Stony Brook University

A New Approach to the Synthesis of the Bicyclic Core of the Immunosuppressants SNF4435 C & SNF4435 D via Silicon Tethering

A Thesis Presented by

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Abstract of Thesis

A New Approach to the Synthesis of the Bicyclic Core of the Immunosuppressants SNF4435 C & SNF4435 D via Silicon Tethering

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The total synthesis of immunosuppressant and multidrug resistant (MDR) reversal agents SNF4435 C and SNF4435 D, isolated from the culture broth of an Okinawan strain of Streptomyces spectabilis in 2001, has been accomplished in a fourteen step process. The key reaction utilizes a Stille coupling en route to the final products. Considering the limitations of the Stille coupling, we are currently adjusting the procedure to allow for a new approach, which involves the use of a molecular tether to join the two precursor molecules. This thesis describes the synthesis of a new pair of precursors as well as our efforts toward linking said molecules together via an appropriate silicon bridge.

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My friends and the rest of my family. Your support and love mean more than you could know.

I

Introduction

I.1 Background & Previous Synthesis of SNF4435 C & SNF4435 D

SNF4435 C **1** and SNF4435 D **2** are immunosuppressant agents, isolated from the culture broth of an Okinawan strain of *Streptomyces spectabilis* in 2001. Both compounds selectively block induced B-cell proliferation versus induced T-cell proliferation and display potent immunosuppressive activity in vitro.[1] These molecules are expected to exhibit a pharmacological profile that is different from established immunosuppressant drugs such as cyclosporine A (CsA) or FK-506 and they represent important new lead compounds for drug development. In addition, since they have been shown to reverse multidrug resistance in tumor cells, the SNF compounds could prove useful in anticancer therapy.[2]

The SNF compounds have small compact structures, each with a rigid tricyclic core that features five chiral centers, four of which are adjacent on the periphery of the cyclobutane ring. (Figure 1).

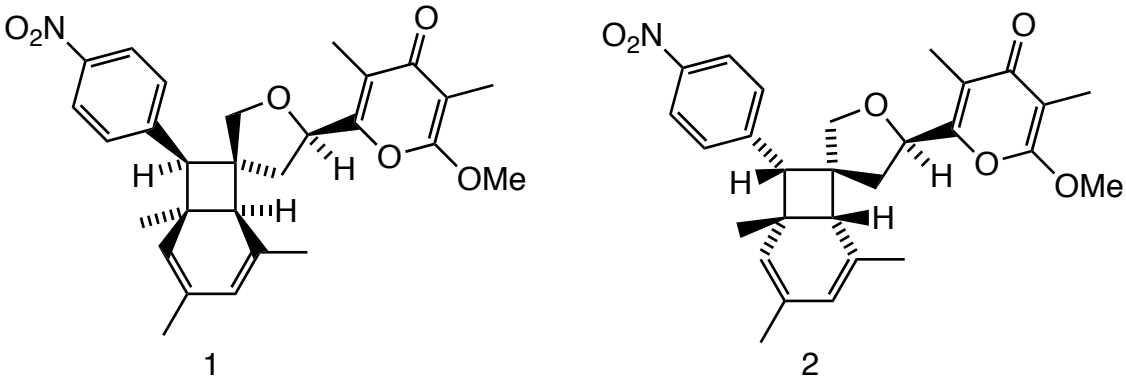


Figure 1 Structures of SNF4435 C **1** & SNF4435 D **2**.

Two thermal electrocyclizations of substituted tetraenes have been recognized as possible steps in the biosynthetic construction of the bicyclo[4.2.0]octadiene substructure of the SNF compounds.[3,4,5]

Kathlyn Parker and Yeon- Hee Lim[6] as well as Dirk Trauner[7] accomplished a syntheses of the SNF compounds from the two iododiene precursors shown in Figure 2.

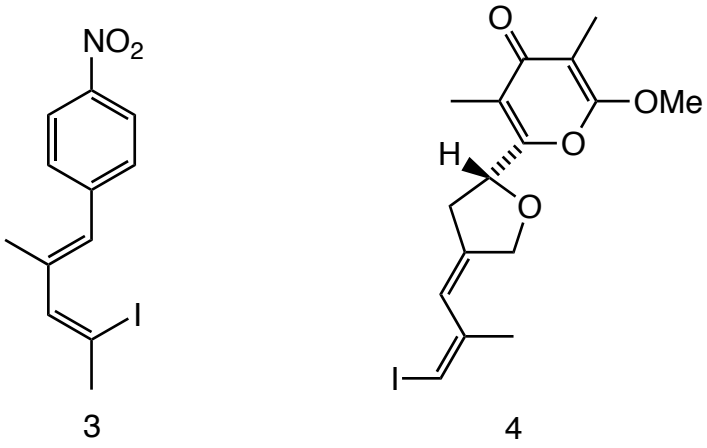


Figure 2 Iodo-diene precursors in previous Parker Group synthesis.

In the Parker/Lim synthesis, the iodine substituent in iodo-diene **4** was converted to a trimethyltin substituent (Figure 3).

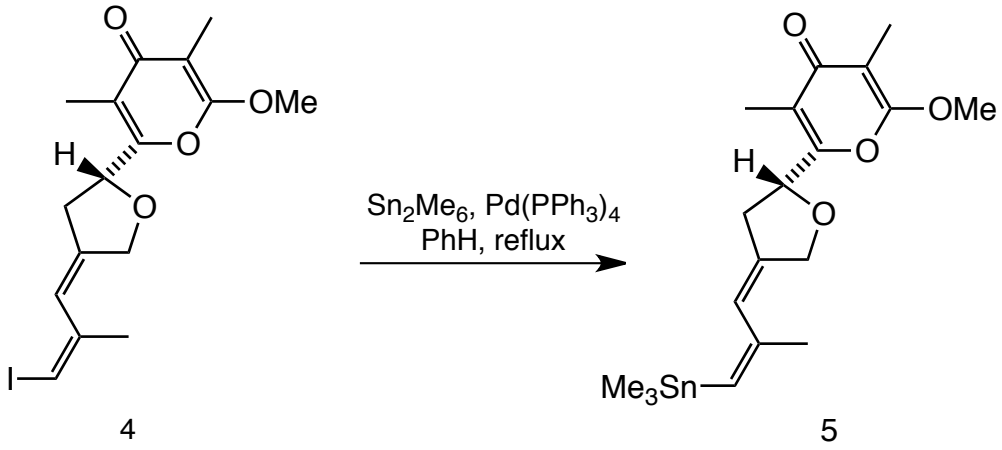


Figure 3 Creation of substrate **5** for subsequent coupling reaction.

Finally, precursors **3** and **5** afforded cyclooctatetraene **6** via the aforementioned Stille coupling. Compound **6** goes on to form the SNF compounds after two electrocyclic ring closings (Figure 4).

