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Treball Final de Grau

Synthesis of protected 1,3-diols and 1,2-diols via C–H activation processes.
Síntesi d'1,3-diols i 1,2-diols protegits via processos activació C–H.

Pep Mòdol Balanzat
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B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

AGRAÏMENTS

Primer de tot, voldria agrair al meu tutor, el Dr. Xavier Ariza per tot el temps dedicat i els coneixements que he après durant aquests últims mesos.

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REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

This Bachelor's Thesis, focused on the metal-catalysed synthesis of protected 1,3-diols and 1,2-diols as acetals through Rh-catalysed cyclisation of bishomoallylic and homoallylic alcohols using propanal as the aldehyde component, aligns with several United Nations Sustainable Development Goals. The project integrates advanced scientific training, innovation in catalytic synthetic methodology, and more sustainable laboratory practices. By employing catalytic processes, generating intermediates *in situ*, and opting for less hazardous reagents, the work contributes to global objectives in education, responsible production, industrial innovation, and health-related scientific progress.

SDG 3: Good Health and Well-Being

The present research contributes indirectly to SDG 3 by advancing synthetic methodologies relevant to the development of bioactive molecules. The 1,3-diol and 1,2-diol motifs targeted in this work are common structural elements in natural products, pharmaceutical intermediates, and other biologically active compounds. By exploring an efficient Rh-catalysed cyclisation assisted by propanal, this project generates fundamental knowledge that may support future progress in medicinal chemistry and drug development.

SDG 4: Quality Education

This project directly supports SDG 4 by fostering advanced scientific training and strengthening competencies in organic synthesis, catalysis, and experimental design. The work promotes hands-on learning, critical thinking, and research-based education within the field of synthetic organic chemistry. By engaging with modern catalytic methodologies, analysing reaction outcomes, and applying rigorous laboratory practices, this TFG enhances both technical expertise and scientific literacy, contributing to high-quality education in chemical sciences.

SDG 9: Industry, Innovation and Infrastructure

The development of new or improved synthetic routes aligns with SDG 9 by promoting innovation in chemical processes relevant to high-value industries such as pharmaceuticals, fine chemicals, and materials science. The Rh-catalysed cyclisation strategy investigated in this work offers an alternative approach to accessing 1,3-diol and 1,2-diols frameworks, evaluating the feasibility of forming hemiacetal intermediates *in situ*. Such methodological advancements have the potential to influence future synthetic work, enabling more efficient, selective, or versatile transformations that can be applied in industrial research and development.

SDG 12: Responsible Consumption and Production

This project supports SDG 12 by applying principles of green chemistry and promoting more sustainable synthetic practices. The use of catalytic processes, the generation of intermediates *in situ*, and the avoidance of toxic reagents contribute to reducing chemical waste and minimising the environmental footprint associated with organic synthesis. By exploring streamlined reaction pathways and choosing less hazardous reagents, this work reinforces responsible resource management and encourages more environmentally conscious approaches in chemical research.

CONTENTS

1. SUMMARY

This work investigates the synthesis of protected 1,3- and 1,2-diols through Rh(III)-catalysed C–H activation processes, focusing on the intramolecular cyclisation of hemiacetals of bishomoallylic alcohols and exploring a new approach using homoallylic alcohols. The study is framed within the ongoing research efforts in our research group, aimed at the development of novel and efficient synthetic methodologies to access 1,3-diol and 1,2-diol motifs. Given the recurrent presence of these structural units in natural products, pharmaceuticals, and other bioactive compounds, the development of efficient and stereoselective synthetic methodologies remains a fundamental challenge in organic chemistry.

The synthetic strategy explored is based on the *in situ* formation of hemiacetals from different alcohols and propanal, a process that involves a hemiacetal formation equilibrium that is key for obtaining the desired compounds. This synthetic route avoids the use of prefunctionalised substrates and enables the direct formation of protected *cis*-1,3-diols and 1,2-diols through the generation of six- and five-membered cyclic intermediates. The influence of substrate structure, particularly the differences among various bishomoallylic alcohols, on reactivity, cyclisation efficiency, and stereochemical outcome has been studied, and for the first time within the research group, experiments using a primary homoallylic alcohol have been carried out.

Hemiacetals of bishomoallylic alcohols exhibit a greater tendency to undergo cyclisation, which is attributed to their increased conformational flexibility, favouring hemiacetal formation and intramolecular attack on the π-allyl–Rh intermediate. Conformational analysis allows the observed diastereoselectivity to be rationalised, highlighting a preference for chair conformations in which the bulkier substituents occupy equatorial positions.

Keywords: 1,3-diols, 1,2-diols, C–H activation, rhodium catalysis, allylic functionalisation, cyclisation of hemiacetals.

2. RESUM

En aquest treball s'estudia la síntesi d'1,3- i 1,2-diols protegits mitjançant processos d'activació d'enllaços C–H catalitzats per Rh(III), centrant-se en la ciclització intramolecular d'hemiacetals d'alcohols bishomoal·lílics i explorant un nou enfocament amb alcohols homoal·lílics. Aquest estudi s'emmarca dins dels esforços de recerca actuals orientats al desenvolupament de noves i eficients metodologies sintètiques per a l'obtenció de motius 1,3-diol i 1,2-diol. Donada la presència recurrent d'aquests motius en productes naturals, fàrmacs i altres compostos bioactius, el desenvolupament de metodologies sintètiques eficients i estereoselectives continua sent un repte fonamental en química orgànica.

L'estratègia sintètica investigada es basa en la formació *in situ* d'hemiacetals a partir de diferents alcohols i propanal, procés que implica un equilibri de formació hemiacetàlic clau per a l'obtenció dels compostos desitjats. Aquesta ruta sintètica evita l'ús de substrats prefuncionalitzats i permet l'obtenció directa de *cis*-1,3-diols i 1,2-diols protegits mitjançant la formació d'intermediaris cíclics de sis i cinc membres. S'ha estudiat la influència de l'estructura del substrat, especialment les diferències entre diversos alcohols bishomoal·lílics, sobre la reactivitat, l'eficiència de la ciclació i el resultat estereoquímic, i s'han realitzat, per primer cop dins del grup de recerca, assaigs amb un alcohol homoal·lílic primari.

Els hemiacetals d'alcohols bishomoal·lílics mostren una major tendència a ciclar, atribuïda a la seva major flexibilitat conformacional, que afavoreix la formació de l'hemiacetal i l'atac intramolecular sobre l'intermedi π-al·lil–Rh. L'anàlisi conformacional permet entendre la diastereoselectivitat observada, destacant la preferència per conformacions de cadira en què els substituents més voluminosos ocupen posicions equatorials.

Paraules clau: 1,3-diols, 1,2-diols, activació C–H, catàlisi amb rodi, funcionalització al·lílica, ciclització d'hemiacetals.

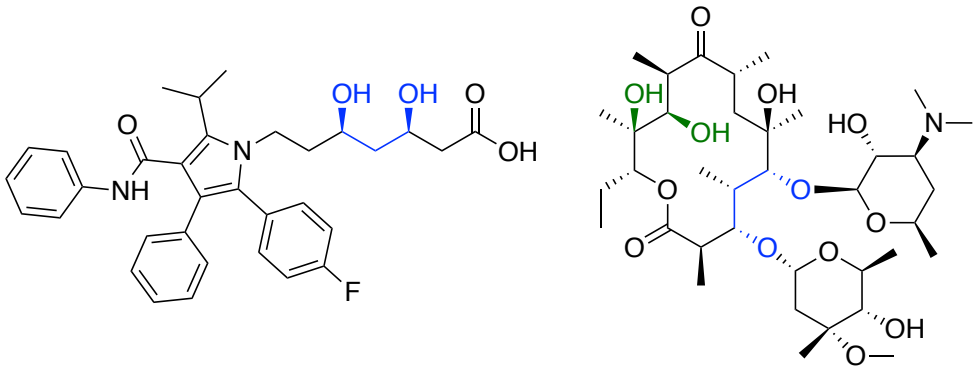
3. INTRODUCTION

At present, drug research and production are mainly focused on the synthesis of compounds that structurally resemble biologically active natural products, those which commonly exhibit useful effects and applications for human health. One of the most common moieties present in these drugs are polyols, including 1,3- and 1,2-diols, which feature in various families of compounds such as polyketides, statins and sugars.[1,2]

Polyketides, which take part in essential metabolic pathways, vary a lot in structure, which gives them different biological activities, acting as antibiotics, cancer chemotherapeutics, and cholesterol lowering agents.[3] Among them, for example, Erythromycin A is an antibiotic used for clinical medicine, pulmonary infections and as a substitute for penicillin-allergic patients, it is formed by a macrolide skeleton, a polyketide derived subgroup, with two sugars attached. If we were to consider only the aglycon, we would find a 1,3-diol and even several 1,2-diols, some protected and others unprotected, as we see in Figure 1.[4]

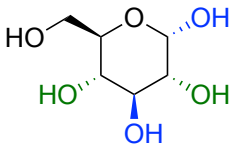
Statins, on the other hand, are known for their powerful ability to regulate cholesterol in the metabolism, thus making them useful for preventing cardiovascular diseases. In atorvastatin's structure we can clearly find this relevant motif (Figure 1).[1]

Simple carbohydrates, such as sugars, frequently contain 1,3-diol and 1,2-diols motifs, with D-glucose being the most representative example. This compound features the 1,3-diol and 1,2-diol arrangements not only in its linear form but also within its cyclic pyranose structure.



Atorvastatin

Erythromycin A



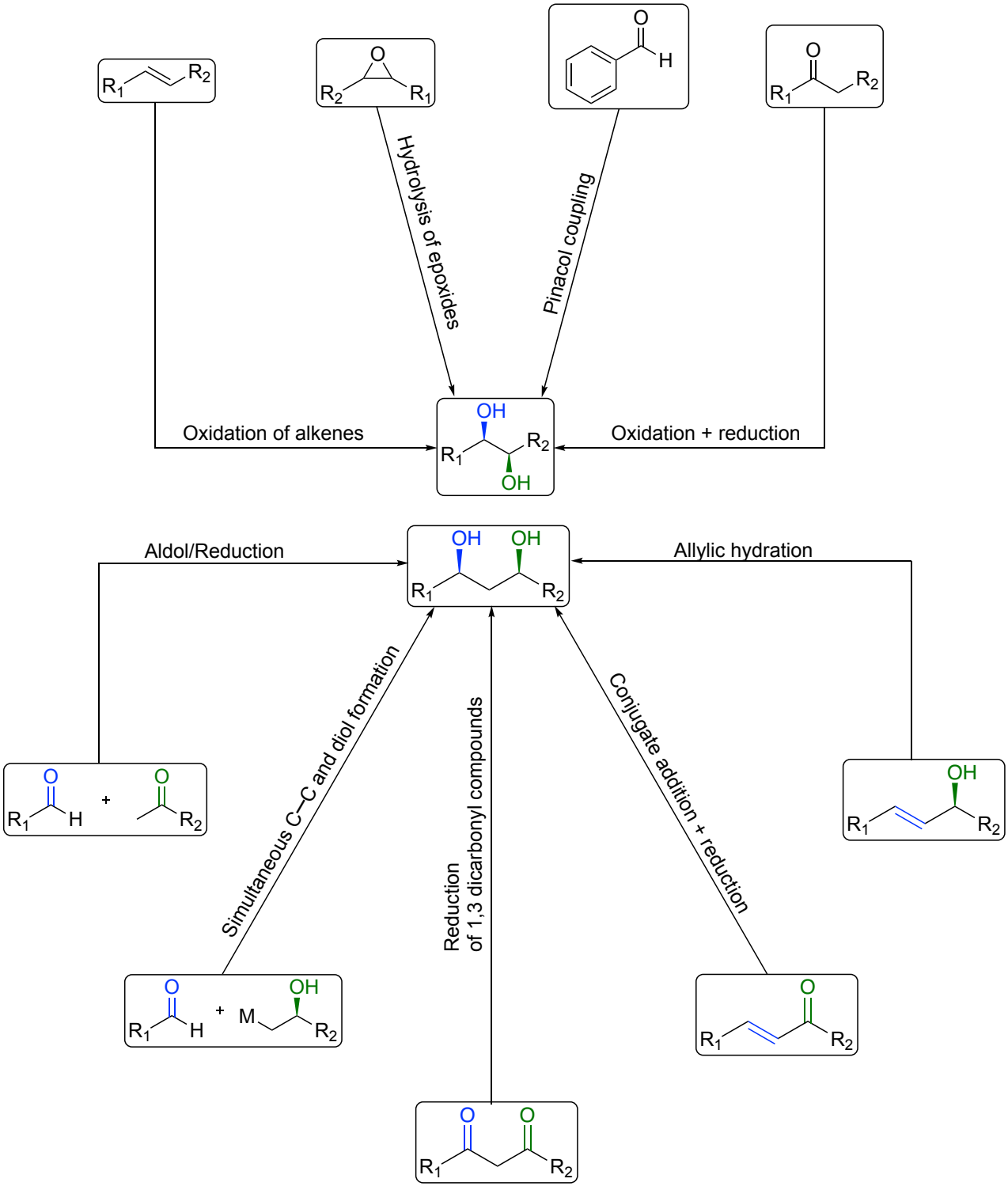
α-D-glucopyranose

Figure 1. Examples of 1,3- and 1,2-diol containing molecules.

Owing to these structural and biological properties, the stereoselective synthesis of both 1,3- and 1,2-diols has become a central goal in organic chemistry. Natural products such as macrolides, polyketides and polyols often contain multiple contiguous stereogenic centres, making the controlled formation of 1,3- and 1,2-diol motifs a persistent synthetic challenge.[5,6]

3.1. CLASSICAL SYNTHETIC METHODS FOR THE OBTENTION OF 1,3-DIOLS AND 1,2-DIOLS

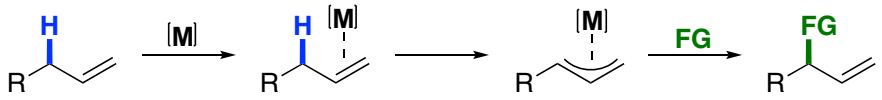
Over the decades, numerous methodologies for the synthesis of both 1,3- and 1,2-diols have been explored and thoroughly studied. Classical approaches include carbonyl addition reactions, allylic hydration and conjugate addition followed by reduction for 1,3-diols, as well as alkene oxidation processes, epoxide hydrolysis, pinacol-type couplings and sequential oxidation–reduction strategies for the preparation of 1,2-diols, as we see in Scheme 1.[6,7,8] However, many of these synthetic routes rely on prefunctionalised substrates, the use of harsh or stoichiometric reagents, or lengthy multistep sequences, and often suffer from limitations in step economy and regio- or stereocontrol. These drawbacks have led to growing interest in the development of alternative strategies, such as direct C–H activation approaches, particularly those mediated by transition-metal catalysis.[5,9,10]



Scheme 1. Classical synthetic methods to obtain 1,2-diols and 1,3-diols.

