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Isocarbacyclin, a synthetic form of prostacyclin, has been recognized as a potential neuroprotective drug which could be used for patients of ischaemic stroke. The first goal described in this thesis was to create a new set of analogs of isocarbacyclin which had a saturated ring system and perform biological testing on these compounds using conditions that mimicked ischaemic stroke symptoms. The synthesis of these compounds was to contain three transition metal catalyzed steps which installed a great deal of complexity into the molecule in only a few steps. These three steps included a palladium catalyzed decarboxylation, a rhodium catalyzed cycloaddition, and a ruthenium catalyzed cross metathesis. However, when the first of these three steps, a decarboxylation, failed to yield product, efforts went to the discovery of the mechanism of this reaction. A second generation synthesis was then conceived, which also contained the same three transition metal catalyzed steps, but the decarboxylation step again failed to yield sufficient product. Due to the complications discovered with transition metal catalyzed decarboxylation reactions, the final investigations described include the results of experiments which give light to the necessary elements for decarboxylation to occur. Herein is presented the efforts of the total synthesis of isocarbacyclin analogs along with the results of explorations into palladium catalyzed decarboxylations.

INVESTIGATIONS IN THE SYNTHESIS OF ISOCARBACYCLIN ANALOGS INVOLVING TRANSITION METAL CATALYSIS WITH EXPLORATIONS INTO PALLADIUM CATALYZED DECARBOXYLATION

by

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CHAPTER I

ISOCARBACYCLIN AND ANALOGS

Background

Prostacyclin (**1**, Figure 1) is known as the gold standard for vasodilation (or the enlargement of blood vessels) and also causes platelet aggregation.[1] It is commonly prescribed under the names of Flolan or Epoprostenol for patients dealing with high blood pressure.[2] Prostacyclin was discovered by the research group of John Vane, a biochemist in the United Kingdom, who went on to win the Nobel Prize in 1982 for his work with prostaglandins.[3]

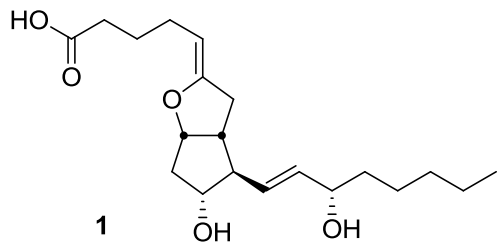

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Figure 1. Prostacyclin

Biologically, prostacyclin is a member of the prostaglandin eicosanoid family and is classified as a lipid.[4] The biological synthesis of prostacyclin begins with arachidonic acid and proceeds via three enzymes (Figure 2).[5] Arachidonic acid (**2**) is first oxygenated by a cyclooxygenase to form an endo-peroxide, PGG_2 (**3**). A peroxidase then cleaves the terminal peroide thereby reducing the molecule from PGH_2 (**4**). Finally, prostacyclin

synthase cyclizes the molecule and the result is prostacyclin, or PGI_2. Other compounds made by a similar pathway from arachidonic acid include the prostaglandins $PGF_{2\alpha}$ (**5**), PGE_2 (**6**), and PGD_2 (**7**, Figure 3).[5]

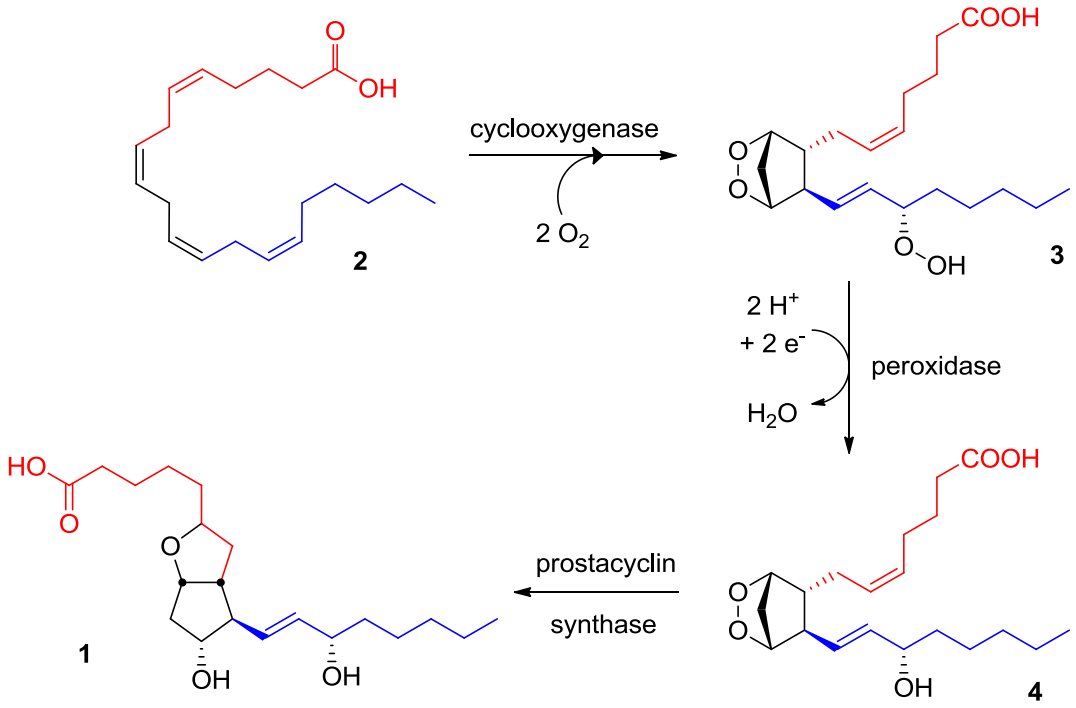


Figure 2. The biosynthesis of prostacyclin from arachidonic acid

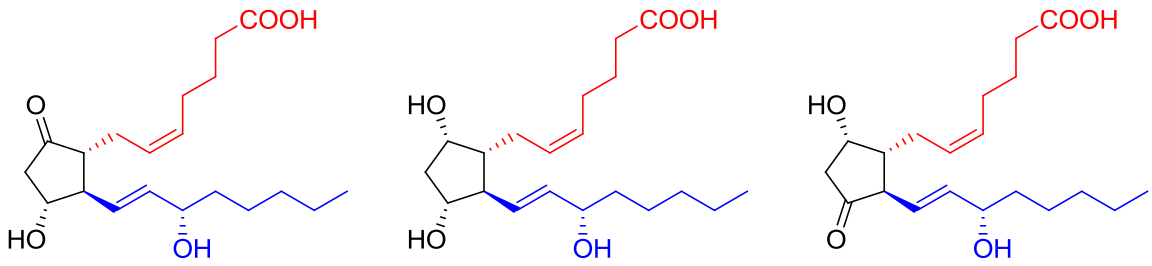
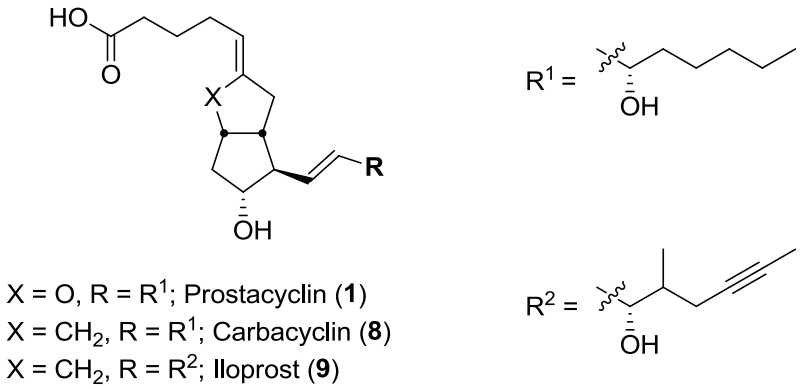


Figure 3. The structures of $PGF_{2\alpha}$, PGE_2, and PGD_2

Biological Activity of Prostacyclin and Analogs

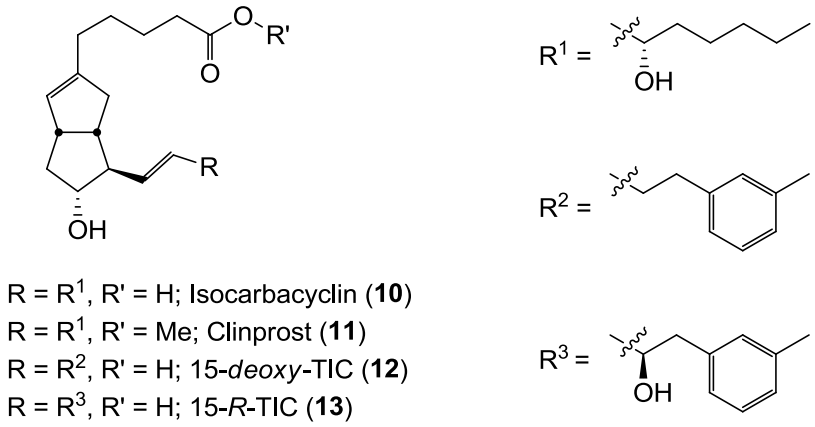
While prostacyclin is highly effective and useful as a vasodilating compound, it is also inherently unstable due to the vinyl ether found in the bicyclic ring system which is reactive with the carboxylic acid. With a half-life of 3 minutes *in vivo*[6], chemists and biochemists were inspired to develop and test new analogs of prostacyclin. The first generation of analogs simply replaced the ethereal oxygen with a methylene group and made no changes to the side chains of the molecule. This compound, known as carbacyclin (**8**, Figure 4), was thought to perform in the same way as prostacyclin however, during clinical trials, significant side effects such as headache and severe facial flushing were noticed.[7] These observations led to the development of iloprost (**9**) which removed the alkyl side chain of carbacyclin and replaced it with an alkyne. Iloprost is currently on the market as Ventavis and can be inhaled to achieve maximum potency.[8]



X = O, R = R^1; Prostacyclin (**1**)
X = CH_2, R = R^1; Carbacyclin (**8**)
X = CH_2, R = R^2; Iloprost (**9**)

Figure 4. Structures of prostacyclin, carbacyclin, and iloprost

The next logical step in formation of analogs was to isomerize the exo-alkene which led to the development of the compounds isocarbacyclin (**10,** Figure 5) and clinprost (**11**). Clinprost is believed to have slightly better biological activity than isocarbacyclin since the methyl ester form is able to cross the blood brain barrier. Enzyme esterases are then able to cleave the methyl moiety resulting in the active isocarbacyclin molecule.[9]



R = R^1, R' = H; Isocarbacyclin (**10**)
R = R^1, R' = Me; Clinprost (**11**)
R = R^2, R' = H; 15-*deoxy*-TIC (**12**)
R = R^3, R' = H; 15-*R*-TIC (**13**)

Figure 5. Structures of isocarbacyclin, clinprost, 15-*deoxy*-TIC, and 15-*R*-TIC

As research continued, scientists endeavored to understand the importance of the alcohol containing ω-side chain of isocarbacyclin. The compounds 15-*deoxy*-tetranorisocarbacyclin (TIC) (**12**, Figure 5) and 15-*R*-TIC (**13**) were designed to test the necessity of the alcohol functional group as well as the need for stereochemistry in that position.[10] It was found that when the alcohol stereochemistry was reversed or completely removed the activity of the compound changed drastically. While removing or reversing the stereochemistry of the alcohol had little effect on the neuroprotective nature of the compounds, it almost completely diminished the vasodilating effect.[10]

As previously stated, the vasodilating capabilities of prostacyclin have been well known for decades. While this is helpful to patients with high blood pressure, it was also hypothesized to be helpful to victims of ischaemic stoke. There are two types of stroke, hemorrhagic and ischaemic. Hemorrhagic strokes occur when blood vessels in the brain are weakend and burst causing bleeding on the brain.[11] Ischaemic strokes, however, are

caused by blood clots in the brain and account for the majority of strokes.[11] Through the opening of the blood vessels in the brain, it was believed that prostacyclin and its analogs could help alleviate the neuronal damage caused by ischaemic strokes.

It was already known that prostacyclin and several of its analogs bind to G-protein coupled receptors known as PGI_2 receptors.[12] Takechi and co-workers published in 1996 that subtle differences in structure caused the molecules to have lower affinity when binding to the known PGI_2 receptors of the peripheral nervous system and to have higher affinity with a novel receptor of the central nervous system. The novel receptor was found to be present in the rostral regions of the brain which include the hippocampus, cerebral cortex, thalamus, striatum, and septum.[12] Multiple tests on a variety of animals including rats,[13] rhesus monkeys,[14] and gerbils[15] show that this receptor is common across multiple species.

Since it had been discovered that isocarbacyclin has the potential for neuroprotection, multiple tests have been designed to test its efficacy. These tests mostly include placing neural cells in stressful conditions and dosing with different amounts of compound to deduce how well the compound protects the cells. Two methods of stressing the cells include exposing them to a high oxygen atmosphere or dosing them with xanthine and xanthine oxidase.[10] Both of these methods cause the mitochondria of cells to release of reactive oxygen species (such as oxygen ions or peroxides) which in turn damage the neural cells.[16] During stroke it is most often not the oxygen deprivation that degenerates the cells, but a process known as reperfusion, which is the rapid influx of

reactive oxygen species after circulation is restored.[17] Also, since isocarbacyclin and other analogs have shown potent neuroprotective activity it can be reasoned that they may also have effect against neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's. It is therefore reasonable to conceive that isocarbacyclin or closely related analogs could enter the pharmaceutical field as aids against neurodegenerative diseases.

Synthesis of Clinprost

It is commonly the goal in organic synthesis, especially where medicinal or biologically active compounds are concerned, not only to create new or existing compounds, but to synthesize them in the fewest number of steps possible. Also, if diversification of key components is installed in the last steps then the overall synthesis is much more attractive. With both of these concepts in mind Dr. Mitchell Croatt conceived a retrosynthesis (Figure 6) of the methyl ester of isocarbacyclin known as clinprost (**11**) and the complete synthesis has been published in Organic Letters.[18] A look at previous synthetic routes shows that many of them contained over twenty steps and allowed for very little diversification of the key ω-side chain. This conceived synthesis, having only nine steps, beat the shortest previous synthesis by six steps.

