in the final target and that would facilitate selective hydrogenation of the second double bond. The X-ray structure of 2.76 suggests that, in this rigid structure, the ketone would not be in the same plane as the double bonds and, therefore, it would be very difficult to either bring one double bond into conjugation with the ketone while the other was still present or have both double bonds in conjugation with the ketone. We carried out a hydrogenation of 3.48 which we had hoped would give us compound 3.51, where the double bond left behind could be made to slip into conjugation with the ketone. Instead, subjecting 3.48 to hydrogenation conditions using Raney-Nickel gave 3.52 in a 97% yield, as a mixture of diastereomers. No change was observed when the mixture was subjected to conditions which would favour the conjugation of a β,γ-double bond with a ketone.

Scheme 3.19 Hydrogenation of 3.48

We also tried the hydrogenation of the mixture of alcohols 3.45, 3.46 and 3.47 using Pd/C and PtO₂, but only with Raney-Nickel did we observe consumption of both exo isomers (3.45 and 3.46). Unfortunately, these conditions did not result in the reduction of both exo isomers. Hydrogenation of all double bonds would provide us with a single exo structure which could subsequently be taken to the α,β-unsaturated ketone; however, submission of the mixture to Raney-Nickel under hydrogen atmosphere for prolonged periods of time did not result in the hydrogenation of all double bonds. An attempt was also made to isomerize 3.48 using rhodium(III) catalysis. Treating 3.48 with RhCl₃•xH₂O in ethanol at 100 °C in a sealed tube did seem to provide us with 3.53 as one of the major products of a
mixture of products. Further investigation is required to determine the identity of the other products and to find the optimal reaction conditions.

Scheme 3.20 Isomerization of 3.48
Addendum to Chapter 3

Synthesis of the Magellanine core

We were able to obtain a crystal structure of the \textit{exo} isomer 3.56 (Figure 3.1) from the mixture products provided by the gold(I) catalyzed transformation of substrate 3.54 (Scheme 3.21). The structure showed that the configuration between the C and D rings of the Magellanine core and thus the configuration between the rings of enal 3.15 was indeed \textit{cis}, as we desired. All aldol condensation conditions which gave an enal product from dialdehyde 3.14 therefore had produced the \textit{cis} enal 3.15, and not the \textit{trans} enal 3.16, as was previously believed (Scheme 3.22). A product having a \textit{trans} relationship between the 6- and 5-membered rings would be more strained than the corresponding \textit{cis} product, indicating that the

\textit{Figure 3.1 Crystal structure of 3.56}
cis isomer is the thermodynamic product. Although the cis dialdehyde 3.14 was isomerized to the trans dialdehyde trans-3.14, the thermodynamic product, the cis isomer, prevails under the thermodynamic reaction conditions (Scheme 3.23), such as many of the aldol condensation conditions which are presented in Table 3.1. Kinetic conditions also provided the cis enal #, as one would have expected.

Scheme 3.21 Preparation and cyclization of substrate 3.54

Scheme 3.22 Lemieux-Johnson and aldol condensation
Now that the configuration of the enal 3.15 has been confirmed, it is evident why only one diastereomer was obtained from the formal 1,4-addition of the malonate chain 2.44: only one face of the enal 3.15 is accessible to the large nucleophile (Scheme 3.21). With the desired configuration between the C and D rings, we have successfully achieved the construction of the core of Magellanine, with the correct relative configuration (Scheme 3.21). We can conclude that through the use of the intramolecular Diels-Alder approach, the oxidative cleavage of 3.13 and the subsequent aldol condensation represent a viable route for the synthesis of Magellanine.
4. Future Directions and Conclusions

Accessing the 5-\textit{exo-dig}/Prins precursor

Although there are still options to explore for the ring contraction of an epoxialcohol, and the use of a kinetic protonation could be further investigated, we believe at this point that there are alternative routes that should be explored and that show much promise in being able to bring us to the key enal intermediate 3.4. One of these would include the Pauson-Khand reaction of propargyllic and allylic amine 4.2. The resulting $\alpha,\beta$-unsaturated ketone 4.3 would then be converted to enal 3.4 by means of 1,4-addition of a hydride and trapping to form a vinyl triflate, and palladium-catalyzed carbonylation.

\textit{Scheme 4.1 Possible route to enal 3.4 featuring a Pauson-Khand reaction}

Another option would also involve accessing an enal through a vinyl triflate intermediate. The preparation of vinyl triflate 4.6 from starting material 4.5 begins the Overman synthesis of Magellanine (Scheme 4.3). As with 4.4, the vinyl triflate would be converted to the enal 3.4 through palladium-catalyzed carbonylation, and from this point, the synthesis would continue as planned. Reaching structure 4.8 would constitute a formal synthesis, as Yen and Liao took 4.8 to Magellanine via oxidative cleavage of the cyclopentene ring and ring-closing double reductive amination (Scheme 4.4). The advantage with this approach is that, similarly to the Diels-Alder route, the \textit{cis} configuration between the C and D rings is inherent in the starting material and therefore established from the beginning of the synthesis and, in this case, there should not be any opportunity for isomerisation. The cyclopentene ring would be present throughout the synthesis and we would not anticipate this to be problematic for the other steps, including the possible hydroxyl-directed hydrogenation (see next section). If difficulties are encountered, the cyclopentene ring can be converted to a protected piperidine ring earlier in the synthesis, as Overman’s group had done3.
Once we successfully attain substrate 3.4 and apply our methodology to the synthesis of Magellanine, we still need to take the cyclized products to our final goal. Our work done so far on the steps following the gold(I) catalyzed 5-exo-dig/Prins of the model substrate suggests that perhaps the order in which the steps are carried out should be revisited. Although the initial results of the rhodium(III) catalyzed isomerization of 3.48 were promising, we believe that a more efficient strategy would involve conversion of the esters from 4.10 to the alcohol prior to the removal of the TIPS group (Scheme 4.5). This would be followed by a hydroxyl-directed hydrogenation. If the second alkene remained, it could
slip into conjugation with the ketone after removal of the TIPS group and oxidation, or otherwise simply be installed in conjugation with the ketone.

**Scheme 4.5 Alternative route to Magellanine following the S-exo-dig/Prins reaction**

Another Opportunity for the Development and Application of a Gold(I) Catalyzed Transformation

An entirely different approach to Magellanine was also envisioned and would be interesting to carry out. This approach would also feature gold catalysis, only this time in the form of a gold(I) catalyzed Prins/Pinacol cyclization (Scheme 4.6). We anticipate that treating precursor 4.14 with a gold(I) catalyst will result in coordination of the gold(I) species to the allene, followed by nucleophilic attack of the alkene onto the activated allene in a Prins fashion. The resulting intermediate 4.16 would be poised to undergo a Pinacol rearrangement, where the bond aligned periplanar to the empty p orbital would migrate in a 1,2-alkyl shift. Three of the four rings of the Magellanine core would be established from this sequence.
Scheme 4.6 Proposed alternative approach to Magellanine featuring a gold(I) catalyzed Prins/Pinacol cyclization

General Conclusions

In summary, we were successful in achieving the 5-exo-dig/Prins cyclization on the model substrate. The x-ray of compound 2.76 confirmed that the reaction, which forms the crucial quaternary carbon centre, provides us with the correct configuration for the application to the synthesis of Magellanine, as we had anticipated. This reaction also proceeded in good yields, in high exo:endo ratios and under favourable reaction conditions: reactions were run at room temperature and were complete in short periods of time, and precautions to keep air and moisture out were not necessary. Further exploration, with additional varied substrates, is required to complete the evaluation of the scope of the reaction.

We began the synthesis of Magellanine through the diastereoselective intramolecular Diels-Alder route. Unfortunately, complications due to isomerization prevented us from accessing the enal precursor with the correct cis relationship at the ring junction. We therefore did not attain the desired 5-exo-dig/Prins substrate; however, we were able to show that our methodology should be applicable to such a substrate and to the synthesis of Magellanine by the successful preparation and 5-exo-dig/Prins cyclization of substrate 3.41. Although our efforts so far in the Diels-Alder route were not fruitful, there
not only remain avenues to explore in greater depth with this strategy, but we have developed other, very promising approaches to the desired enal intermediate 3.4, and we do not doubt that this goal is attainable.

We have made progress in the steps following the key transformation with the model substrate. This has given us an opportunity to evaluate these steps prior to the synthesis, and the order in which they are carried out. We have determined that this order should be reviewed as other routes may allow us to reach our final goal more efficiently.

In conclusion, the studies presented in this document are strong evidence that the 5-exo-dig/Prins reaction can be applied successfully to the synthesis of Magellanine. Our methodology constitutes a novel and efficient approach to the magellanane core. We have also shown a different approach to Magellanine, one which would allow for the development and study of a different gold(I) catalyzed transformation, a Prins/Pinacol cyclization. Both the Prins/Pinacol and 5-exo-dig/Prins cyclizations would make excellent examples of gold(I) catalysis in organic synthesis, demonstrating well its value as a synthetic tool.

**Claims to Original Research**

1. Development and optimization of the gold(I) catalyzed 5-exo-dig/Prins reaction.
2. Investigation of the gold(I) catalyzed 5-exo-dig/Prins reaction on various cyclopent-1-ene carboxaldehyde silyl enol ether substrates.
3. Investigation into the synthesis of (±)-Magellanine and (±)-Magellaninone using a 5-exo-dig/Prins reaction.
4. Development and proposal of multiple routes to the 5-exo-dig/Prins reaction precursor for the synthesis of (±)-Magellanine and (±)-Magellaninone.
5. Exploration of the transformation of the functionalized core into the natural product.
Experimental

General Experimental

All reactions were carried out under argon atmosphere with glassware flame dried under vacuum unless otherwise indicated. Solvents for reactions were distilled prior to use unless otherwise indicated; dichloromethane, toluene, DMF and TMEDA were distilled over calcium hydride, and THF and diethyl ether were distilled over sodium in the presence of benzophenone. Solvents which were not distilled (benzene, DMSO, acetonitrile, methanol and acetone) were taken from a bottle and were of ACS grade unless otherwise indicated. Reactions were monitored by thin layer chromatography (TLC) using glass or aluminum backed 250 μm ultrapure silica gel TLC plates and visualized using a short wave-length UV lamp and p-anisaldehyde or KMnO₄ stain. Column chromatography was performed with 60 silica gel (230-400 mesh, Merck). Fridge temperature was -4 °C. All ¹H and ¹³C spectra were recorded on either a Bruker Avance 400MHz spectrometer or a Bruker Avance 300MHz spectrometer. Chemical shifts (δ) were reported in ppm relative to solvent residual peak. Spectral features for characterization are reported in the following order for ¹H spectra: chemical shifts (δ, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet); coupling constant (J in Hertz); number of protons. For ¹³C spectra: chemical shifts (δ, ppm); multiplicity (C, CH, CH₂, CH₃). Infrared (IR) spectra were recorded with a Bomen Michaelson 100 Fournier instrument. IR spectra were obtained as a thin film of pure compound on sodium chloride plates. HRMS (EI) spectra were obtained on a Kratos Analytical Concept instrument.