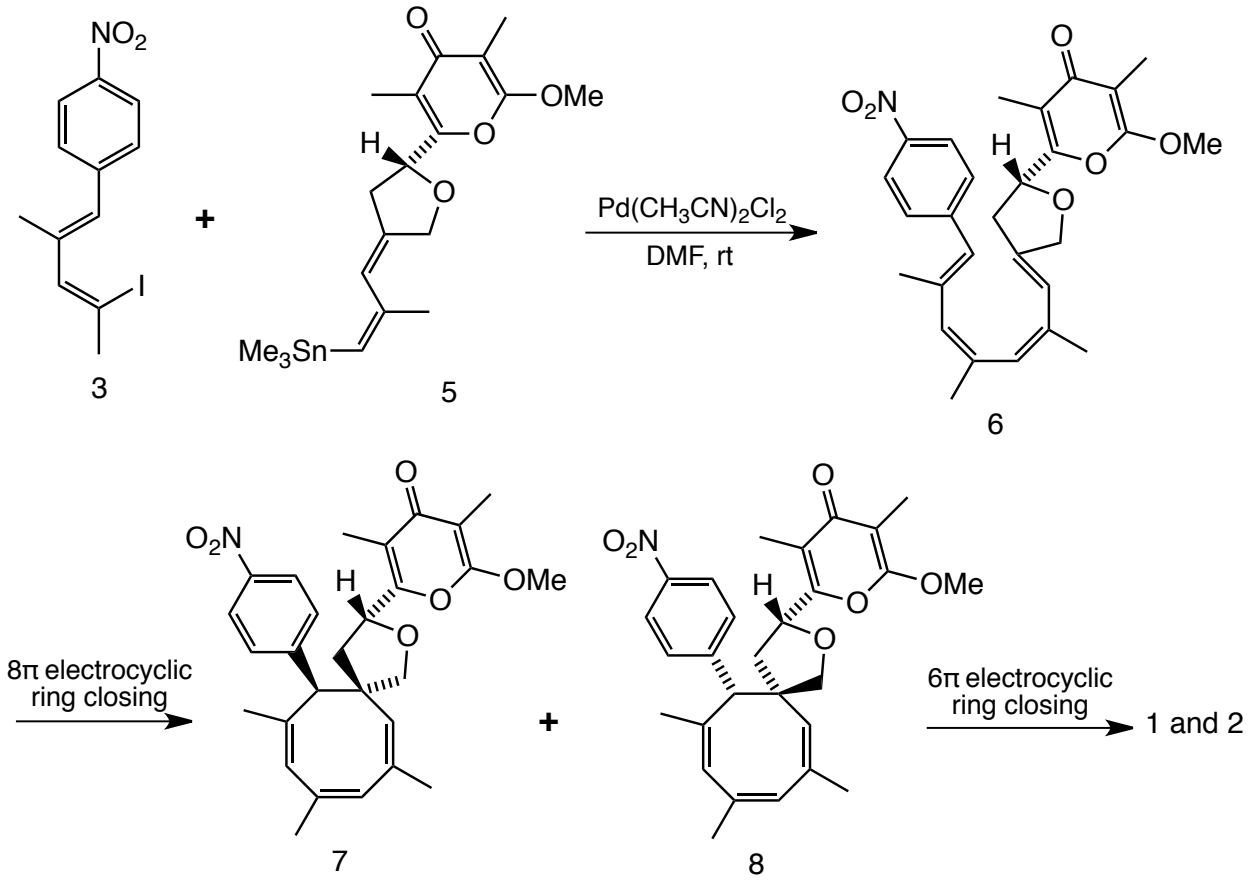


Figure 4 Stille coupling and subsequent electrocyclic ring forming reactions.

Our goal is to develop a synthetic scheme that does not require the use of toxic tin reagents. Wender's work with nickel-catalyzed [4+4] cycloadditions[8] provides an attractive alternative for the synthesis of cyclooctatriene precursors **7** and **8**. Shown in Figure 5 is a specific [4+4] cycloaddition, reported by Wender, in which there is as much as a 40:1 product ratio in favor of cis isomer **10**.

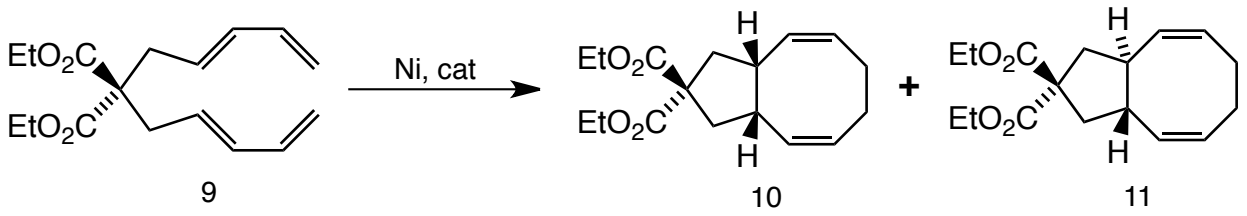


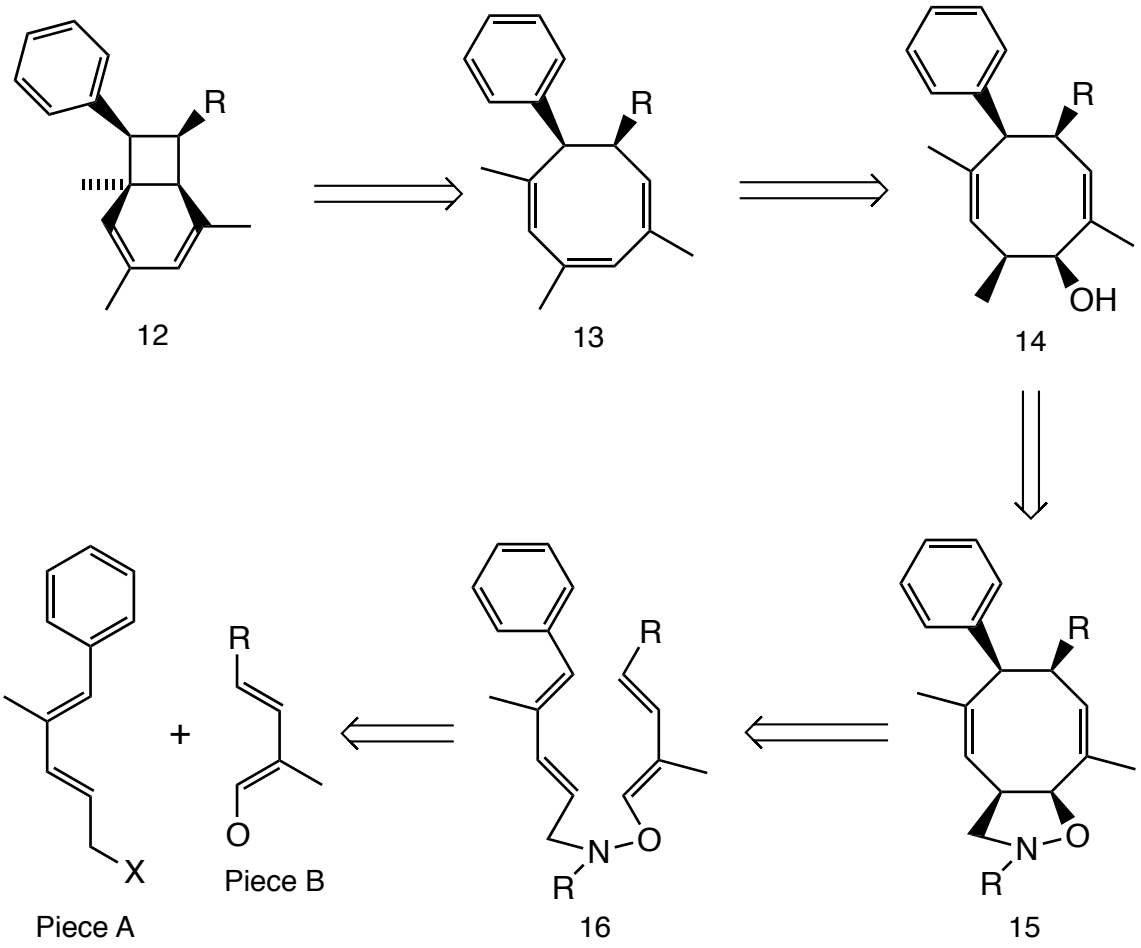
Figure 5 Nickel-catalyzed [4+4] cycloaddition showing a 40:1 product ratio between **10** and **11**.