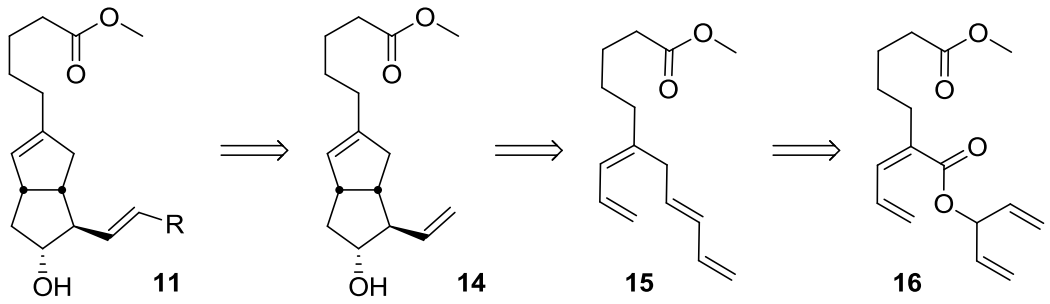


Figure 6. Retrosynthesis of clinprost

Retrosynthetic design began with the installation of the ω-side chain via cross metathesis so that diversity could be installed from a single compound (**14**) in the final step. From there the molecule was deconstructed to a tetraene (**15**) which could undergo a [2+2+1] reaction catalyzed by a Rh^{I} catalyst. This tetraene, which appeared simple at first, proved to be a difficult molecule to synthesize due to the methylene interrupting conjugation of all four double bonds. With little hope for success, a Tsuji-Trost type decarboxylation of diester **16** was attempted and the result was a surprisingly high yield of tetraene **15**.

The rhodium catalyzed cycloaddition is a step in which three important stereocenters are set and reduction using sodium borohydride sets the last stereocenter. The method through which this reaction proceeds (Figure 7) is quite elegant.

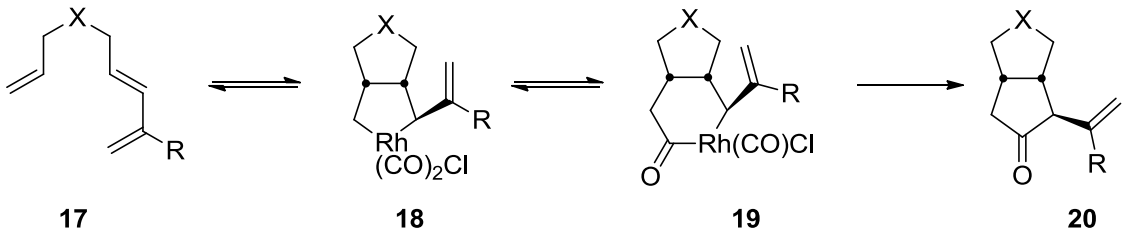


Figure 7. Rhodium catalyzed [2+2+1] cycloaddition

When the rhodium catalyst comes into contact with the tetraene it coordinates to the conjugated system and forms the first ring of the bicycle as seen by compound **18**. The rhodium then inserts one of its carbonyl ligands into the second ring thereby expanding it by one carbon. Finally, reductive elimination occurs and the reduced rhodium species is released from the compound. The carbon monoxide atmosphere that the reaction is kept under allows coordination of another carbonyl ligand and the rhodium catalyst is then ready to reenter the catalytic cycle.

The rhodium catalyzed cycloaddition, in addition to a palladium catalyzed decarboxylation and ruthenium catalyzed cross-metathesis, make up the final steps of the synthesis. These three transition metal catalyzed steps install a large degree of complexity from a relatively simple molecule. The synthesis of clinprost that has just been described (Figure 8) begins with pimelic acid (**21**) which undergoes a mono-esterification with divinyl carbinol followed by an aldol condensation with acrolein, methylation with diazomethane, and finally dehydration with mesyl chloride.

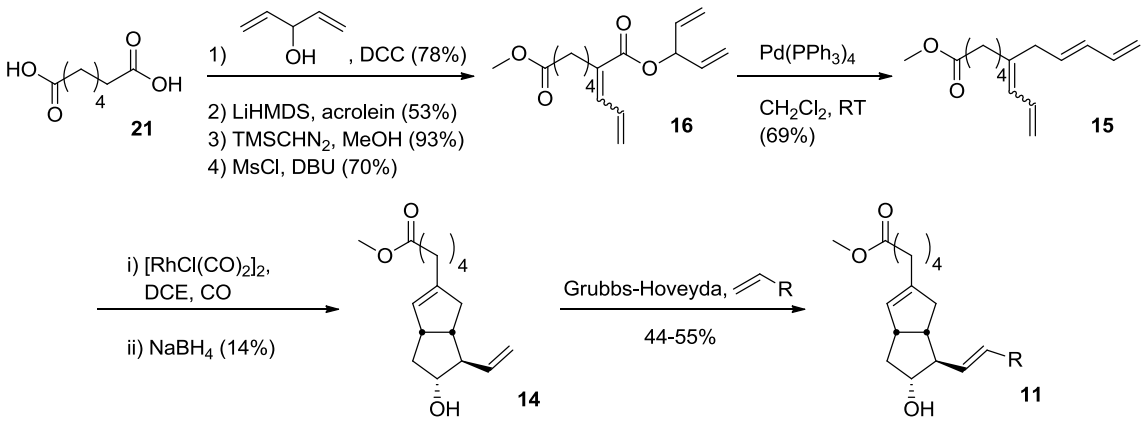


Figure 8. Synthesis of clinprost

The resulting ester (**16**) is then subjected to Pd^0 which results in simultaneous decarboxylation of the allyl ester and allylic rearrangement to form tetraene **15**. This compound is then reacted with a Rh^I catalyst followed by an *in situ* reduction; the four stereocenters of bicycle **14** are set in this process. Finally, various terminal alkenes can be installed using Grubbs-Hoveyda cross metathesis to form the final product (**11**). The concept of using cross metathesis to install diversity in the latter stages of synthesis has been used before and has been shown to have excellent yields.[19]

First Generation Synthesis of Analogs

It was thought that a new type of analog which does not contain the cyclic alkene could be synthesized in almost exactly the same manner. Instead of the mono-esterified pimelic acid undergoing the aldol reaction with acrolein, an allyl group could be installed via a simple enolate reaction. Then the methylation, decarboxylation, cycloaddition, and

cross-metathesis steps could be performed in the same manner as before with the result being a more saturated analog (Figure 9).

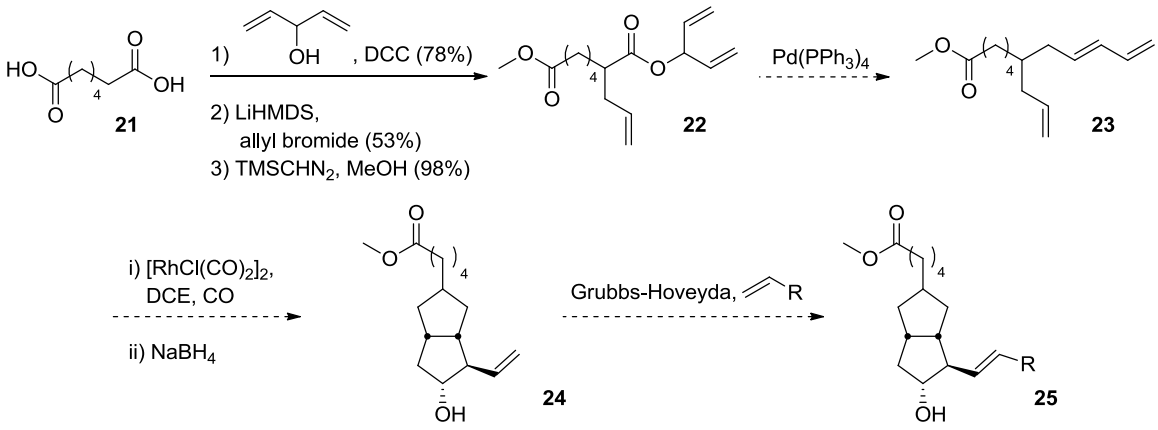


Figure 9. Proposed synthesis of saturated analog 25

Since an alkyl group in the alpha position did not appear to be very different chemically or electronically from the alkene it was believed that the palladium catalyzed decarboxylation would be as successful as the previous example. Interestingly, when saturated diester **22** was subjected to the same decarboxylation conditions as those published for the synthesis of clinprost, the expected product was not observed. This result gave further evidence to the uniqueness of the previously described decarboxylation that will be discussed in greater detail in Chapter III.

Results and Discussion

The mono-esterification of pimelic acid (**21**) is a relatively simple reaction that proceeds through the well-known coupling mechanism using dicyclohexyl carbodiimide (DCC). The DCC, when combined with dimethyl amino pyridine (DMAP), facilitates an esterification reaction between carboxylic acids and alcohols. The reaction resulted in high yields so long as the DCC solution was added in a dropwise fashion so as to prevent di-esterification of the pimelic acid.

Addition of the allyl group to the alpha position of the ester also proved to be relatively facile. At least two equivalents of a strong base (LiHMDS) were used to deprotonate the carboxylic acid as well as the most acidic α-proton which formed an enolate. This enolate was then able to react with the allyl bromide forming the desired product.

Methylation using trimethylsilyl diazomethane in methanol resulted in exceedingly high yields of the necessary diester **22**. This compound was then subjected to the same decarboxylation conditions that had been used previously in the synthesis of clinprost (Figure 10).

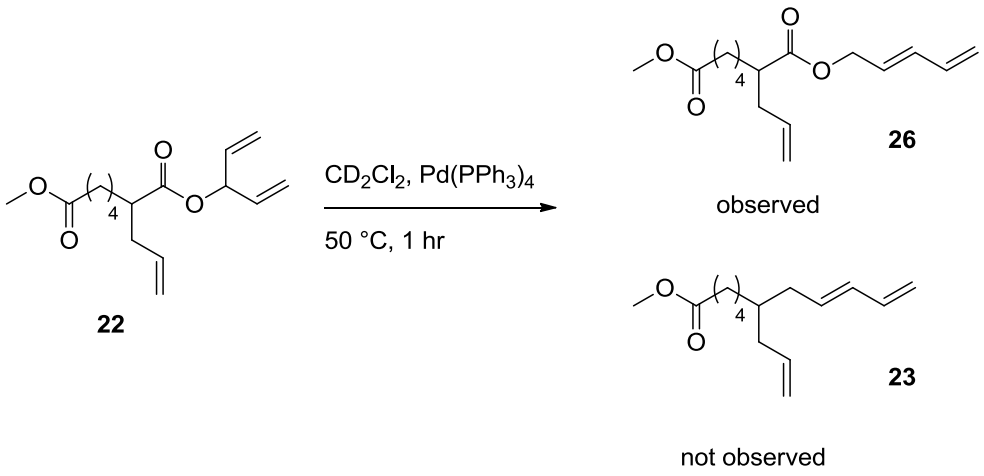


Figure 10. Decarboxylation of substrate 13

Diester **22** was weighed out in 40 mg quantities and added to microwave flasks containing a stir bar. Dichloromethane was added as the solvent and palladium tetrakis triphenylphosphine was used as the palladium catalyst. After one hour in the microwave at 50 °C the reaction was checked by thin layer chromatography. Since no product was observed it was resubjected to microwave conditions but at a higher temperature (70 °C). After three hours at these conditions there was still no formation of desired product (**23**). The mixture was purified via column chromatography and the purified compounds were analyzed using NMR spectroscopy. The results showed that the bis-allylic portion of the starting material had rearranged into the linear form but that no decarboxylation had occurred (**26**). Multiple trials were conducted (Table 1) and all yielded the same result; the starting material isomerized but did not undergo decarboxylation.

Table 1. Decarboxylation conditions attempted with substrate 22

Entry	Time	Temperature	Result
1	1 hour	50 °C	Rearrangement
2	Overnight	Room Temperature	Rearrangement
3	1 hour	70 °C	Rearrangement
4	3 hours	50 °C	Rearrangement

Since it was perplexing that a vinyl group alpha to the carbonyl would enable decarboxylation more efficiently than an alkyl group, the direction of this project switched from a total synthesis to an investigation of the method through which the decarboxylation reaction proceeded. Although this research did not lead to the total synthesis of a biologically active compound as originally planned, the reactions, techniques, and strategies were used to create a second generation synthesis which is described in Chapter II. Also, the information that came from the decarboxylation efforts helped determine the value of the novel decarboxylation from the synthesis of clinprost (Chapter III).

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CHAPTER II

SECOND GENERATION SYNTHESIS

Background

The synthesis of natural product analogs has many benefits. Often times it is possible to make minor changes to the structure of a biologically active compound and exponentially increase the activity or make the drug more marketable. Prostacyclin, the gold standard for vasodilation, shows excellent activity, but due to its reactivity and short half-life researchers sought out analogs that would be more stable compounds. This is how compounds such as iloprost, carbacyclin, isocarbacyclin, and clinprost were created.[1]

As certain changes were made to the structure of prostacyclin scientists began to notice that the drug lost its efficacy for vasodilation but showed high activity for neuroprotection.[2] These changes, correlating with the presence and stereochemistry of the alcohol on the ω-side chain, have helped direct researchers to a new goal, neuroprotection.[3] While it is known that prostacyclin binds to a G-protein coupled receptor which is contained in the peripheral nervous system, the new analogs appear to bind to a novel receptor associated with the central nervous system.[4]

Multiple analogs have been created of isocarbacyclin but the majority of them revolve around changes to the ω-side chain. To date, no syntheses are known that contain

a saturated bicyclic ring system. The synthesis described in Chapter I was designed to create analogs of this nature and send them for biological testing. However, since the synthesis failed to get past the decarboxylation barrier, analogs were never synthesized. It was at this point that a new synthesis was conceived involving a compound that contained the anion stabilizing group necessary for decarboxylation (Figure 11).