3.2. TRANSITION METAL CATALYSED ALLYLIC C–H ACTIVATION AND FUNCTIONALISATION

A possible key step to prepare a wide variety of bioactive molecules and ligands containing 1,3- and 1,2-diols could involve a transition-metal catalysed allylic C–H bond activation and functionalisation. This transformation allows a rather inert bond like C–H to become more reactive through its cleavage, for a further later introduction of other functional groups, as we see in Scheme 2. Consequently, this has awakened a high interest in modern organic synthesis. Transition metal catalysts have been found as a magnific tool to achieve this type of activation with palladium, rhodium and iridium as main elements.[11]



Scheme 2. Activation and functionalisation of an allylic C–H bond.

In every organic reaction, conformation of molecules, chemical environment and reaction conditions play a crucial role, and in order to make this functionalisations work, we need to acknowledge different features.

Regioselectivity is the most limiting factor in these specific reactions as the coexisting of different C–H bonds with similar reactivity, other functional groups possibly coordinating with transition metals and even molecule conformation can affect reaction yields by forming undesired products. To address it, these limitations must be optimized and can, indeed, work to our advantage when properly directed. For instance, certain functional groups, such as those who contain oxygen or nitrogen, can act as directing groups to coordinate the metal toward the desired C–H bond, forming 5 or 6 membered rings depending on the molecule skeleton (Figure 2).

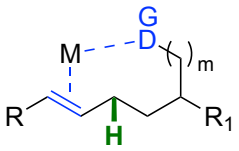
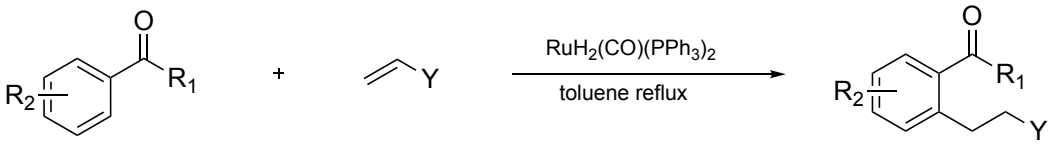


Figure 2. Metal-directing group coordination.

Each of the previously mentioned transition metals gives the reaction a different approach. Palladium complexes, which are by far the most studied, with different allylic transformations achieved such as oxidation, amination, alkylation and arylation,[9] usually achieve linear-type selective functionalisation of terminal alkenes, while rhodium and iridium ones obtain branch selective functionalisation not only in terminal alkenes but also in internal olefins.[8,12]

3.3. PREVIOUS RESEARCH

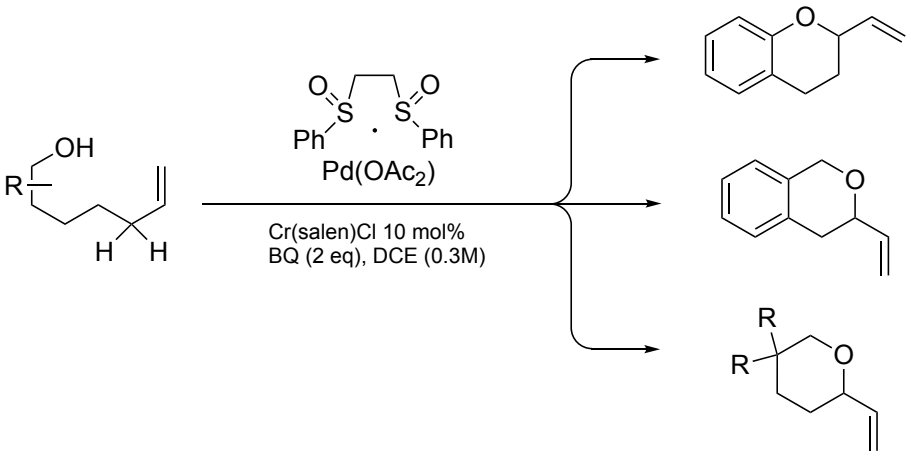
The development of allylic C–H activation has not always been as straightforward as it may appear today. In fact, it has undergone a profound transformation from a mechanistic curiosity to a fundamental tool in modern organic synthesis. In the early 1990s Chatani and co-workers presented an efficient alternative to classical prefunctionalised pathways for C–H bond activation, in which they used a rhodium catalyst to alkylate, alkenylate and acylate, selectively, aromatic compounds, through the usage of directing groups such as carbonyls and olefins (Scheme 3).[10,13]



Scheme 3. Chatani's and co-workers C–H bond activation.

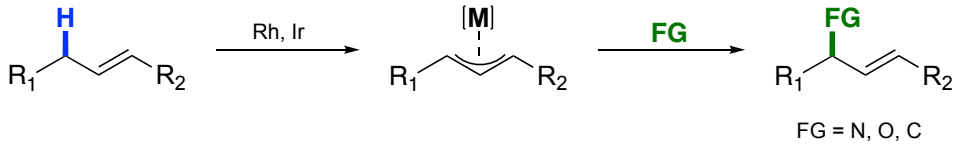
Later on, Murai, Kakiuchi and co-workers, including Chatani himself, reported a new ruthenium catalytic reaction, which enabled regioselective arylation of aromatic ketones and amides, with alkyl boron compounds and involving C–H bond cleavage. These advances introduced a new paradigm in organic synthesis, where the inert C–H bond itself could serve as a reactive handle.[11,14]

Among all C–H transformations, allylic C–H activation has proven to be one of the most versatile and powerful, allowing direct conversion of alkenes into oxygenated, aminated, or alkylated products. White and co-workers, reported the Pd(II)-catalysed allylic oxidation of terminal alkenes, a pioneer intramolecular conversion of alkenes into oxygenated products, concretely oxygen heterocycles such as chromans, isochromans and pyrans, by using phenols and aliphatic alcohols as nucleophiles under uniform and mild conditions, as shown in Scheme 4.[12,15]This same group years later, developed the enantioselective synthesis of isochroman motifs using, this time, a novel chiral ligand (ArSOX).[13,16]



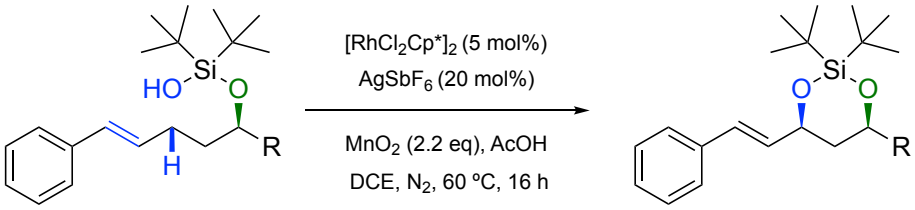
Scheme 4. Pd(II)-catalysed allylic oxidation of terminal alkenes.

Even though both these studies represented a big step forward in the C–H functionalization with hydroxyls as nucleophiles, they were limited to terminal olefins, thus, Blakey and co-workers introduced a method in which they studied the intermolecular allylic C–H etherification of internal olefins. Branch selective allylic etherification and amination were accomplished by using a rhodium(III) catalyst in a wide variety of alcohols and olefins, even with the usage of another metal-catalyst from the IX group such as Ir(III) (Scheme 5).[17,18]



Scheme 5. IX group metal-catalysed allylic functionalisation.

Following these advances, our research group carried out a study in which they used the same rhodium catalyst to functionalise an allylic C–H bond to obtain selectively protected syn-1,3-diols. This was accomplished by employing silanols as nucleophiles which underwent intramolecular cyclisation to form six-membered silaketal rings (Scheme 6).

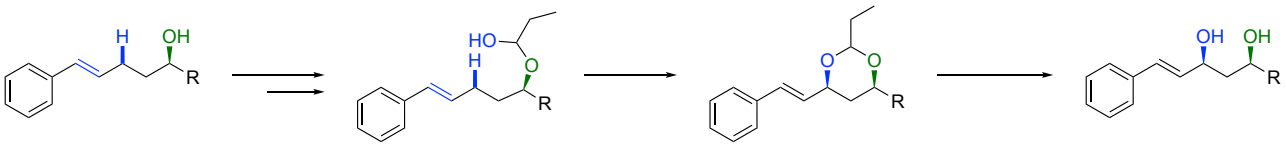


Scheme 6. Synthesis of protected 1,3-diols through silaketal intermediate.

It is worth noting the importance of the reaction conditions which were refined regarding Blakey's earlier work,[18] which had a great success in the very beginning. A significant cut down on silver salts such as silver acetate, replaced by manganese dioxide was done not only to lower the cost of the reaction, but also to achieve a more controlled reaction medium in terms of free metal ions in solution, which could cause undesired products. In addition, $AgSbF_6$ concentration was gently reduced from a 30 mol% to 20 mol% for the same reasons explained above.

Overall, these studies turned out to be a great variant for this type of functionalisations as the reaction proceeded smoothly, affording good yields and diastereoselectivity across different substrates. The only drawback of the reaction was that it occurred exclusively when the olefin moiety was conjugated to a phenyl group.

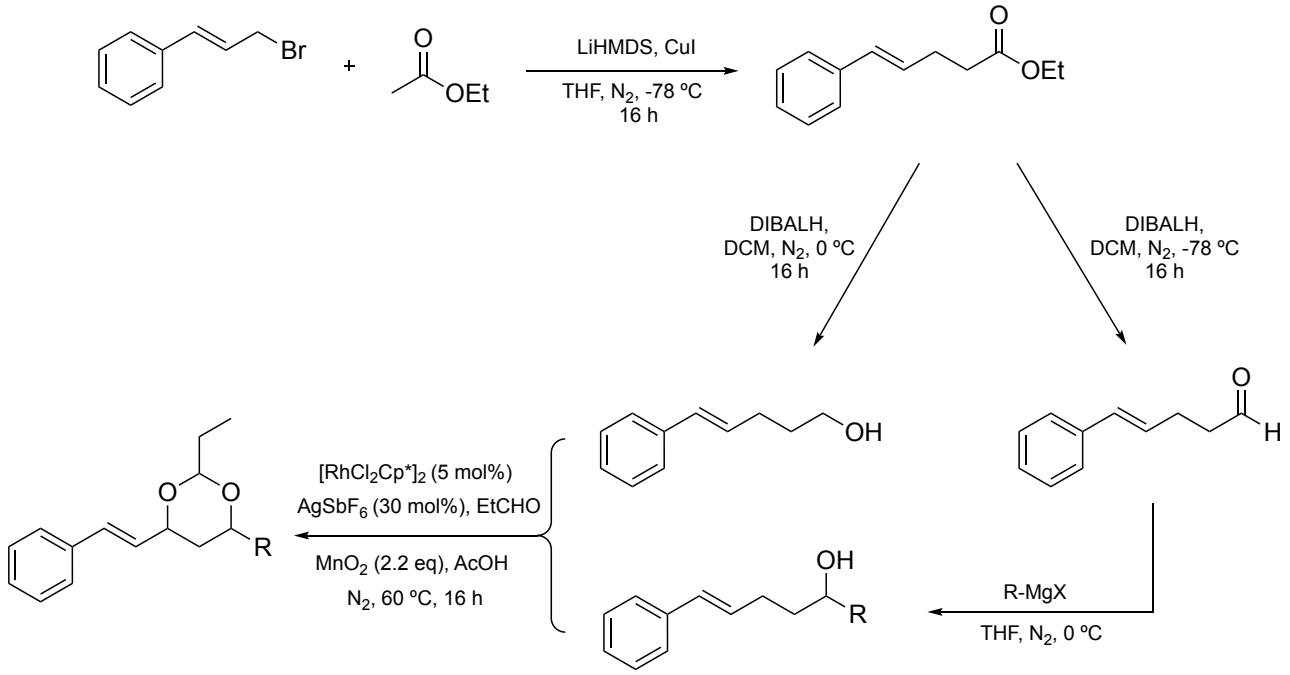
In recent work, our group accomplished the rhodium catalysed functionalisation of C–H allylic positions, which yielded selectively protected *syn*-1,3-diols in the form of six-membered acetal ring intermediates. The followed strategy was the cyclisation of hemiacetals prepared from the corresponding bishomoallylic alcohols. Such moieties can then be deprotected through classic methodologies to afford the diol (Scheme 7).



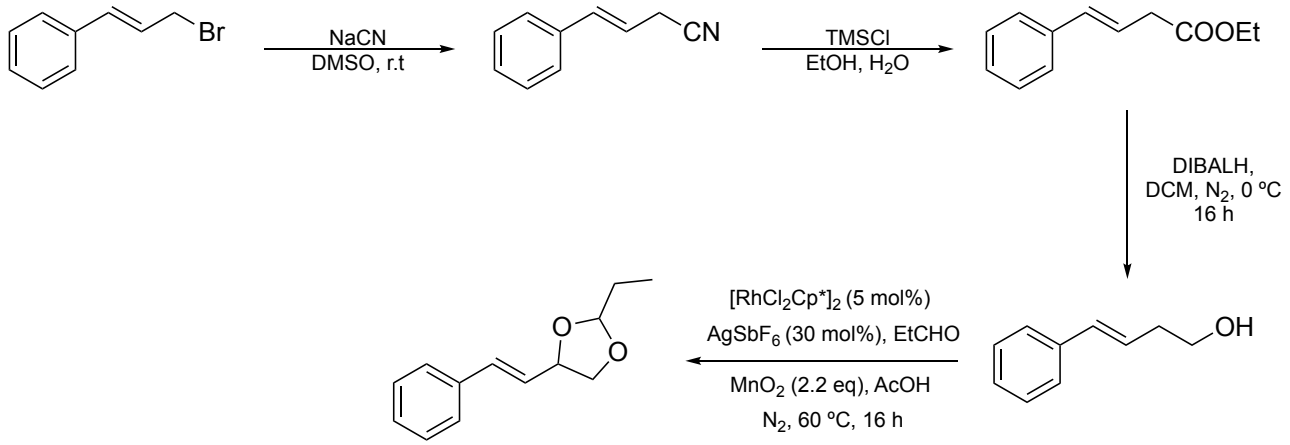
Scheme 7. Proposed synthetic route in this work.