Adaptation of the Wender methodology as a route to an SNF precursor requires the use of an appropriate tether between the two diene precursors. This tether must allow for easy removal after the required bonds between the diene precursors are formed.

I.2 Retrosynthetic Analysis

To simplify matters, we set our sights on an analogue of the SNF compounds, molecule **12** shown in Scheme 1. The retrosynthesis involves five steps, one of which is the same 6π electrocyclic ring closing that afforded **1** and **2** in the previous synthetic procedure (now **13** → **12**). Other than that, out of necessity, the steps outlined in Scheme 1 have been adapted to allow for the use of tether **N**. In our new scheme, it is necessary to remove tether **N** (**15** → **14**) and form the third olefin (**14** → **13**) in cyclooctatriene **13** before the aforementioned reaction (**13** → **12**) can occur.

Tether **N** and the new diene precursors **Piece A** and **Piece B** are linked in the convergent step of the synthesis (**16** → **Piece A** & **Piece B**).



Scheme 1 Retrosynthetic analysis.

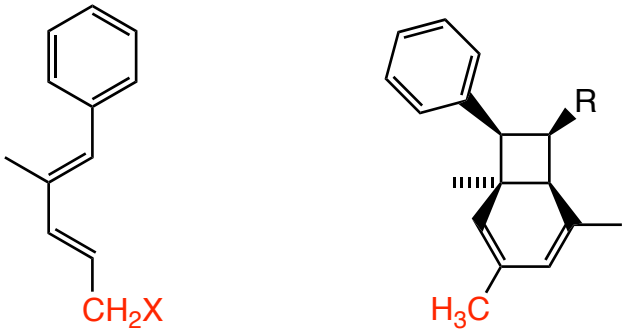
So **Piece A** and **Piece B** enter into the story. Moving from conception to execution, it was necessary to make specific decisions regarding the structures of **Piece A** and **Piece B**.

II

Synthesis of Pivotal Precursors

II.1 Synthesis of Alcohol 19 from α-Methyl Cinnamaldehyde

Switching from the concept of **Piece A**, to the actual molecule required consideration of the following key points: First, the compound must be a diene. Second, as seen in Figure 6, the methyl group in **12** has only hydrogens attached to it, whereas the corresponding methyl group in **Piece A**, in order to facilitate coupling with tether **N**, will start off by having substituent X.



Piece A 12

Figure 6 Methyl group with substituent X and eventually with only hydrogens.

Therefore, substituent X must be removable en route to the final product. One way that this might be accomplished, as shown in Scheme 1, is by achieving, through any one of several substitution reactions, a direct bond between the C-1 carbon of **Piece A** and tether **N**. It is also conceivable that a direct bond between the methyl carbon and the tether not be achieved. This possibility is discussed in greater detail later on in the paper.

We chose α-methyl cinnamaldehyde **17** as the starting material for the first pivotal piece. We utilized a simple Horner-Wadsworth-Emmons (HWE) homologation[9] to afford ester **18** in 86% yield after distillation. Diisobutylaluminum hydride reduced ester **18** to alcohol **19** in 70% yield (Figure 7).

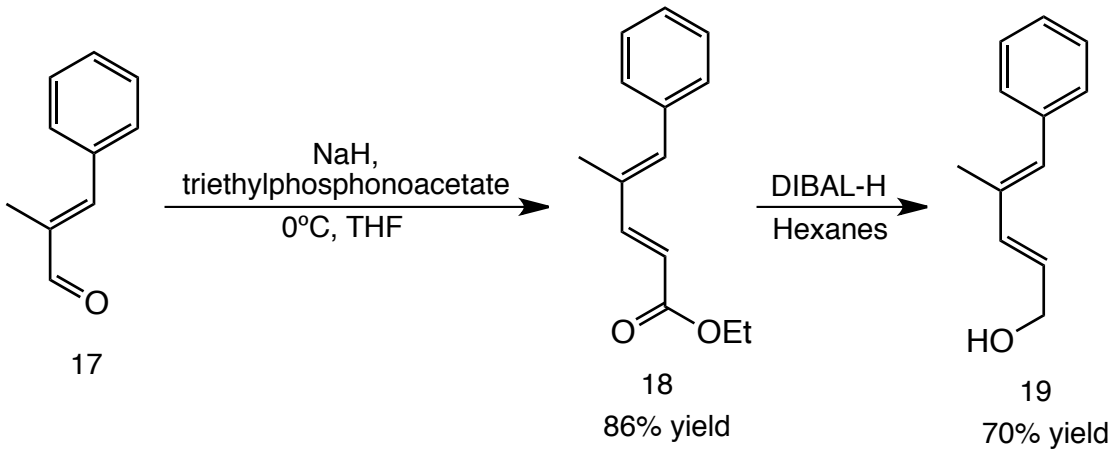
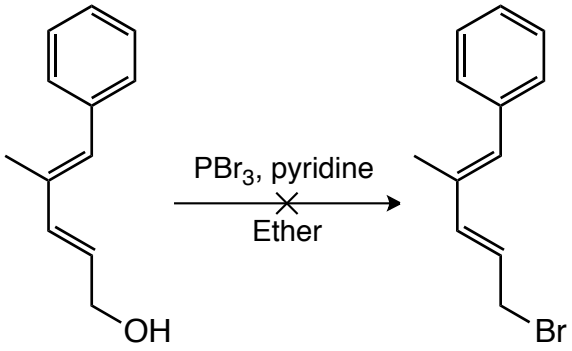


Figure 7 HWE homologation and subsequent reduction.

The oxygen in alcohol **19** must, at some point during the course of the synthesis, be exchanged for a hydrogen, as the methyl group in **12** has only hydrogens attached to it (shown previously in Figure 6). Therefore, it is necessary either to remove it as the next step en route to a direct bond between tether **N** and the methylene, or remove it later by a deoxygenation procedure. We chose first to exchange the alcohol oxygen with a halide. PBr_3 and pyridine were utilized in our attempt to brominate the alcohol. However, the material decomposed in each attempt to isolate the product (Figure 8).



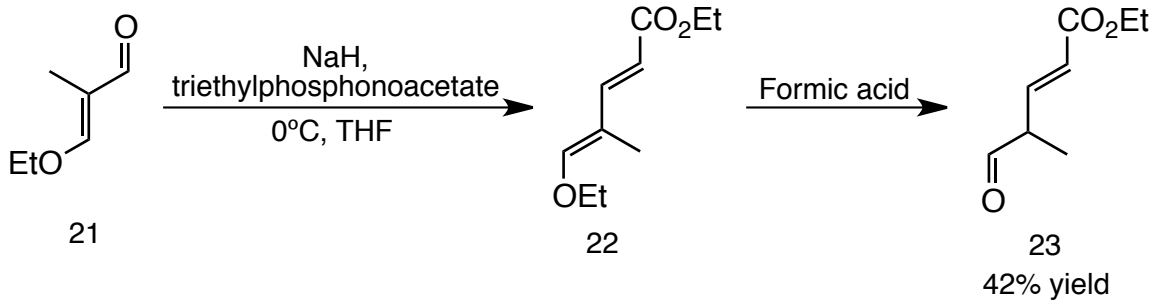
19 20

Figure 8 Bromination of alcohol.

With many different methods of halogenation available to us, we decided to put that problem aside and focus on the execution of **Piece B** and on finding a candidate for tether **N**.