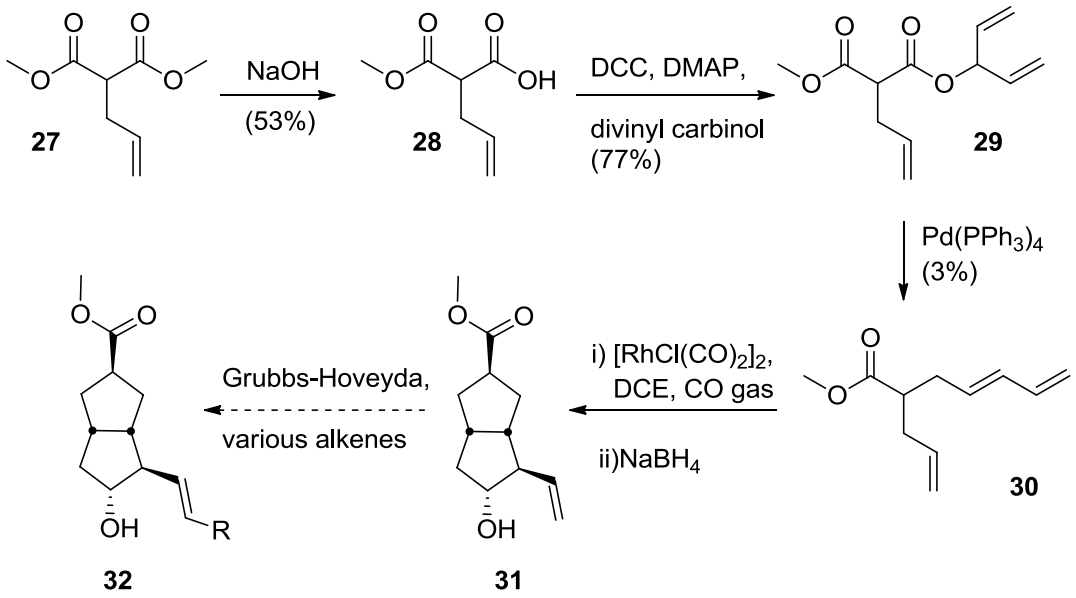

Figure 11. Second generation synthesis of saturated analogs

Results and Discussion

This second generation synthesis begins with commercially available dimethyl allyl malonate (**27**) which undergoes mono-saponification with sodium hydroxide to yield mono-acid **28**. The carboxylic acid of **28** is then coupled with divinyl carbinol to yield diester **29**. From this diester the synthesis mimics that of clinprost[5] and the first generation synthesis of a saturated analog as described in Chapter I.

The first step of the second generation synthesis is a mono-saponification with sodium hydroxide (Figure 12). After multiple attempts, it was noticed that a significant amount of THF was required in order to solubilize the compound in the aqueous base. Even with this knowledge, the products of the reaction always contained unreacted starting material, the desired mono-acid, and di-acid which had both methyl groups removed. Conveniently, the unreacted starting material was retrieved during purification and could be reused.

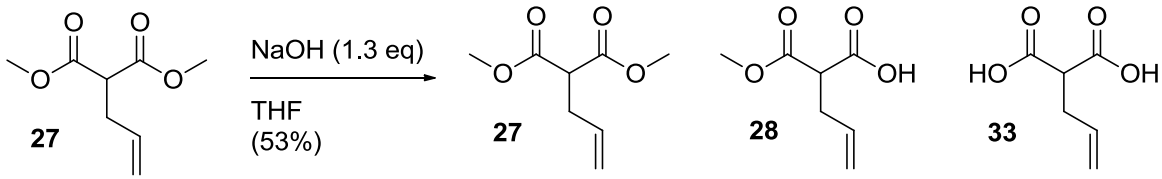

Figure 12. Mono-saponification of dimethyl allylmalonate

Following saponification, the compound was coupled with divinyl carbinol to form diester **29** (Figure 13). Ideal conditions for this reaction were found to be when 2 equivalents of dicyclohexyl carbodiimide were used along with 1.2 equivalents of divinyl carbinol.

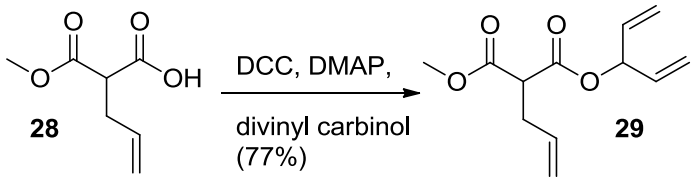

Figure 13. Coupling of methyl malonate and divinyl carbinol

With ester **29** in hand, decarboxylation with concomitant allylic transposition was attempted (Figure 14). Despite the presence of an anion-stabilizing group, the decarboxylation of diester **29** failed to produce significant amounts of product (**30**), with the major isolated compound being the rearranged product (**34**). The details of these trials are covered extensively in Chapter III.

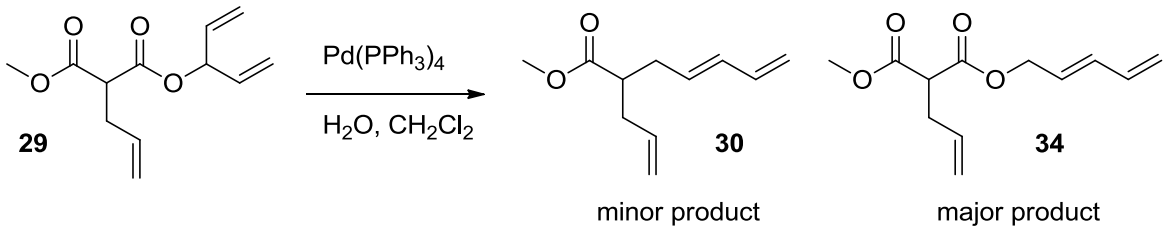

Figure 14. Decarboxylation of diester 27

A sufficient amount of ester **30** was produced to proceed to the rhodium catalyzed cycloaddition (Figure 15), although it could only be run on a test scale (< 5 mg). With only 3 mg of triene **30** we were able to observe the cycloaddition but the product was not able to be purified. Also, the final stereocenter of the alcohol was not able to be set because the sodium borohydride reaction was not attempted. The final product of the rhodium catalyzed cycloaddition is compound **35**. Fortunately, future endeavors to create saturated isocarbacyclin analogs should be able to have good results with the cycloaddition from triene **30** based on the preliminary results obtained along with the results of previous published rhodium catalyzed cycloaddition reactions.[6]

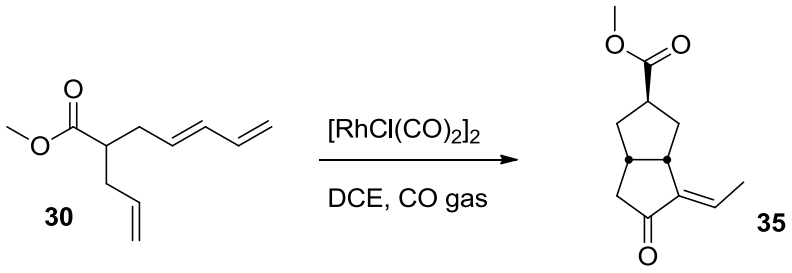

Figure 15. Rhodium catalyzed cycloaddition of triene 28

With the unexpected low reactivity for the decarboxylation trials of diester **27,** it was determined that the final efforts for this thesis should be to investigate decarboxylations of anion stabilized bis-allylic systems. The results of these efforts are contained in Chapter III.

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CHAPTER III

DECARBOXYLATION

Background

Reactions involving the loss of carbon dioxide or "decarboxylation reactions" are well known in the realms of organic chemistry and biochemistry. Decarboxylations happen frequently inside living systems and the class of reactions is one of the oldest known in the organic repertoire.[1] When most students think of decarboxylation reactions, they envision a carboxylic acid decomposing and giving off carbon dioxide while a new carbon-hydrogen bond is formed. While these reactions can be useful, they are extremely limited when it comes to desired products and usually require harsh conditions such as pyrolysis.[2]

Decarboxylative coupling is a decarboxylation reaction that closely resembles other known cross coupling reactions (Figure 16). In these types of reactions metals, such as silver or copper, are used to facilitate decarboxylative carbometalation which is necessary before the cross coupling can occur.[3] Often times the metalated species are protonated before the desired carbon-carbon or carbon-heteroatom bond can be formed which drastically reduces the yield of the desired product.[4]

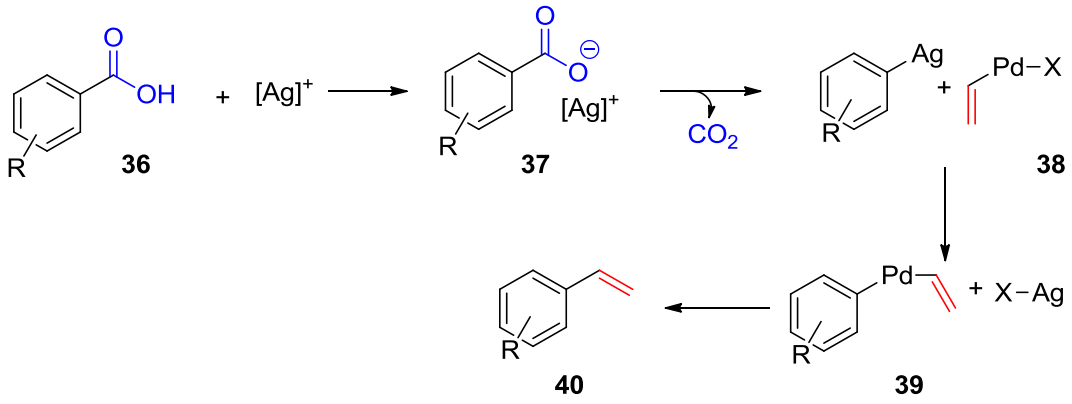

Figure 16. Decarboxylative coupling example

Recent advances have shown that organometallic catalysts are capable of assisting in the decarboxylation of molecules much more complex than simple carboxylic acids.[2] A Tsuji-Trost type decarboxylation (Figure 17) utilizes esters that have an anion stabilizing group that can stabilize the alpha carbon.[5, 6] The reaction proceeds as the Pd^0 catalyst coordinates to the double bond and cleaves the oxygen-carbon bond. The carbon dioxide is then free to leave the system and finally a new carbon-carbon bond is formed through a process called decarboxylative allylation.[7]

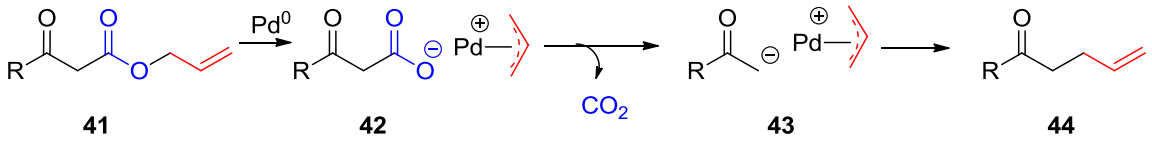

Figure 17. Tsuji-Trost decarboxylation example

The conditions that are required for this type of decarboxylation often include high temperatures or the presence of a strong acid in order to force the extrusion of the carbon dioxide.[8] While helpful for decarboxylation, often times these extreme conditions will result in the degradation of the compound and little desired product will be formed.

Dr. Jon Tunge at the University of Kansas has compiled a review of recent decarboxylation advances that resemble the Tsuji-Trost model.[9] While the review covers a broad range of substrates, conditions, and catalysts the common thread through all of the reactions is that the starting compound is either a malonate, carbonate, or ketoester. This is to say that all of the compounds form a stable anion which facilitates the extrusion of carbon dioxide.

Results and Discussion

In the decarboxylation reaction used for the synthesis of clinprost discussed in Chapter I, it is obvious that there is no anion stabilizer present (Figure 18).[10] It was therefore assumed that any substrate that contained the bis-allylic system would decarboxylate in the same manner and yield the desired product (Figure 19). As can be seen in Table 2, multiple conditions were attempted but the only product observed was the rearrangement of the bis-allylic system.

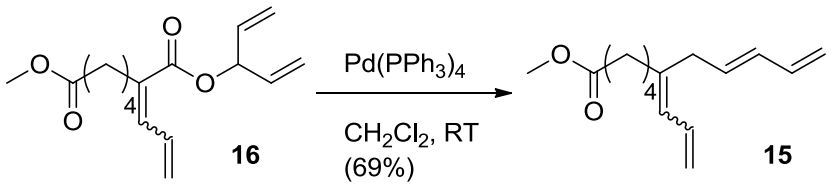

Figure 18. Decarboxylation reaction from the synthesis of clinprost

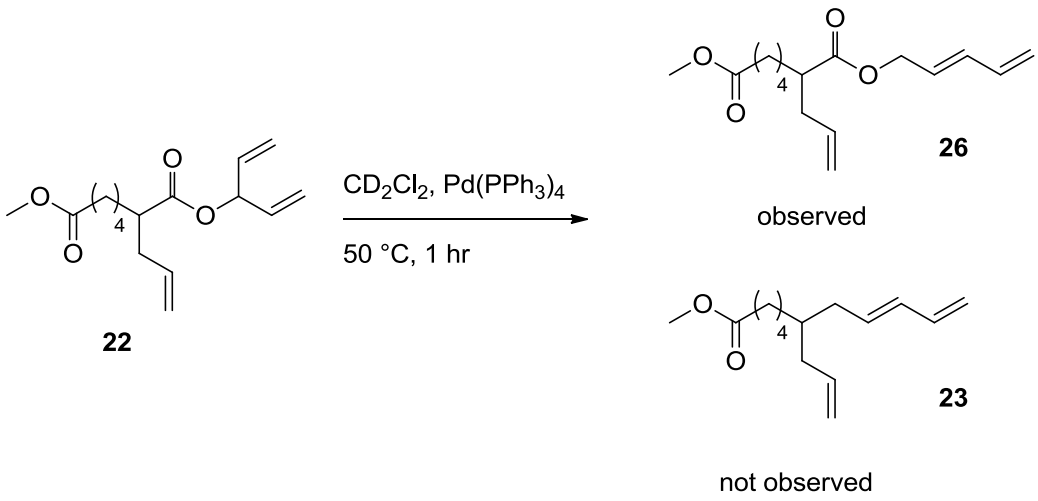

Figure 19. Decarboxylation attempts with ester 22

Table 2. Conditions for decarboxylation attempts with substrate 22

Entry	Time	Temperature	Result
1	1 hour	50 °C	Rearrangement
2	Overnight	Room Temperature	Rearrangement
3	1 hour	70 °C	Rearrangement
4	3 hours	50 °C	Rearrangement

The next step was to try decarboxylation conditions with a compound that resembled the previous substrate but was easier to make. In two steps ester **47** was made from succinic anhydride in large quantities (Figure 20).

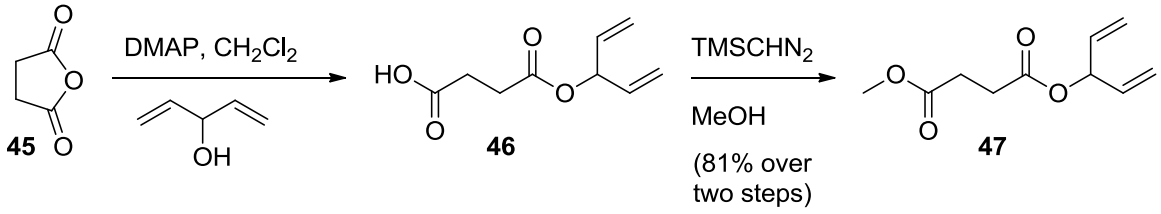

Figure 20. Synthesis of ester 47 from succinic anhydride

Decarboxylation conditions similar to those previously attempted with ester **22** were tried, however the reaction yielded no desired product (Figure 21). It was at this point that additives were considered. A variety of additives which are shown in Table 3 include Lewis and Brønsted acids. Since other decarboxylation reactions require acidic conditions in order to force extrusion of the carbon dioxide, it was hypothesized that catalytic amounts of Lewis or Brønsted acids would facilitate decarboxylation.