4. OBJECTIVES

The present work aims to study and portray the ongoing research on the development of novel synthetic methodologies to obtain 1,3-diol and 1,2-diol moieties. The proposed methods rely on the Rh-catalysed allylic C–H activation of bishomoallylic (Scheme 8) and homoallylic (Scheme 9) alcohols that have been reacted *in situ* to form hemiacetals, which are expected to act as directing groups for stereoselective allylic functionalisation reactions.

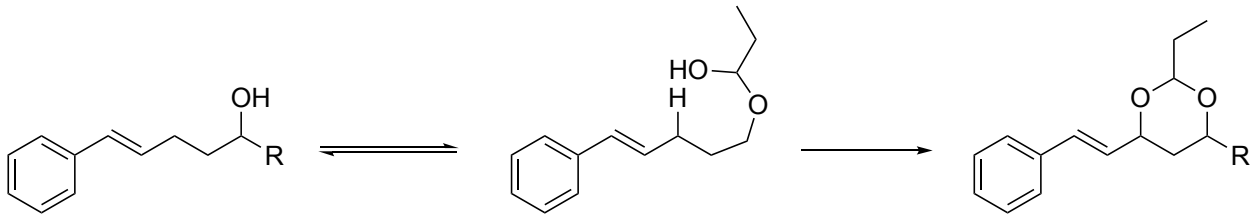


Scheme 8. Synthetic route proposed for the obtention of protected 1,3-diols.



Scheme 9. Proposed synthetic route for the obtention of protected 1,2-diols.

The reaction mechanism involves a pre-equilibrium for the formation of the corresponding hemiacetals, which is shifted toward the formation of the desired protected *syn*-1,3-diols or 1,2-diols under the applied reaction conditions, as shown in Scheme 10.



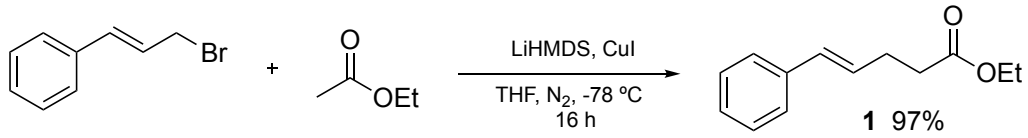
Scheme 10. Proposed route for the obtention of the cyclised product.

Although the reaction has not yet been fully optimized, the main objective at this stage is to isolate and characterize the obtained protected *syn*-1,3-diols, in order to subsequently perform the deprotection step and access the free 1,3-diol motifs. This process also applies for the obtention of *syn*-1,2-diols.

5. PREPARATION OF HOMOALLYLIC AND BISHOMOALLYLIC SUBSTRATES

5.1. SYNTHESIS OF ESTER 1

For the first reaction of our synthetic pathway, the one we show below in Scheme 11, ethyl acetate undergoes an allylic alkylation type reaction with commercial cinnamyl bromide in presence of copper (I) iodide.

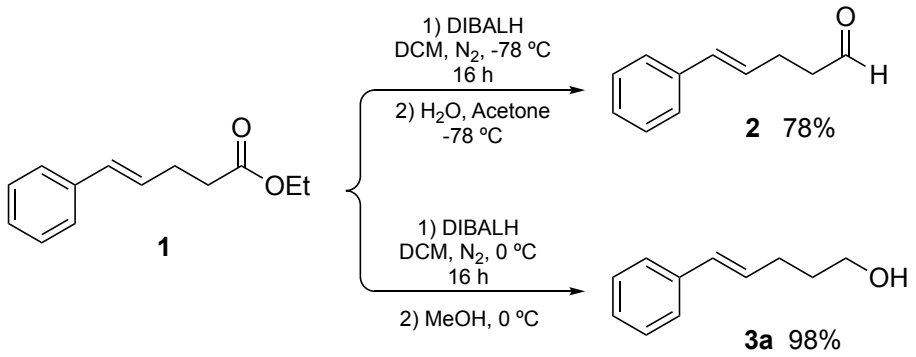


Scheme 11. Reaction to obtain ester **1**.

The overall success and efficiency of this transformation is influenced by the role of CuI, both parts, iodide anion and copper (I) cation play different and essential functions. Initially an iodide–bromide exchange takes place, generating the corresponding cinnamyl iodide, which is more reactive toward nucleophilic substitution, as iodide is a better leaving group than bromide. Simultaneously, a Cu(I) enolate is generated from ethyl acetate enabling a transmetalation step followed by an allylic substitution, leading to the desired product with high yield and regioselectivity.[19]

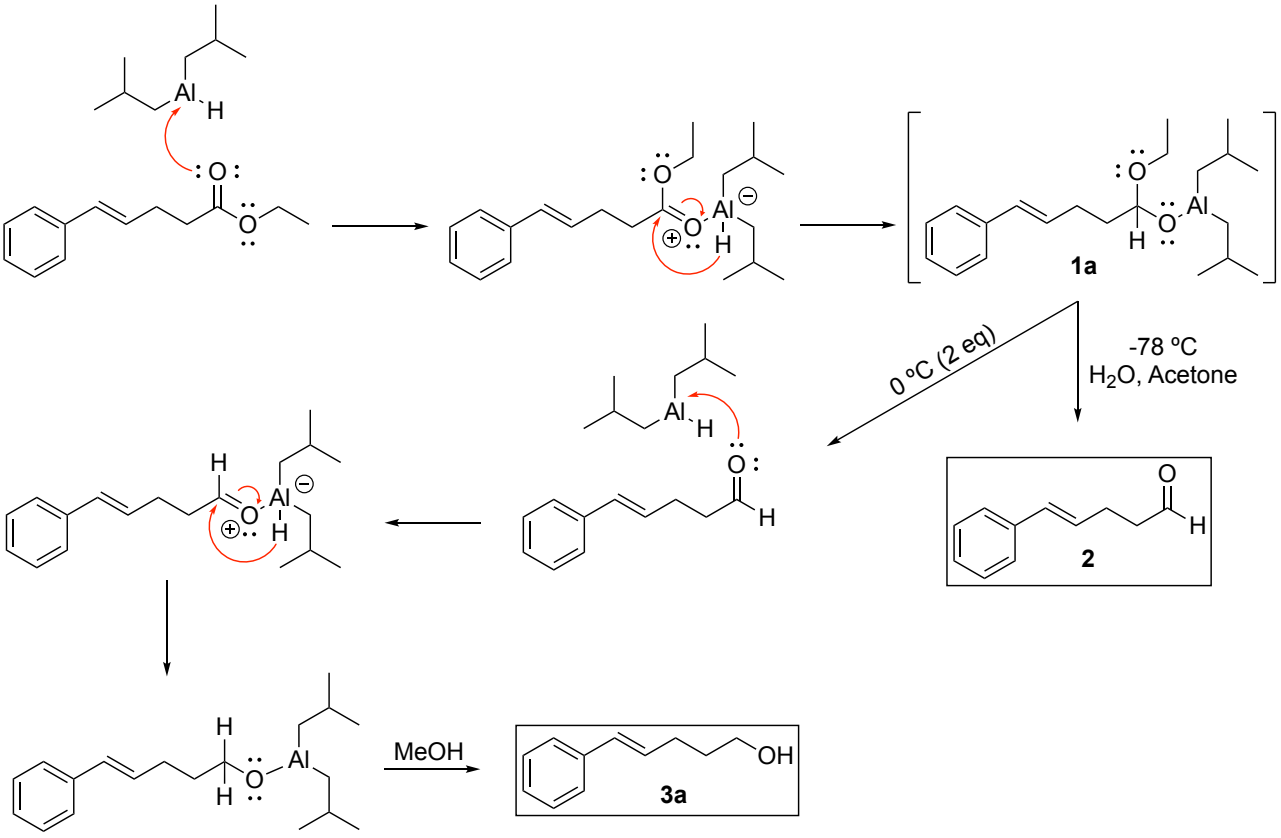
5.2. REDUCTION OF ESTER 1

The following step is the reduction of ester **1**, which is afforded with DIBALH, but we must consider that a slight variation of the reaction conditions leads to two different outcomes as we show in Scheme 12. Temperature and DIBALH equivalents control the final oxidation state.



Scheme 12. Possible pathways for the reduction of ester **1**.

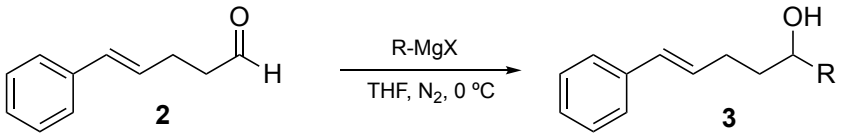
When the reaction is performed at −78 °C, the reduction stops at the aldehyde stage. However, when the reaction is carried out at a higher temperature (0 °C), the reduction proceeds to completion, giving the corresponding primary alcohol **3a** instead. This difference arises because lower temperatures slow down the second hydride transfer due to stabilisation of intermediate **1a**, allowing selective formation of the aldehyde, whereas higher temperatures and DIBALH equivalents favour further reduction to the alcohol (Scheme 13).[20] For the obtention of primary homoallylic alcohol **7** we used the same conditions as for the obtention of primary alcohol **3a.**



Scheme 13. Mechanism for the reduction of ester **1.**

5.3. General procedure for the formation of secondary alcohols

For the obtention of secondary alcohols, aldehyde **2** was subjected to nucleophilic attack of several organomagnesium compounds (Scheme 14), commonly known as Grignard reagents. In Table 1, results of three different attacks of this type of compounds with different substituents are shown, with their respective yields. This well-established reaction allowed to obtain the desired secondary alcohols with fairly good yields.



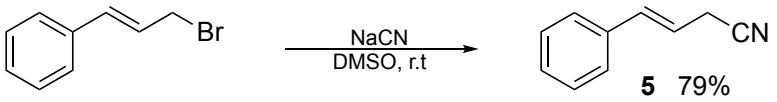
Scheme 14. Obtention of secondary alcohols.

R	Product	Yield (%)
$Ph(CH_2)_2$	**3b**	87
^{i}Pr	**3c**	81
Ph	**3d**	87

Table 1. Results for secondary alcohols.

5.4. Cyanation of cinnamyl bromide

As the first step toward accessing the 1,2-diol moiety, the corresponding nitrile was prepared through the classical Kolbe nitrile synthesis, in which commercially available cinnamyl bromide undergoes a nucleophilic substitution with 2 equivalents of sodium cyanide in DMSO (Scheme 15). This S_N2-type transformation is known to proceed efficiently, rapidly and exothermically for allylic halides, leading to the formation of the nitrile in high yields. After completion, the crude reaction mixture is poured into cold hexane, where the product precipitates as a solid in suspension. This precipitation-based work-up is consistent with literature reports and avoids prolonged handling of cyanide-containing mixtures which lead to brownish solutions and poor yields. [21,22,23]



Scheme 15. Reaction for the obtention of cyanide compound **5**.

Entry	Rate of addition	Reaction time (h)	Temperature	Yield (%)
Initial conditions	Slow	Overnight	r.t	17
Modified conditions	Dropwise	2	r.t	80
Kawai *et al.* [22]	n.d	5 min	r.t	82
Friedman *et al.* [23]	Dropwise	0.6	60-90º C	92
Komabayashi *et al.* [21]	n.d	24	40 ºC	>99

Table 2. Conditions for the cyanation reaction.

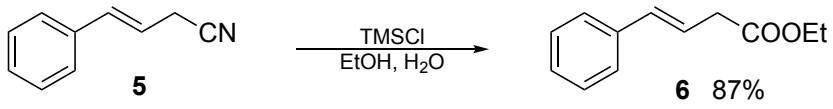
The first time this reaction was performed, it was done with reflux of ACN and DMF overnight, results turned out to be very poor, thus the next time we used the conditions shown in Table 2 which yielded only a 17% of the desired nitrile. Consequently, several parameters were modified in order to improve the efficiency of the transformation.

The main change was the rate of addition of the cinnamyl bromide solution in DMSO to the NaCN suspension in DMSO. Initially, the reagent was added relatively slowly but not dropwise, and was later replaced by a strictly dropwise addition, which allowed for better yields. Throughout the addition, the reaction mixture was stirred and submerged in a water bath to moderate the temperature, thus, the reaction temperature was adjusted. According to precedents in literature, elevated temperatures are required for complete conversion in Kolbe nitrile syntheses. However, given the highly exothermic nature of the reaction, external heating was avoided, as the heat released during the addition was considered sufficient to provide the thermal energy required for the reaction to proceed efficiently, and higher temperatures usually favour side product formation.

After complete addition of the cinnamyl bromide, the reaction mixture was allowed to stir for an additional 5 minutes before being worked up following the standard decantation and extraction procedure, thus the colour of the solution came out to be clearer than before, longer resting periods lead to the brownish solution mentioned before. The solution was not cooled down in an ice bath after completion of the addition nor during the course of the reaction, as DMSO has a relatively high freezing point (18–19 °C), excessive cooling would significantly increase the viscosity of the medium and could lead to partial solidification.

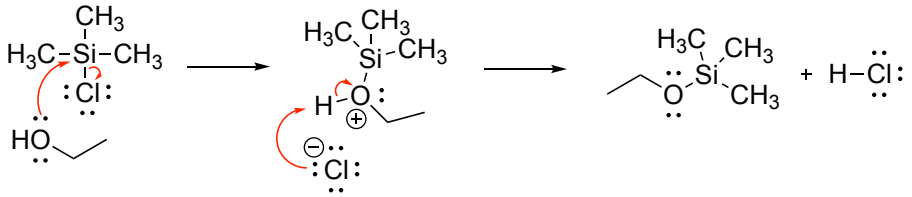
Overall, these modifications led to a significant increase in product yield, affording a yellowish-white crude material in 80% yield, as summarised in Table 2. It is worth noting the importance of the polar aprotic solvent, DMSO, which is crucial for the development of the reaction as it helps with the nucleophilicity of NaCN by minimizing its solvation.[23]

5.5. SYNTHESIS OF ESTER 6



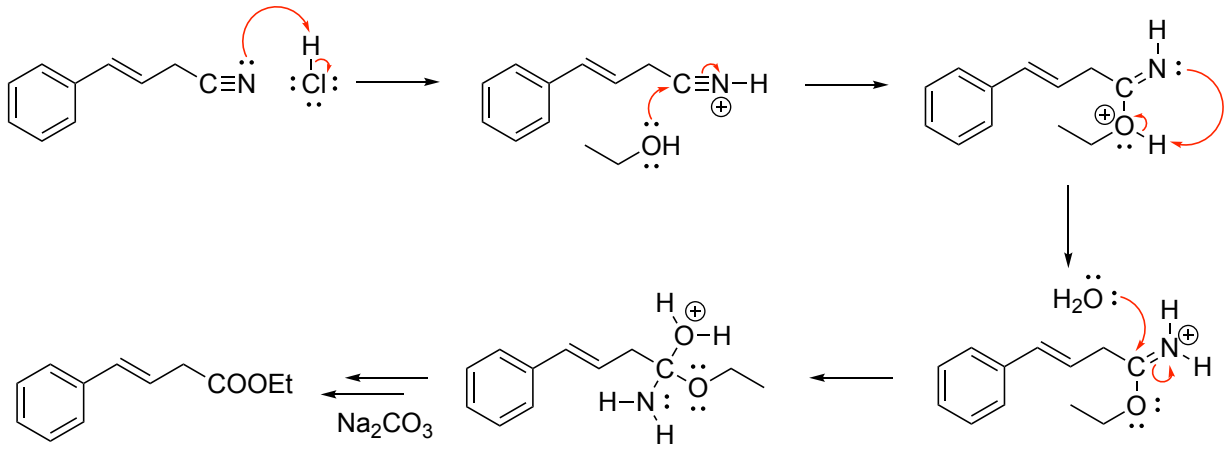
Scheme 16. Reaction for the obtention of ester **6**.