Procedures: Chapter 2

Cyclopent-1-enecarbaldehyde (2.42)

A solution of cyclohexene (2.4 mL, 23.7 mmol) in DCM (15.3 mL) and 15% MeOH (2.7 mL) was ozonized at -78 °C until the solution turned a persistent blue colour. The solution was then degassed with argon and then kept under an argon atmosphere. Dimethyl sulfide (2.37 mL, 32.3 mmol) was added dropwise and the solution was left to stir from -78 °C to 0 °C for 1.5 hours, then at 0 °C for 30 minutes. At this point, the reaction mixture was usually stored in the fridge overnight. The colourless solution was stirred at room temperature for 1 hour before volatiles were carefully evaporated. The residue was dissolved in
benzene (48 mL), and piperidine (0.12 mL, 1.19 mmol) and acetic acid (0.07 mL, 1.19 mmol) were added. The mixture was refluxed with a Dean-Stark until TLC indicated all starting material was consumed (1.5 hours). The resulting orange solution was washed twice with each 2N HCl, sat. aqu. NaHCO₃ and brine. Then 25 mg of hydroquinone were added and most of the benzene was distilled off using a Vigreux column, leaving a dark brown mixture of the desired product **2.42** (1.69 g, 74%) in benzene. Spectral data agree with the literature values.³⁶

**Diethyl 2-(prop-2-ynyl)malonate (2.43)**

Diethyl malonate (30 mL, 0.198 mol) was added slowly to NaH (60% wt in mineral oil, 8.30 g, 0.207 mol) in THF (150 mL) at 0 °C. After stirring for 30 minutes at room temperature, this mixture was added dropwise over 2 hours to a solution of propargyl bromide (80% wt in toluene, 26.4 mL, 0.237 mol) and sodium iodide (29.6 g, 0.198 mol) in THF (160 mL) at room temperature. The milky yellow reaction mixture was left to stir overnight, then was quenched with ammonium chloride and extracted three times with DCM. The combined organic layers were dried with MgSO₄ and concentrated. Fractional distillation (using a Vigreux column) of the crude mixture under reduced pressure (≤2 Torr) provided a mixture composed primarily of the monoalkylated product **2.43** (15.0 g, 38%) and some dialkylated malonate as a colourless oil. Mixtures are inevitable; however, a slow distillation will allow for the complete removal of the excess malonate with minimal loss of product and low dialkylated product content in the desired monoalkylated product fractions. Spectral data are in accordance with values reported in the literature.³⁷

**Tetrakis(triphenylphosphine)palladium(0)**

A flask containing palladium(II) chloride (1.00 g, 5.64 mmol) and triphenylphosphine (7.40 g, 28.2 mmol) in DMSO (70 mL) was heated to 130 °C for 1 hour. The flask was then left to cool to room temperature, stirring vigorously, for 20 minutes. Hydrazine monohydrate (1.10 mL, 22.6 mmol) was added dropwise and the mixture was left to stir slowly at room temperature for 45 minutes, and then put into an ice bath. The mixture was filtered on a coarse fritted funnel and the yellow solid was rinsed with ethanol, then with ether and then dried under vacuum. The yellow powder (5.91 g, 91%) was stored under argon in the fridge.
Diethyl 2-(4-methylpent-4-en-2-ynyl)malonate (2.44)

Propargyl malonate 2.43 (2.31 g, 11.6 mmol, as part of a mixture of diethyl malonate and dialkylated product from the previous step weighing 3.3 g total) was added neat to a solution of Pd(PPh₃)₄ (965 mg, 0.832 mmol) and copper(I) iodide (317 mg, 1.66 mmol) in benzene (167 mL). The solution was then degassed with argon for 10 minutes. 2-bromopropene (4.4 mL, 50.0 mmol) was then added via syringe and the mixture was left to stir for 5 minutes. Diethyl amine was then added dropwise and the dark brown reaction mixture was left to stir at room temperature overnight. The stir bar was removed, silica gel was added directly and the solvent was removed. The dry pack was placed on a column and flashed (3% EtOAc in hexanes) to give 2.44 (2.41 g, 86%) as a yellow oil. Spectral data match values reported in the literature.³⁸

(±)-Diethyl 2-(4-methylpent-4-en-2-ynyl)-2-(2-((triisopropylsilyloxy)methylene)cyclopentyl)malonate (2.41)

A first solution was prepared as follows: To a solution of cyclopent-1-enecarbaldehyde (2.42) (99.7 mg, 1.04 mmol) in THF (5 mL) at -78 °C was added TIPSOTf (0.42 mL, 1.56 mmol). After stirring for 5 minutes, dimethyl sulfide (0.23 mL, 3.12 mmol) was added dropwise. This solution was stirred at -78 °C for 40 minutes, then the second solution was added. This second solution was prepared by adding a solution of 2.44 (396 mg, 1.66 mmol) in THF (1.5 mL) to a suspension of NaH (60% in mineral oil, 84.0 mg, 2.10 mmol) in THF (5 mL) at 0 °C. The second solution was stirred at room temperature for 30 minutes and then added to the first solution at -78 °C, dropwise and along the side of the flask. The reaction mixture was stirred for 1.5 hours, starting from -78 °C and left to warm, then was quenched with sat. aq. NaHCO₃. The mixture was extracted with ether (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (2 % ethyl acetate in hexanes) afforded 2.41 (389 mg, 76%, E:Z 11:1) as a pale yellow oil. The excess of malonate chain 2.44 can be recovered.
(±)-(E)-Diethyl 2-(4-methylpent-4-en-2-ynyl)-2-(2-((triisopropylsilyloxy)methylene)cyclopentyl)malonate (2.41-E)

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.99-1.18 (m, 21H), 1.25 (t, $J=7.1$ Hz, 6H), 1.47-1.63 (m, 2H), 1.82 (dd, $J=1.4$, 1.1 Hz, 3H), 1.94-2.08 (m, 3H), 2.52 (dddd, $J=16.2$, 8.4, 4.8, 1.8 Hz, 1H), 2.88 (d, $J=17.1$ Hz, 1H), 3.06 (d, $J=17.1$ Hz, 1H), 3.42 (m, 1H), 4.09-4.26 (m, 4H), 5.13 (m, 1H), 5.16 (m, 1H), 6.48 (m, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): δ 12.1 (CH), 14.1 (CH$_3$), 14.2 (CH$_3$), 17.9 (CH$_3$), 17.9 (CH$_3$), 23.7 (CH$_3$), 24.0 (CH$_2$), 25.1 (CH$_2$), 27.6 (CH$_2$), 29.8 (CH$_2$), 44.0 (CH), 60.7 (C), 61.3 (CH$_2$), 61.5 (CH$_2$), 84.8 (C), 84.9 (C), 121.1 (CH$_2$), 122.6 (C), 127.0 (C), 135.7 (CH), 170.5 (C), 170.5 (C); IR (neat, cm$^{-1}$): 3101, 2945, 2868, 2226, 1731, 1669, 1268, 1181, 883; HRMS (El) m/z calcld for C$_{28}$H$_{46}$O$_5$Si (M)$^+$ 490.3115, found 490.31041.

(±)-(Z)-Diethyl 2-(4-methylpent-4-en-2-ynyl)-2-(2-((tert-butyldimethylsilyloxy)methylene)cyclopentyl)malonate (2.41-Z)

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.02-1.13 (m, 21H), 1.25 (t, $J=7.17$ Hz, 3H), 1.27 (t, $J=7.17$ Hz, 3H), 1.73-1.89 (m, 4H), 2.23-2.42 (m, 4H), 2.79 (d, $J=17.1$ Hz, 1H), 2.95 (d, $J=17.2$ Hz, 1H), 4.09-4.30 (m, 4H), 5.12 (m, 1H), 5.15 (m, 1H), 5.33 (s, 1H), 5.78 (s, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): δ 13.1 (CH), 14.1 (CH$_3$), 14.2 (CH$_3$), 18.2 (CH$_3$), 18.3 (CH$_3$), 23.6 (CH$_2$), 23.7 (CH$_3$), 24.1 (CH$_2$), 32.1 (CH$_3$), 32.2 (CH$_2$), 61.3 (CH$_2$), 61.4 (CH$_2$), 62.6 (C), 73.7 (CH), 84.2 (C), 85.3 (C), 120.8 (CH$_2$), 127.1 (C), 131.1 (CH), 143.4 (C), 169.0 (C), 169.8 (C); IR (neat, cm$^{-1}$): 2944, 2867, 2230, 1730, 1273, 1190, 884; HRMS (El) m/z calcld for C$_{28}$H$_{46}$O$_5$Si (M)$^+$ 490.3115, found 490.31171.

(±)-Diethyl 2-((tert-butyldimethylsilyloxy)methylene)cyclopentyl)-2-(4-methylpent-4-en-2-ynyl)malonate (2.68)

A first solution was prepared as follows: To a solution of cyclopent-1-enecarbaldehyde (2.42) (300 mg, 3.12 mmol) in THF (18 mL) at -78 °C was added TIPSOTf (1.08 mL, 4.68 mmol). After stirring for 5 minutes, dimethyl sulfide (0.69 mL, 9.36 mmol) was added dropwise. This solution was stirred at -78 °C for 40 minutes, and then the second solution was added. This second solution was prepared by adding a solution of 2.44 (1.12 g, 4.68 mmol) in THF (5 mL) to a suspension of NaH (60% in mineral oil, 250 mg, 6.24 mmol) in THF (12 mL) at 0 °C. The second solution was stirred at room temperature for 30 minutes, and then added to the first solution at -78 °C, dropwise and along the side of the flask. The reaction
mixture was stirred for 1.5 hours, starting from -78 °C and left to warm, then was quenched with sat. aq. NaHCO₃. The mixture was extracted with ether (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (2 % ethyl acetate in hexanes) afforded 2.68 (1.07 g, 76%, E:Z 6:1) as a colourless oil. The excess of malonate chain 2.44 can be recovered.