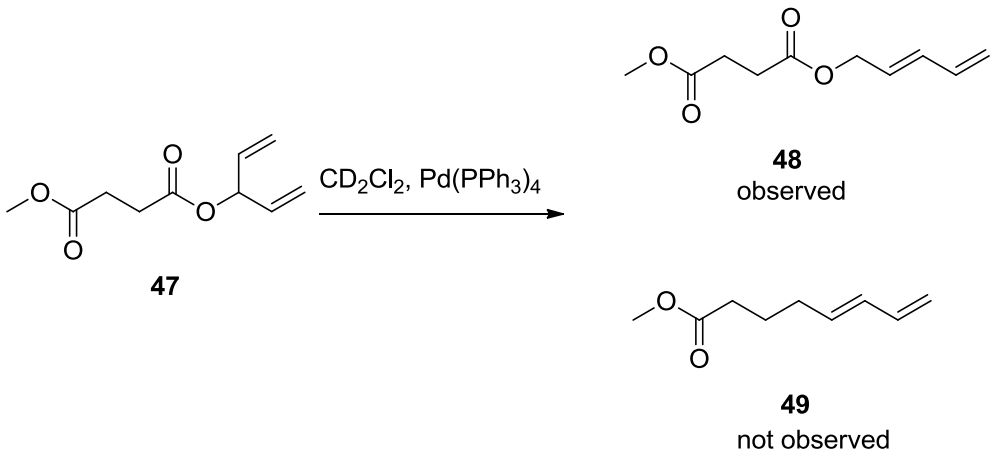

Figure 21. Decarboxylation reaction with ester 47

Table 3. Conditions for decarboxylation attempts with ester 47

Entry	Additive	Time	Temperature	Result
1	n/a	1 hour/overnight	50 °C/ RT	Rearrangement
2	Glacial Acetic Acid	1 hour/overnight	50 °C/ RT	Rearrangement
3	$BF_3{\cdot}OEt_2$	1 hour/overnight	50 °C/ RT	Rearrangement
4	$AlCl_3$	1 hour/overnight	50 °C/ RT	Rearrangement

After examining the results from the aforementioned experiments, it was determined that the additives were not helping to facilitate decarboxylation and that the original vinyl system was more crucial than originally expected. With this in mind it was determined that a bis-allylic benzoate ester should resemble the stability that was in the original compound since the α-carbon was sp^2 hybridized and that decarboxylation

should easily occur with this molecule (Figure 22). Table 4 shows the many various conditions that were attempted.

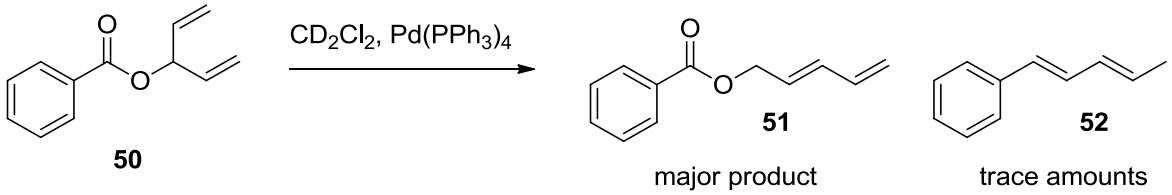

Figure 22. Decarboxylation reaction with benzoate ester 50

As can be seen in Table 4, the first attempts were to recreate conditions that had already been tried with the previous systems. Deuterated solvents were then used so that crude NMR spectra could be obtained without exposing the reactions to air. In an attempt to create decarboxylative coupling conditions similar to those discussed at the opening of this chapter, salts such as silver oxide and zinc bromide were used only to yield the same undesired product.

Table 4. Conditions for decarboxylation trials of benzoate ester 50

Entry	Additive	Solvent	Time/ Temperature	Results
1)	DPPE	$CDCl_3$	1 hr/50 °C, overnight/ RT	Rearranged
2)	$ZnBr_2$	THF	1 hr/50 °C, overnight/ RT	Rearranged
3)	AgO_2	d8-Toluene	1 hr/70 °C, overnight/ RT	Rearranged
4)	$BF_3{\cdot}OEt_2$	CD_2Cl_2	1 hr/50 °C, overnight/ RT	Rearranged
5)	Glacial Acetic Acid	CD_2Cl_2	1 hr/50 °C, overnight/ RT	Rearranged
6)	n/a	Trifluoroethanol	1 hr/50 °C, overnight/ RT	Rearranged
7)	n/a	Trifluoroethanol	Overnight/ RT	Rearranged
8)	n/a	d_6-Acetone (wet)	Overnight/ RT	Rearranged
9)	n/a	d_4-Methanol	Overnight/ RT	Rearranged
10)	n/a	Glacial Acetic Acid	1 hr/50 °C, overnight/ RT	Rearranged
11)	n/a	CD_2Cl_2	1 hr/50 °C, overnight/ RT	Rearranged
12)	n/a	DMSO	1 hr/RT, 10 min/reflux	Decomposition
13)	n/a	d_8-Toluene	1 hr/100 °C, overnight/ RT	Rearranged, **52**
14)	n/a	d_8-Toluene	1 hr/120 °C, overnight/ RT	Rearranged, **52**
15)	n/a	d_8-Toluene	1 hr/140 °C, overnight/ RT	Rearranged, **52**
16)	n/a	d_8-Toluene	1 hr/180 °C, overnight/ RT	Rearranged, **52**

Testing with the original system showed that no decarboxylation was apparent when chloroform was used; therefore trials with multiple solvents were attempted. When inspected via TLC, reactions carried out in toluene showed a promising non-polar compound, however when visualized with NMR it quickly became apparent that it was not the desired product. A small amount of decarboxylated product seemed to have formed in reaction 13-16 but isomerization had occurred resulting in the conjugated system ending with a methyl (ester **52**).

The final compound lacking anion stabilization that was to be tested was a cinnamic ester (Figure 23). It was suspected that this compound would decarboxylate and reproduce the original results due to the double bond between the ester and phenyl ring.

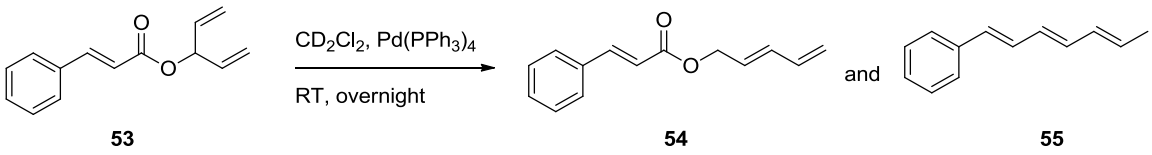

Figure 23. Decarboxylation reaction for cinnamic ester

As it turned out, ester **53** proved difficult to make and decarboxylation attempts did not yield the product that was expected. Similar to the results seen in entries 13-16 of the benzoate system, the compound did show some decarboxylation but any decarboxylated product had rearranged to the terminal methyl (**55**) shown in Figure 6. The only condition that was attempted for this compound was leaving it overnight at room temperature.

With the results of many failed decarboxylation reactions, several conclusions were made. It was first determined that a dienoate must be formed in order for decarboxylation to occur when an anion stabilizing group was not present. This gave explanation as to why the cinnamate ester failed to decarboxylate as well as the reaction from the synthesis of clinprost. Finally, other members of the Croatt group ran experiments testing the necessity of the bis-allylic system as opposed to the typical allyl system often seen with decarboxylative allylation.[8] Interestingly, the bis-allylic ester was necessary along with the dienoate for decarboxylation to occur.

As previously stated, the decarboxylation of compounds containing anion stabilizing groups is a known reaction. The review written by Jon Tunge[11] contains numerous examples of ketoesters, malonates, and carbonates which readily undergo decarboxylation when introduced to catalysts. It was with this knowledge that the second generation synthesis of a saturated isocarbacylin analog was derived (discussed in Chapter II). Although there was no proof of bis-allyl systems undergoing decarboxylation in the literature, there was no reason to believe that the compounds would not proceed through the same Tsuji-Trost type mechanism. However, once subjected to the same conditions as were described in the literature, the compound yielded only small amounts of the desired product (Figure 24).

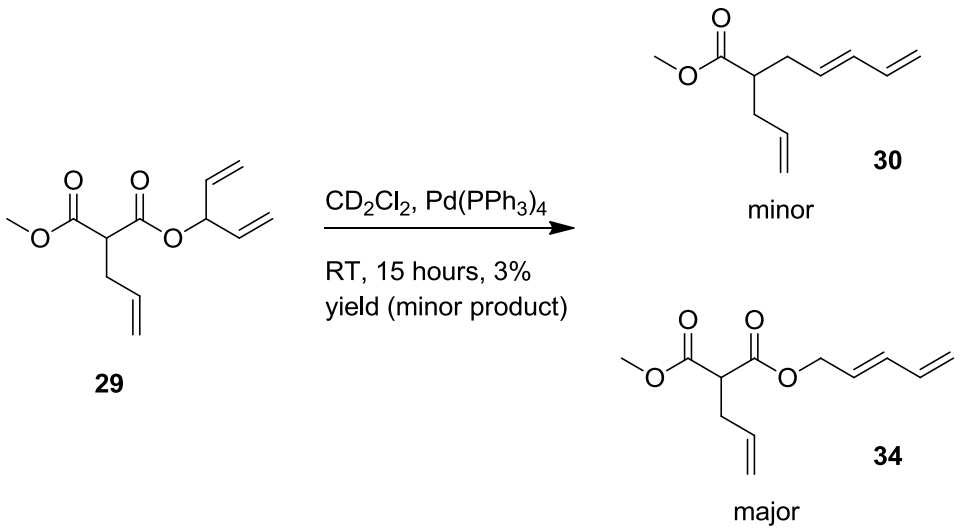

Figure 24. Decarboxylation reaction with malonate ester 29

Since the yields of the decarboxylation reactions were so low, efforts once again moved from the total synthesis of isocarbacyclin analogs to the methodology of decarboxylation reactions. Other solvents were used such as dimethyl formamide, tetrahydrofuran, and toluene but no positive changes were observed in product yield. Finally it was hypothesized that the bis-allylic system was too stable to decarboxylate at room temperature so higher temperatures were used. Unfortunately, the higher temperatures only forced decomposition and no product formation.

The final experiment was to test if a diallyl allylmalonate system would decarboxylate. According to the literature references, allyl systems decarboxylated with high yields. Diallyl allylmalonate was synthesized via a coupling reaction between di-acid allylmalonate (**33**) and allyl alcohol and was then subjected to decarboxylation conditions (Figure 25).

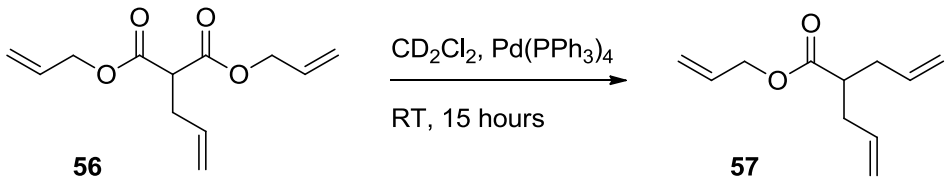

Figure 25. Decarboxylation reaction with diallyl allylmalonate

Although the product was not able to be recovered, crude NMR gave proof that decarboxylation was occurring. The triplet which represented the proton between the carbonyls was observed to shrink while a pentet developed more upfield. This corresponds to the anticipated results as the newly formed carbon-carbon bond is identical to the allyl group which was already in place.

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CHAPTER IV

EXPERIMENTAL

General Information

All anhydrous reactions were performed with dry solvents in oven dried glassware under a nitrogen atmosphere. Unless otherwise noted, all solvents and reagents were obtained from commercial sources and used without further purification. Chromatographic purification was performed using silica gel (60 Å, 32-63 μm). NMR spectra were recorded using a JEOL ECA spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of triplets (tt), multiplet (m), etc. IR data was obtained with a Perkin Elmer FTIR spectrometer with ATR sampling accessory with frequencies reported in cm^{-1}. High Resolution Mass Spectra were acquired on a ThermoFisher Scientific LTQ Orbitrap XL MS system.

Pimelic acid ester 21a

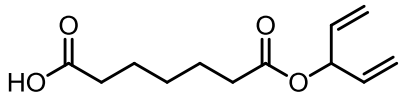

Figure 26. Pimelic acid ester 21a[1]

A solution of DCC (2.45 g, 11.9 mmol) in THF (15 mL) was added to a solution of pimelic acid (9.54 g, 59.4 mmol), 1,4-pentadien-3-ol (1.16 mL, 11.9 mmol), and DMAP (145 mg, 1.19 mmol) in THF (90 mL) slowly via an additional funnel over 3 hours. After 2 days, the reaction was filtered through Celite and washed with THF. Silica gel was added to the concentrated mixture and the solvent was removed after which the dry powder was added to a silica gel column. The product was purified (7:3, hexanes/EtOAc) to yield acid **21a** (2.1 g, 78%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.34 - 11.00 (s, 1H), 5.88 - 5.79 (m, 2H), 5.74 - 5.69 (m, 1H), 5.34 - 5.21 (m, 4H), 2.36 (t, *J* = 7.4 Hz, 4H), 1.72 - 1.63 (m, 4H), 1.44 - 1.35 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 179.5, 172.4, 135.1 (2C), 117.4 (2C), 74.9, 34.2, 33.7, 28.4, 24.5, 24.3 ppm.

HRMS (ESI) $C_{12}H_{18}O_4Na$ $[M+Na]^+$, calculated: 249.1103, found: 249.1098.

IR (neat) 2935, 2866, 1732, 1705, 1641, 1170, 925 cm^{-1}.