The next step in this synthetic pathway is a modified Pinner reaction (Scheme 16). In its classical form, the Pinner reaction requires anhydrous gaseous HCl through a mixture of a nitrile and an alcohol to generate the corresponding imidate hydrochloride. However, these conditions require a source of gaseous HCl.[21] To avoid this limitation, we employed a milder variant in which HCl is generated *in situ* through the reaction of trimethylsilyl chloride (TMSCl) with ethanol (Scheme 17).[23]



Scheme 17. Mechanism for the *in situ* formation of gaseous hydrogen chloride.

Under these conditions, protonation of the nitrile produces the corresponding nitrilium ion, which is subsequently attacked by ethanol to afford the imidate intermediate (Scheme 18). Although milder than the classical protocol, this system still creates a strong enough acidic medium, which is essential for activating the nitrile but may also promote side pathways depending on the substrate. Water and Na_2CO_3 are used to quench the reaction which yielded an 82% of the desired ester.



Scheme 18. Mechanism for the formation of ester **6**.

6. CYCLISATIONS TO OBTAIN PROTECTED 1,3-DIOLS AND 1,2-DIOLS

6.1. CYCLISATION CONTEXT

Early efforts in the research group focused on promoting cyclisation through hemisilaketal intermediates, which were first prepared prior to the Rh-catalysed step. Subsequent studies explored whether this transformation could be achieved in a single step, directly from bishomoallylic alcohols, thus bypassing the need to isolate or preform the hemisilaketal intermediate. To favour this pathway, aldehydes such as chloral were selected because of their strong electrophilicity, which makes them prone to shifting the equilibrium toward hemiacetals, the reactive oxygenated species. Under these favourable conditions, the bishomoallylic alcohols can condense with the aldehyde to form the hemiacetal *in situ*, which is then competent to enter the Rh-catalysed allylic C–H activation sequence, leading to the cyclised product.

In addition to this, the former master student Josep Castellà also demonstrated that the methodology was not limited to chloral.[24] He examined a variety of electrophiles with different electronic profiles, showing that the efficiency of the cyclisation strongly depends on the aldehyde ability to shift the hemiacetal equilibrium. These results highlighted that achieving productive cyclisation requires a delicate balance between electrophilicity, stability of the intermediate, and compatibility with the Rh(III)-catalysed manifold.

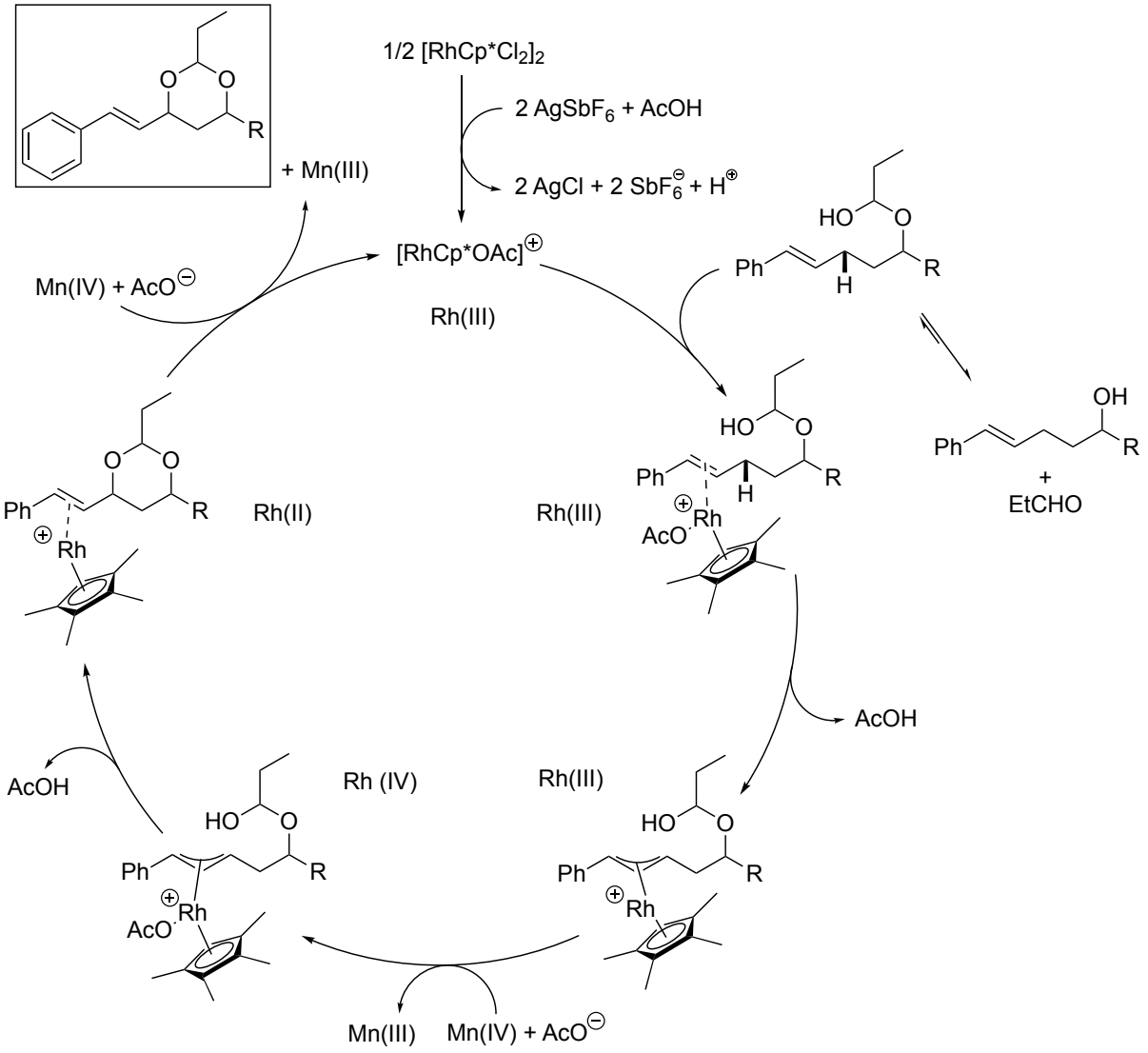
In the present work, we reuse the same conceptual strategy used previously, Rh(III)-catalysed allylic C–H activation of homoallylic or bishomoallylic alcohols in the presence of an aldehyde, but with a different aldehyde, a more volatile one easier to eliminate from the reaction crude. Unlike chloral, propanal does not strongly favour hydrate or hemiacetal formation,[25] meaning that the equilibrium is less biased toward the nucleophilic species, and the hemiacetal must be generated and maintained *in situ* under milder thermodynamic conditions. Therefore, our system requires a finer control of the equilibrium between alcohol, aldehyde, and hemiacetal, and the Rh(III)-catalysed step must operate under conditions where the nucleophile might be in low concentration.

6.2. CATALYTIC CYCLE

Although the proposed catalytic cycle is consistent with established Rh(III) reactivity and with previous literature precedents, it should be noted that the actual mechanism operating under our conditions and nucleophile has not been experimentally verified. The sequence shown therefore represents a plausible mechanistic hypothesis rather than a demonstrated pathway.

The catalytic cycle followed in Rh(III)-catalysed allylic C–H functionalisation has been thoroughly described by Blakey and co-workers, who demonstrated that these transformations proceed through chloride abstraction of the precatalyst, substrate coordination, and acetate-assisted C–H activation via concerted metalation deprotonation pathway (Scheme 19). This generates the key π-allyl–Rh(III) intermediate, which undergoes nucleophilic attack followed by reductive elimination to release the functionalised product. The metal is then restored to its active Rh(III) oxidation state through reoxidation by a terminal oxidant.[17] This general mechanism is very similar to the one proposed for our system, where the *in situ*-generated hemiacetal acts as the nucleophile and MnO_2 serves as the stoichiometric oxidant required to complete the catalytic cycle.

In addition, the efficiency of this transformation strongly depends on the presence of acetate and the terminal oxidant. As shown by Boutadla and co-workers, acetate ligands are crucial for enabling the C–H activation step through a concerted metalation deprotonation pathway, ensuring productive formation of the π-allyl–Rh(III) intermediate.[26] Likewise, MnO_2 plays an essential role in reoxidising Rh(II) back to Rh(III) after reductive elimination, a process known to prevent catalyst deactivation in oxidative cyclisations.[27]

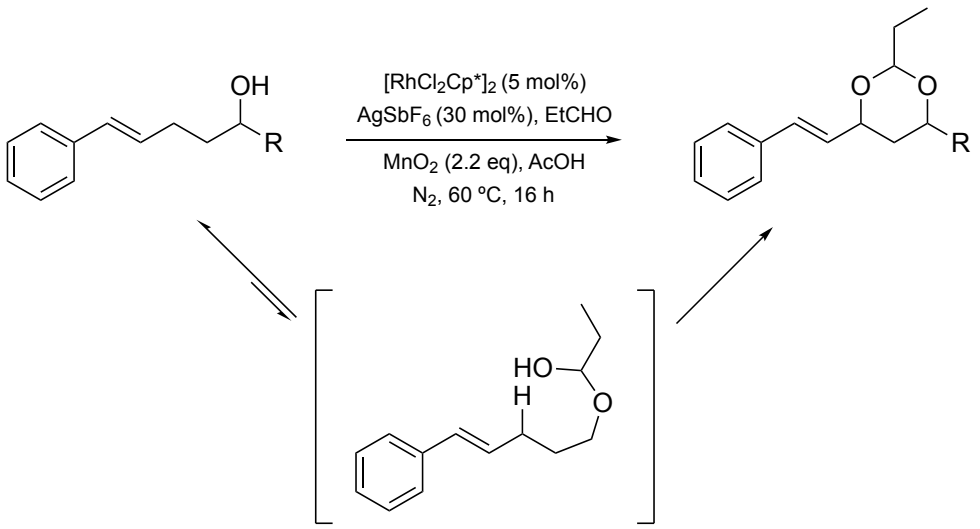


Scheme 19. Proposed catalytic cycle to obtain cyclised product.[17]

6.3. CYCLISATION WITH PROPANAL

6.3.1. Cyclisation of bishomoallylic alcohols

We first evaluated the behaviour of bishomoallylic alcohols under the optimised Rh(III) conditions (Scheme 20). These substrates, which possess additional conformational flexibility compared to homoallylic analogues, can adopt geometries that favour hemiacetal formation and subsequent intramolecular attack on the π-allyl intermediate. Results are shown in Table 3.



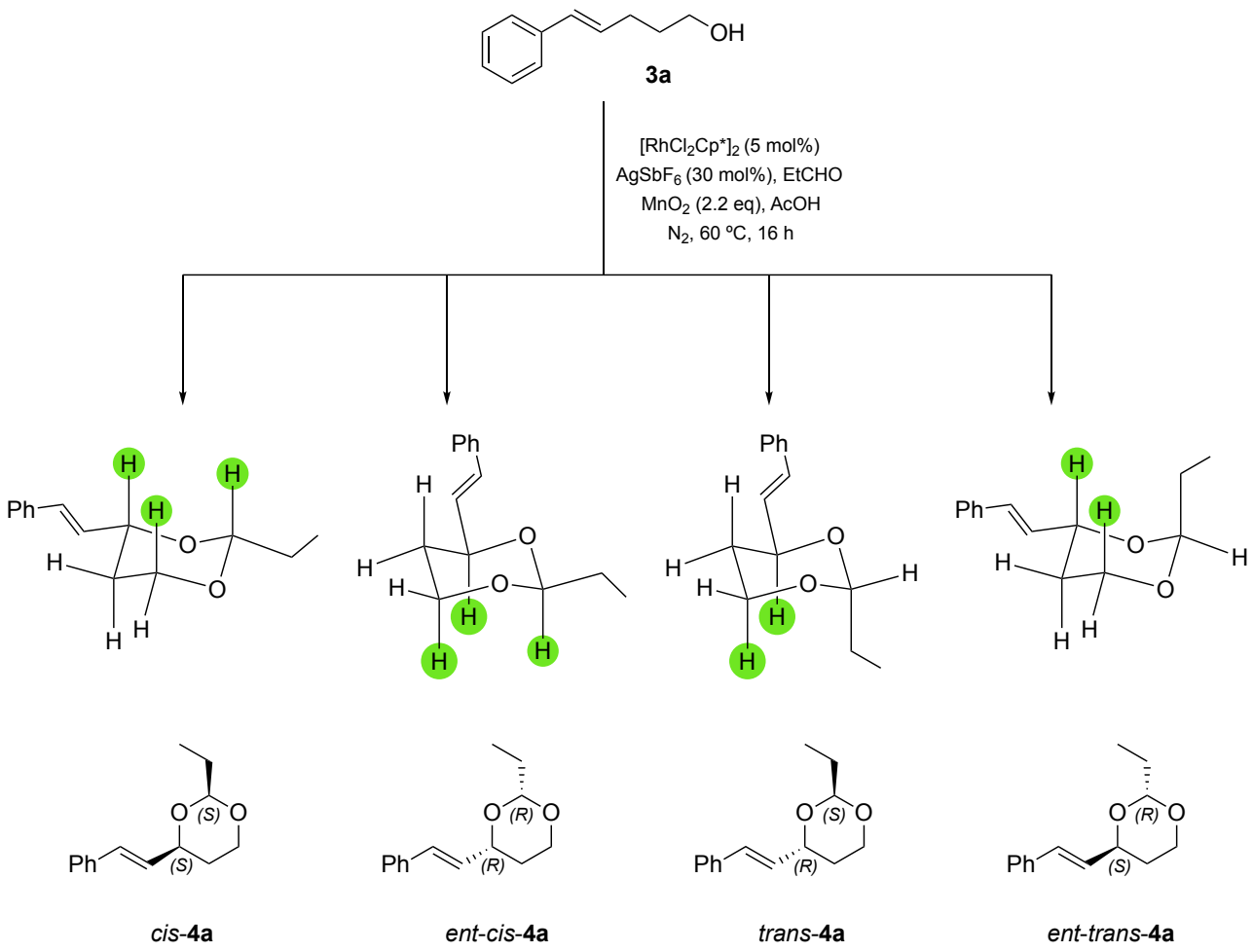
Scheme 20. Reaction for the obtention of protected 1,3-diols.