Major isomer: (±)-(E)-Diethyl 2-((tert-butylidimethylsilyloxy)methylene)cyclopentyl)-2-(4-methylpent-4-en-2-ynyl)malonate (2.68-E)

^1^H NMR (400 MHz, CDCl₃): δ 0.12-0.11 (m, 6H), 0.91-0.92 (m, 9H), 1.23-1.28 (m, 6H), 1.42-1.67 (m, 2H), 1.81-1.84 (m, 3H), 1.93-2.08 (m, 3H), 2.50 (dddd, J=16.0, 8.4, 4.4, 1.8 Hz, 1H), 2.88 (d, J=17.1 Hz, 1H), 3.04 (d, J=17.1 Hz, 1H), 3.39-3.45 (m, 1H), 4.10-4.27 (m, 4H), 5.12-5.14 (m, 1H), 5.17 (s, 1H), 6.36-6.38 (m, 1H); ^1^C NMR (400 MHz, CDCl₃): δ -5.1 (CH₃), -5.1 (CH₃), 14.1 (CH₃), 14.2 (CH₃), 18.4 (C), 23.7 (CH₃), 24.1 (CH₂), 25.1 (CH₂), 25.8 (CH₃), 27.8 (CH₂), 29.7 (CH₂), 44.0 (CH), 60.8 (C), 61.4 (CH₂), 61.5 (CH₂), 84.8 (2xC), 121.1 (CH₂), 123.6 (C), 127.0 (C), 135.3 (CH), 170.5 (C), 170.5 (C); IR (neat, cm⁻¹): 3101, 2957, 2858, 2230, 1734, 1670, 1260; HRMS (EI) m/z calcd for C₂₅H₄₀O₅Si (M)+ 448.2645, found 448.2658.

NHC (2.45)
Silver hexafluoroantimonate(V) (53.3 mg, 0.151 mmol) was placed in a flask in the glovebox. A solution of chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) (93.6 mg, 0.151 mmol) in acetonitrile (2 mL) was added and the mixture was left to stir at room temperature for 2.5 hours before being placed on a pad of silica and rinsed with DCM. The collected washings were concentrated and dried in vacuo to give a greyish white solid (124 mg, 95%). Stored at room temperature. Spectral data agree with literature values.
General procedure for Au(I) catalyzed cyclization reactions

All experiments were performed with glassware which was not flame dried and were not kept under an argon atmosphere. To a solution of the starting material in the appropriate solvent (0.05 M) was added the appropriate catalyst (2.5 mol%). The solution was left to stir at room temperature until judged complete by TLC. The solvent was evaporated and the crude mixture was placed on a silica column. Flash chromatography (3 % ethyl acetate in hexanes) provided the product(s).

Mixture of cyclized products 2.49, 2.50 and 2.51

Obtained as a pale yellow oil.

(±)-(3aR,9R,9’R)-Diethyl 7-methyl-9-(triisopropylsilyloxy)-3,3a,8,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (2.49)

1H NMR (400 MHz, CDCl3): δ 1.08-1.12 (m, 21H), 1.21 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.34-1.46 (m, 2H), 1.51-1.61 (m, 2H), 1.66-1.76 (m, 4H), 1.86-1.95 (m, 1H), 2.14-2.24 (m, 2H), 3.56 (d, J=8.0 Hz, 1H), 4.04-4.30 (m, 5H), 5.29 (s, 1H), 5.94 (s, 1H); 13C NMR (400 MHz, CDCl3): δ 13.1 (CH), 14.2 (CH3), 14.3 (CH3), 18.4 (CH3), 23.3 (CH3), 25.2 (CH2), 29.6 (CH2), 31.5 (CH2), 40.2 (CH2), 48.8 (CH), 61.1 (CH2), 61.5 (CH2), 64.7 (C), 71.5 (C), 73.3 (CH), 118.9 (CH), 119.0 (CH), 140.1 (C), 149.8 (C), 171.2 (C), 171.3 (C); IR (neat, cm⁻¹): 2944, 2867, 1734, 1254; HRMS (EI) m/z calcd for C28H46O5Si (M⁻) 490.3115, found 447.25489 (M - iPr)⁺.

(±)-(3aR,9R,9’R)-Diethyl 7-methylene-9-(triisopropylsilyloxy)-3,3a,5,7,8,9-hexahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (2.50)

1H NMR (400 MHz, CDCl3): δ 1.05-1.22 (m, 29H), 1.54-1.63 (m, 1H), 1.66-1.79 (m, 1H), 1.82-1.90 (m, 1H), 2.17-2.25 (m, 1H), 2.41-2.51 (m, 2H), 2.61 (d, J=14.4 Hz, 1H), 3.20 (dt, J=14.8, 0.9 Hz, 1H), 3.28 (t, J=7.7 Hz, 1H), 4.06-4.27 (m, 5H), 4.72 (d, J=12.0 Hz, 2H), 5.79 (d, J=2.0 Hz, 1H); 13C NMR (400 MHz, CDCl3): δ 13.1 (CH), 14.3 (CH3), 14.3 (CH3), 18.4 (CH3), 18.4 (CH3), 27.7 (CH2), 31.5 (CH2), 34.8 (CH2), 37.8 (CH2), 39.6 (CH2), 51.1 (CH), 58.3 (C), 61.3 (CH2), 61.4 (CH2), 63.0 (C), 74.3 (CH), 110.1 (CH2), 121.2 (CH), 142.7 (C), 147.7 (C), 170.4 (C), 171.5 (C); IR (neat, cm⁻¹): 2944, 2867, 1734, 1254; HRMS (EI) m/z calcd for C28H46O5Si (M⁻) 490.3115, found 447.25568 (M - iPr)⁺.
(±)-(3aR,9R,9'R)-Diethyl 7-methyl-9-(triisopropylsilyloxy)-3,3a,8,9-tetrahydro-1H-cyclopenta[d]indene-4,4(2H)-dicarboxylate (2.51)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 0.85 (td, J=12.3, 6.4 Hz, 1H), 1.05-1.28 (m, 28H), 1.42-1.59 (m, 2H), 1.61-1.69 (m, 4H), 2.26-2.43 (m, 3H), 3.14 (dd, J=10.6, 7.7 Hz, 1H), 4.02 (dq, J=7.1, 10.8 Hz, 1H), 4.10 (dq, J=10.8, 7.1 Hz, 1H), 4.21 (q, J=7.11 Hz, 2H), 4.87 (t, J=7.9 Hz, 1H), 6.15 (J=9.7 Hz, 1H), 6.49 (d, J=9.9 Hz, 1H); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): δ 12.7 (CH), 14.0 (CH\(_3\)), 14.3 (CH\(_3\)), 14.8 (CH\(_3\)), 18.3 (CH\(_3\)), 18.3 (CH\(_3\)), 25.5 (CH\(_2\)), 29.9 (CH\(_2\)), 34.2 (CH\(_2\)), 45.0 (CH\(_2\)), 48.7 (CH), 58.0 (C), 59.3 (C), 61.1 (CH\(_2\)), 61.3 (CH\(_2\)), 80.6 (CH), 125.9 (CH), 126.4 (CH), 129.5 (C), 135.6 (C), 169.2 (C), 170.5 (C); IR (neat, \text{cm}^{-1}): 2949, 2873, 1740, 1248; HRMS (EI) m/z calcd for C\(_{28}\)H\(_{46}\)O\(_5\)Si (M\(^+\)) 490.3115, found 490.30898.

Mixture of cyclized products 2.69, 2.70 and 2.71

Obtained as a pale yellow oil. IR (neat, \text{cm}^{-1}): 2955, 2861, 1733, 1253; HRMS (EI) m/z calcd for C\(_{25}\)H\(_{40}\)O\(_5\)Si (M\(^+\)) 448.2645, found 448.26318.

(±)-(3aR,9R,9'R)-Diethyl 9-(tert-butyldimethylsilyloxy)-7-methyl-3,3a,8,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (2.69)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 0.06-0.18 (m, 6H), 0.85-0.97 (m, 9H), 1.11-1.93 (m, 15H), 2.05-2.46 (m, 2H), 3.42 (dd, J=8.2, 1.9 Hz, 1H), 3.90-4.31 (m, 5H), 5.27 (s, 1H), 5.94 (s, 1H); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): δ -4.5 (CH\(_3\)), -4.0 (CH\(_3\)), 14.3 (CH\(_3\)), 14.3 (CH\(_3\)), 18.1 (C), 23.3 (CH\(_3\)), 25.3 (CH\(_2\)), 26.0 (CH\(_3\)), 29.8 (CH\(_2\)), 31.5 (CH\(_2\)), 40.1 (CH\(_3\)), 48.8 (CH), 61.1 (CH\(_2\)), 61.5 (CH\(_2\)), 64.3 (C), 71.4 (C), 72.6 (CH), 118.7 (CH), 119.0 (CH), 140.3 (C), 149.9 (C), 171.3 (C), 171.4 (C).
(±)-(3aR,9R,91R)-Diethyl 9-(tert-butylidemethylsilyloxy)-7-methylene-3,3a,5,7,8,9-hexahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (2.70)

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.06-0.18 (m, 6H), 0.85-0.97 (m, 9H), 1.11-1.93 (m, 11H), 2.05-2.46 (m, 3H), 2.61 (d, $J=14.4$ Hz, 1H), 3.15 (t, $J=7.9$ Hz, 1H), 3.18 (d, $J=15.1$ Hz, 1H), 3.90-4.31 (m, 5H), 4.72 (d, $J=15.0$ Hz, 2H), 5.79 (d, $J=2.0$ Hz, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): δ -4.3 (CH$_3$), -4.1 (CH$_3$), 14.3 (CH$_3$), 18.1 (C), 26.1 (CH$_3$), 27.7 (CH$_2$), 31.4 (CH$_2$), 34.8 (CH$_2$), 37.3 (CH$_2$), 39.5 (CH$_2$), 51.1 (CH), 57.9 (C), 61.4 (CH$_2$), 61.4 (CH$_2$), 62.9 (C), 73.8 (CH), 110.2 (CH$_2$), 121.4 (CH), 142.7 (C), 147.5 (C), 170.4 (C), 171.6 (C).

(±)-(3aR,9R,91R)-Diethyl 9-(tert-butylidemethylsilyloxy)-7-methyl-3,3a,8,9-tetrahydro-1H-cyclopenta[d]indene-4,4(2H)-dicarboxylate (2.71)

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.06-0.18 (m, 6H), 0.85-0.97 (m, 10H), 1.11-1.93 (m, 13H), 2.05-2.46 (m, 3H), 3.01 (dd, $J=10.5$, 7.7 Hz, 1H), 3.90-4.31 (m, 4H), 4.68-4.72 (m, 1H), 6.14 (d, $J=9.8$ Hz, 1H), 6.49 (d, $J=9.9$ Hz, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): δ -4.4 (CH$_3$), -4.2 (CH$_3$), 14.1 (CH$_3$), 14.3 (CH$_3$), 14.7 (CH$_3$), 18.2 (C), 25.8 (CH$_2$), 26.1 (CH$_3$), 31.6 (CH$_2$), 34.0 (CH$_2$), 44.6 (CH$_2$), 48.7 (CH), 57.6 (C), 59.2 (C), 61.1 (CH$_2$), 61.3 (CH$_2$), 80.4 (CH), 125.9 (CH), 126.3 (CH), 129.7 (C), 135.6 (C), 169.4 (C), 170.5 (C).