II.2 Synthesis of Aldehyde 23 & Trapping of Enolate 24

We chose 3-ethoxymethacrolein **21** as the starting material and utilized a simple Horner-Wadsworth-Emmons homologation, followed by a hydrolysis of enol ether **22** to form aldehyde **23** (Figure 9) in 42% yield after chromatography.[10]



21 22 23

42% yield

Figure 9 HWE homologation and subsequent hydrolysis to afford aldehyde **23**.

When treated with a base, aldehyde **23** should form enolate **24** (Figure 10) and, with it, the necessary diene for the [4+4] cycloaddition reaction.

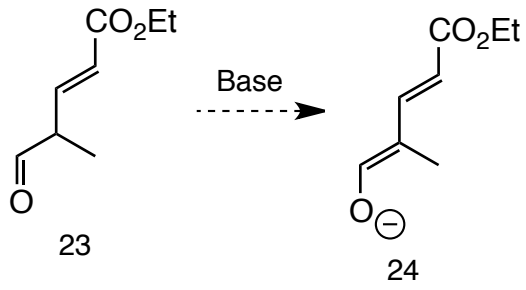


Figure 10 Enolate formed from aldehyde **23**.

While we believe that aldehyde **23** possesses enough enol character to achieve a successful tethering without necessitating a trapping procedure, we did run an experiment[11] with aldehyde **23** and a common trapping agent (t-butyl dimethyl silyl triflate). The reaction afforded a very clean product in 80% yield (Figure 11).

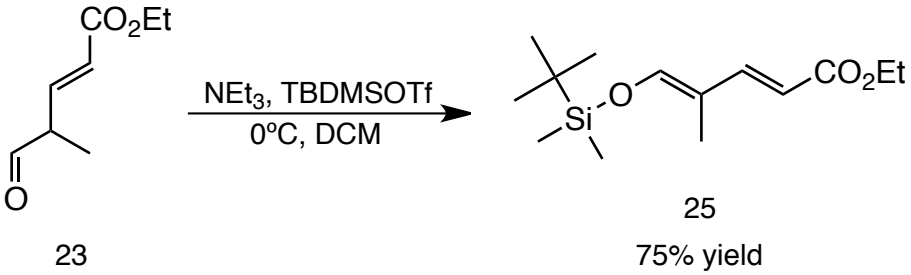


Figure 11 Trapping of the enolate of aldehyde **23**.

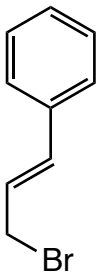
After the syntheses of alcohol **19** & aldehyde **23** were complete, the task became choosing an appropriate tether and finding a reaction that would successfully link the two pieces together for the [4+4] cycloaddition reaction.

III

Tether Reactions

III.1 Tether Reactions with Model Bromide 26

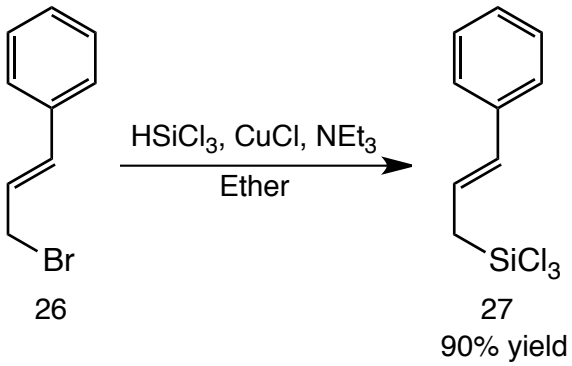
The next step en route to our final product was to chose our tether. Silicon provides a promising option as there are many commercially available reagents at our disposal and the silicon is removed easily with a fluoride ion source such as HF. Therefore, with significant progress made on the synthesis of our precursors, we purchased model bromide **26** (Figure 12) and began our search for a workable reagent and tethering reaction.



26

Figure 12 Model bromide.

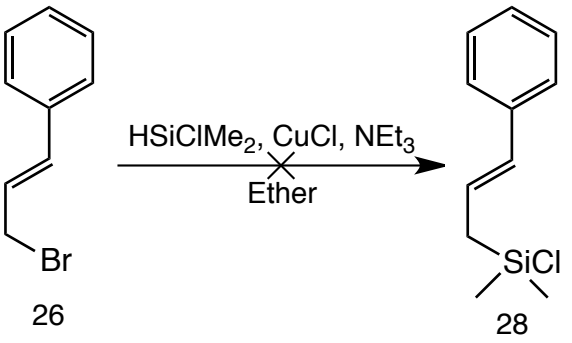
Upon perusal of the reaction database, the first reaction we chose was a simple silation with trichlorosilane.[12] The reaction was successful and afforded silane **27** in 90% yield (Figure 13).



26 27
90% yield

Figure 13 First silation of model bromide **26**.

There was no proper aqueous work up for this reaction, because the reactive chlorides on the silane substituent would have been lost and the molecule made useless for our purposes. However, the reagents used were volatile enough to be removed while evaporating under reduced pressure. This reaction was noteworthy; however, it presented another problem that needed to be addressed. The silicon in silane **27** has three chlorides on it when only one is necessary. Therefore, we attempted to alter the procedure by using a different silicon reagent, one that had fewer chlorides so that, at most, one reactive species would exist after displacing the bromide in model **26**. We repeated the reaction with dimethylchlorosilane (Figure 14). Unfortunately, the reaction yielded only starting material



26 28

Figure 14 Silation attempt with alkylated silicon reagent.

The next move was to attempt to selectively defunctionalize two of the three chlorides in silane **27**, thereby leaving one to react with enolate **24**. Since oxygen has such a strong affinity for silicon, we first attempted to attach pinacol (2,3-dimethyl-2,3-butanediol) to the molecule, thereby displacing the two excess chlorine substituents.[13] Several attempts were made; however, none proved successful. Since this reaction also required a non-aqueous work up, the primary problem became removing the excess pinacol and 1,8-diazabicycloundec-7-ene (DBU), with each being far less volatile than the reagents used in Figure 13, in order to see whether or not the reaction actually worked. We attempted to utilize sodium hydride in place of DBU, in order to test the efficacy of the base in this reaction and also to provide a crude product with a more transparent NMR spectrum. However, sodium hydride did not produce the desired result. The reaction outline for both is shown in Figure 15.

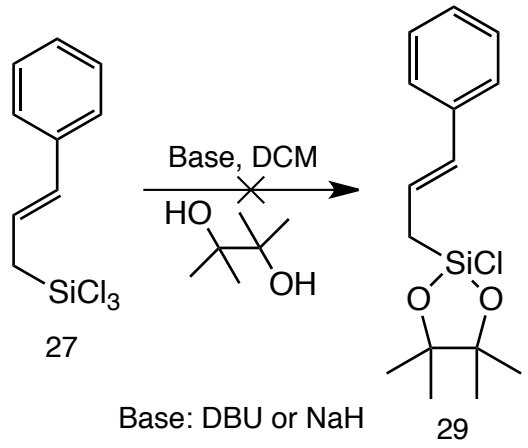


Figure 15 Pinacol reaction for attempted selective defunctionalization.

The next attempt to selectively defunctionalize silane **27** involved phenylmagnesium bromide in a 2:1 ratio of reagent to starting material. We hoped that two phenyl Grignard molecules would react with each molecule of starting material and leave one chloride on

the molecule as desired. Thus, it was important to monitor the number of equivalents of each molecule that was used as well as the rate at which they were added. We hoped that steric hindrance would also help to prevent three phenyl Grignard molecules from adding to one molecule of starting material. The worries were for naught though, as the Grignard reagent did not react with the starting material. Similar attempts were also made with phenyllithium and t-butyllithium as reagents (Figure 16). Starting material was consumed and no desired products were seen in the ^{1}H NMR spectra.