R	Product	Yield (%)
H	**4a**	40
$Ph(CH_2)_2$	**4b**	4
^{i}Pr	**4c**	-

Table 3. Results for the obtention of protected 1,3-diols.

To rationalise the differences observed in reactivity and yield, we considered both the conformational preferences and relative stability of the hemiacetal intermediates involved in the cyclisation process. While steric effects at the R position influence the accessible chair conformations, the dominant factor appears to be the equilibrium for the hemiacetal formation. Substrates bearing less sterically hindered substituents at R favour hemiacetal formation, thereby increasing the effective concentration of the cyclisation-competent intermediate and leading to higher conversions and yields. In contrast, increased steric bulk disfavours hemiacetal formation, shifting the equilibrium toward the open-chain form and resulting in reduced cyclisation efficiency and lower yields, as summarised in Table 3. These steric effects not only account for the lower yields observed experimentally but also explain the diastereoselectivity of the reaction.

The conformational analysis depicted in Scheme 21 is intended to provide a qualitative rationale for the observed reactivity trends and diastereoselectivity. In principle, the cyclisation of bishomoallylic alcohols could lead to four possible stereoisomers, two pairs of enantiomers, arising from different relative configurations of the newly formed chiral centres. In Scheme 21, the protons highlighted in green indicate those expected to display diagnostic NOESY correlations, allowing differentiation between the possible stereoisomers.



cis-**4a** *ent-cis*-**4a** *trans*-**4a** *ent-trans*-**4a**

Scheme 21. Representative chair conformation for protected 1,3-diols.

Although more than one stereoisomer is likely formed during the reaction, only one diastereomer as a racemic mixture has been characterised, the *cis* isomer (*cis*-**4a** and *ent-cis*-**4a**), as confirmed by COSY and NOESY NMR experiments (Figures 3 and 4). The preferential formation of this diastereomeric pair can be rationalised by the adoption of the most stable chair conformation, in which the bulkier substituents occupy equatorial positions, thereby minimising steric interactions.

For the remaining substrates, the relative configuration of the cyclised products could not be conclusively assigned due to low conversion or insufficient material for full spectroscopic characterisation.

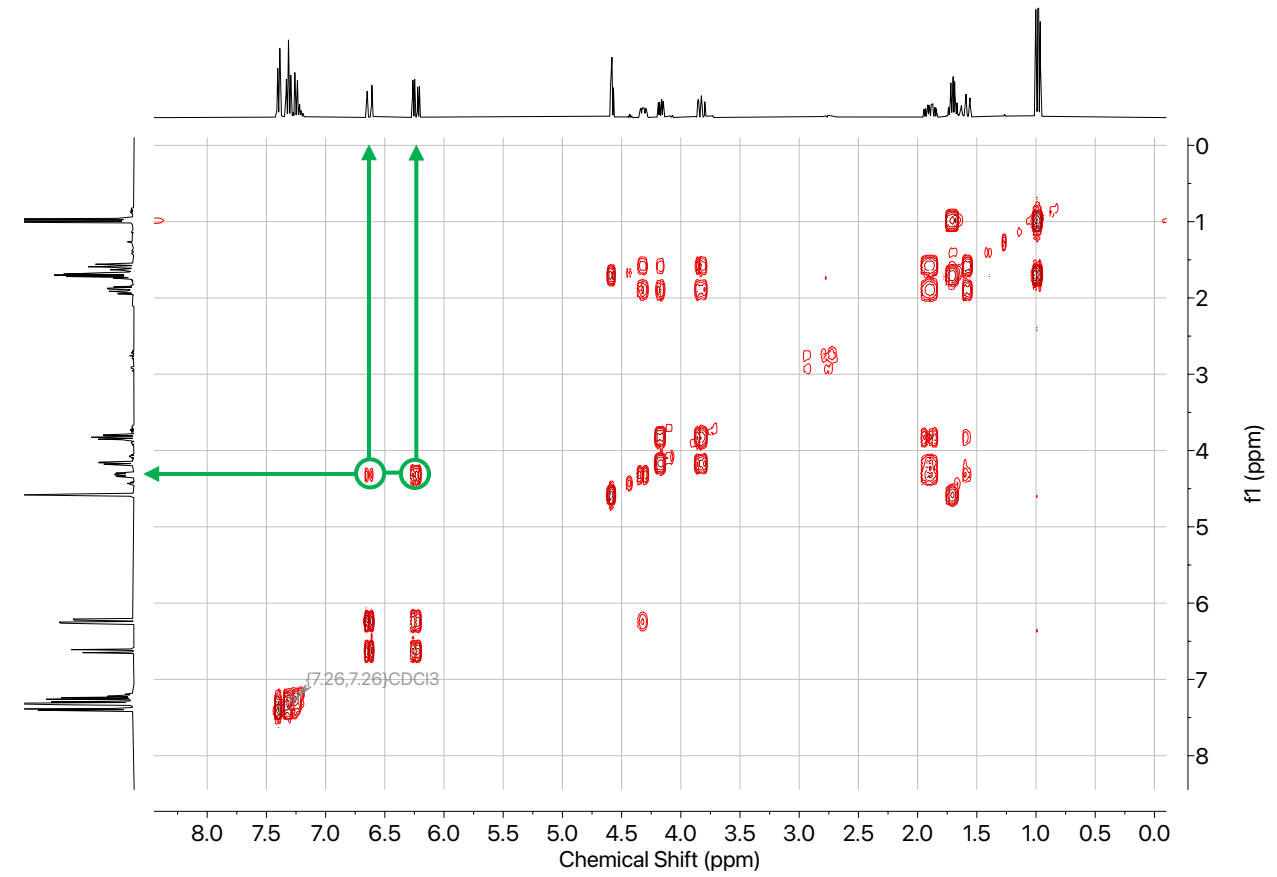


Figure 3. COSY NMR spectrum of **4a.**

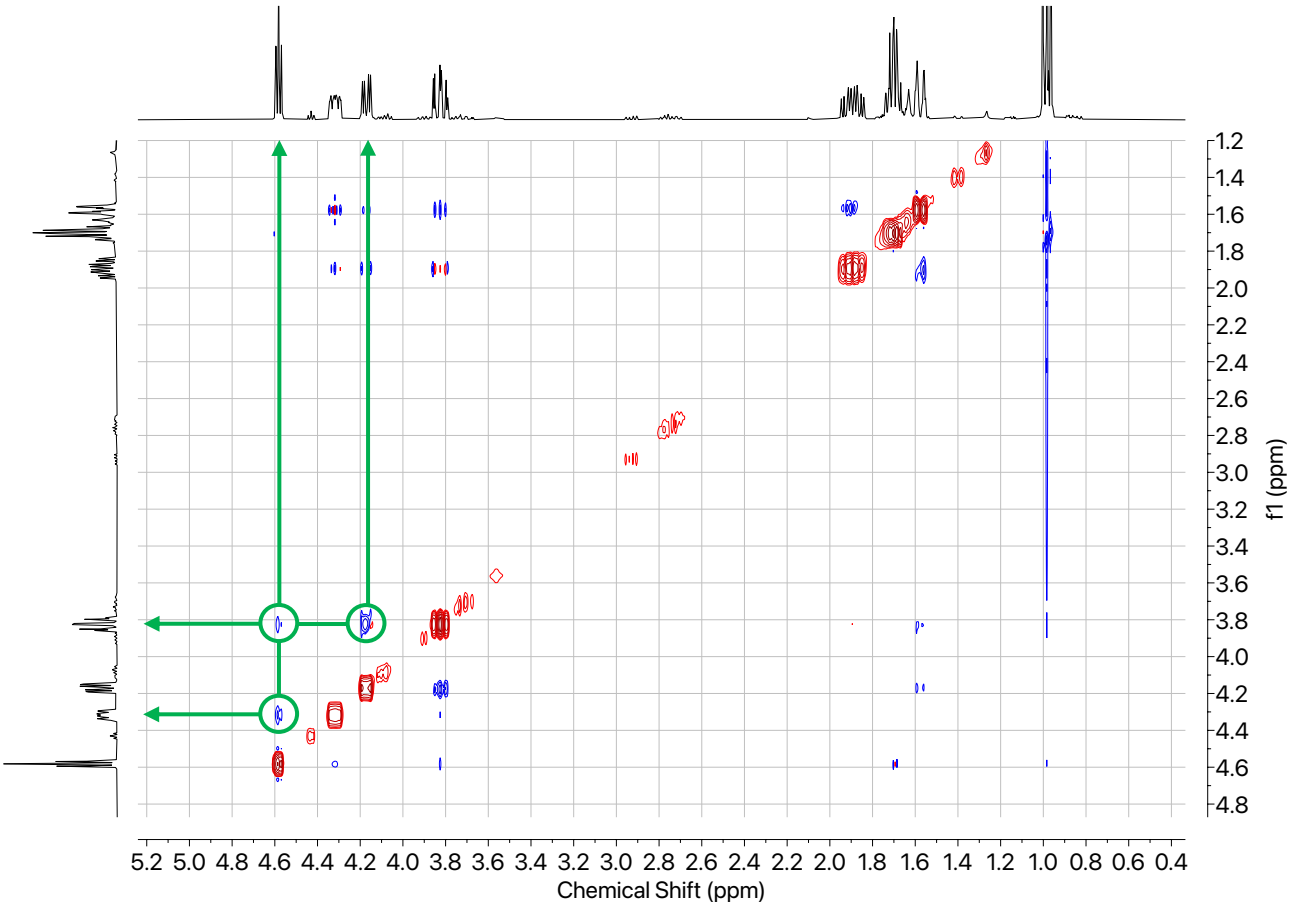
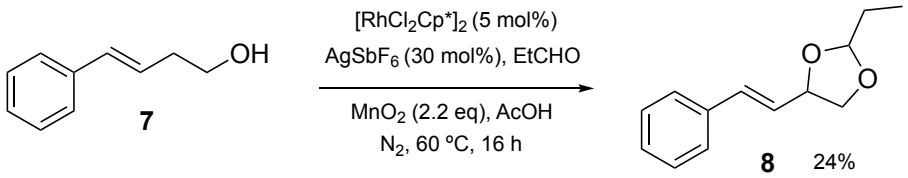


Figure 4. NOESY NMR spectrum of **4a.**

COSY experiments allowed the assignment of the proton spin couplings, while NOESY correlations provided key through-space interactions that enabled the relative stereochemical assignment of the cyclised product.

6.3.2. Cyclisation of homoallylic alcohol

We next examined the primary homoallylic alcohol, which lacks the extra methylene spacer present in bishomoallylic substrates. This structural difference affects both the equilibrium toward hemiacetal formation and the geometric alignment required for nucleophilic attack. As a result, the homoallylic substrate typically showed poorer yields than bishomoallylic substrates, and the cyclisation proceeded with a 24% yield under the standard conditions (Scheme 22).



Scheme 22. Reaction for the obtention of protected 1,2-diol.

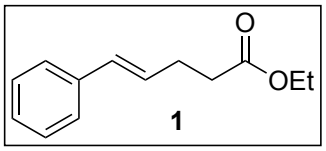
7. EXPERIMENTAL SECTION

7.1. MATERIALS AND METHODS

Commercially available materials, solvents, and reagents were used as received from commercial suppliers unless specifically indicated. Solvents like DCM or THF used in reactions were purified and converted into the corresponding anhydride following standard procedures. Room temperature encompasses a temperature range between 20 and 25 ºC. Unless otherwise stated, all reactions were carried at atmospheric pressure. Column chromatography was carried out using as stationary phase VWR BDH Chemicals silica gel (technical grade, 40-63 μm particle size) on regular columns. The eluents are indicated in each case. Analytical TLC was performed using Merck pre-coated silica gel 60 F254 plates and visualized by UV light (λ = 254 nm). ^{1}H, ^{13}C, COSY were recorded on a Bruker Avance III (^{1}H at 400 MHz, ^{13}C at 101 MHz) spectrometer at 25 ºC. The coupling constants (*J*) are reported in Hz and chemical shifts (δ) are in ppm. $CDCl_3$ (99.8%) was used as solvent. Signal assignments were derived from ^{1}H and ^{13}C spectra when necessary. Spectra were processed using MestreNova 14.2.3.

7.2. SYNTHESIS OF STARTING MATERIALS

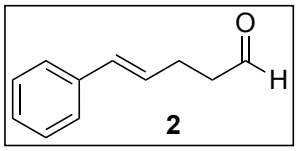
7.2.1. Synthesis of ester 1



1

Copper(I) iodide (19.472 g, 98.8 mmol) was added to a round-bottom flask under N_2 atmosphere, dissolved in anhydrous THF (125 mL) and ethyl acetate (50 mL, 56.30 mmol) was added. The mixture was cooled to -78 ºC and a solution of LiHMDS (60 mL, 1 M in THF, 60.89 mmol) was added and stirred for one hour. After an hour, commercially available *trans*-cinnamyl bromide (10.013 g, 50.81 mmol) was added dropwise, still at -78 ºC. The suspension was allowed to warm to room temperature and stirred for 16 h. The resulting suspension was quenched with saturated NH_4Cl aq. (150 mL). The solvent was removed under reduced pressure. The crude mixture was diluted in DCM (100 mL) and water (100 mL) and filtered under vacuum. The phases were portioned, and the aqueous phase was extracted with DCM (2x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain 10.045 g (49.18 mmol) of ester **1** as a dark yellow oil in 97% yield.