(±)-Diethyl 2-(prop-2-ynyl)-2-((triisopropylsilyloxy)methylene)cyclopentylmalonate (2.72)

A first solution was prepared as follows: To a solution of cyclopent-1-enecarbaldehyde (2.42) (1.70 g, 17.7 mmol) in THF (100 mL) at -78 °C was added TIPSOTf (7.13 mL, 26.5 mmol). After stirring for 10 minutes, dimethyl sulfide (3.90 mL, 53.0 mmol) was added dropwise. This solution was stirred at -78 °C for 40 minutes, and then the second solution was added. This second solution was prepared by adding a solution of 2.43 (5.26 g, 26.5 mmol) in THF (15 mL) to a suspension of NaH (60% in mineral oil, 1.41 g, 35.4 mmol) in THF (65 mL) at 0 °C. The second solution was stirred at room temperature for 30 minutes, and then was added to the first solution at -78 °C, dropwise and along the side of the flask. The reaction mixture was stirred for 1 hour, starting from -78 °C and left to warm, then was quenched with saturated aqueous NaHCO$_3$. The mixture was extracted with ether (3X) and the combined organic layers were
dried over MgSO₄, filtered and concentrated. The crude mixture (E:Z 12:1) was purified by flash chromatography (3 % ethyl acetate in hexanes). Fractions containing only the E isomer were combined and concentrated then put on the Kugelrohr apparatus for 35 minutes at 110 °C (≤2 Torr) and put through a short silica pad to give **2.72-E** (5.78 g, 72%) as a colourless oil. The excess of malonate chain **2.43** can be recovered.

**Major isomer: (±)-(E)-Diethyl 2-(prop-2-ynyl)-2-(2-((triisopropylsilyloxy)methylene)cyclopentyl)malonate (2.72-E)**

[Diagram of molecule]

**1H NMR (400 MHz, CDCl₃):** δ 1.03-1.17 (m, 21H), 1.25 (t, J=7.1 Hz, 6H), 1.39-1.63 (m, 2H), 1.89-2.07 (m, 4H), 2.53 (dddd, J=16.0, 8.5, 4.6, 1.6 Hz, 1H), 2.78 (dd, J=17.0, 2.68 Hz, 1H), 2.93 (d, J=17.0, 2.68 Hz, 1H), 3.40-3.46 (m, 1H), 4.11-4.26 (m, 4H), 6.47-6.49 (m, 1H); **13C NMR (400 MHz, CDCl₃):** δ 12.1 (CH), 14.1 (CH₃), 14.2 (CH₃), 17.9 (CH₃), 17.9 (CH₃), 24.0 (CH₂), 24.3 (CH₂), 27.7 (CH₂), 29.7 (CH₂), 43.8 (CH), 60.4 (C), 61.4 (CH₂), 61.5 (CH₂), 71.4 (CH), 80.2 (C), 122.4 (C), 135.8 (CH), 170.3 (C), 170.4 (C); **IR (neat, cm⁻¹):** 3283, 2945, 1730, 1667; **HRMS (EI) m/z calcd for C₂₅H₄₂O₅Si (M)⁺ 450.2802, found 407.2143 (M - i-Pr)⁺.

**Pd(η³-1-PhC₃H₄)(η⁵-C₅H₅) (2.75)**

To a solution of palladium(π-cinnamyl) chloride dimer (601 mg, 1.16 mmol) in THF (20 mL) at -78 °C was added dropwise a solution of sodium cyclopentadienylide (2.0 M in THF, 1.45 mL, 2.90 mmol) in THF (20 mL) and the mixture turned from a bright yellow to a dark burgundy colour. After stirring for 10 minutes at -78 °C, the flask was brought to room temperature and the mixture was concentrated. Hexanes was added and the mixture was filtered, rinsing with hexanes until washings were colourless. The collected filtrate was then concentrated to a minimum amount of hexanes, enough for the oil-like substance to stay together (has a low surface tension). This was then brought to -40 °C. The liquid which had collected at the surface was removed and the resulting solid was warmed and dried to give a dark burgundy powder (580 mg, 87%). Stored in the fridge. Spectral data are in accordance with values reported in the literature.[a]
(±)-(E)-Diethyl 2-(pent-4-en-2-ynyl)-2-(2-((triisopropylsilyloxy)methylene)cyclopentyl)malonate (2.73-E)

Benzene (22 mL) was added to a flask containing \([\eta^5-C_5H_5]Pd(\eta^3-1Ph-C_3H_4)]\) (32.0 mg, 0.111 mmol), triphenylphosphine (58.2 mg, 0.222 mmol) and copper(I) iodide (42.2 mg, 0.222 mmol). The mixture was degassed with argon for 10 minutes. During this time, 2.72-E (1.00 g, 2.22 mmol) was added neat via syringe. Once degassing was stopped, vinyl bromide (1.0M solution in THF, 6.66 mL, 6.66 mmol) was added. After 5 minutes, diethyl amine (1.15 mL, 11.1 mmol) was added dropwise and the mixture was stirred at room temperature overnight, changing from a dark yellow colour to a brown colour. The stir bar was removed and silica gel was added directly to the reaction mixture. After removal of the solvent, the dry pack was placed on a column and flash chromatography (3% ethyl acetate in hexanes) afforded 2.73-E (792 mg, 75%) as a yellow oil.

\[\text{1H NMR (400 MHz, CDCl}_3\): } \delta 1.02-1.17 (m, 21H), 1.24 (t, J=7.2 Hz, 6H), 1.45-1.62 (m, 2H), 1.90-2.06 (m, 3H), 2.52 (dddd, J=16.0, 8.3, 4.6, 1.5 Hz, 1H), 2.88 (dd, J=17.2, 1.7 Hz, 1H), 3.02 (dd, J=17.2, 1.9 Hz, 1H), 3.39-3.44 (m, 1H), 4.07-4.29 (m, 4H), 5.36 (dd, J=11.0, 2.1 Hz, 1H), 5.50 (dd, J=17.5, 2.1 Hz, 1H), 5.71 (ddt, J=17.5, 11.0, 1.8 Hz, 1H), 6.48 (s, 1H); \text{13C NMR (400 MHz, CDCl}_3\): } \delta 12.1 (CH), 14.1 (CH3), 14.2 (CH3), 17.9 (CH3), 24.0 (CH2), 25.2 (CH2), 27.7 (CH2), 29.7 (CH2), 44.0 (CH), 60.7 (C), 61.4 (CH2), 61.5 (CH2), 82.3 (C), 86.4 (C), 117.4 (CH), 122.5 (C), 126.4 (CH2), 135.8 (CH), 170.5 (C), 170.5 (C); \text{IR (neat, cm}^{-1}\): 2944, 2234, 1732, 1670, 1268, 1182, 883; \text{HRMS (EI) m/z calcd for C}_{27}H_{46}O_5Si (M)^+ 476.2958, found 476.29774.

General procedure for the Au(I) catalyzed cyclization reaction of 2.73-E

All experiments were performed with glassware which was not flame dried and were not kept under an argon atmosphere. To a solution of 2.73-E in toluene (0.05 M) was added the appropriate catalyst (2.5 mol%). The solution was left to stir at room temperature until judged complete by TLC. The solvent was evaporated and the crude mixture was placed on a silica column. Flash chromatography (5 % ethyl acetate in hexanes) provided the cyclized product 2.76 as white crystals. Recrystallization from 5% ethyl acetate in hexanes allowed for X-ray crystallography.
(±)-(3aR,9R,91R)-Diethyl 9-(triisopropylsilyloxy)-3,3a,8,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (2.76)

1H NMR (400 MHz, CDCl3): δ 1.07-1.15 (m, 21H), 1.22 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.35-1.48 (m, 2H), 1.53-1.64 (m, 2H), 1.66-1.78 (m, 1H), 1.89-1.97 (m, 1H), 2.20 (ddt, J=18.1, 9.6, 2.4 Hz, 1H), 2.38 (ddt, J=18.1, 5.7, 0.7 Hz, 1H), 3.59 (d, J=8.1 Hz, 1H), 4.05-4.31 (m, 5H), 5.41 (s, 1H), 5.73 (ddd, J=9.6, 5.4, 2.4 Hz, 1H), 6.17 (dd, J=9.7, 2.4 Hz, 1H) 13C NMR (400 MHz, CDCl3): δ 13.1 (CH), 14.2 (CH3), 14.3 (CH3), 18.4 (CH3), 18.4 (CH3), 25.2 (CH2), 29.5 (CH2), 31.6 (CH2), 35.2 (CH2), 49.0 (CH), 61.2 (CH2), 61.6 (CH2), 65.0 (C), 71.4 (C), 73.4 (CH), 121.3 (CH), 123.3 (CH), 130.7 (CH), 149.4 (C), 171.0 (C), 171.2 (C); IR (neat, cm⁻¹): 3040, 2944, 2867, 1733, 1248; HRMS (EI) m/z calcd for C27H44O5Si (M)⁺ 476.2958, found 433.24080 (M - iPr)⁺. MP= 89.6-91.0 °C.

(±)-(E)-Diethyl 2-((E)-5-phenylpent-4-en-2-ynyl)-2-(2-((triisopropylsilyloxy)methylene)cyclopentyl)malonate (2.74-E)

Benzene (22 mL) was added to a flask containing [(η⁵-C₅H₅)Pd(η³-1Ph-C₃H₄)] (32.0 mg, 0.111 mmol), triphenylphosphine (58.2 mg, 0.222 mmol) and copper(I) iodide (42.2 mg, 0.222 mmol). The mixture was degassed with argon for 10 minutes. During this time, 2.72-E (1.00 g, 2.22 mmol) was added neat via syringe. Once degassing was stopped, β-bromo styrene (0.85 mL, 6.66 mmol) was added. After 5 minutes, diethyl amine (1.15 mL, 11.1 mmol) was added dropwise and the dark brown reaction mixture was stirred at room temperature overnight. The stir bar was removed and silica gel was added directly to the reaction mixture. After removal of the solvent, the dry pack was placed on a column and flash chromatography (3% ethyl acetate in hexanes) afforded 2.74-E (987 mg, 80%) as a yellow oil.

1H NMR (400 MHz, CDCl3): δ 1.03-1.18 (21H), 1.27 (t, J=7.1 Hz, 6 H), 1.48-1.65 (m, 2H), 1.94-2.10 (m, 3H), 2.50-2.59 (m, 1H), 2.96 (dd, J=17.2, 2.0 Hz, 1H), 3.12 (dd, J=17.2, 2.0 Hz, 1H), 3.44-3.49 (m, 1H), 4.11-4.29 (m, 4H), 6.10 (dt, J=16.2, 2.2 Hz, 1H), 6.51-6.53 (m, 1H), 6.83 (d, J=16.2 Hz, 1H), 7.23-7.36 (m, 5H);

13C NMR (400 MHz, CDCl3): δ 12.1 (CH), 14.2 (CH₃), 14.2 (CH₃), 17.9 (CH₃), 17.9 (CH₃), 24.1 (CH₂), 25.6 (CH₂), 27.7 (CH₂), 29.8 (CH₂), 44.0 (CH), 60.8 (C), 61.4 (CH₂), 61.5 (CH₂), 82.8 (C), 88.1 (C), 108.5 (CH), 122.5 (C), 126.2 (CH), 128.5 (CH), 128.8 (CH), 135.8 (CH), 136.5 (C), 140.8 (CH), 170.5 (C), 170.5 (C); IR
(neat, cm⁻¹): 2944, 2215, 1730, 1672, 1178; HRMS (EI) m/z calcd for C₃₃H₄₈O₅Si (M⁺) 552.3271, found 552.32876.