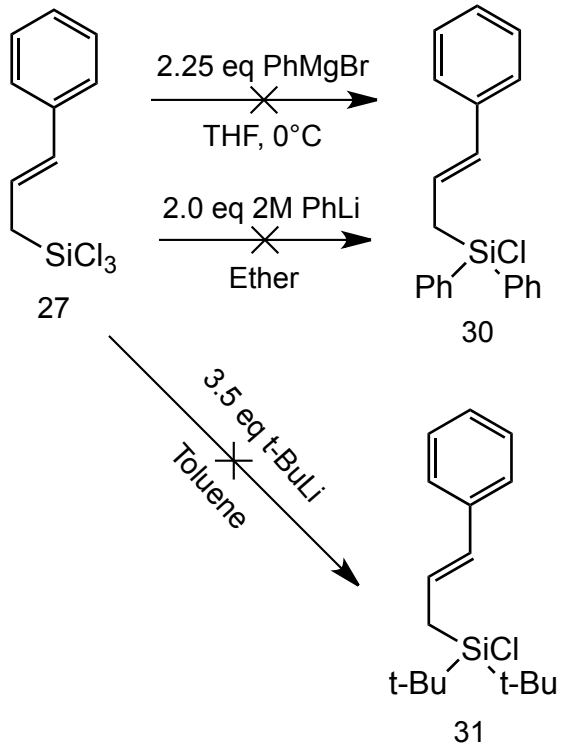


Figure 16 Continued attempts toward selective defunctionalization.

Next, we tried turning bromide **26** into a Grignard species and treating it with chlorodimethylsilane. We used mercuric chloride to promote the reaction (Figure 17).

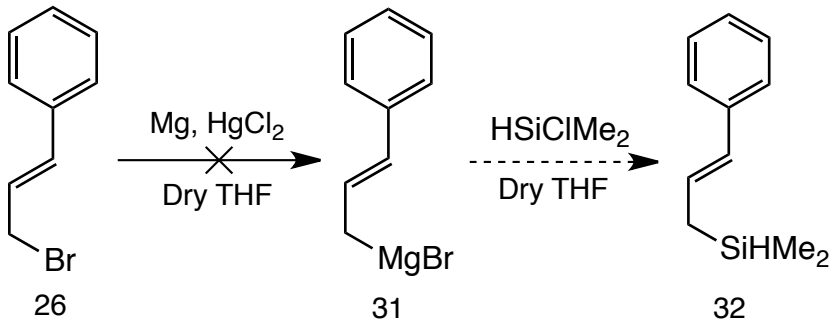


Figure 17 Attempt to turn bromide **26** into a reactive Grignard species.

The proton NMR spectrum of silane **32** showed no trace of the methyl groups on the silicon. Had that worked, the plan was to halogenate the silyl substituent or attempt the reaction with a more halogenated silicon reagent such as dimethyldichlorosilane. We were perplexed as to why the simple model bromide **26** did not form a reactive Grignard species. We postulated that the Grignard species may have formed and precipitated out of solution. Indeed, during the experiment, a white solid, that could have been reactive Grignard, formed in the reaction flask. Therefore, when the reaction was later quenched with water, the Grignard reagent would have been instantly hydrolyzed and the silicon reagent left to evaporate under reduced pressure. The 1H NMR spectrum shows evidence of both reduced products (shown in Figure 18), supporting the notion that the Grignard did precipitate out of solution.

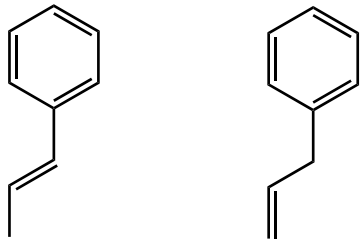
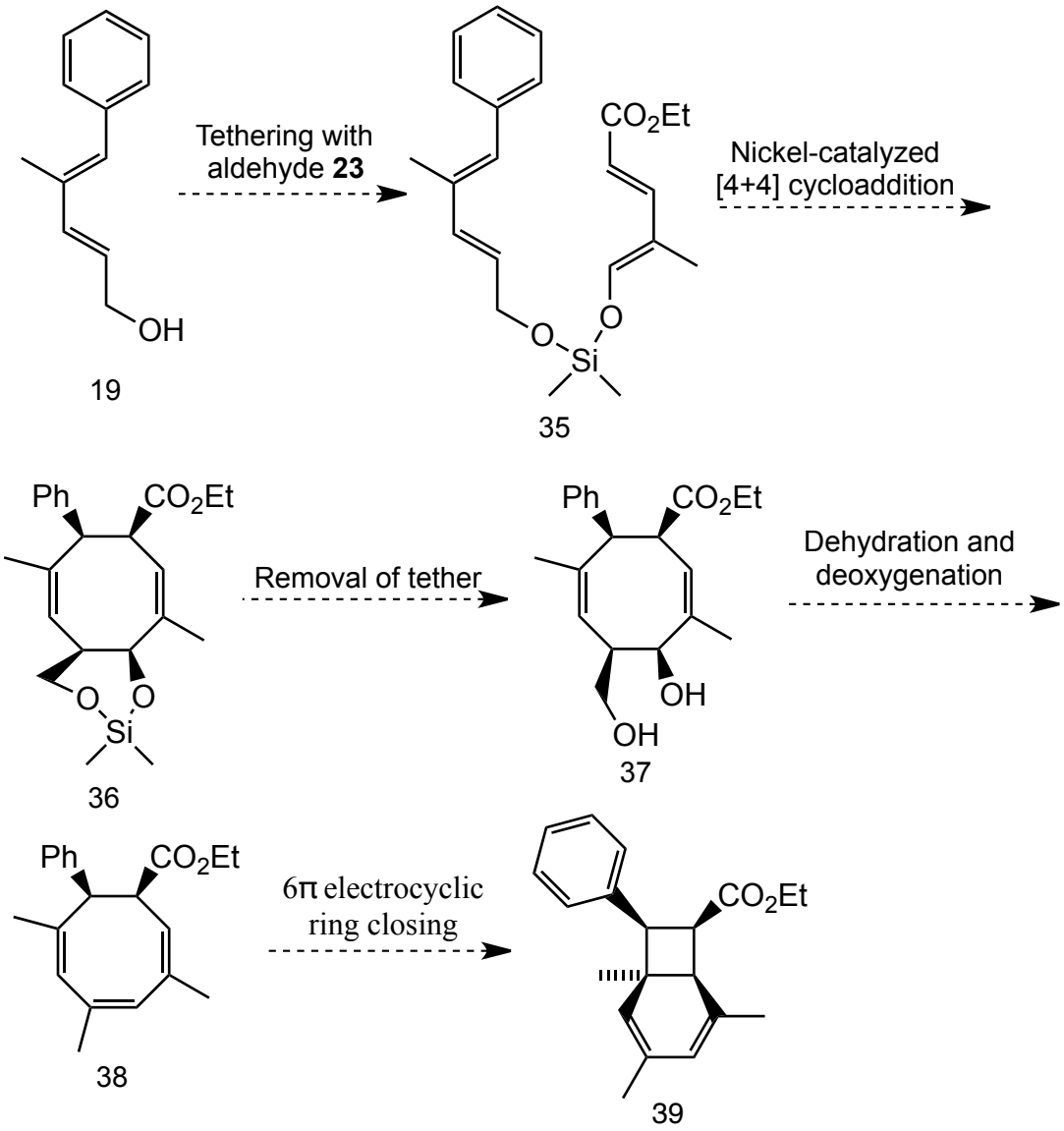


Figure 18 Reduced products formed during quenching of Grignard species **31**.