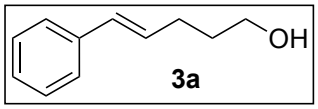
7.2.2. Synthesis of aldehyde 2



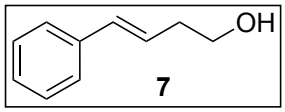
2

The corresponding ester **1** (7.269 g, 35.58 mmol) was dissolved, under N_2 atmosphere, in anhydrous DCM (125 mL) and cooled to -78 ºC. A DIBALH solution (50 mL, 1 M in DCM) was added dropwise and stirred for two hours at -78 ºC. The reaction was quenched by swiftly pouring the flask content into a beaker containing a 1:1 H_2O/acetone solution (200 mL) under vigorous stirring. The mixture was allowed to cool down to room temperature and solvent was evaporated at reduced pressure. To the resulting crude H_2O and NaOH (50 mL, 1 M) was added. The phases were portioned and filtered under vacuum. Aqueous phase was washed with DCM (2x50 mL). Then, combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain 4.446 g (27.74 mmol) of aldehyde **2** as a yellow oil in 78% yield.

7.2.3. Preparation of bishomoallylic and homoallylic primary alcohols 3a and 7



3a

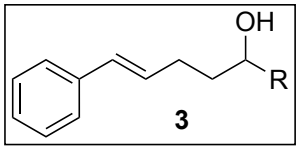


7

The corresponding ester (1eq.) was dissolved under N_2 atmosphere in anhydrous DCM (75 mL) and cooled to 0 ºC. A DIBALH solution (2.5 eq., 1 M in DCM) was added dropwise and stirred for 16 h still at 0 ºC. The resulting suspension was quenched by gradually adding distilled methanol (30 mL) in an ice bath under vigorous stirring. The solvent was removed under reduced pressure. The crude mixture was diluted in DCM (75 mL) and water (75 mL) and filtered under vacuum. The phases were portioned, and the aqueous phase was washed twice with brine and twice with an

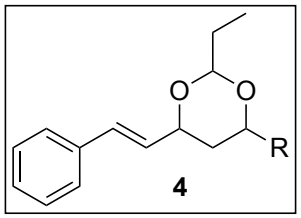
NaOH aqueous solution (1 M). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the desired primary alcohols **3a** and **7** as yellow oils.

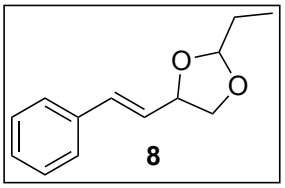
7.2.4. General procedure for the preparation of secondary alcohols



The corresponding aldehyde **2** (1 eq.) was dissolved under N_2 atmosphere in anhydrous THF (3.5 mL/mmol) and cooled to 0 ºC in an ice bath. An organomagnesian solution (1.5 eq., 3 M in THF) was added dropwise and stirred for one hour. After an hour, the mixture was allowed to cool down to room temperature and stirred for 16 h. The crude was diluted in saturated NaCl solution (50 mL) and ethyl acetate (50 mL) and filtered under vacuum. The phases were portioned, and the aqueous phase was extracted with ethyl acetate solution (2x50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain alcohols **3b**, **3c** and **3d** as yellow oils.

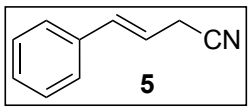
7.2.5. General procedure for the synthesis of protected 1,3-diols and 1,2-diols as cyclic acetals





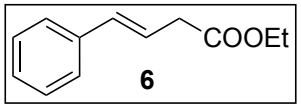
In a small round bottom flask, the selected alcohol (1 eq.), MnO_2 (2.2 eq.), $AgSbF_6$ (30% mol) and [$RhCl_2Cp^*$] (5% mol) are weighted and an inert atmosphere is done with N_2. Then 0,44mL (10eq.) of EtCHO and 2 drops of AcOH are added carefully. This solution is constantly stirred overnight at a temperature of 60ºC. After completion, the mixture is allowed to cool down to room temperature. DCM is used to dissolve the oil formed, and then the mixture is filtered through a porous glass plate with a Celite pad by vacuum filtration. The solvent is evaporated under reduced pressure, and the crude product is purified by flash column chromatography using hexane/AcOEt 95:5 as eluent to obtain the desired products **4a, 4b, 4c** and **8** as colourless oils.

7.2.6. Synthesis of cyanide compound 5



Commercially available cinnamyl bromide (25.000 g, 126.86 mmol) was weighed into a 100-mL round-bottom flask and placed under a nitrogen atmosphere. DMSO (50 mL) was then added. In a separate 250-mL round-bottom flask, NaCN (12.389 g, 252.83 mmol) was charged and suspended in DMSO, under a nitrogen atmosphere, with gentle stirring in a water bath. The cinnamyl bromide solution was added dropwise to the stirred suspension of NaCN under vigorous stirring. Upon complete addition, the reaction mixture was allowed to warm to room temperature and stirred for an additional 5 min after removing the water bath. The mixture was transferred to a 500 mL separatory funnel, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. While still warm, cold hexane was added to the concentrated residue to precipitate the product. The resulting solid was collected by vacuum filtration and dried to give 14.300 g (99.87 mmol) of cyanide **5** in a 79% yield.

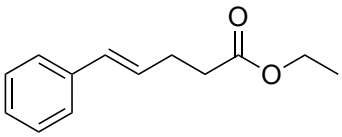
7.2.7. Synthesis of ester 6



The previously synthesized nitrile **5** (5.893 g, 41.2 mmol) was dissolved in absolute ethanol (60 mL) in a 250 mL round-bottom flask under a nitrogen atmosphere. TMSCl (21 mL) was added, and the reaction mixture was heated to 60 °C and stirred overnight under temperature control. The next morning, the reaction was cooled to room temperature, and water (1.48 mL, 82.13 mmol), DCM (200 mL) and Na_2CO_3 (28.310 g, 267.5 mmol) were added. The biphasic mixture was stirred for 30 min at room temperature. The mixture was then transferred to a separatory funnel, the organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. Volatiles were removed under reduced pressure to afford 6.779 g (35.64 mmol) of ester **6** as a dark red oil in an 87% yield.

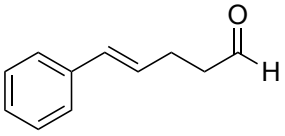
7.3. CHARACTERISATION OF COMPOUNDS

7.3.1. Ethyl (*E*)-5-phenylpent-4-enoate (1)



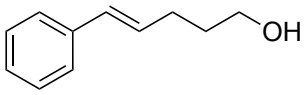
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 7.23 – 7.18 (m, 1H), 6.44 (d, *J* = 1.4 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.58 – 2.46 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).[28]

7.3.2. (*E*)-5-Phenylpent-4-enal (2)



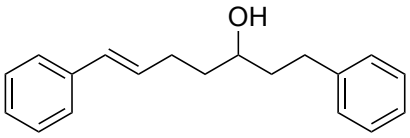
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.5 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.5 Hz, 1H), 2.66 – 2.51 (m, 4H).[29]

7.3.3. (*E*)-5-Phenylpent-4-en-1-ol (3a)



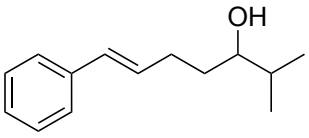
Alcohol **3a** was obtained as a yellow oil in a 98% yield (2.031 g, 12.52 mmol) after purification by silica gel column chromatography (hexane/EtOAc 90:10). The reduction was performed starting from ester **1** (3.060 g, 14.98 mmol) using DIBALH (37 mL, 36.72 mmol) in anhydrous DCM (75 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H), 7.25 – 7.20 (m, 1H), 6.45 (d, *J* = 1.5 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.70 (t, *J* = 6.5 Hz, 2H), 2.38 – 2.26 (m, 2H), 1.76 (p, *J* = 6.5 Hz, 2H).[30]

7.3.4. (*E*)-1,7-Diphenylhept-6-en-3-ol (3b)



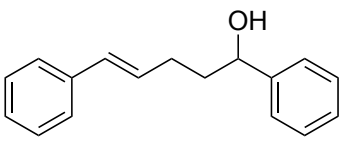
Alcohol **3b** was obtained (2.134 g, 8.01 mmol) as a yellow oil in 87% yield after purification by silica gel liquid chromatography (Hexane/AcOEt 90:10) using (1.478 g, 9.22 mmol) of aldehyde **2** dissolved in anhydrous THF (30 mL) and a commercially available phenetylmagnesium chloride solution (13.83 mL, 1 M in THF). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 7H), 7.24 – 7.19 (m, 3H), 6.44 (d, 1H), 6.24 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.72 (ddt, *J* = 7.7, 6.5, 4.7 Hz, 1H), 2.92 – 2.78 (m, 1H), 2.75 – 2.64 (m, 2H), 2.46 – 2.25 (m, 2H), 1.86 – 1.78 (m, 2H), 1.72 – 1.64 (m, 2H).[31]

7.3.5. (*E*)-2-Methyl-7-phenylhept-6-en-3-ol (3c)



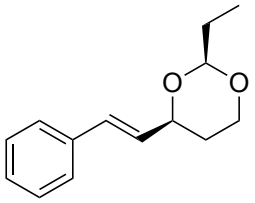
Alcohol **3c** was obtained (1.531 g, 7.49 mmol) as a yellow oil in 81% yield after purification by silica gel liquid chromatography (Hexane/AcOEt 90:10) using (1.476 g, 9.21 mmol) of aldehyde **2** dissolved in anhydrous THF (30 mL) and a commercially available isopropylmagnesium chloride solution (6.91 mL; 2 M in THF). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H), 7.23 – 7.17 (m, 1H), 6.43 (d, *J* = 1.5 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 2.47 – 2.24 (m, 3H), 1.60 – 1.51 (m, 2H), 0.94 (d, *J* = 2.5 Hz, 6H).[32]

7.3.6. (*E*)-1,5-Diphenylpent-4-en-1-ol (3d)



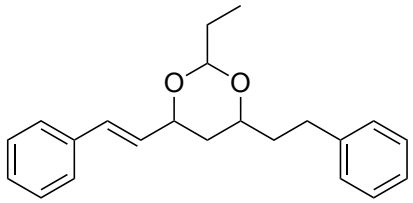
Alcohol **3d** was obtained (1.814 g, 7.62 mmol) as a yellow oil in 87% yield after purification by silica gel liquid chromatography (Hexane/AcOEt 90:10) using (1.397 g, 8.72 mmol) of aldehyde **2** dissolved in anhydrous THF (30 mL) and a commercially available phenylmagnesium bromide solution (4.36 mL, 3 M in THF). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 9H), 7.23 – 7.18 (m, 1H), 6.42 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.75 (dd, *J* = 7.7, 5.5 Hz, 1H), 2.40 – 2.23 (m, 2H), 2.06 – 1.83 (m, 3H).[33]

7.3.7. *cis*-2-Ethyl-4-((*E*)-styryl)-1,3-dioxane (4a)



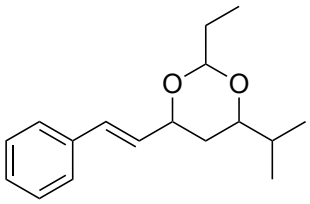
Protected 1,3-diol **4a** was obtained following **general procedure for the preparation of protected 1,3-diols and 1,2-diols as cyclic acetals** using alcohol **3a** (105.1 mg, 0.48 mmol) and propanal (0.44 mL, 6.160 mmol) to yield 40% (56.6 mg, 0.26 mmol) of the cyclised product as a colourless oil after purification by silica gel liquid chromatography (Hexane/AcOEt 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.27 (m, 2H), 7.26 – 7.12 (m, 1H), 6.63 (dd, *J* = 16.0, 1.3 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.58 (t, *J* = 5.2 Hz, 1H), 4.32 (dddd, *J* = 11.3, 6.1, 2.6, 1.3 Hz, 1H), 4.17 (ddd, *J* = 11.4, 5.0, 1.4 Hz, 1H), 3.82 (ddd, *J* = 12.4, 11.4, 2.5 Hz, 1H), 1.89 (dddd, *J* = 13.4, 12.4, 11.3, 5.0 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.58 (dtd, *J* = 13.3, 2.5, 1.4 Hz, 1H), 0.98 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.74, 130.81, 129.36, 128.64, 127.84, 126.65, 103.13, 66.53, 31.77, 28.39, 8.56.

7.3.8. (*E*)-2-Ethyl-4-phenethyl-6-styryl-1,3-dioxane (4b)



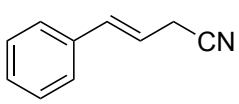
Protected 1,3-diol **4b** was obtained following **general procedure for the preparation of protected 1,3-diols and 1,2-diols as cyclic acetals** using alcohol **3b** (100.3 mg, 0.38 mmol) and propanal (0.44 mL, 6.160 mmol) to yield 4% (5.0 mg, 0.02 mmol) of the cyclised product as a colourless oil after purification by silica gel liquid chromatography (Hexane/AcOEt 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 6H), 7.25 – 7.16 (m, 4H), 6.60 (d, *J* = 1.3 Hz, 1H), 6.22 (dd, *J* = 16.0, 6.1 Hz, 1H), 4.55 (t, *J* = 5.3 Hz, 1H), 4.27 (dddd, *J* = 10.6, 6.3, 2.8, 1.3 Hz, 1H), 3.63 (dddd, *J* = 10.9, 8.4, 4.4, 2.5 Hz, 1H), 2.77 (dddd, *J* = 29.9, 13.7, 8.9, 6.4 Hz, 2H), 1.67 – 1.47 (m, 6H), 1.02 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.06, 136.80, 130.78, 129.40, 128.67, 128.65, 128.52, 127.82, 126.66, 125.97, 102.81, 77.48, 76.84, 37.56, 37.43, 31.27, 28.36, 8.84.

7.3.9. (*E*)-2-Ethyl-4-isopropyl-6-styryl-1,3-dioxane (4c)



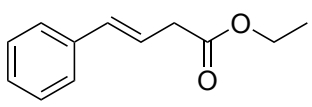
Protected 1,3-diol **4c** was obtained following **general procedure for the preparation of protected 1,3-diols and 1,2-diols as cyclic acetals** using alcohol **3c** (127.6 mg, 0.62 mmol) and propanal (0.44 mL, 6.160 mmol). The cyclised product was isolated as a colourless oil after purification by silica gel liquid chromatography (Hexane/AcOEt 95:5), however the isolated yield could not be accurately determined. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 6.57 (d, *J* = 1.9 Hz, 1H), 6.41 (dd, *J* = 16.3, 4.6 Hz, 1H), 4.85 – 4.76 (m, 2H), 3.44 (ddd, *J* = 11.9, 7.1, 2.3 Hz, 1H), 1.97 (ddt, *J* = 13.7, 12.1, 6.1 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.66 – 1.61 (m, 2H), 0.96 (d, *J* = 2.0 Hz, 3H), 0.94 – 0.89 (m, 6H).