**General procedure for the Au(I) catalyzed cyclization reaction of 2.74-E**

All experiments were performed with glassware which was not flame dried and were not kept under an argon atmosphere. To a solution of 2.74-E in toluene (0.05 M) was added the appropriate catalyst (2.5 mol%). The solution was left to stir at room temperature until judged complete by TLC. The solvent was evaporated and the crude mixture was placed on a silica column. Flash chromatography (3% ethyl acetate in hexanes) provided product 2.77 as a pale yellow oil and 2.78 as a sticky off-white solid.

(±)-(3aR,9R,9¹R)-Diethyl 8-phenyl-9-(triisopropylsilyloxy)-3,3a,8,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (2.77)

1H NMR (400 MHz, CDCl₃): δ 0.49-0.61 (m, 3H), 0.88-1.16 (m, 18H), 1.25 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.39-1.81 (m, 5H), 2.15 (td, J=12.0, 6.6 Hz, 1H), 3.42 (dt, J=8.4, 2.4 Hz, 1H), 3.54 (d, J=8.2 Hz, 1H), 4.09-4.33 (m, 5H), 5.52 (s, 1H), 5.59 (dd, 9.6, 2.3 Hz, 1H), 6.22 (dd, J=9.6, 2.8 Hz, 1H), 7.16-7.32 (m, 5H); 13C NMR (400 MHz, CDCl₃): δ 14.2 (CH), 14.3 (CH₃), 14.3 (CH₃), 18.6 (CH₃), 18.8 (CH₃), 25.0 (CH₂), 30.2 (CH₂), 31.5 (CH₂), 49.1 (CH), 52.9 (CH), 61.3 (CH₂), 61.6 (CH₂), 66.4 (C), 71.9 (C), 80.2 (CH), 121.6 (CH), 121.8 (CH), 127.0 (CH), 128.4 (CH), 129.6 (CH), 136.5 (CH), 143.1 (C), 149.1 (C), 170.9 (C), 171.0 (C); IR (neat, cm⁻¹): 3062, 3028, 2946, 2867, 1732, 1732, 1249; HRMS (EI) m/z calcd for C₃₃H₄₈O₅Si (M⁺) 552.3271, found 552.32636.

(±)-(3aR,6aR,Z)-diethyl 3a-formyl-3-((E)-3-phenylallylidene)hexahydopentalene-1,1(2H)-dicarboxylate (2.78)

1H NMR (400 MHz, CDCl₃): δ 1.24 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.30-1.43 (m, 1H), 1.53-1.66 (m, 2H), 1.76-1.93 (m, 2H), 2.70-2.80 (m, 1H), 2.90 (d, J=17.3 Hz, 1H), 3.32 (t, J=8.8 Hz, 1H), 3.48 (dd, J=17.3, 2.4 Hz, 1H), 4.12-4.28 (m, 4H), 6.24 (dd, J=11.0, 1.9 Hz, 1H), 6.47 (d, 15.5 Hz, 1H), 6.54 (dd, J=15.3, 10.8
Hz, 1H), 7.18-7.34 (m, 5H), 9.73 (s, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 14.2 (CH$_3$), 14.3 (CH$_3$), 27.9 (CH$_2$), 30.6 (CH$_2$), 36.8 (CH$_2$), 41.3 (CH$_2$), 54.6 (CH), 61.7 (CH$_2$), 62.0 (C), 62.0 (CH$_2$), 67.5 (C), 124.4 (CH), 125.2 (CH), 126.6 (CH), 127.9 (CH), 128.8 (CH), 133.4 (CH), 137.2 (C), 143.2 (C), 169.6 (C), 171.9 (C), 202.7 (CH); IR (neat, cm$^{-1}$); IR (neat, cm$^{-1}$): 2964, 1730, 1713, 1447, 1254; HRMS (El) m/z calcd for C$_{24}$H$_{28}$O$_5$ (M)$^+$ 396.1937, found 396.19419.

**Procedures: Chapter 3**

(E)-Ethyl hexa-3,5-dienoate (3.8)

To a solution of diisopropyl amine (44.0 mL, 0.311 mol) in THF (206 mL) at -10 °C was added n-BuLi (10M in pentane, 31.0 mL, 0.310 mol). The solution was stirred at -10 °C for 30 minutes before being brought to -78 °C. HMPA (68.8 mL, 0.395 mol) was then added slowly via syringe and the mixture was allowed to stir for 20 minutes at -78 °C. Ethyl sorbate (24.0 mL, 0.164 mol) in THF (69.0 mL) was added dropwise and the mixture was left to stir for 10 minutes. The resulting bright red solution was poured directly into acetic acid (62.0 mL) and ice water (320 mL). The mixture was extracted three times with hexanes and the combined organic layers were washed with sat. aqu. NaHCO$_3$ and with brine. The organic layer was dried with MgSO$_4$ and concentrated to afford 3.8 as a yellow oil (20.8 g, 83%). The crude product was used in the next step without further purification. Spectra match values reported in the literature.$^{39}$

(E)-Hexa-3,5-dien-1-ol (3.9)

LiAlH$_4$ (8.06 g, 0.202 mol) was added to ether (88.5 mL) in a flask which was then brought to 0 °C. Ester 3.8 (20.8 g, 0.148 mol) in ether (19 mL) was added slowly and the mixture was left to stir at room temperature overnight. The reaction was quenched with aqueous sodium L-tartrate (25 g/L) at 0 °C and was left to stir at room temperature for 30 minutes. The phases were separated and the aqueous layer was extracted 3 times with ether. The combined organic layers were washed with brine, dried with MgSO$_4$ and concentrated to give alcohol 3.9 (12.8 g, 88%) as a yellow oil. The crude product was used directly in the following step. Spectra match values reported in the literature.$^{39}$
(E)-Hexa-3,5-dienyl 4-methylbenzenesulfonate (3.10)

To a flask containing alcohol 3.9 (12.8 g, 0.130 mol) in triethylamine (73 mL) was added TsCl (27.6, 0.145 mol) at 0 °C in portions over 15 minutes. The mixture was left to stir at room temperature overnight then was poured into water and extracted three times with ether. The combined organic extracts were washed twice with 1M HCl, once with sat. aqu. NaHCO₃ and once with brine, then dried over MgSO₄ and concentrated to yield the tosylated alcohol 3.10 (26.1 g, 79%) as an orange oil. The crude product was used without further purification. Spectra match values reported in the literature.⁴₀

(E)-6-Azidohexa-1,3-diene (3.11)

Sodium azide (3.94 g, 60.6 mmol) was added to a solution of tosylate 3.10 (10.2 g, 40.4 mmol) in DMSO (48.0 mL). The mixture was stirred at room temperature overnight and was then diluted with water at 0 °C and extracted three times with ether. The combined ethereal layers were washed with water and with brine, dried with MgSO₄ and concentrated to give azide 3.11 (4.95 g, 99%) as an orange oil. The crude product was used in the following step without further purification. Spectra match values reported in the literature.⁴¹

(E)-Hexa-3,5-dien-1-amine (3.1)

LiAlH₄ (4.33g, 0.108 mol) was added to ether (1.0 L) in a flask which was then brought to 0 °C. Azide 3.11 (12.7 g, 0.103 mol) was added slowly and the mixture was left to stir at room temperature for 4 hours. The reaction was quenched with aqueous sodium L-tartrate (25 g/L) at 0 °C and was left to stir at room temperature for 1.5 hours. The phases were separated and the aqueous layer was extracted 3 times with ether. The combined organic layers were washed with brine, dried with MgSO₄ and concentrated, affording the crude amine 3.1 as a yellow oil. The crude product was distilled (heat gun, ≤ 2 Torr) to a colourless oil (6.82 g, 68%). Caution should be exercised during the distillation as over-heating of this product can result in polymerization. Spectra match values reported in the literature.

(E)-N-(Hexa-3,5-dienyl)acrylamide (3.2)

Triethylamine (1.5 mL,10.6 mmol) was added to a flask containing amine 3.1 (940 mg, 9.67 mmol) in DCM (22 mL) at room temperature. This mixture was then added slowly and along the side of the flask to a solution of acryloyl chloride (0.79 mL, 9.67 mmol) in DCM (22 mL) at -78 °C. This transparent yellow
reaction mixture was then left to warm to room temperature and stirred for 4 hours, then sat. aqu. 
NaHCO₃ was added and the mixture was extracted 3 times with ethyl acetate. The combined organic 
layers were washed with brine, dried with MgSO₄ and concentrated under reduced pressure. Flash 
chromatography (40% ethyl acetate in hexanes) gave amide 3.2 (1.07 g, 73%) as a colourless oil. 
Polymerization of this compound was observed with a sample of lesser purity stored in the fridge. 
Spectra match values reported in the literature⁴².

(±)-(4aR,8aS)-2,3,4,4a,8,8a-Hexahydroisoquinolin-1(7H)-one (3.3)

This experiment was performed with glassware which was not flame dried and was not kept under an 
argon atmosphere. In(OTf)₃ (375 mg, 0.668 mmol) was added to a flask containing amide 3.2 (505 mg, 
3.34 mmol) in a mixture of distilled water (40 mL) and isopropanol (6.5 mL). The mixture was brought to 
50 °C and stirred overnight. The reaction mixture was then brought to room temperature and extracted 
three times with ethyl acetate. The combined organic layers were washed with brine and dried with 
MgSO₄ and concentrated in vacuo to give lactam 3.3 as a pale yellow solid (360.1 mg, 71%). 
Recrystallization from THF and Et₂O gave 3.3 as white crystals. Attempts at scaling up the reaction to 
more than 2 g of amide 3.2 resulted in significantly decreased yields. Spectra match values reported in 
the literature.

(±)-(4aR,8aS)-2-Tosyl-1,2,3,4,4a,7,8,8a-octahydroisoquinoline (3.13)

LiAlH₄ (1.06 g, 2.66 mmol) was added to THF (67 mL) in a flask which was then brought to 0 °C. Lactam 
3.3 (1.83 g, 12.1 mmol) in THF (93 mL) was added slowly and the mixture was left to stir at room 
temperature overnight. The reaction was quenched with aqueous sodium L-tartrate (25 g/L) at 0 °C and 
was left to stir at room temperature for 1 hour and 30 minutes. The phases were separated and the 
aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were washed with 
brine, dried with MgSO₄ and concentrated. The crude amine 3.12 was carried on without further 
purification.