We plan to try this reaction over again with dry ether, instead of THF, to see if it might beget the desired result.

III.2 Tether Reactions with Alcohol 19

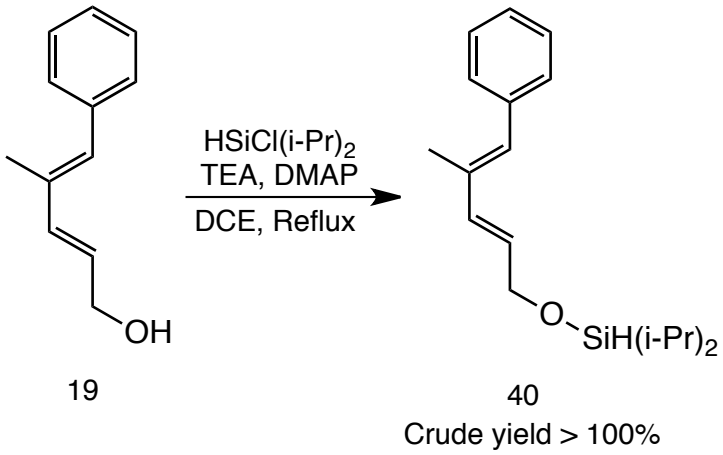
While it would not be ideal, another option for introducing the tether is to attach the silicon directly to the oxygen in alcohol **19**. Only if this makes the tethering easier would it be an advantageous option as it adds the complicated step of removing the oxygen later on in the sequence (after the nickel-catalyzed [4+4] cycloaddition and removal of silicon). This would be accomplished by using a reaction such as the Barton deoxygenation. We anticipate that this would prove difficult, but if it is the only way to achieve the tether, it is worth exploring. The reaction sequence is shown in Scheme 2.



Scheme 2 Probable reaction sequence with alcohol **19** as a precursor.

Since alcohol **19** was obtained in good yields, we decided to use the actual molecule in our experiments instead of another model compound. The first reaction we chose involved a displacement of the chloride on chlorodiisopropylsilane with the use of TEA and 4-dimethylaminopyridine (DMAP).[14] The reaction was heated to reflux and, because of its higher boiling point, dichloroethane (DCE) was used instead of dichloromethane.

The crude yield of silyl ether **40** was over 100%, with the spectra being clean enough to move to the next step without further purification (Figure 19).

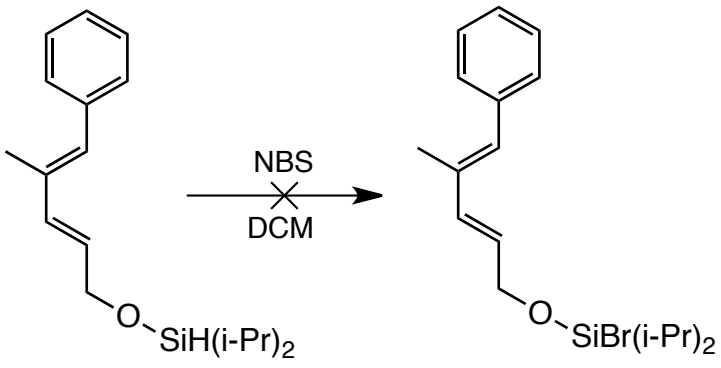


19 40

Crude yield > 100%

Figure 19 Reaction of silicon reagent with alcohol **19**.

With the hydrogen on the silicon molecule, the next step was to replace it with a leaving group that would allow for reaction with enolate **24**. We chose to attempt a reaction with n-bromosuccinimide (NBS) in DCM (Figure 20).



40 41

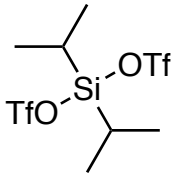
Figure 20 Attempted bromination with n-bromosuccinimide.

As shown above, the reaction did not yield the desired product. Instead, every time we ran the reaction, starting material was consumed and no desired products were seen in the ^{1}H NMR spectrum. We believed that the starting material decomposed. This was

evidenced by the loss of peaks in the proton NMR corresponding to the olefinic protons. When we tried to purify silane **40**, it decomposed on the column.

III.3 Future Research

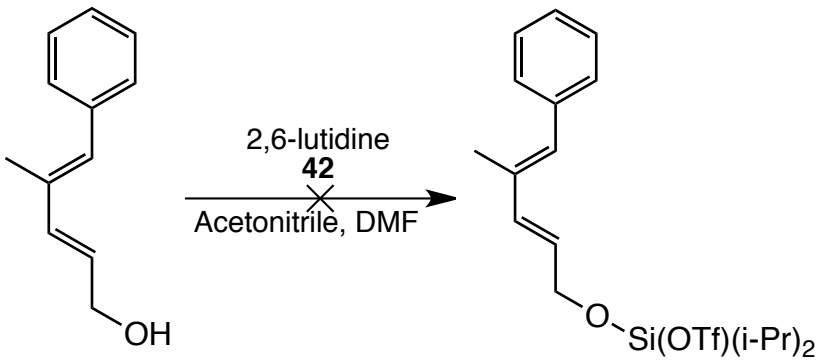
One linker we've recently considered, shown in Figure 21, is diisopropylsilyl bis(trifluoromethanesulfonate) **42**. Moving forward, it looks to be a promising candidate as we try to tether alcohol **19** and aldehyde **23**.



Diisopropylsilyl Bis(trifluoromethanesulfonate)
42

Figure 21 New reagent candidate for tethering.

We found, in the reaction database, a procedure utilizing silane **42** and decided to adopt it for our own purposes (Figure 19).[15]



19 43

Figure 22 Silation attempt with tether **42**.

However, starting material was again consumed and no desired products were seen in the ^{1}H NMR spectrum. This was evidenced by the loss of peaks in the proton NMR corresponding to the olefinic protons. In the future we hope to solve the problem of substrate decomposition.

IV

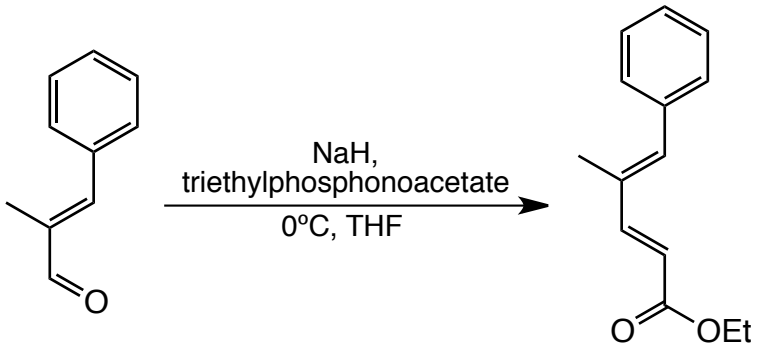
Conclusion

The tethering step of the initial analysis has proven itself formidable. Once we have a stable tether and manage to accomplish the [4+4] cycloaddition to connect the two precursors. Many of the remaining steps will have been done already on the substrate of the previous, successful Parker group synthesis. The biggest difficulty at this point is overcoming the problem of substrate decomposition. Many times when we attempt to introduce the leaving group onto the silyl tether (as either a halide or a trifyl species like diisopropylsilyl bis(trifluoromethanesulfonate)) the substrate decomposes and turns to a black, murky liquid. Use of a less complex model compound may shed some light on this problem. Since the olefinic protons of our substrate continue to be lost, it may be beneficial to work with a model compound without such regions, in order to see if the reagents are more successful in attaching the leaving group without compromising the integrity of the substrate. The large number of available silicon reagents is promising, as there are still many more avenues that we may explore on our way to successfully coupling the two pivotal pieces.