Acid with allylic side chain 21b

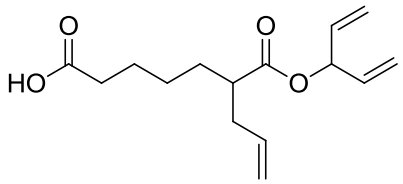

Figure 27. Acid with allylic side chain 21b[2]

A solution of LiHMDS (3.4 mL, 3.39 mmol) in THF (2.5 mL) was made in a round bottom flask at -78 °C. Slowly a solution of mono-ester **21a** (200 mg, 1.13 mmol) in THF (1.2 mL) was added and allowed to react with the base for 15 minutes. The solution was then transferred via cannula to another round bottom flask containing allyl bromide (1.25mL, 11.3 mmol) in THF (6 mL). The reaction was allowed to progress for 2 hours before being quenched with saturated aqueous ammonium chloride (approximately 2 mL). Extraction using EtOAc was followed with evaporation and then purification using flash silica gel chromatography. A mixture of 10% hexanes in ethyl acetate was used to elute the product which was then verified to be pure via NMR and TLC. Reaction yielded acid **21b,** a pale yellow oil, at 53% (159.5 mg, 0.598 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.91 - 10.15 (s, 1H), 5.88 - 5.79 (m, 2H), 5.78 - 5.68 (m, 2H), 5.34 - 5.28 (m, 2H), 5.26 - 5.21 (m, 2H), 5.10 - 5.00 (m, 2H), 2.51 - 2.44 (m, 1H), 2.43 - 2.32 (m, 3H), 2.28 - 2.20 (m, 1H), 1.72 - 1.59 (m, 3H), 1.57 - 1.48 (m, 1H), 1.41 - 1.31 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 179.3, 174.3, 135.2, 135.1 (2C), 117.6, 117.5, 117.0, 74.9, 45.1, 36.4, 33.7, 31.3, 26.6, 24.4 ppm.

HRMS (ESI) $C_{15}H_{22}NaO_4$ [M+Na]+, calculated: 289.1416, found: 289.1410.

Ester with allylic side chain 22

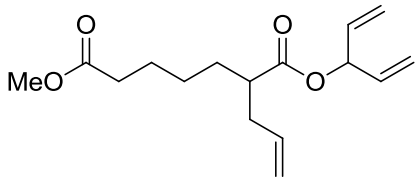

Figure 28. Ester with allylic side chain 22[3]

A solution was made in a round bottom flask at 0 °C of acid **21b** (50 mg, 0.19 mmol) and methanol (1.82 mL). Slowly, trimethylsilyl diazomethane (1 mL, 1.82 mmol) was added and the solution was left to stir for 10 minutes. Nitrogen bubbles were observed in the solution indicating reaction progress. Nitrogen gas was bubbled through the solution for 20 minutes in a well-ventilated hood to remove the toxic gases. Following immediate evaporation the resulting colorless oil was subjected to a flash silica gel chromatography (95:5 hexanes/EtOAc) to yield methyl ester **21b** (49.1 mg, 96%). Product purity was determined by thin layer chromatography and NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.82 (ddd, *J* = 6.2, 10.6, 17.0 Hz, 1H), 5.81 (ddd, *J* = 6.2, 10.6, 17.0 Hz, 1H), 5.78 - 5.68 (m, 2H), 5.32 - 5.27 (m, 2H), 5.24 - 5.20 (m, 2H), 5.10 - 4.99 (m, 2H), 3.71 - 3.60 (m, 3H), 2.51 - 2.43 (m, 1H), 2.42 - 2.34 (m, 1H), 2.30 (t,

J = 7.4 Hz, 2H), 2.27 - 2.20 (m, 1H), 1.70 - 1.59 (m, 3H), 1.56 - 1.47 (m, 1H), 1.37 - 1.28 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.3, 174.0, 135.2, 135.1 (2C), 117.5, 117.5, 117.0, 74.8, 51.5, 45.2, 36.4, 33.8, 31.3, 26.7, 24.7 ppm.

HRMS (ESI) $C_{16}H_{25}O_4$ $[M+H]^+$, calculated: 303.1572, found: 303.1567.

Malonic mono-acid 28

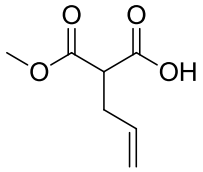

Figure 29. Malonic mono-acid 28[5]

Dimethyl allylmalonate (2 mL, 12.4 mmol) and THF (2 mL) were combined and 4 M NaOH (9.6 mL) was added dropwise. The solution was left to stir at room temperature until the pH reached seven (approximately one hour). The resulting solution was then acidified with HCl and extracted three times using ethyl acetate. The product was purified by chromatography (9:1, hexanes, EtOAc) to yield acid **28** (1.04 g, 53%) as a pale yellow oil. Spectral data was in agreement with previous reports.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.80 - 5.74 (m, 1H), 5.14 (dd, *J* = 1.4, 16.9 Hz, 1H), 5.09 (dd, *J* = 1.1, 10.3 Hz, 1H), 3.76 (s, 3H), 3.50 (t, *J* = 7.2 Hz, 1H), 2.69 – 2.65 (m, 2H) ppm.

Malonic ester 29

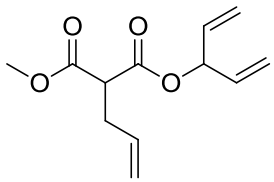

Figure 30. Malonic ester 29[1]

A solution was made of malonic mono-acid **28** (834 mg, 5.27 mmol), DMAP (64.7 mg, 0.53 mmol), divinyl carbinol (0.65 mL, 6.32 mmol), and THF (24 mL). A solution of DCC (2.17 g, 10.54 mmol) in THF (20 mL) was then added dropwise at the rate of about one drop per two seconds. The solution was left to stir overnight while solids formed. After one day the reaction was filtered through Celite to get rid of solids. The product was purified (7:3, hexanes/EtOAc) to yield malonic ester **29** (908 mg, 77%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.84 - 5.72 (m, 4H), 5.30 (dd, *J* = 1.7, 17.2 Hz, 2H), 5.24 - 5.22 (m, 2H), 5.13 - 5.09 (m, 1H), 5.06 – 5.04 (m, 1H), 3.72 (s, 3H), 3.48 (t, *J* = 7.4 Hz, 1H), 2.67 - 2.63 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.31, 167.82, 134.54 (2C), 133.92, 117.97, 117.84 (2C), 76.15, 52.54, 51.69, 32.87 ppm.

Triene 30

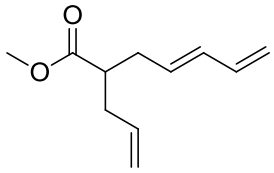

Figure 31. Triene 30[7]

A solution was made of malonic ester **29** (42.4 mg, 0.19 mmol), dichloromethane (1 mL), and water (2.5 μL, 0.19 mmol). Palladium tetrakis triphenylphosphine (25 mg, 0.02 mmol) was then added and the reaction was left to stir for 15 hours. The reaction changed from a dark orange color to a pale yellow during this time. Purification via silica gel chromatography (95:5, hexanes:EtOAc) yielded triene **30** (1 mg, 3%) as a colorless oil. Analytically pure spectral data was not obtained due to the low yield. However, 1H NMR spectral analysis showed similarities to related structures.[8]

Bicycle 35

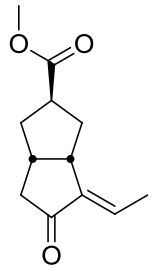

Figure 32. Bicycle 35[8]

Triene **30** (3 mg, 0.016 mmol) in dichloroethane (2 mL) was added to an oven-dried test tube. $[RhCl(CO)_2]_2$ (0.6 mg, 0.016 mmol) was then added before purging thoroughly with CO. A CO filled balloon was used to maintain a constant CO atmosphere and the reaction was heated to 80 °C using an oil bath for 4 hours. TLC and crude NMR showed evidence of product formation based on related structures.[8] No product was purified.

Succinate mono-acid 46

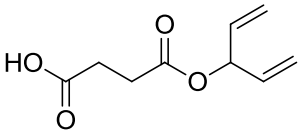

Figure 33. Succinate mono-acid 46[1]

A solution of divinyl carbinol (0.3 mL, 2.97 mmol) and dimethyl aminopyridine (72 mg, 0.59 mmol) was made in dichloromethane (5 mL). Slowly solid succinic

anhydride (482 mg, 4.81 mmol) was added and the solution was left to stir at room temperature overnight. The resulting mixture was filtered through celite to get rid of get rid of solids and then purified via silica gel chromatography (85:15 hexanes/EtOAc) to yield mono-acid **46** (726 mg, 3.94 mmol, 82%). The resulting colorless oil was determined pure via NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.17 - 9.46 (br. s, 1H), 5.83 (ddd, J = 5.7, 10.3, 16.6 Hz, 2H), 5.74 - 5.70 (m, 1H), 5.31 (td, J_t = 1.1 Hz, J_d = 17.2 Hz, 2H), 5.25 (td, J_t = 1.1 Hz, J_d = 10.3 Hz, 2H), 2.73 - 2.65 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.3, 171.1, 134.7 (2C), 117.7 (2C), 75.6, 29.0, 29.1 ppm.

HRMS (ESI) $C_9H_{13}O_4$ $[M+H]^+$, calculated: 185.0814, found: 207.0627.

Succinate di-ester 47

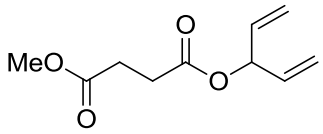

Figure 34. Succinate di-ester 47[3]

A solution was made in a round bottom flask at 0 °C of succinate mono-acid **46** (125 mg, 0.679 mmol) and methanol (6.8 mL). Slowly, trimethylsilyl diazomethane (3.4 mL, 6.79 mmol) was added and the solution was left to stir for 10 minutes. The solution

was then degassed with nitrogen for 20 minutes to rid the flask of toxic gases. Following immediate evaporation the resulting colorless oil was subjected to a flash silica gel chromatography (95:5 hexanes/EtOAc) to yield succinate diester **47** (128 mg, 0.644 mmol, 95%). Product purity was determined by thin layer chromatography and NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.81 (ddd, J = 5.7, 10.3, 16.6 Hz, 2H), 5.71 - 5.67 (m, 1H), 5.28 (td, J_t = 1.1 Hz, J_d = 17.2 Hz, 2H), 5.21 (td, J_t = 1.1 Hz, J_d = 10.3 Hz, 2H), 3.66 (s, 3H), 2.68 - 2.60 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.6, 171.1, 134.8 (2C), 117.4 (2C), 75.3, 51.7, 29.2, 28.7 ppm.

HRMS (ESI) $C_{10}H_{15}O_4$ $[M+H]^+$, calculated: 199.0970, found: 221.0782.

Benzoate ester 50

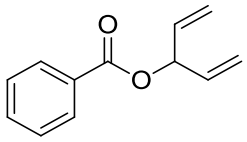

Figure 35. Benzoate ester 50[4]

To a precooled solution of divinyl carbinol (1.05 mL, 10.8 mmol), DMAP (132 mg, 1.08 mmol), and pyridine (1.3 mL, 16.2 mmol) in dichloromethane (32 mL) at 0 °C. was slowly added benzoyl chloride (1.5 mL, 12.9 mmol) and the resulting mixture was left stirring at 0 °C for 20 minutes. The solution was left to stir at room temperature

overnight. After 24 hours the solution was quenched with a saturated solution of sodium bicarbonate (approximately 5 mL) and then extracted with dichloromethane. The organic layer was then evaporated and purified via silica gel chromatography (9:1 hexanes/EtOAc) to yield benzoate **50** (1.92 g, 10.2 mmol, 94%). The spectroscopic data for this compound matched reported data.[9]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.09 (dd, *J* = 1.0, 8.0 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 6.01 - 5.92 (m, 3H), 5.44 - 5.37 (m, 2H), 5.32 - 5.25 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.6, 135.2 (2C), 133.1, 130.4, 129.8 (2C), 128.5 (2C), 117.7 (2C), 75.6 ppm.

Cinnamate ester 53

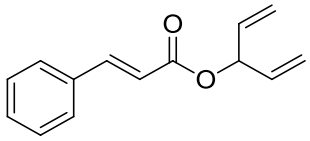

Figure 36. Cinnamate ester 53[1]

A solution of DCC (1.74 g, 8.45 mmol) in THF (10 mL) was added to a solution of cinnamic acid (1.25 g, 8.45 mmol), 1,4-pentadien-3-ol (0.82 mL, 8.45 mmol), and DMAP (206 mg, 1.69 mmol) in THF (90 mL) slowly via an additional funnel over 3 hours at 0 °C. After 16 hours, the reactionwas filtered through celite and washed with

THF. The product was purified by chromatography (95:5, hexanes, EtOAc) to yield acid **53** (0.83 g, 43%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 16.0 Hz, 1H), 7.57 - 7.52 (m, 2H), 7.42 - 7.38 (m, 3H), 6.49 (d, *J* = 16.0 Hz, 1H), 5.93 (ddd, *J* = 6.3, 10.3, 16.6 Hz, 2H), 5.88 - 5.84 (m, 1H), 5.38 (td, J_t = 1.1 Hz, J_d = 17.2 Hz, 2H), 5.28 (td, J_t = 1.1 Hz, J_d = 10.3 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.9, 145.1, 135.0 (2C), 134.3, 130.3, 128.9 (2C), 128.1 (2C), 118.0, 117.5 (2C), 75.1 ppm.

HRMS (ESI) $C_{14}H_{15}O_2$ $[M+H]^+$, calculated: 215.1072, found: 215.10724.

Malonic di-acid 33

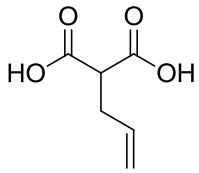

Figure 37. Malonic di-acid 33[5]

Dimethyl allylmalonate (1 mL, 6.2 mmol) in THF (2 mL) was added to 4 M NaOH (6.2 mL). The reaction was left to stir for 1 hour before being acidified with HCl and extracted using EtOAc. The product was dried and required no purification to yield

acid **35** (885 mg, 99%) as a white crystalline solid. The spectroscopic data for this compound matched reported data.[10]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.83 (m, 1H), 5.20-5.11 (m, 2H), 3.54 (t, *J* = 7.2 Hz, 1H), 2.71 – 2.68 (m, 2H) ppm.

Diallyl allylmalonate 56

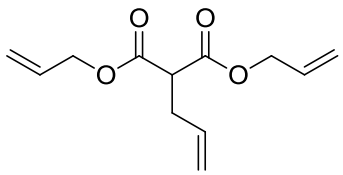

Figure 38. Diallyl allylmalonate 56[1]

A solution was made of malonic di-acid starting material (371 mg, 2.57 mmol), DMAP (31 mg, 0.26 mmol), allyl alcohol (0.87 mL, 12.9 mmol), and THF 15 mL). A solution of DCC (1.59 g, 7.71 mmol) in THF (10 mL) was then added dropwise at the rate of about one drop per two seconds. The solution was left to stir overnight while solids formed. After one day the reaction was filtered through Celite to get rid of solids. The product was purified (95:5, hexanes/EtOAc) to yield diallyl allylmalonate **56** (86 mg, 14%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.89 (ddt, J_d = 5.7, 17 Hz, J_t = 7.2 Hz, 2H), 5.78 (ddt, J_d = 10.3, 17.2 Hz, J_t = 6.9 Hz, 1H), 5.34 - 5.30 (m, 2H), 5.25 – 5.22 (m, 2H), 5.15 – 5.10

(m, 1H), 5.08 – 5.05 (m, 1H), 4.67 – 4.60 (m, 4H), 3.50 (t, *J* = 7.2), 2.69 – 2.66 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.65 (2C), 133.96, 131.60 (2C), 118.81 (2C), 117.93, 66.07 (2C), 51.62, 32.96 ppm.