To a flask containing amine 3.12 in pyridine (6.8 mL) was added TsCl (2.54 g, 13.3 mmol) at 0 °C in 
portions over 15 minutes. The mixture was left to stir at room temperature overnight, and then poured 
into water and extracted three times with ethyl acetate. The combined organic extracts were washed 
twice with 2M HCl, once with sat. aqu. NaHCO₃ and once with brine, then dried over MgSO₄ and
concentrated. Flash chromatography (15% Et2O in hexanes) yielded the tosylated amine 3.13 (2.77 g, 79% over 2 steps) as a white crystalline solid.

1H NMR (400 MHz, CDCl3): δ 1.56-1.66 (m, 2H), 1.72-1.87 (m, 2H), 1.91-2.14 (m, 4H), 2.43 (s, 3H), 2.63-2.69 (m, 1H), 2.82 (J=11.4, 3.7 Hz, 1H), 3.11-3.20 (m, 2H), 5.46 (ddt, J=9.9, 3.8, 1.9 Hz, 1H), 5.63, (ddt, J=10.0, 3.5, 1.8 Hz, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.63 (d, J=8.2 Hz, 2H); 13C NMR (400 MHz, CDCl3): δ 21.7 (CH3), 23.4 (CH2), 24.2 (CH2), 29.5 (CH2), 33.0 (CH), 33.4 (CH), 45.2 (CH2), 49.6 (CH2), 127.7 (CH), 127.8 (CH), 129.7 (CH), 129.8 (CH), 133.7 (C), 143.4 (C); IR (neat, cm⁻¹): 3017, 2925, 2838, 1489, 1349; HRMS (EI) m/z calcd for C16H21NO2S (M)+ 291.1293, found 291.1276. MP: 93.5-94.5 °C.

(±)-(35,45)-3-(3-oxopropyl)-1-Tosylpiperidine-4-carbaldehyde (3.14)

This experiment was carried out with glassware which was not flame dried and was not kept under an argon atmosphere. To a flask containing tosyl amine 3.13 (570 mg, 1.96 mmol) in a mixture of THF (23 mL) and water (7.7 mL) was added a solution of osmium tetroxide (4% wt in water, 1.3 mL, 0.198 mmol). After stirring for 5 minutes at room temperature, NMO (465 mg, 3.97 mmol) was added. Once all starting material was judged consumed by TLC, NaIO4 (1.27 mg, 5.95 mmol) was added. When the second step was complete by TLC, the reaction was quenched with 20% aqu. Na2S2O3 and the aqueous layer was extracted 3 times with ether. The combined organic layers were washed with 20% aqu. Na2S2O3 and with brine, dried over MgSO4 and concentrated in vacuo (rotary evaporator water bath temperatures ≤ 40 °C) to give dialdehyde 3.14 (622.2 mg, 98%, 13:1 cis:trans) as an off-white solid. Yields for this reaction ranged between 76% and 98% and cis:trans ratios varied between 7:1 and 14:1. This product can be stored for extensive periods of time without gradual conversion to the trans isomer if kept as a solid in the fridge.

1H NMR (400 MHz, CDCl3): δ 1.55-1.65 (m, 1H), 1.80-2.01 (m, 3H), 2.20-2.28 (m, 1H), 2.36-2.44 (m, 4H), 2.47-2.70 (m, 4H), 3.40 (dd, J=11.9, 5.0 Hz, 1H), 3.46-3.53 (m, 1H), 7.30-7.34 (m, 2H), 7.59-7.64 (m, 2H), 9.70 (s, 1H), 9.78-9.79 (m, 1H); 13C NMR (400 MHz, CDCl3): δ 19.6 (CH2), 21.5 (CH2), 21.7 (CH3), 34.12 (CH), 41.3 (CH2), 45.2 (CH2), 48.4 (CH2), 50.6 (CH), 127.7 (CH), 129.9 (CH), 133.3 (C), 143.9 (C), 201.4 (CH), 202.4 (CH); IR (neat, cm⁻¹): 2926, 2846, 2728, 1719, 1337; HRMS (EI) m/z calcd for C16H21NO4S (M)+ 323.1191, found 323.11808. MP: 87.6-88.5.
(±)-(4aS,7aS)-2-Tosyl-2,3,4,4a,7,7a-hexahydro-1H-cyclopenta[c]pyridine-6-carbaldehyde (3.16)

To a solution of dialdehyde 3.14 (127 mg, 0.393 mmol) in benzene (1 mL) were added piperidine (1 drop, ca. 0.0687 mmol) and acetic acid (1 drop, ca. 0.137 mmol). The flask was equipped with a Dean-Stark and a reflux condenser, and the solution was refluxed for about 1 hour or until all starting material was consumed by TLC. The resulting orange solution was washed twice with each 2N HCl, sat. aqu. NaHCO₃ and brine. The organic layer was dried MgSO₄, filtered and concentrated to give enal 3.16 (87.6 mg, 73%) as an off-white powder.

1H NMR (400 MHz, CDCl₃): δ 1.74 (dtd, J=14.0, 6.4, 3.5 Hz, 1H), 1.99-2.07 (m, 1H), 2.25-2.35 (m, 1H), 2.42 (s, 3H), 2.53-2.64 (m, 3H), 2.80 (ddd, J=11.6, 9.0, 3.5 Hz, 1H), 2.90-2.97 (m, 1H), 3.09-3.25 (m, 2H), 6.65-6.67 (m, 1H), 7.29-7.33 (m, 2H), 7.60-7.64 (m, 2H), 9.70 (s, 1H); 13C NMR (400 MHz, CDCl₃): δ 21.7 (CH₃), 26.6 (CH₂), 31.9 (CH₂), 37.2 (CH), 42.8 (CH), 44.1 (CH₂), 47.0 (CH₂), 127.7 (CH), 129.9 (CH), 133.5 (C), 143.7 (C), 147.1 (C), 154.2 (CH), 189.7 (CH); IR (neat, cm⁻¹): 2930, 2857, 1678; HRMS (EI) m/z calcd for C₁₆H₁₉NO₃S (M)+ 305.1086, found 305.10673. MP: 100.9-102.8.

Dibenzylammonium trifluoroacetate

This reaction was performed with glassware which was not flame dried and was not kept under an argon atmosphere. A solution of TFA (15.4 mL, 200 mmol) in deionized water (84.6 mL) was added dropwise with an addition funnel to a flask containing dibenzylamine (1.93 mL, 10.0 mmol) with stirring. A white solid was formed immediately and once the addition was complete, the solid was collected by vacuum filtration, washed with water and dried (1.41 g, 45 %). Spectral data are in accordance with values reported in the literature.⁴³

(±)-(4aR,8aS)-2-Tosyl-1,2,3,4,4a,7,8,8a-octahydroisoquinolin-7-ol (3.37)

Palladium(II) acetate (6.0 mg, 0.0267 mmol), copper(II) acetate (4.8 mg, 0.0264 mmol), hydroquinone (5.7 mL, 0.0536 mmol) and acetic acid (2.7 mL) were placed into a flask under an atmosphere of oxygen and stirred 5 minutes. The starting material 3.13 (46.9 mg, 0.161 mg) was added and the mixture was
brought to ca. 55 °C and left to stir for 24 hours, still under an atmosphere of oxygen. The mixture was then brought back to room temperature, filtered through celite and extracted three times with EtOAc, and the combined organic layers were washed once with sat. aq. NaHCO₃ and once with brine, then dried over MgSO₄ and concentrated.

A solution of the crude mixture in methanol (1 mL) was then added slowly to a flask containing sodium methoxide (10.0 mg, 0.185 mmol) in methanol (1 mL) and was stirred at room temperature overnight. The reaction was quenched with sat. aq. NH₄Cl and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. Flash chromatography (40% ethyl acetate in hexanes) provided a mixture of isomers of 3.37 as a white solid (30.7 mg, 62% over 2 steps).

**Major isomer of 3.37**

$^1$H NMR (300 MHz, CDCl₃): δ 1.44-1.77 (m, 4H), 2.02-2.22 (m, 3H), 2.34-2.47 (m, 4H), 2.68 (dd, J=12.0, 3.1 Hz, 1H), 3.36 (d, J=11.8 Hz, 1H), 3.43-3.53 (m, 1H), 4.20-4.26 (m, 1H), 5.71-5.83 (m, 2H), 7.32 (d, J=8.0 Hz, 2H), 7.61-7.65 (m, 2H); $^{13}$C NMR (300 MHz, CDCl₃): δ 21.7 (CH₃), 27.7 (CH₂), 29.0 (CH), 32.2 (CH₂), 33.8 (CH), 45.8 (CH₂), 50.4 (CH₂), 64.4 (CH), 127.8 (CH), 128.5 (CH), 129.8 (CH), 133.4 (C), 134.1 (CH), 143.6 (C); IR (neat, cm⁻¹): 3051, 2961, 2874, 2233, 1658, 1588, 1451, 1342; HRMS (EI) m/z calcd for C₁₆H₂₁NO₃S (M)+ 307.1242, found 307.12579. MP: 112.3-113.6 °C.

(±)-(3aS,7aS)-5-Tosyldecahydroxireno[2,3-f]isoquinolin-2-ol (cis-3.38)

A solution of m-CPBA (87.5 mg, 0.507 mmol) in DCM (1 mL) was stirred until the solid had dissolved. A solution of allylic alcohol 3.37 (54.1 mg, 0.0.176 mmol) in DCM (1 mL) then solid NaHCO₃ (41.0 mg, 0.440 mmol) were added at 0 °C. The reaction mixture was left to stir at room temperature for 3.5 hours then was quenched with 20% aqueous Na₂S₂O₃. The mixture was filtered and extracted three times with DCM. The organic layer was washed twice with sat. aq. NaHCO₃ and once with brine, dried with MgSO₄ and concentrated under reduced pressure. Flash chromatography (80% ethyl acetate in hexanes) provided the epoxyalcohol 3.38 (39.3 mg, 69%) as white crystals.

$^1$H NMR (300 MHz, CDCl₃): δ 1.38-2.47 (m, 10H), 3.16 (dd, J=3.5, 1.6 Hz, 1H), 3.32-3.51 (m, 3H), 3.64-3.79 (m, 2H), 4.14-4.23 (m, 1H), 7.28-7.34 (m, 2H), 7.58-7.64 (m, 2H).
(±)-(3aS,7aS)-5-Tosyldecahydrooxireno[2,3-f]isoquinoline (3.39)

A solution of m-CPBA (125 mg, 0.725 mmol) in DCM (1.5 mL) was stirred until the solid had dissolved, and a solution of 3.13 (102 mg, 0.349 mmol) in DCM (1 mL) was added. The reaction mixture was left to stir at room temperature for 2 hours, and then quenched with 20% aqueous Na₂S₂O₃. The mixture was filtered and the organic layer was washed twice with sat. aq. NaHCO₃ and once with brine, dried with MgSO₄ and concentrated under reduced pressure. Flash chromatography (25% ethyl acetate in hexanes) provided the epoxide 3.39 (86.2 mg, 80%, dr 4:1) as white crystals.