IV

Experimental Procedures

General: Reagents were purchased reagent grade from Aldrich and Fisher Scientific/ Acros Organics and used without further purification. Hexanes, acetone, dichloromethane, ethyl ether, and ethyl acetate were purchased from VWR. Solvents were stored over calcium hydride for use in reactions that required dry solvents. $MgSO_4$ was used as the drying agent after aqueous work-up. All reactions were performed under an inert atmosphere of argon gas. Thin-layer Chromatography (TLC) was performed on metal-backed silica gel plates, developed with PMA and visualized by UV light. IR spectra (cm^{-1}) were completed using a Thermo Scientific Nicolet iS10. ^{1}H- and ^{13}C-NMR spectra were taken at rt in $CDCl_3$ using 300 MHz Varient and 400 and 500 MHz Bruker NMR instruments (solvent peak references: 7.26 ppm for ^{1}H-NMR and 77.3 ppm for ^{13}C-NMR).

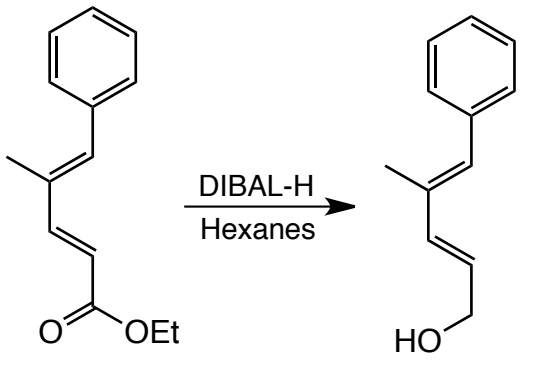


17 18

86% yield

Ester 18

To a clean, oven dried, two-neck round bottom flask (RBF), was added 95% NaH (2.87g, 71.8 mmol) and 60 mL of dry THF. The RBF was then purged with argon gas and cooled to 0°C. After ten minutes, triethylphosphonoacetate (16.75 mL, 75.2 mmol) was added to 30 mL dry THF and transferred **slowly** dropwise via syringe. The solution bubbled as hydrogen gas was liberated and it turned from cloudy to clear. After all of the triethylphosphonoacetate was added, α-methyl cinnamaldehyde **17** (9.55 mL, 68.4 mmol) was added **slowly** dropwise in 20 mL of dry THF. The solution stirred at room temperature for ten minutes and was then quenched with brine. The organic layer was extracted with ethyl ether (3 x 5 mL), and the combined organic solution was dried with MgSO4 and filtered through filter paper. Solvent was evaporated under reduced pressure. The crude product was distilled to afford ester **18** as a yellow liquid (12.72 g, 58.8 mmol, 86% yield). Spectroscopic data matched reported values[9]. IR: 2981, 1713, 1621 cm^{-1}; ^{1}H-NMR (400 mHz) ($CDCl_3$) ∂: 7.50 (dd, *J* = 0.83 Hz, *J* = 15.66 Hz, 1H), 7.28-7.41 (m, 5H), 6.86 (s, 1H), 5.98 (dd, *J* = 0.82 Hz, *J* = 15.66, 1H), 4.24 (q, *J* = 7.15 Hz, 2H), 2.05 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

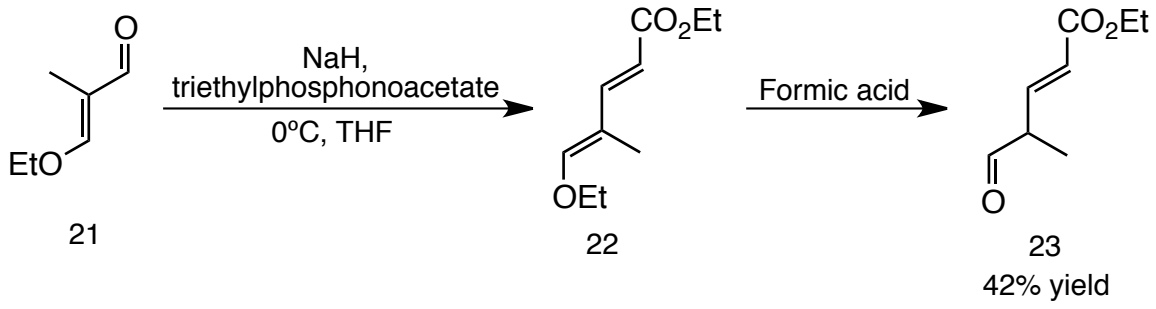


18 19

70% yield

Alcohol 19

To a clean, oven dried, two-neck RBF, was added 4.9ml of ester **18** (23.12 mmol) in 50 mL hexanes. The flask was purged with argon and cooled to 0°C. After ten minutes, 70 mL of DIBAL-H (69.35 mmol) was added **slowly**, dropwise via syringe to the RBF. The reaction was monitored by TLC and upon completion, was quenched with 8 mL of methanol. The reaction solidified and turned a cloudy grey. A solution of 10% potassium sodium tartrate was added (50 mL) and the mixture was allowed to stir until the solid dissolved and became manageable. The contents of the RBF were then transferred to a separation funnel and the organic layer was extracted with ether (3 x 45 mL). The combined organic layers were then washed once with brine and dried over $MgSO_4$. Solvent was evaporated under reduced pressure to afford the product as a cloudy crystal (2.789 g, 16.00 mmol, 70% yield). IR: 3265, 2923 cm^{-1}; ^{1}H-NMR (400 mHz) ($CDCl_3$) ∂: 7.23-7.28 (m, 5H), 6.54 (s, 1H), 6.52 (d, *J* = 16.99 Hz, 1H), 5.94 (dt, *J* = 0.52 Hz, *J* = 15.59 Hz, 1H), 4.29 (t, J = 5.80, 2H), 2.02 (s, 3H).



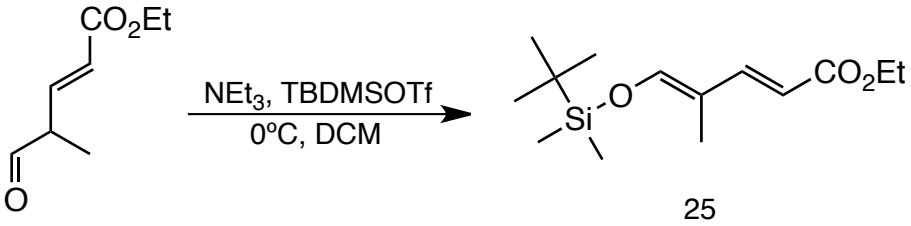
21 22 23

42% yield

Aldehyde 23

To an argon purged, oven dried, two neck RBF at 0°C was added 1.1g NaH (45.87 mmol) in 27 mL dry THF. Next, 9.53 mL of triethylphosphonoacetate (48.06 mmol) in 20 mL THF was added **slowly** dropwise via syringe; hydrogen gas was liberated and the

solution turned from cloudy to clear. Finally, 4.99g (43.69 mmol) of the starting material **21** was diluted with 20 mL of THF and added via syringe to the reaction flask. The reaction was monitored by TLC and quenched with 35 mL of water. The flask's contents were then transferred to a separation funnel and the organic layer was extracted with methylene chloride (DCM) (3 x 5 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated. Next a mixture of 30 mL formic acid per 6 mL water was added to the crude product. The reaction was allowed to stir and upon completion, was diluted with water. The organic layer was extracted with DCM (3 x 5 mL) and quenched with a solution of sodium bicarbonate ($NaHCO_3$). Once the organic layer was isolated, it was dried with $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to afford aldehyde **23** as a yellow liquid (0.57 g, 3.68 mmol, 42% yield)[10]. IR: 3453, 2984, 2360, 1737 cm^{-1}; ^{1}H-NMR (400 mHz) ($CDCl_3$) ∂: 9.48 (s, 1H), 6.71 (dt, *J* = 1.38 Hz, *J* = 6.87 Hz, 1H), 4.20 (q, *J* = 7.14 Hz, 2H), 3.39 (d, *J* = 6.87 Hz, 2H), 1.77 (d, *J* = 1.1 Hz, 3H), 1.29 (t, *J* = 7.14 Hz, 1H).