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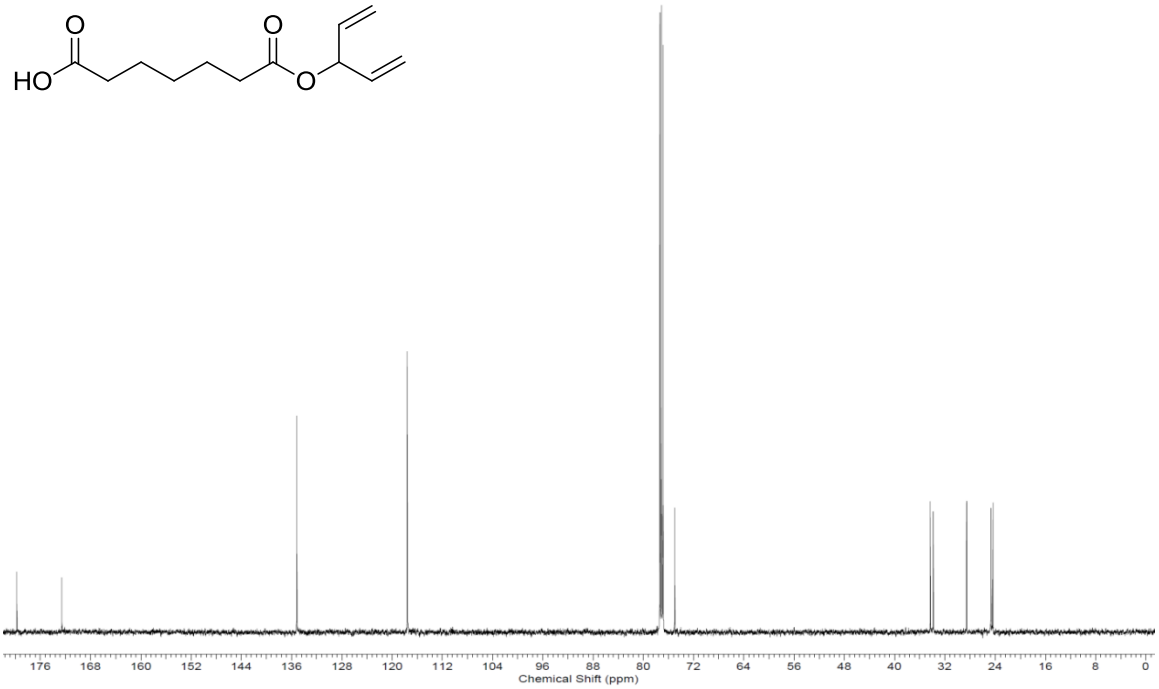
APPENDIX A

NMR SPECTRA OF COMPOUNDS

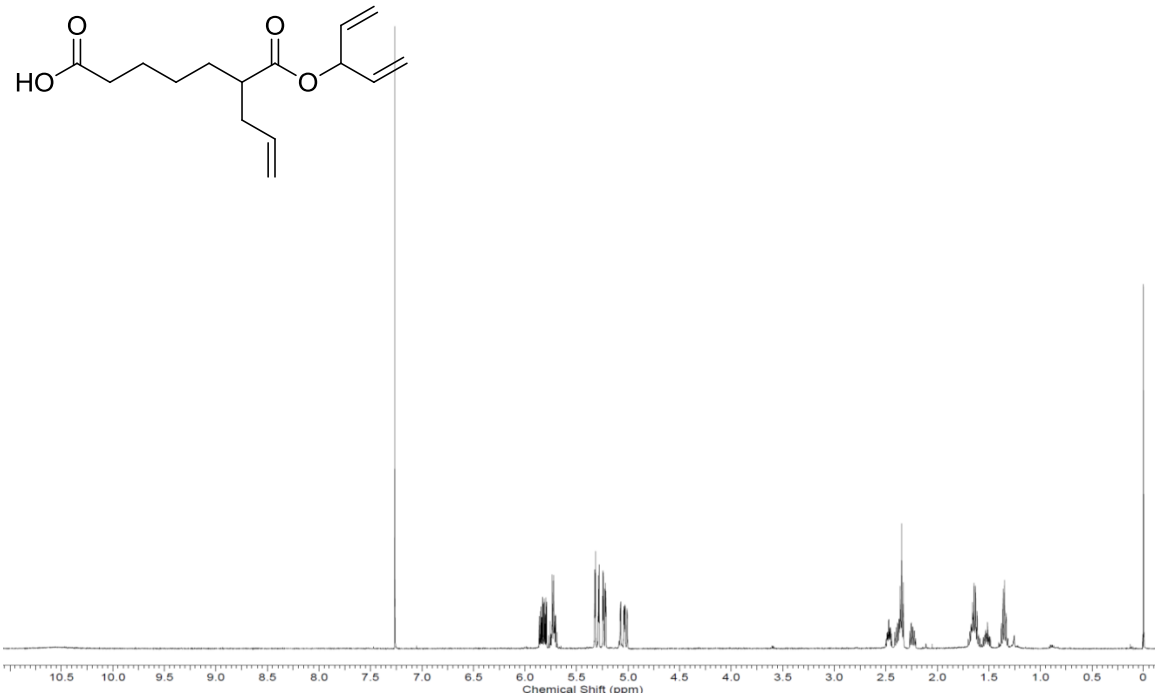
NMR spectra were recorded using a JEOL ECA spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). All spectra were taken at room temperature in deuterated chloroform unless otherwise noted.