Major isomer: (±)-(1aS,3aS,7aS,7bR)-5-Tosyldecahydrooxireno[2,3-f]isoquinoline

1H NMR (400 MHz, CDCl₃): δ 1.23-1.31 (m, 1H), 1.63-2.05 (m, 7H), 2.34 (dd, J=11.4, 3.2 Hz, 1H), 2.39 (dd, J=11.5, 3.3 Hz, 1H), 2.43 (s, 3H), 2.93 (dd, J=3.7, 1.6 Hz, 1H), 3.11 (t, J=4.2 Hz, 1H), 3.38-3.43 (m, 1H), 3.64-3.70 (m, 1H), 7.32 (d, J=7.9 Hz, 2H), 7.60-7.63 (m, 2H); 13C NMR (400 MHz, CDCl₃): δ 19.7 (CH₂), 21.7 (CH₃), 22.7 (CH₂), 24.0 (CH₂), 29.2 (CH), 33.3 (CH), 46.2 (CH₂), 51.1 (CH₂), 51.5 (CH), 56.7 (CH), 127.8 (CH), 129.8 (CH), 133.3 (C), 143.6 (C); IR (neat, cm⁻¹): 2927, 2858, 2251, 1465, 1332; HRMS (EI) m/z calcd for C₁₆H₂₁NO₃S (M)+ 307.1242, found 307.11500. MP: 117.3-120.1 °C.

(±)-Diethyl 2-(4-methylpent-4-en-2-ynyl)-2-((4aS,7aS,E)-2-tosyl-6-((triisopropylsilyloxy)methylene)octahydro-1H-cyclopenta[c]pyridin-5-yl)malonate (3.41)

A first solution was prepared as follows: To a solution of 3.16 (82.2 mg, 0.269 mmol) in THF (1.5 mL) at -78 °C was added TIPSOTf (0.11 mL, 0.404 mmol). After stirring for 5 minutes, dimethyl sulfide (0.06 mL, 0.807 mmol) was added dropwise. This solution was stirred at -78 °C for 40 minutes, then the second solution was added. This second solution was prepared by adding a solution of 2.44 (96.2 mg, 0.404 mmol) in THF (0.5 mL) to a suspension of NaH (60% in mineral oil, 21.5 mg, 0.807 mmol) in THF (1 mL) at 0 °C. The second solution was stirred at room temperature for 30 minutes, and then added to the first solution at -78 °C, dropwise and along the side of the flask. The reaction mixture was stirred for 1 hour, starting from -78 °C and left to warm, then was quenched with sat. aq. NaHCO₃. The mixture was extracted with ethyl acetate (3X), and the combined organic layers were dried over MgSO₄, filtered and
concentrated. Purification by flash chromatography (5%, 10% and 50% ethyl acetate in hexanes) afforded **2.41** (67.6 mg, 36 %) as a sticky, off-white solid. Starting material (36.3 mg, 44%) was recovered, and the excess of malonate chain **2.44** can also be recovered.

**1H NMR** (400 MHz, CDCl₃): δ 1.01-1.26 (m, 28H), 1.51 (dtd, J=12.6, 12.6, 4.0 Hz, 1H), 1.74-1.86 (m, 4H), 1.92-2.01 (m, 1H), 2.11-2.33 (m, 3H), 2.38-2.43 (m, 4H), 2.50 (ddd, J=17.3, 10.4, 2.3 Hz, 1H), 2.83 (d, J=17.2 Hz, 1H), 3.01 (s, 1H), 3.04 (d, J=17.2 Hz, 1H), 3.47 (d, J=11.7 Hz, 1H), 3.60 (d, J=11.4 Hz, 1H), 4.02-4.24 (m, 4H), 5.11 (d, J=1.0 Hz, 1H), 5.56 (s, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.60 (d, J=8.2 Hz, 2H); **13C NMR** (400 MHz, CDCl₃): δ 12.1 (CH), 14.0 (CH₃), 14.1 (CH₃), 17.9 (CH₃), 17.9 (CH₃), 21.6 (CH₃), 23.6 (CH₃), 24.8 (CH₂), 28.1 (CH₂), 29.1 (CH₂), 35.3 (CH), 39.8 (CH), 45.8 (CH₂), 47.1 (CH²), 50.4 (CH), 60.2 (C), 61.5 (CH₂), 61.6 (CH₂), 84.1 (C), 85.3 (C), 119.0 (C), 121.4 (CH₂), 126.6 (C), 127.8 (CH), 129.6 (CH), 133.2 (C), 138.6 (CH), 143.4 (C), 170.4 (C), 170.5 (C); IR (neat, cm⁻¹): 2943, 2867, 1659, 1588, 1451, 1290; HRMS (EI) m/z calcd for C₃₈H₅₇NO₇SSi (M⁺) 699.3625, found 656.30885 (M - iPr)⁺.

**Procedure for Au(I) catalyzed cyclization of 3.41**

This experiment was performed with glassware which was not flame dried and was not kept under an argon atmosphere. To a solution of **3.41** in toluene (0.05 M) was added JohnPhos (2.5 mol%). The solution was left to stir at room temperature until judged complete by TLC. The solvent was evaporated and the crude mixture was placed on a silica column. Flash chromatography (3 % ethyl acetate in hexanes) provided the mixture of cyclized products **3.42**, **3.43** and **3.44** as a sticky pale yellow solid.

**Mixture of cyclized products 3.42, 3.43 and 3.44**

Obtained as a sticky pale yellow solid. IR (neat, cm⁻¹): 2961, 2874, 1659, 1588, 1451, 1290; HRMS (EI) m/z calcd for C₃₈H₅₇NO₇SSi (M⁺) 699.3625, found 656.30674 (M – iPr)⁺.

**(±)-Cyclized product 3.42**

**1H NMR** (400 MHz, CDCl₃): δ 0.83-2.44 (m, 41H), 2.68 (d, J=15.1, 1H), 2.75 (d, J=13.0 Hz, 1H), 3.26 (s, 1H), 3.53-3.61 (m, 1H), 3.63-3.74 (m, 1H), 3.96-4.26 (m, 5H), 5.29 (s, 1H), 5.91 (s, 1H), 7.27-7.32 (m, 2H), 7.57-5.62 (m, 2H); **13C NMR** (400 MHz, CDCl₃): δ 13.5 (CH), 14.2 (CH₃), 14.3 (CH₃), 18.4 (CH₃), 18.5 (CH₃), 21.7
(CH₃), 23.2 (CH₃), 26.3 (CH₂), 29.0 (CH₂), 35.6 (CH), 40.5 (CH₂), 41.0 (CH), 46.2 (CH₂), 46.7 (CH₂), 53.3 (CH), 61.2 (CH₂), 61.6 (CH₂), 65.1 (C), 71.6 (C), 73.0 (CH), 118.6 (CH), 119.1 (CH), 127.9 (CH), 129.6 (CH), 133.6 (C), 140.5 (C), 143.2 (C), 149.8 (C), 170.7 (C), 171.2 (C).

(±)-Cyclized product 3.43

¹H NMR (400 MHz, CDCl₃): δ 0.83-2.44 (m, 40H), 2.51 (dd, J=15.1, 4.4 Hz, 1H), 2.97 (s, 1H), 3.22 (dd, J=15.8 Hz, 1H), 3.53-3.61 (m, 1H), 3.63-3.74 (m, 1H), 3.96-4.26 (m, 5H), 4.74 (d, J=9.3 Hz, 2H), 5.82 (d, J=1.6 Hz, 1H), 7.27-7.32 (m, 2H), 7.57-5.62 (m, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 13.6 (CH), 14.2 (CH₃), 14.3 (CH₃), 18.4 (CH₃), 18.5 (CH₃), 21.7 (CH₃), 27.0 (CH₂), 34.3 (CH₂), 37.5 (CH₂), 38.0 (CH), 41.2 (CH), 42.1 (CH₂), 46.1 (CH₂), 46.5 (CH₂), 56.3 (CH), 59.2 (C), 61.4 (CH₂), 61.6 (CH₂), 63.9 (C), 72.5 (CH), 110.6 (CH₂), 121.8 (CH), 128.0 (CH), 129.6 (CH), 133.2 (C), 142.3 (C), 143.4 (C), 148.4 (C), 170.3 (C), 171.1 (C).

General procedure for deprotection of 2.49, 2.50 and 2.51
The mixture of tricyclic compounds 2.49, 2.50 and 2.51 (219 mg, 0.446 mmol) was dissolved in THF (5.5 mL). A 1.0 M solution of tetra-n-butyrammonium fluoride in THF (2.3 mL, 2.30 mmol) was added via syringe. The pale yellow solution turned darker and eventually reached dark brown as it was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NaHCO₃ and extracted with ethyl acetate (3X). The combined organic layers were dried over MgSO₄, filtered and concentrated. Purification by silica gel chromatography (30% ethyl acetate in hexanes) afforded the mixture of alcohols 3.45, 3.46 and 3.47 (123 mg, 82%) as a sticky pale yellow oil.

(±)-(3a⁹R,9R,9¹R)-Diethyl 9-hydroxy-7-methyl-3,3a,8,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (3.45)

¹H NMR (400 MHz, CDCl₃): δ 1.23 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.39-1.64 (m, 4H), 1.67-1.86 (m, 6H), 2.14 (dd, J=17.7, 9.9 Hz, 1H), 2.25 (dd, J=17.8, 6.1 Hz, 1H), 3.45 (dd, J=8.1, 2.3 Hz, 1H), 3.99 (dd, J=9.4, 6.4 Hz, 1H), 4.04-4.30 (m, 4H), 5.29 (s, 1H), 5.95 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 14.3 (CH₃), 14.3 (CH₃), 23.2 (CH₃), 25.4 (CH₂), 29.6 (CH₂), 31.6 (CH₂), 38.8 (CH₂), 48.5 (CH), 61.3 (CH₂), 61.7 (CH₂), 63.9 (CH), 72.5 (CH), 110.6 (CH₂), 121.8 (CH), 128.0 (CH), 129.6 (CH), 133.2 (C), 142.3 (C), 143.4 (C), 148.4 (C), 170.3 (C), 171.1 (C).
64.2 (C), 71.4 (C), 72.2 (CH), 118.6 (CH), 118.9 (CH), 140.1 (C), 149.8 (C), 171.0 (C), 171.4 (C); IR (neat, cm⁻¹): 3515, 2925, 1732, 1652; HRMS (EI) m/z calcd for C₁₉H₂₆O₅ (M)⁺ 334.1780, found 334.1777.