7.3.10. (*E*)-4-Phenylbut-3-enenitrile (5)



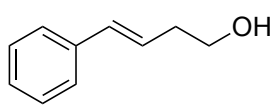
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.74 (d, *J* = 1.8 Hz, 1H), 6.06 (dt, *J* = 15.8, 5.7 Hz, 1H), 3.30 (dd, *J* = 5.7, 1.8 Hz, 2H).[34]

7.3.11. Ethyl (*E*)-4-phenylbut-3-enoate (6)



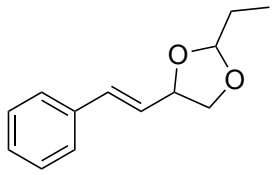
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 2H), 7.27 – 7.22 (m, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 6.33 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.25 (dd, *J* = 7.1, 1.4 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).[35]

7.3.12. (*E*)-4-Phenylbut-3-en-1-ol (7)



Alcohol **7** was obtained as a yellow oil (0.406 g, 2.74 mmol) after purification by silica gel column chromatography (hexane/EtOAc 80:20). The reduction was performed starting from ester **6** (8.008 g, 42,1 mmol) using DIBALH (45 mL, 44.92 mmol) in anhydrous DCM (30 mL). Purification of 1.000 g of the crude material afforded the isolated alcohol in 41% recovery. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 6.21 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.76 (t, *J* = 6.3 Hz, 2H), 2.49 (dtd, *J* = 7.7, 6.3, 1.4 Hz, 2H).[36]

7.3.13. 2-Ethyl-4-((*E*)-styryl)-1,3-dioxolane (8)



Protected 1,2-diol **8** was obtained following **general procedure for the preparation of protected 1,3-diols and 1,2-diols as cyclic acetals** using alcohol **7** (102.1 mg, 0.689 mmol) and propanal (0.44 mL, 6.160 mmol) to yield 24% (33.7 mg, 0.165 mmol) of the cyclised product as a colourless oil after purification by silica gel liquid chromatography (Hexane/Et_2O 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 6.68 (d, *J* = 0.9 Hz, 1H), 6.19 (ddd, *J* = 15.8, 7.6, 1.7 Hz, 1H), 4.98 (t, *J* = 4.7 Hz, 1H), 4.65 (dtd, *J* = 7.7, 6.6, 0.9 Hz, 1H), 4.07 (dd, *J* = 7.9, 6.9 Hz, 1H), 3.71 (dd, *J* = 7.9, 6.5 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H).

8. CONCLUSIONS

Building on previous studies from the research group, a Rh(III)-catalysed allylic C–H activation strategy was investigated for the synthesis of protected 1,3-diols through the *in situ* formation of hemiacetal intermediates, and for the first time, 1,2-diols were introduced into this type of methodology. The scope and limitations of this transformation were evaluated using different allylic alcohol substrates.

Cyclisation of bishomoallylic alcohols revealed a strong dependence on substrate structure and steric effects. Only the primary bishomoallylic alcohol bearing hydrogen atoms at the bishomoallylic position (R = H) afforded a fully characterised cyclised product, highlighting the key role of the equilibrium of hemiacetal formation. Increased steric bulk at R disfavours this equilibrium and restricts the access to productive conformations, resulting in lower yields or no detectable product formation.

Conformational analysis qualitatively rationalised both the observed reactivity trends and the diastereoselectivity of the reaction. Although multiple diastereomers are theoretically possible, steric factors bias the cyclisation toward a single dominant diastereomer under the conditions employed.

Extension of the methodology to homoallylic alcohols resulted in lower cyclisation efficiency, reflecting reduced conformational flexibility and less favourable geometric alignment for intramolecular attack. Notably, cyclisations leading to protected 1,2-diols constitute a new transformation within our research group and represent a preliminary proof of concept for this approach.

Future work could focus on expanding the substrate scope by exploring alternative substituents at the R positions for protected 1,2-diols, optimising reaction conditions, and investigating the deprotection step for both 1,3- and 1,2-diol products to enhance the synthetic utility of this methodology.

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10. ACRONYMS

ACN	Acetonitrile
Ac	Acetyl
COSY	Correlation spectroscopy
Cp*	Pentamethylcyclopentadienyl
DCM	Dichloromethane
DG	Directing group
DIBALH	Diisobutylaluminum hydride
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
FG	Functional group
LiHMDS	Lithium hexamethyldisilazide
M	Metal
Me	Methyl
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect spectroscopy
Ph	Phenyl
Rh	Rhodium
s	Singlet
S_N2	Bimolecular nucleophilic substitution
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
UV	Ultraviolet
X	Halogen
atm	Atmospheric pressure
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dddd	Doublet of doublets of doublets of doublets
ddt	Doublet of doublets of triplets
dt	Doublet of triplets
dtd	Doublet of triplets of doublets
eq.	Equivalent
iPr	Isopropyl
m	Multiplet
n.d.	Not determined
p	Pentet
q	Quadruplet
rt	Room temperature
t	Triplet

APPENDICES

APPENDIX 1: PROTECTED 1,3-DIOLS CHARACTERISATION

CHARACTERISATION OF *CIS*-2-ETHYL-4-((*E*)-STYRYL)-1,3-DIOXANE (4A)