^{1}H NMR of **21a**

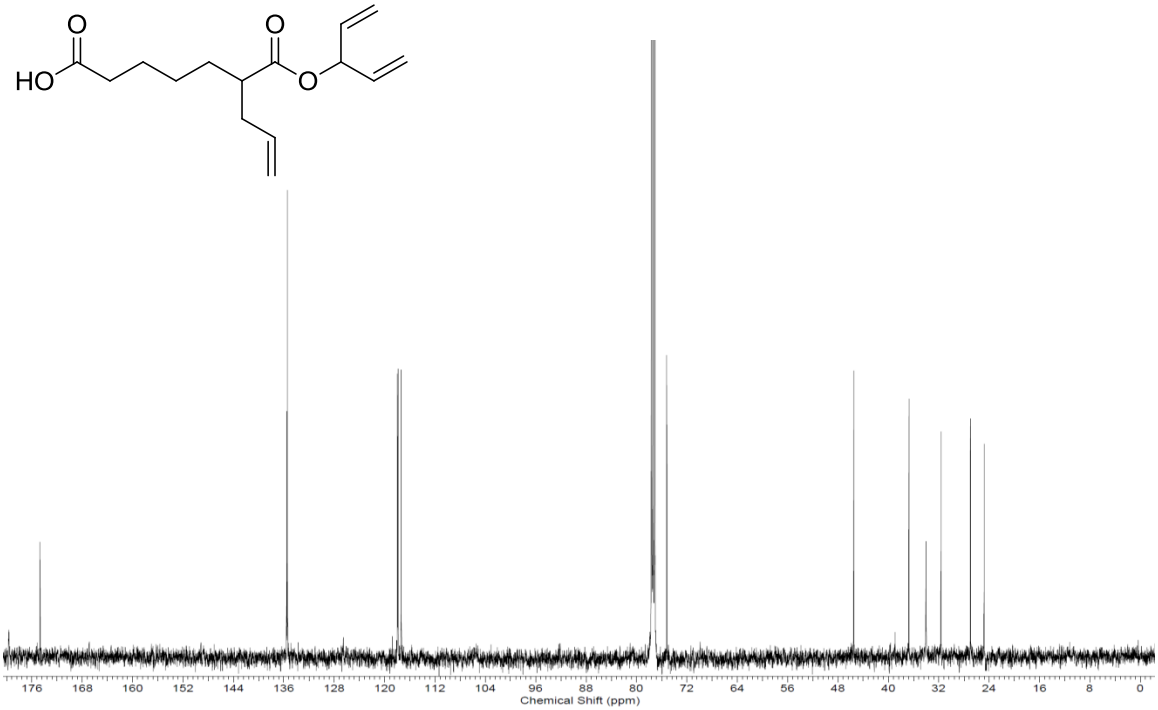
^{13}C NMR of **21a**



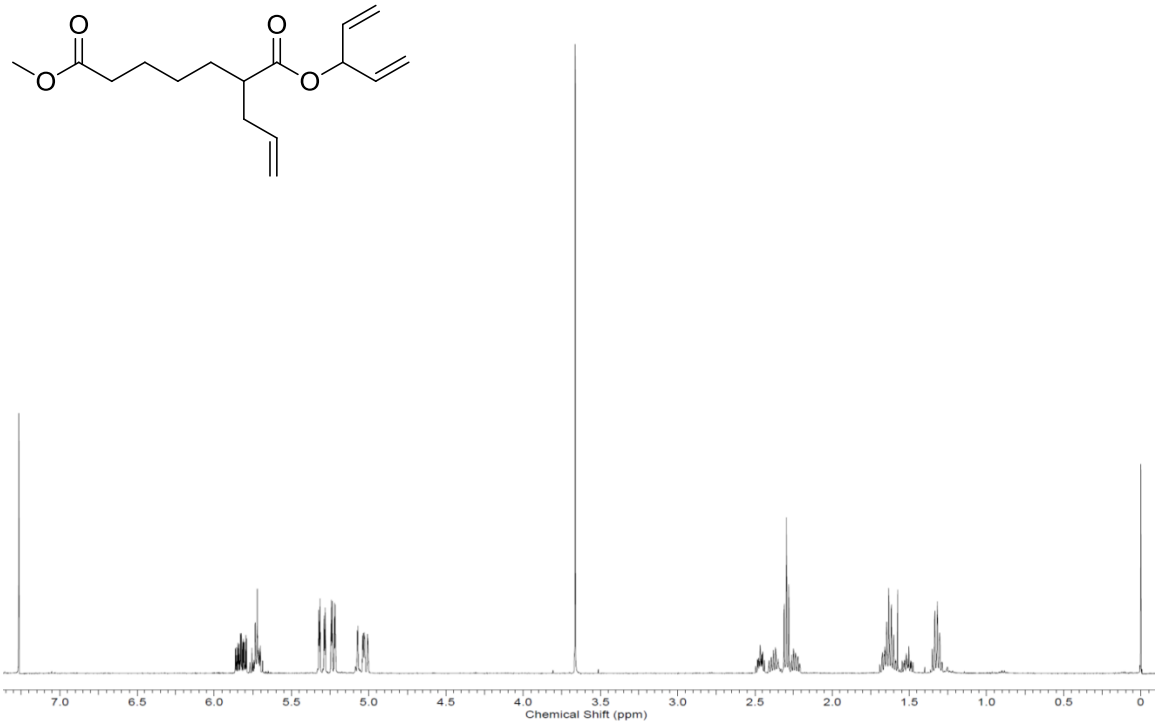
^{1}H NMR of **21b**



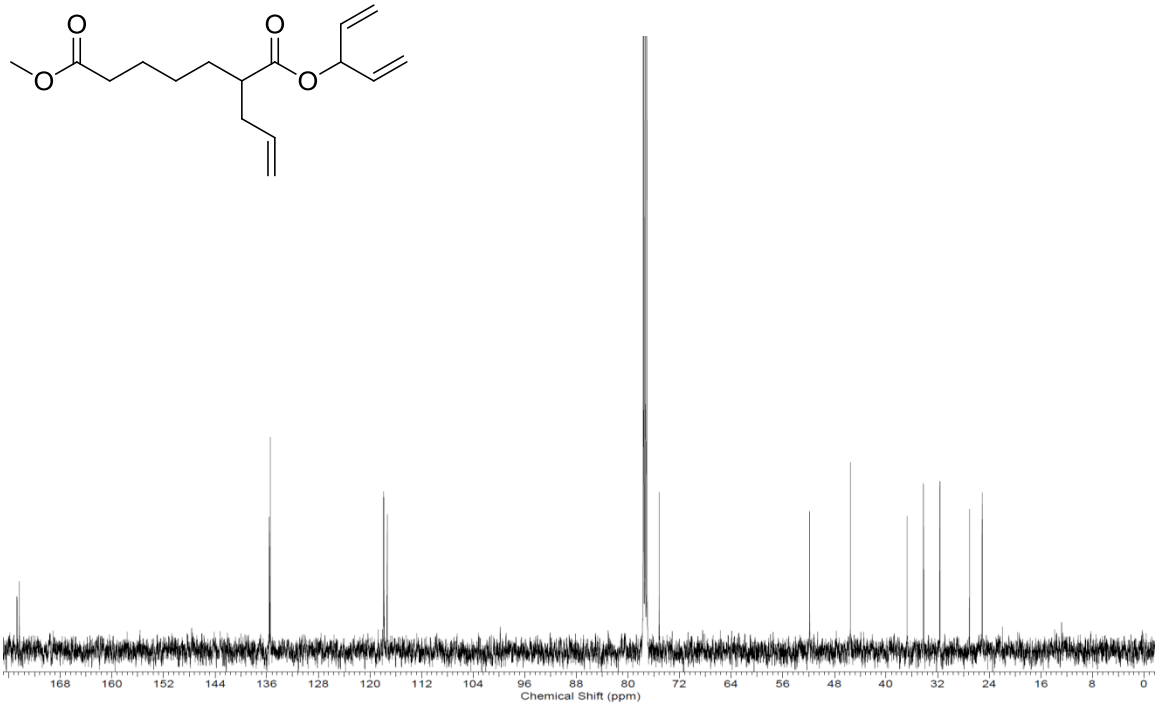
^{13}C NMR of **21b**



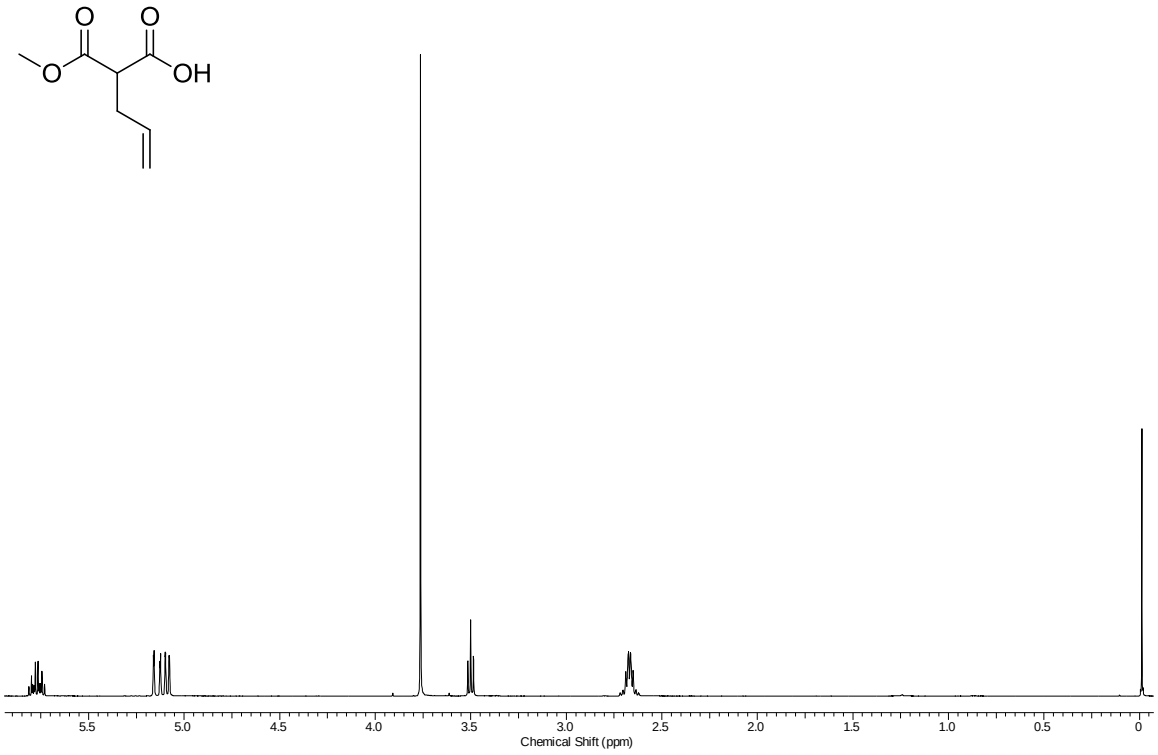
^{1}H NMR of **22**



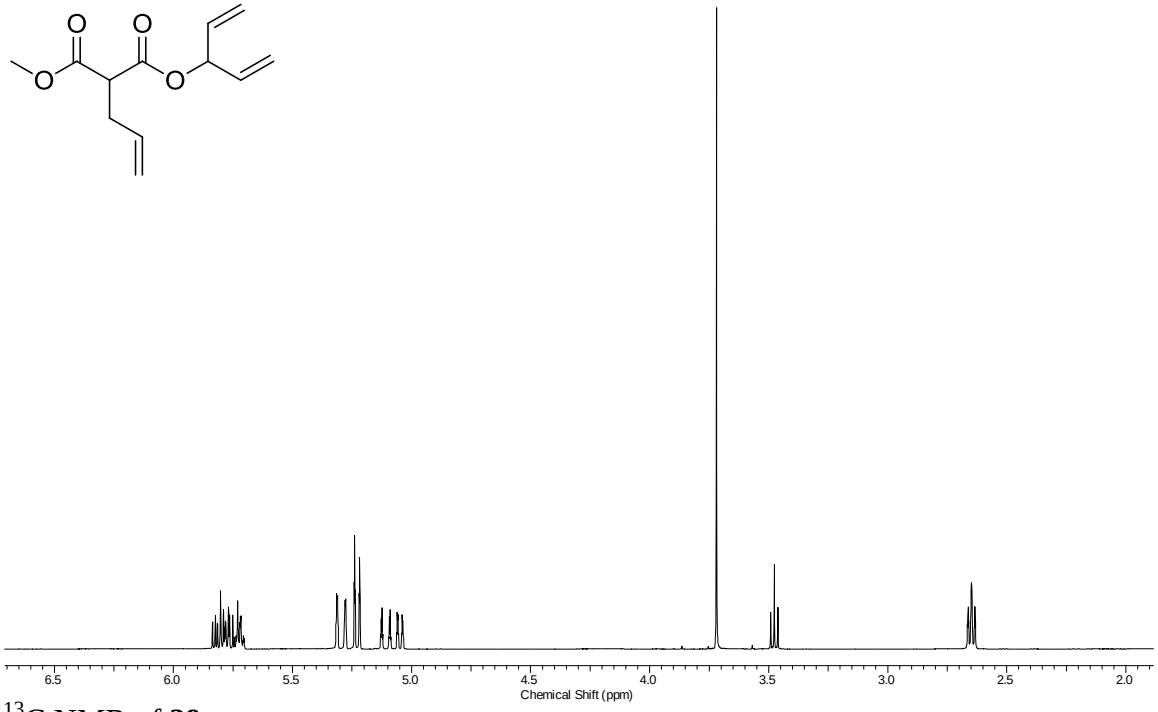
^{13}C NMR of **22**



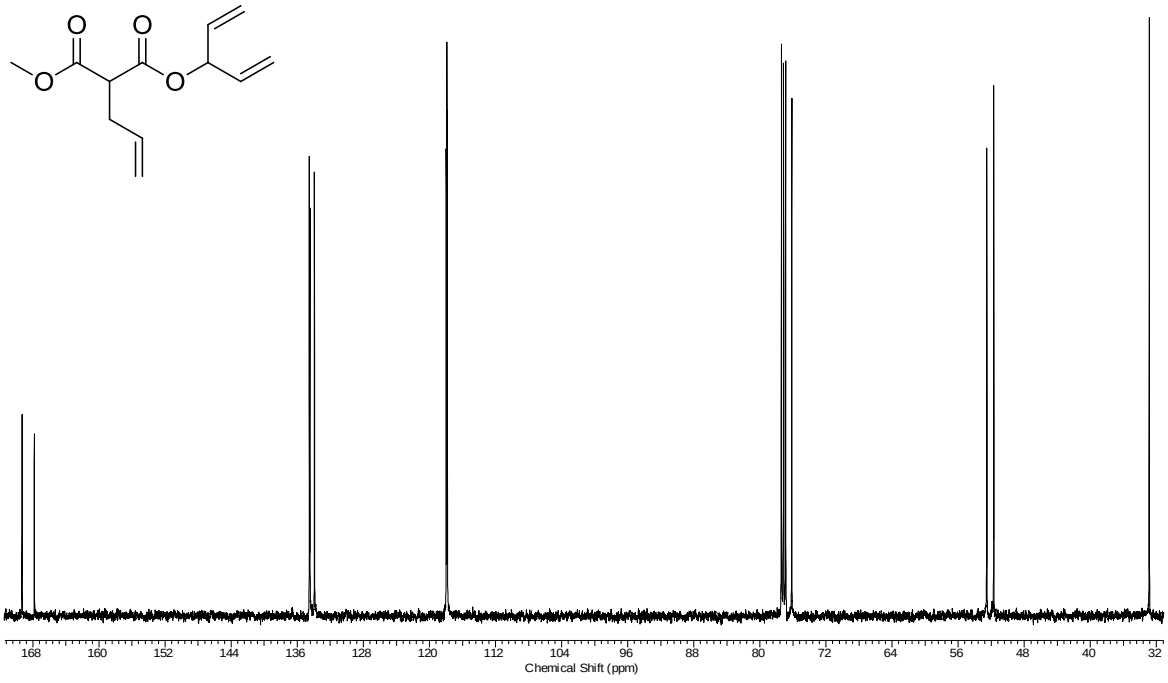
^{1}H NMR of **28**



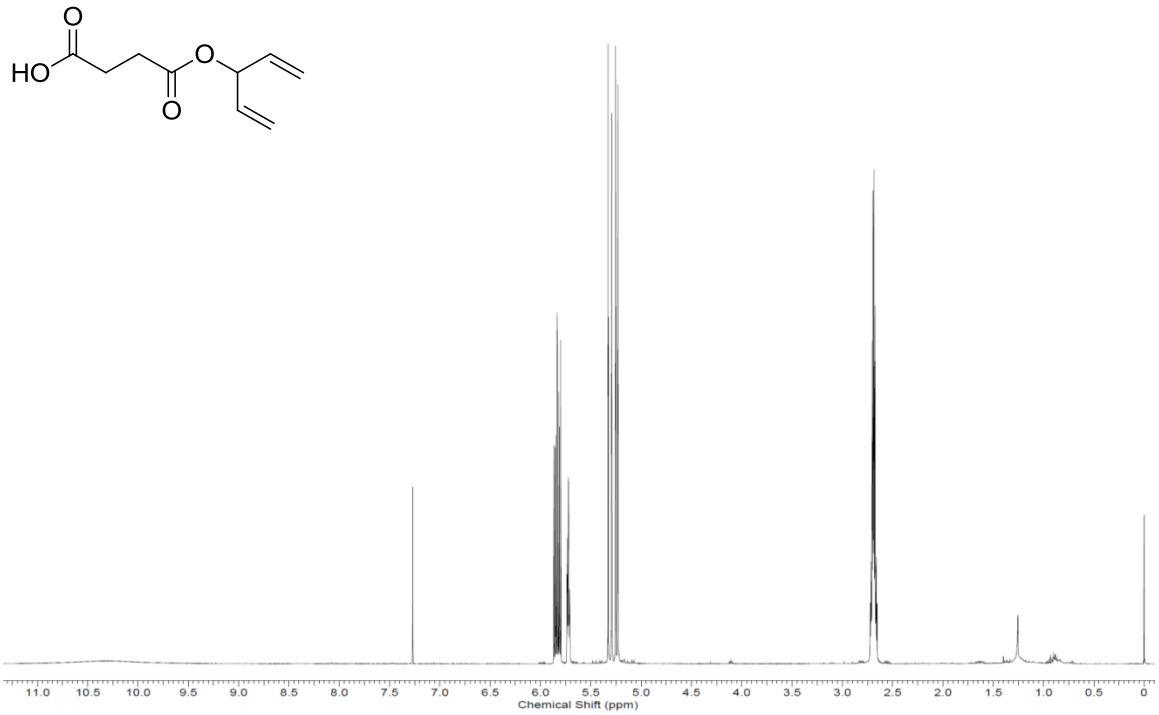
^{1}H NMR of **29**



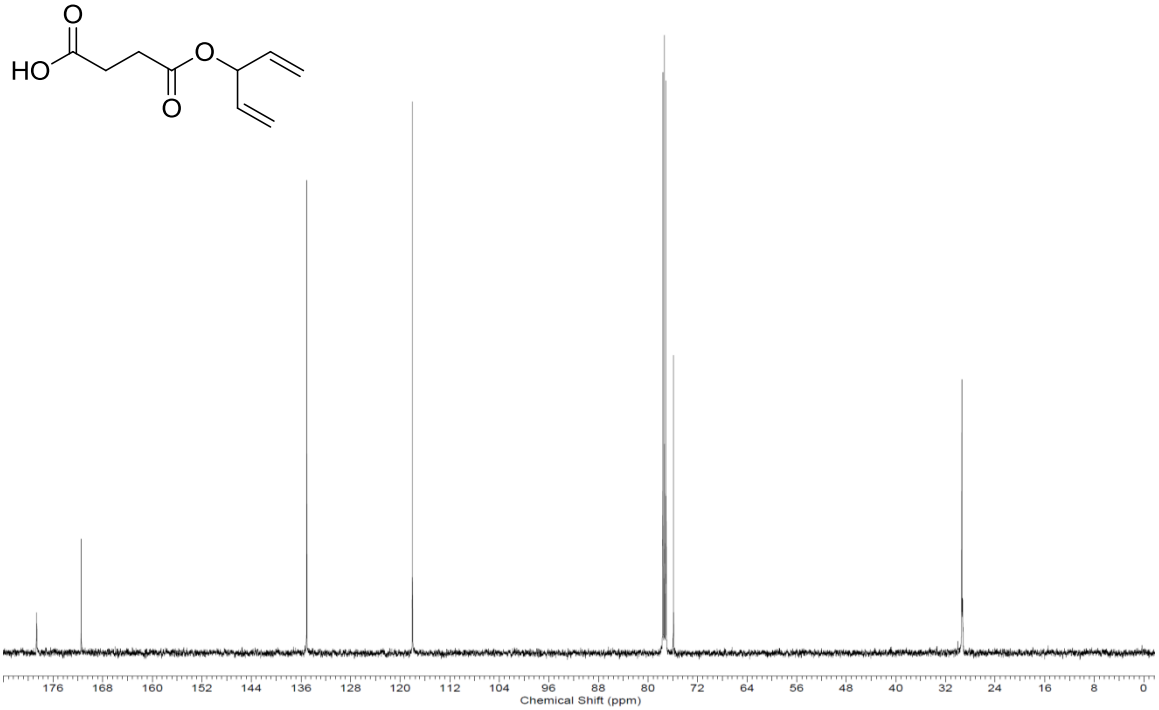