(±)-(3aR,9R,9¹R)-Diethyl 9-hydroxy-7-methylene-3,3a,5,7,8,9-hexahydro-1H-cycloenta[c]indene-4,4(2H)-dicarboxylate (3.46)

¹H NMR (400 MHz, CDCl₃): δ 1.18-1.36 (m, 8H), 1.52-1.63 (m, 3H), 1.85-1.94 (m, 1H), 2.09-2.15 (m, 1H), 2.40-2.53 (m, 2H), 2.63 (d, J=14.4 Hz, 1H), 3.17-3.25 (m, 2H), 3.96-4.01 (m, 1H), 4.08-4.25 (m, 4H), 4.76 (J=11.6 Hz, 2H), 5.83 (d, J=2.0 Hz, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 14.3 (CH₃), 14.3 (CH₃), 27.9 (CH₂), 31.3 (CH₂), 34.6 (CH₂), 36.4 (CH₂), 39.0 (CH₂), 51.0 (CH), 57.4 (C), 61.5 (CH₂), 61.6 (CH₂), 62.8 (C), 73.3 (CH), 110.9 (CH₂), 121.9 (CH), 142.1 (C), 146.8 (C), 170.1 (C), 171.6 (C); IR (neat, cm⁻¹): 3500, 2924, 1729, 1459, 1257; HRMS (EI) m/z calcd for C₁₉H₂₆O₅ (M)⁺ 334.1780, found 334.1771 (334.17592).

(±)-(3aR,9R,9¹R)-Diethyl 9-hydroxy-7-methyl-3,3a,8,9-tetrahydro-1H-cycloenta[d]indene-4,4(2H)-dicarboxylate (3.47)

¹H NMR (400 MHz, CDCl₃): δ 0.95 (td, J=13.0, 6.2 Hz, 1H), 1.04-1.81 (m, 14H), 2.26-2.43 (m, 3H), 3.14 (dd, J=10.6, 7.7 Hz, 1H), 3.95-4.32 (m, 4H), 4.87 (t, J=7.9 Hz, 1H), 6.15 (J=9.7 Hz, 1H), 6.49 (d, J=9.9 Hz, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 14.0 (CH₃), 14.3 (CH₃), 14.7 (CH₃), 25.7 (CH₂), 31.5 (CH₂), 33.7 (CH₂), 43.8 (CH₂), 48.8 (CH), 57.0 (C), 59.1 (C), 61.4 (CH₂), 61.5 (CH₂), 80.5 (CH), 125.9 (CH), 126.4 (CH), 129.8 (C), 135.6 (C), 169.4 (C), 170.3 (C); IR (neat, cm⁻¹): 3519, 2933, 1732, 1440, 1242; HRMS (EI) m/z calcd for C₁₉H₂₆O₅ (M)⁺ 334.1780, found 334.17529.

Oxidation of alcohols 3.45, 3.46 and 3.47

The experiment was performed with glassware which was not flame dried and solvent which was not distilled, and was not kept under an argon atmosphere. The mixture of alcohols 3.45, 3.46 and 3.47 (234 mg, 0.700 mmol) was dissolved in DCM (14 mL). The Dess-Martin periodinane (530 mg, 1.25 mmol) was added, and the mixture was stirred at room temperature for 3 days. The reaction was quenched with 20% aqueous Na₂S₂O₃. The mixture was filtered and the organic layer was washed twice with sat. aq. NaHCO₃ and once with brine, dried with MgSO₄ and concentrated under reduced pressure. Flash
chromatography (20% ethyl acetate in hexanes) provided the oxidized products 3.48 and 3.50 (174 mg, 75%) as an off-white solid.

\( (\pm)-(3aR,9^1R)\)-Diethyl 7-methyl-9-oxo-3,3a,8,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (3.48) 

\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.21 (t, \( J=7.1 \) Hz, 3H), 1.27 (t, \( J=7.1 \) Hz, 3H), 1.47-1.72 (m, 4H), 1.81-1.94 (m, 5H), 2.72 (d, \( J=21.6 \) Hz, 1H), 3.20 (d, \( J=21.7 \) Hz, 1H), 4.04-4.29 (m, 5H), 5.36 (s, 1H), 6.20 (s, 1H); \( ^{13}C \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 14.2 (CH\(_3\)), 14.3 (CH\(_3\)), 22.7 (CH\(_2\)), 25.6 (CH\(_2\)), 31.0 (CH\(_2\)), 39.1 (CH\(_2\)), 44.1 (CH\(_2\)), 44.6 (CH), 61.5 (CH\(_2\)), 61.8 (CH\(_2\)), 70.5 (C), 72.2 (C), 119.6 (CH), 120.3 (CH), 138.2 (C), 146.7 (C), 170.4 (C), 170.8 (C), 205.9 (C); IR (neat, cm\(^{-1}\)): 2925, 1734, 1653, 1456, 1244, 1209; HRMS (El) m/z calcd for C\(_{19}\)H\(_{24}\)O\(_5\) (M\(^+\)) 332.1624, found 332.16332.

\( (\pm)-(3aR,9^1R)\)-Diethyl 7-methyl-9-oxo-3,3a,8,9-tetrahydro-1H-cyclopenta[d]indene-4,4(2H)-dicarboxylate (3.50) 

\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.10 (t, \( J=7.1 \) Hz, 3H), 1.16-1.34 (m, 5H), 1.45-1.63 (m, 2H), 1.72-1.80 (m, 4H), 1.91-1.97 (m, 1H), 2.71 (d, \( J=22.3 \) Hz, 1H), 3.20-3.28 (m, 1H), 3.42 (dd, \( J=10.5, 7.5 \) Hz, 1H), 3.93-4.08 (m, 2H), 4.21 (q, \( J=7.1 \) Hz, 2H), 6.27 (d, \( J=9.6 \) Hz, 1H), 6.65 (d, \( J=9.7 \) Hz, 1H); \( ^{13}C \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 13.9 (CH\(_3\)), 14.2 (CH\(_3\)), 14.7 (CH\(_3\)), 24.8 (CH\(_2\)), 31.4 (CH\(_2\)), 40.5 (CH\(_2\)), 46.3 (CH\(_2\)), 46.3 (CH), 58.4 (C), 60.8 (C), 61.5 (CH\(_2\)), 61.6 (CH\(_2\)), 126.5 (CH), 126.8 (CH), 128.3 (C), 135.1 (C), 168.4 (C), 169.8 (C), 216.8 (C); IR (neat, cm\(^{-1}\)): 2963, 2869, 1725, 1444, 1250; HRMS (El) m/z calcd for C\(_{19}\)H\(_{24}\)O\(_5\) (M\(^+\)) 332.1624, found 332.16130.

\( (\pm)-(3aR,9^1R)\)-Diethyl 7-methyl-9-oxo-3,3a,6,7,8,9-hexahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (3.52) 

This experiment was performed with glassware which was not flame dried and was not kept under an argon atmosphere. To a solution of tricyclic ketone 3.48 (35 mg, 0.105 mmol) in 99% ethanol (1 mL) was added 2 drops of Raney-Nickel (slurry in H\(_2\)O). The flask was purged three times with argon and the
mixture was then put under 1 atmosphere of hydrogen and stirred for 3.5 hours at room temperature. The mixture was then filtered through celite, rinsing with ethanol. The collected washings were concentrated to give a mixture of the 2 diastereomers of 3.52 (34.2 mg, 97%, dr 5:1).

**Major isomer of 3.52**

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.80 (d, $J=7.0$ Hz, 3H), 0.81-2.04 (m, 12H), 2.16 (ddd, $J=14.9, 3.9, 1.6$ Hz, 1H), 2.22-2.44 (m, 2H), 2.63 (ddd, $J=13.7, 5.5, 1.8$ Hz, 1H), 2.68 (dd, $J=14.8, 5.3$ Hz, 1H), 3.97 (dd, $J=8.5, 6.8$ Hz, 1H), 4.03-4.29 (m, 4H), 5.35 (d, $J=1.7$ Hz, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): δ 14.2 (CH$_3$), 14.3 (CH$_3$), 19.3 (CH$_3$), 26.4 (CH$_2$), 29.3 (CH), 31.2 (CH$_3$), 32.5 (CH$_2$), 37.9 (CH$_2$), 45.6 (CH$_2$), 46.7 (CH), 61.3 (CH$_2$), 61.7 (CH$_2$), 69.3 (C), 73.3 (C), 123.2 (CH), 147.2 (C), 170.7 (C), 170.7 (C), 209.8 (C); IR (neat, cm$^{-1}$): 2922, 1731; HRMS (EI) m/z calcd for C$_{19}$H$_{26}$O$_5$ (M)$^+$ 334.1780, found 334.17608.

(±)-(3a$R$,9$R$)-Diethyl 7-methyl-9-oxo-3,3a,6,9-tetrahydro-1H-cyclopenta[c]indene-4,4(2H)-dicarboxylate (3.53)

This experiment was performed with glassware which was not flame dried and was not kept under an argon atmosphere. Tricyclic ketone 3.48 (17.5, 0.0526 mmol) was placed into a sealed tube with ethanol (95%, 0.2 mL) and RhCl$_3$•xH$_2$O (1.1 mg, 0.00526 mmol) and was heated to 100 °C overnight. The mixture was then filtered through celite, rinsing with DCM, and the collected washings were concentrated. Flash chromatography (10% ethyl acetate in hexanes) provided compound 3.53 (5.2 mg, 30%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.16-1.80 (m, 10H), 1.95-2.06 (m, 4H), 3.01 (d, $J=19.4$ Hz, 1H), 3.09-3.17 (m, 1H), 3.90 (dd, $J=8.7, 6.9$ Hz, 1H), 4.05 (dq, $J=10.7, 7.2$ Hz, 1H), 4.14-4.29 (m, 4H), 5.43 (d, $J=1.8$ Hz, 1H), 5.86-5.88 (m, 1H).
Glossary of Abbreviations

Ac  acetate
BHT  butylated hydroxytoluene (2,6-bis(1,1-dimethylethyl)-4-methylphenol)
Bn  benzyl
Bu  butyl
n-BuLi  n-butyl lithium
tBu  tert-butyl
COSY  COrrrelation SpectroscopY
m-CPBA  meta-chloroperoxybenzoic acid
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCM  dichloromethane
DIPEA  N,N-diisopropylethylamine
DMF  dimethylformamide
DMSO  dimethyl sulfoxide
dr  diastereomeric ratio
Et  ethyl
Ether  Diethyl ether
EtOAc  ethyl acetate
EI  electron ionization
HMBC  Heteronuclear Multiple Bond Correlation
HMPA  Hexamethylphosphoramide
HMQC  Heteronuclear Multiple Quantum Coherence
HRMS  High-Resolution Mass Spectrometry
IR  Infra-Red
LDA  lithium diisopropylamide
Me  methyl
MP  melting point
NMO  4-Methylmorpholine N-oxide
NMR  Nuclear Magnetic Resonance
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References


Supporting Information
TIPSO
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CO₂Et
2.41-E