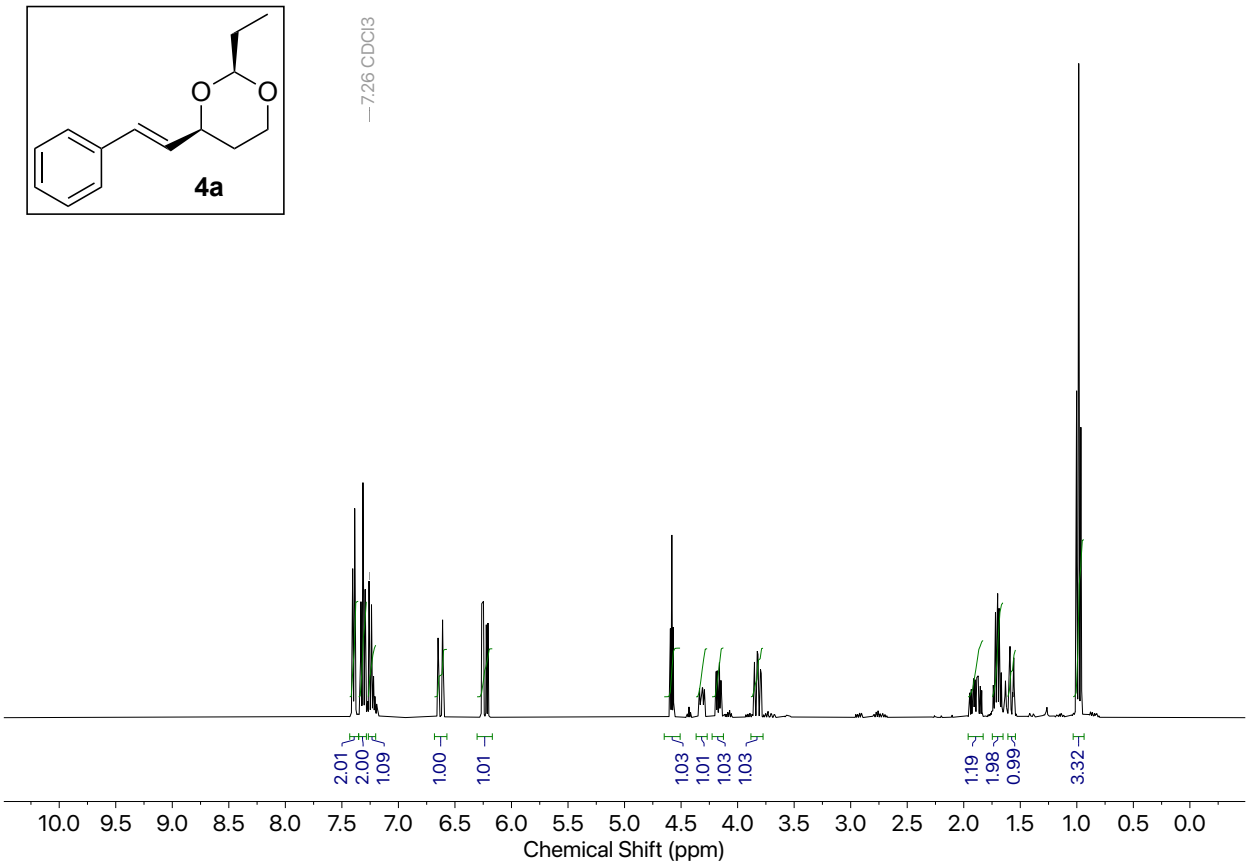

Figure 5. ^{1}H NMR of compound **4a.**

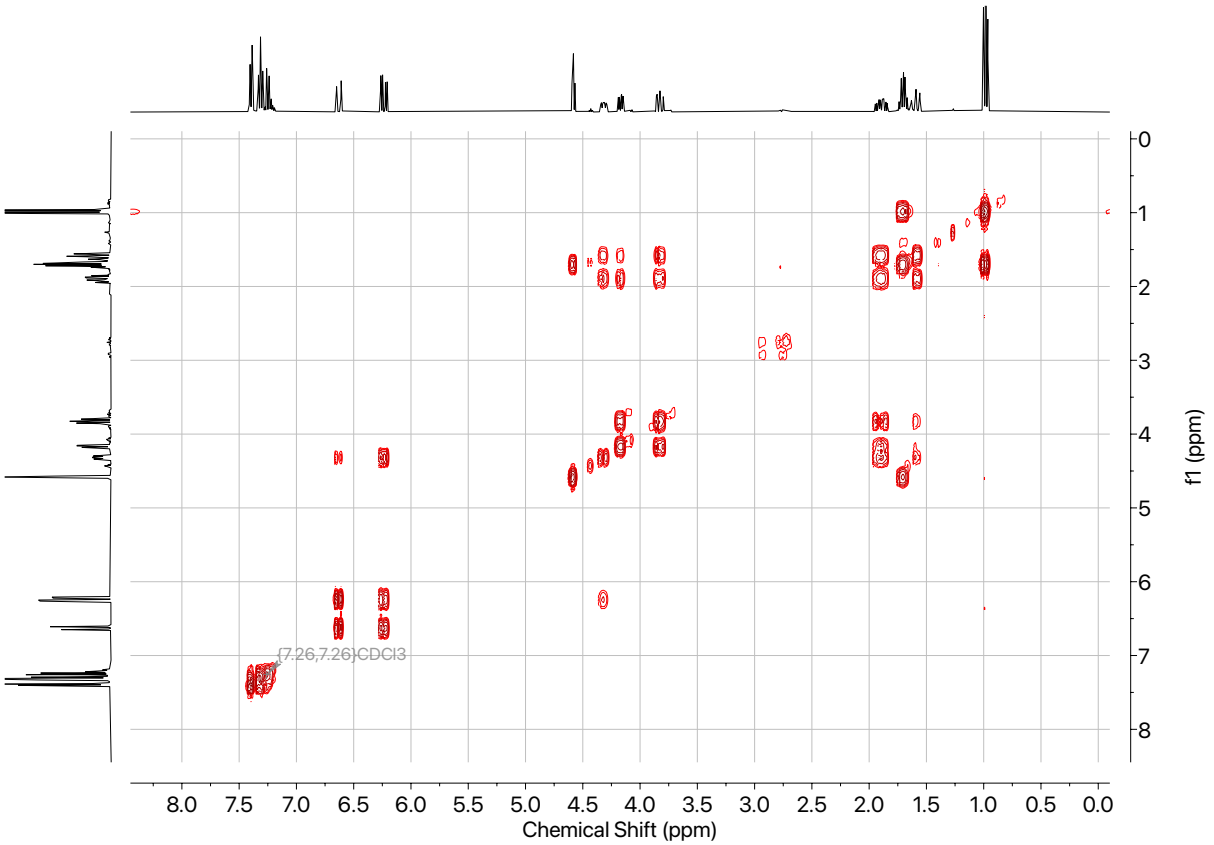

Figure 6. COSY NMR of compound **4a.**

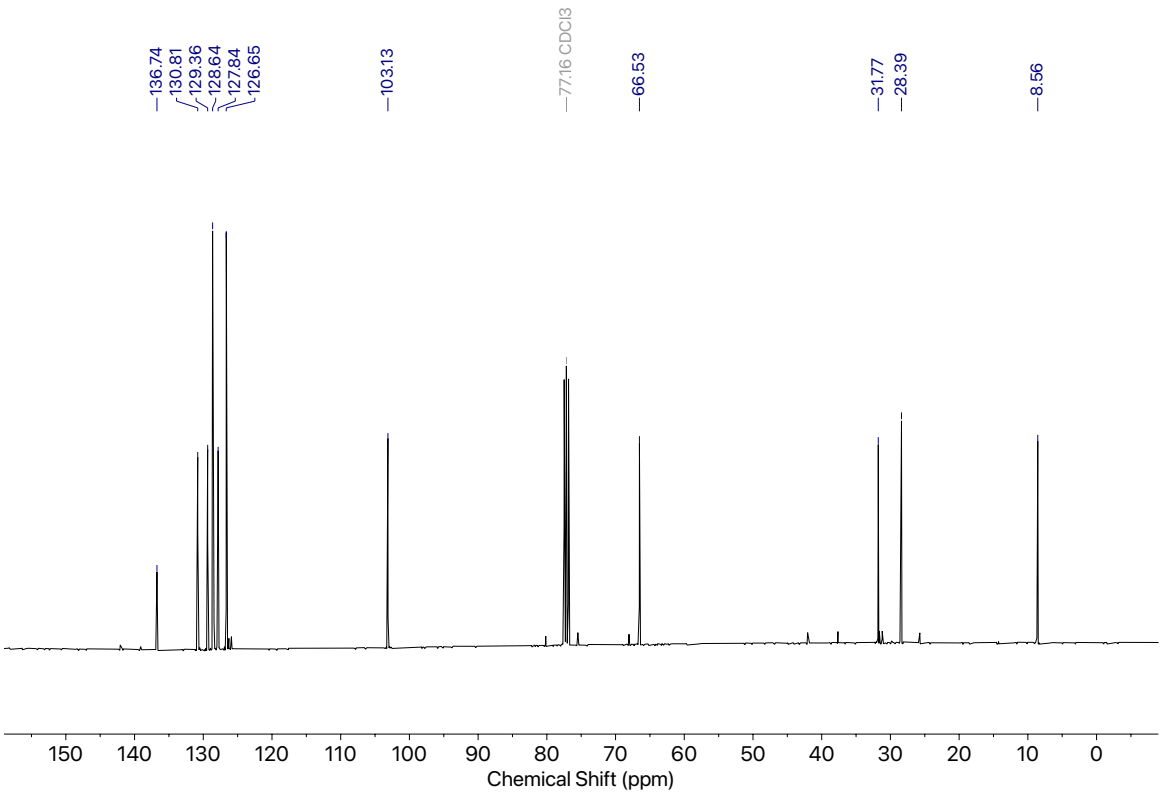

Figure 7. ^{13}C NMR of compound **4a.**

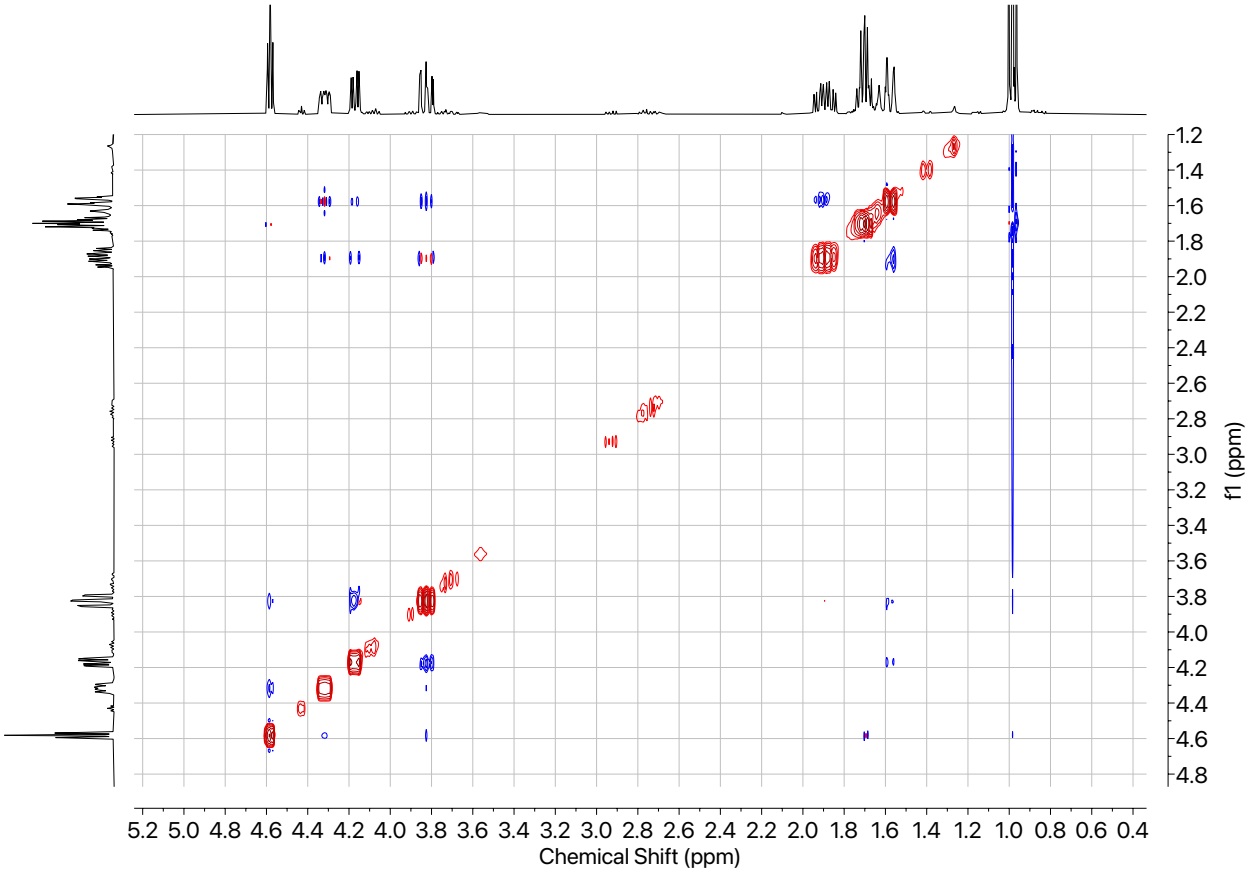

Figure 8. NOESY NMR of compound **4a.**

CHARACTERISATION OF (*E*)-2-ETHYL-4-PHENETHYL-6-STYRYL-1,3-DIOXANE (4B)

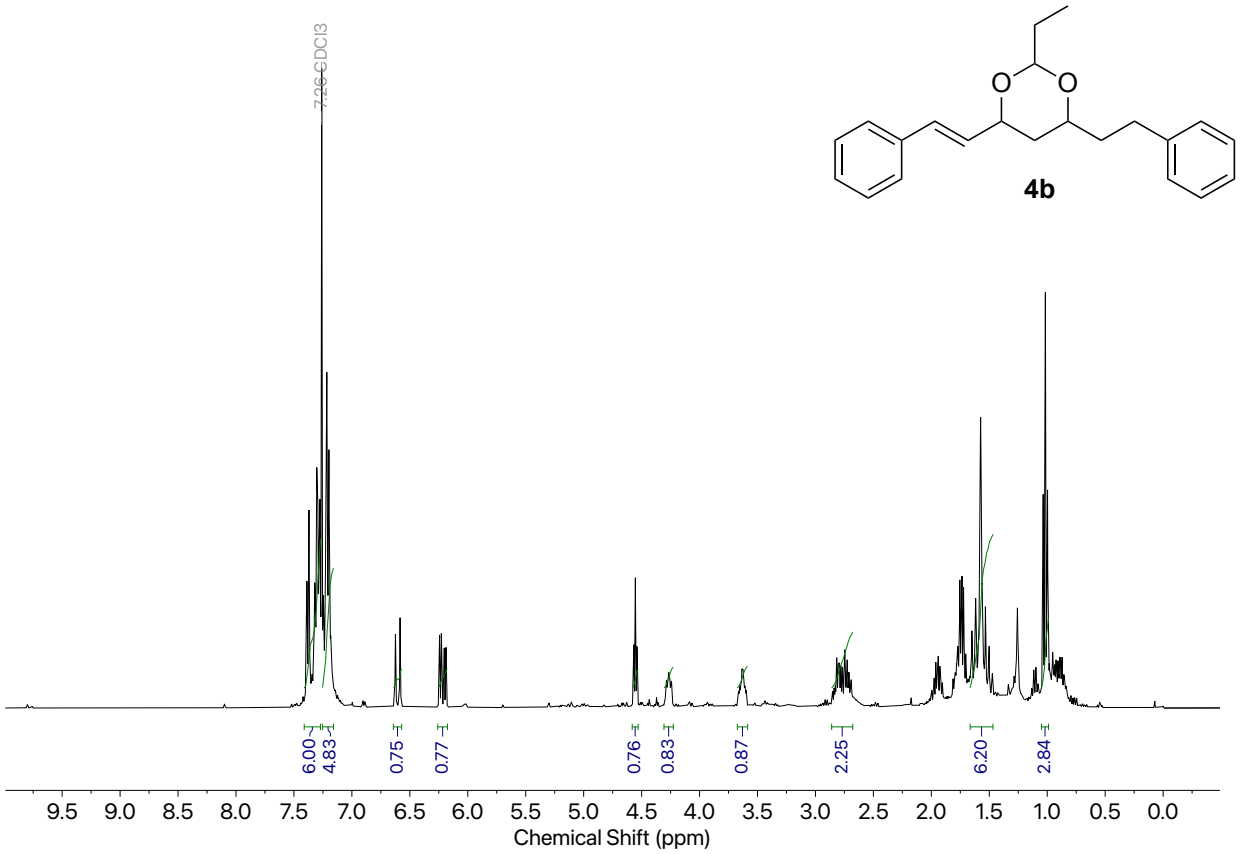

Figure 9. ^{1}H NMR of compound **4b.**

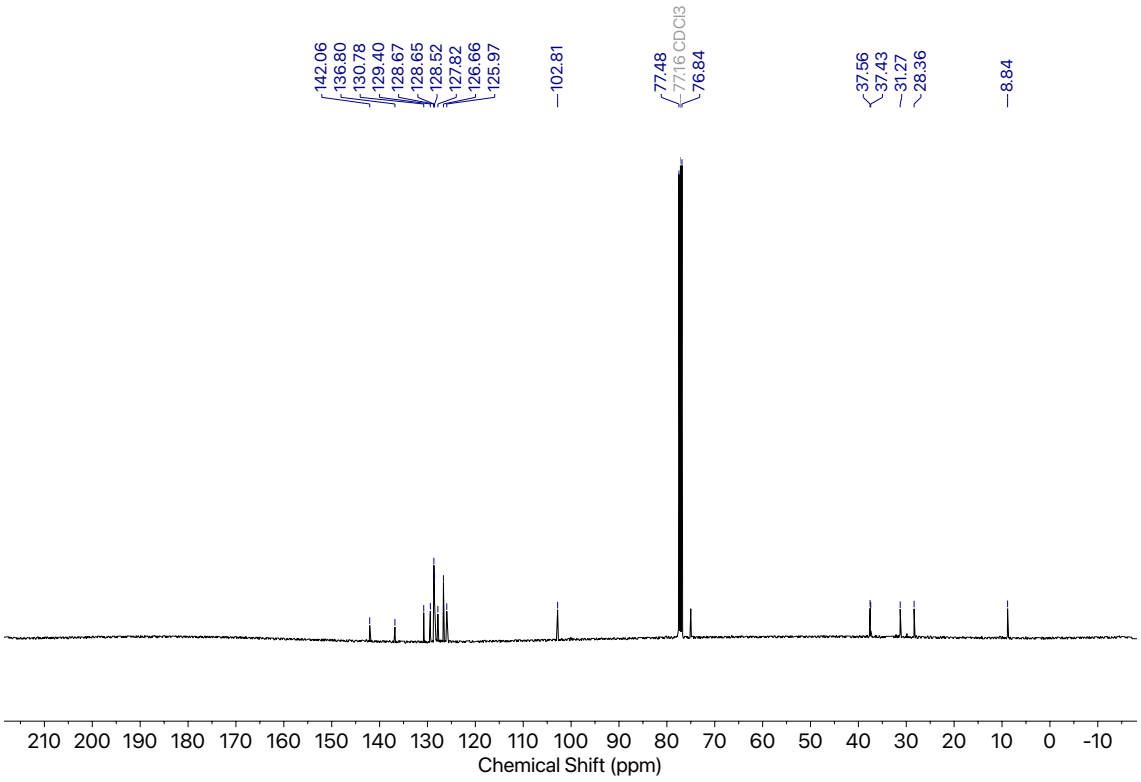

Figure 10. ^{13}C NMR of compound **4b.**

APPENDIX 2: PROTECTED 1, 2-DIOL CHARACTERISATION

CHARACTERISATION OF 2-ETHYL-4-((*E*)-STYRYL)-1,3-DIOXOLANE (8)

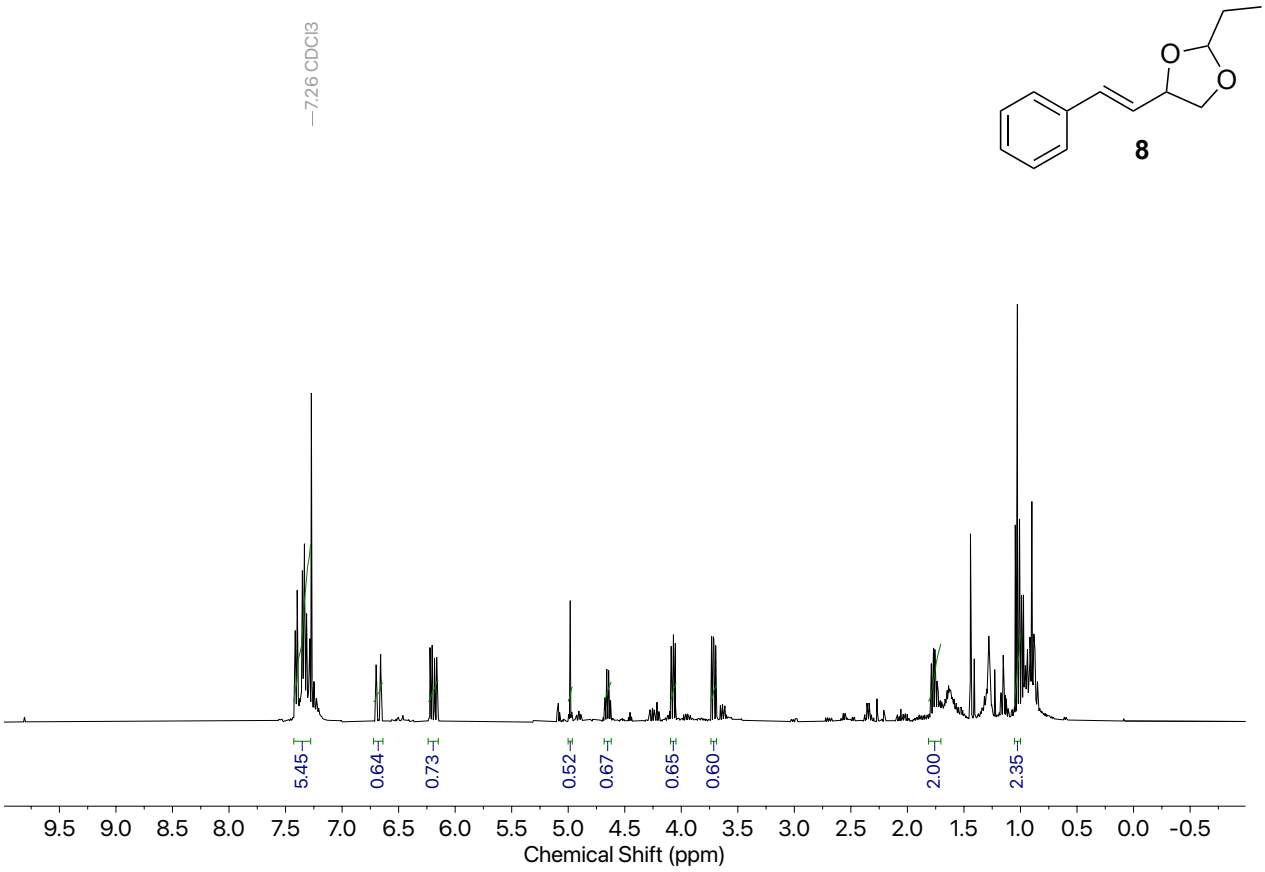

Figure 11. ^{1}H NMR of compound **8.**