^{13}C NMR of **29**



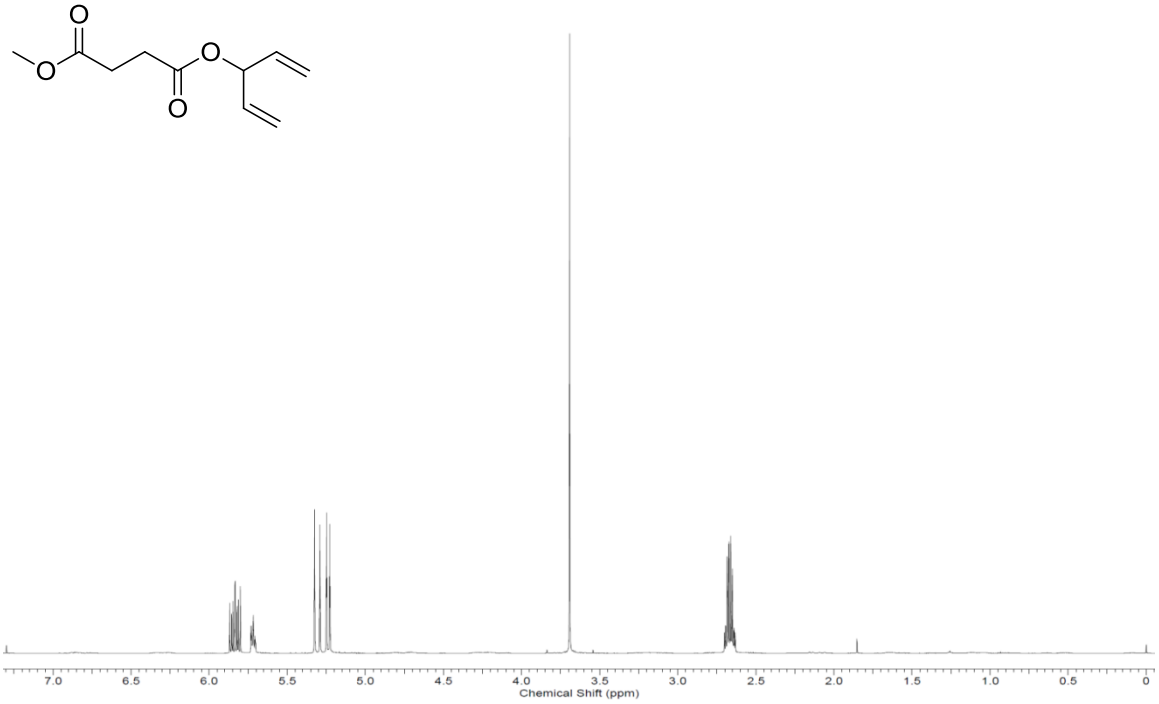
^{1}H NMR of **46**



^{13}C NMR of **46**

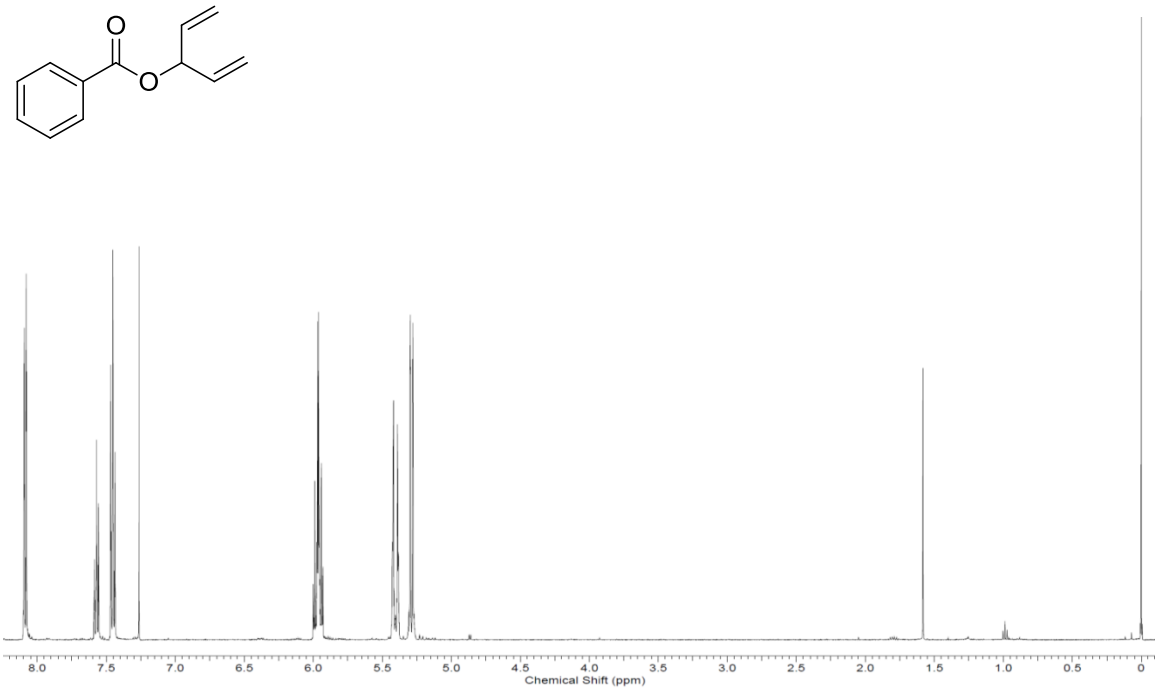


^{1}H NMR of **47**

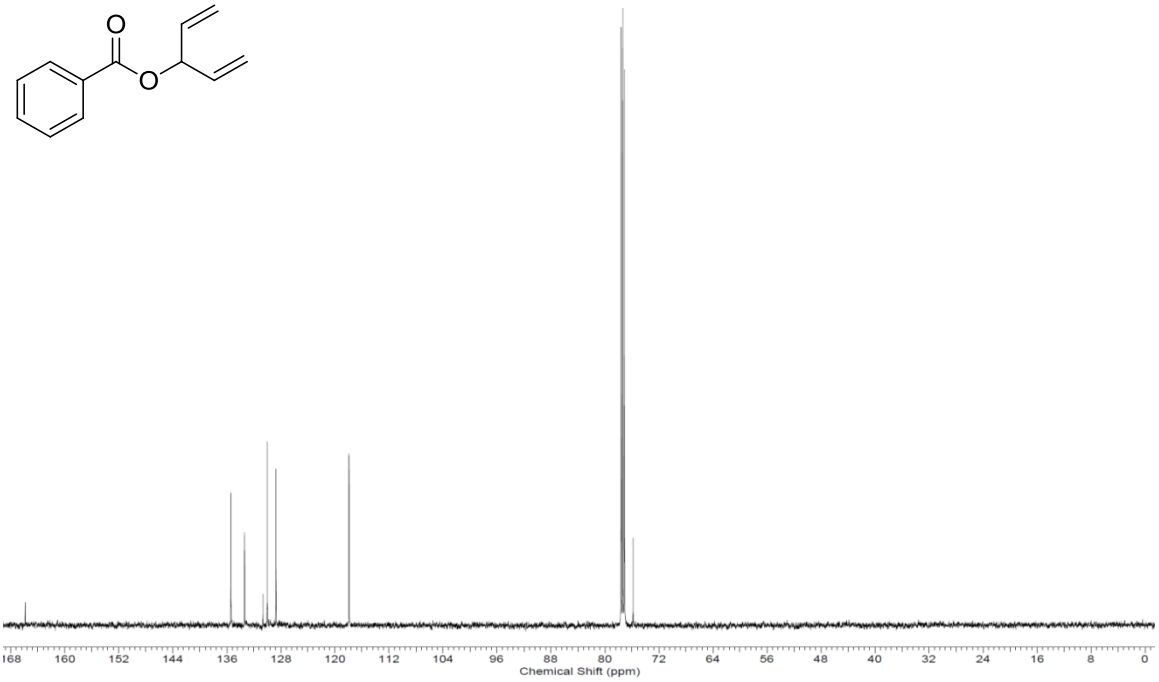


^{13}C NMR of **47**

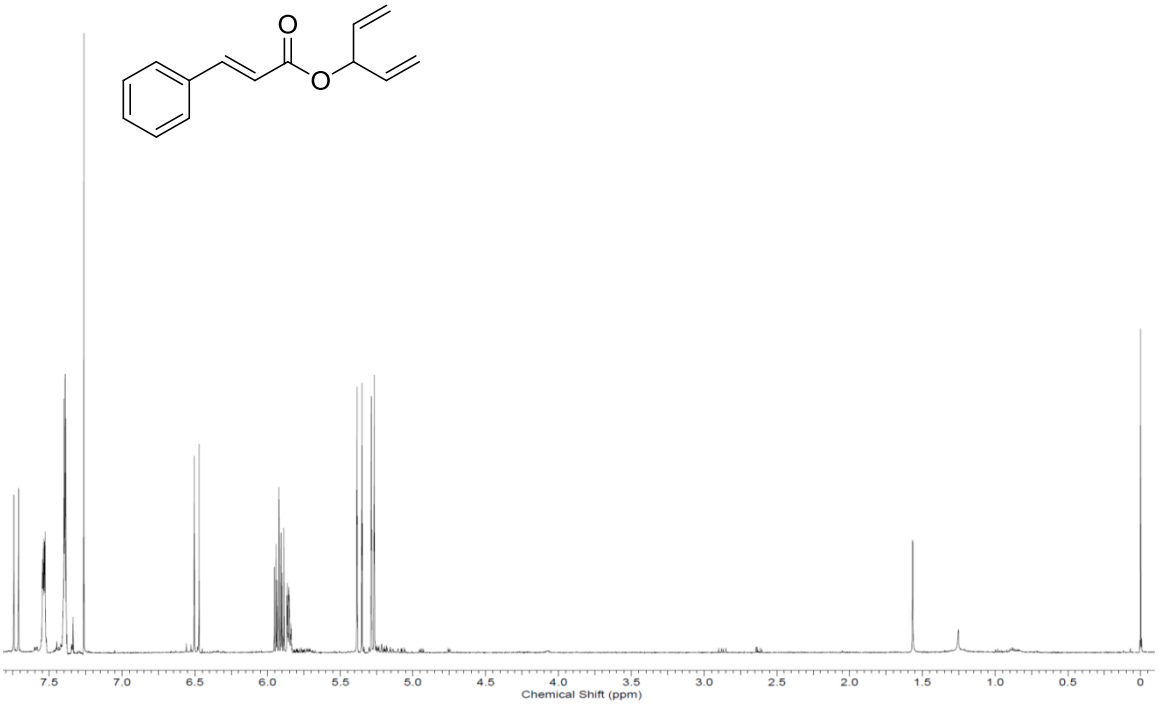
^{1}H NMR of **50**



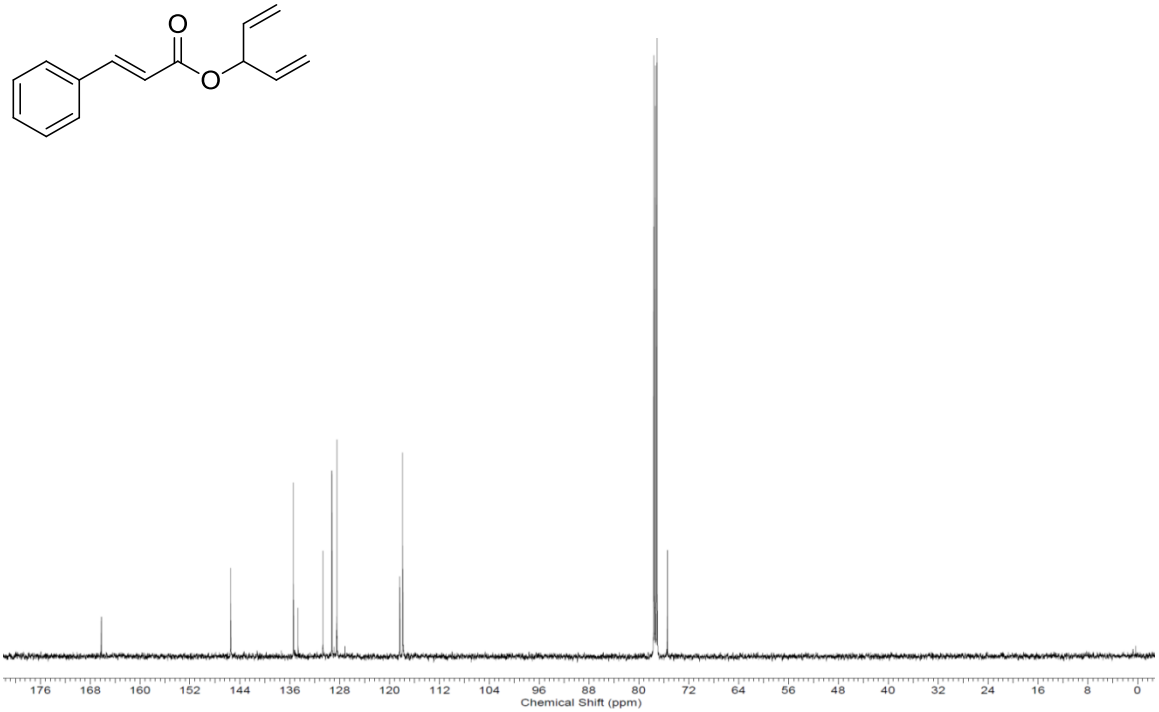
^{13}C NMR of **50**



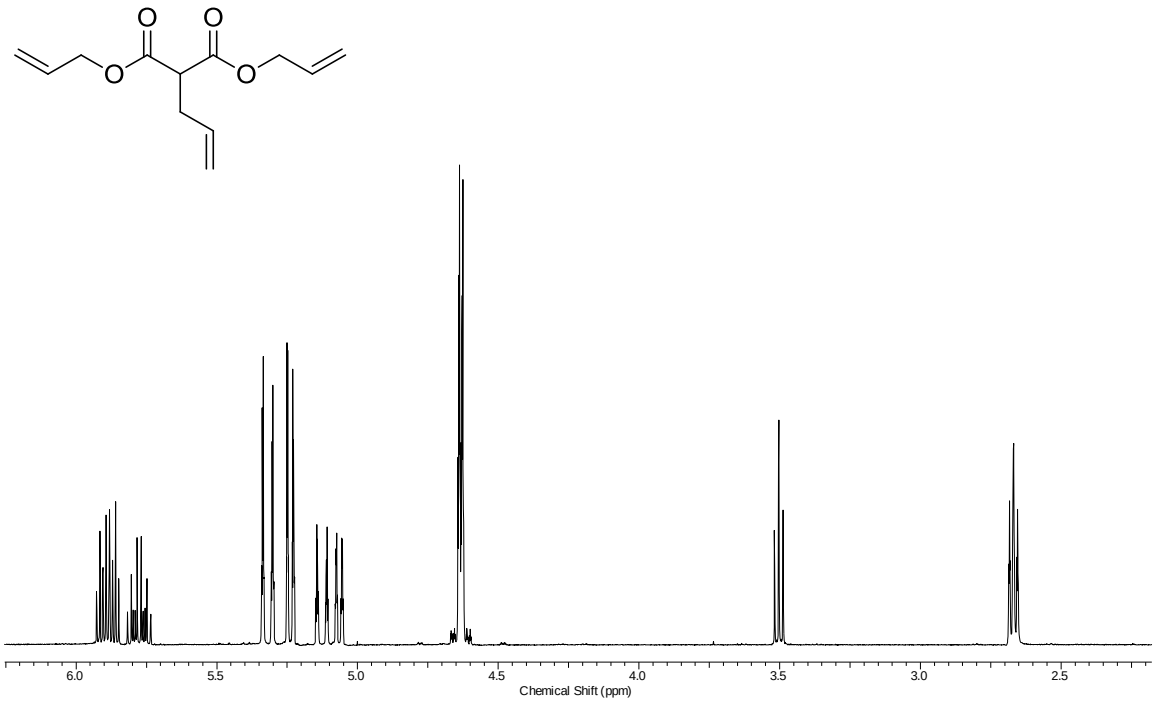
^{1}H NMR of **53**



^{13}C NMR of **53**



^{1}H NMR of **56**



^{13}C NMR of **56**