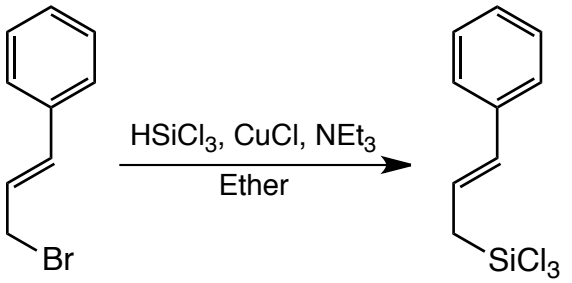
23 25

75% yield

Silyl Ether 25

We adopted Welmaker's procedure[11] for this reaction. To an oven dried, argon purged RBF in an ice bath was added 341.8 mg (2.19 mmol) of aldehyde **23** in 3.6 mL dry DCM. Next 0.34 mL (2.41 mmol) triethyl amine (TEA) was added dropwise to the RBF

and the reaction was left to stir. After ten minutes, 0.5 mL (2.19 mmol) TBDMSOTf was added to the reaction flask. The reaction was monitored by TLC. Upon completion, the reaction was diluted with 13.0 mL DCM and transferred to a separation funnel. The mixture was then washed with potassium bicarbonate (3 x 10 mL) and brine (1 x 10 mL). Afterwards, the combined organic solution was dried with MgSO4 and filtered through filter paper. The solvent was evaporated under reduced pressure, affording silyl ether **25** as a yellow liquid (443.5 mg, 1.64 mmol, 80% yield). IR: 3497, 2933, 2859, 2360 cm^{-1}; ^{1}H-NMR (400 mHz) ($CDCl_3$) ∂: 7.02 (d, *J* = 16.11 Hz, 1H), 6.65 (d, *J* = 16.11 Hz, 1H), 4.27 (q, *J* = 7.12 Hz, 2H), 2.36 (s, 3H), 1.33 (t, *J* = 7.16 Hz, 4H), 0.91 (s, 9H), 0.10, (s, 6H); 13C-NMR ($CDCl_3$) ∂: 197.9, 165.8, 140.2, 131.9, 61.8, 28.4, 25.9, 18.2, 14.5, -3.3.



26 27

90% yield

Silane 29

We adopted Sakurai's procedure[12] for this reaction. To an oven dried, two-neck, argon purged RBF was added 0.8 mL (5.66 mmol) TEA and 0.015 g (0.15 mmol) CuCl in 5.0 mL of dry ether. To the reaction flask was added dropwise via syringe a mixture of 1.01 g (5.15 mmol) of bromide **28** and 0.78 mL (7.72 mmol) $HSiCl_3$ in another 5.0 mL of dry ether. The reaction was allowed to stir over night. After twenty-four hours, the solvent

was evaporated under reduced pressure to afford silane **29** (1.17g, 4.65 mmol, 90% yield). ^{1}H-NMR (400 mHz) ($CDCl_3$) ∂: 7.32 (m, 5H), 6.52 (d, J = 15.66 Hz, 1H), 6.14 (m, J = 7.96 Hz, 1H), 2.51 (d, J = 7.96 Hz, 2H).

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Appendix

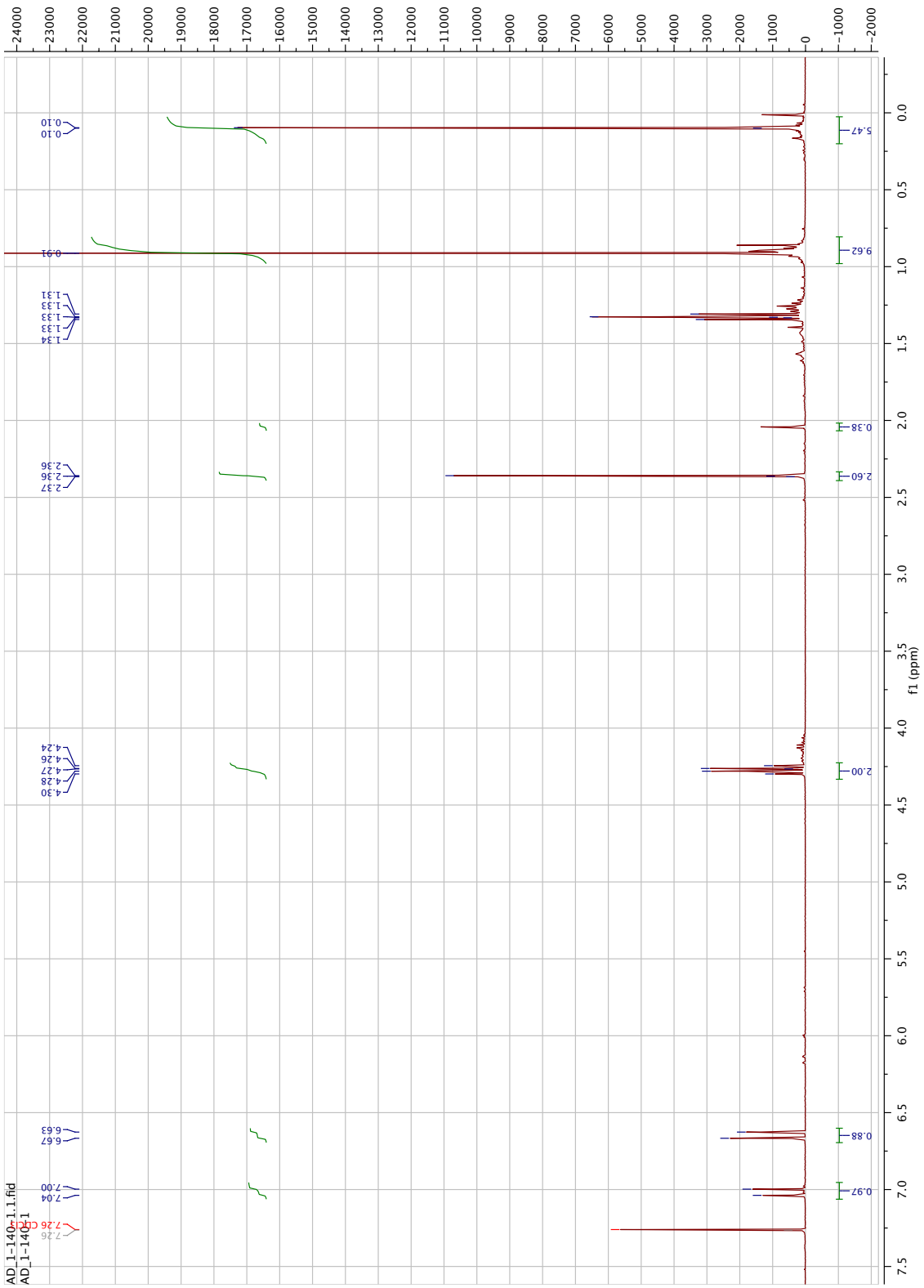

Figure A.1 ^{1}H-NMR spectrum of compound **25** in $CDCl_3$ (400 MHz).

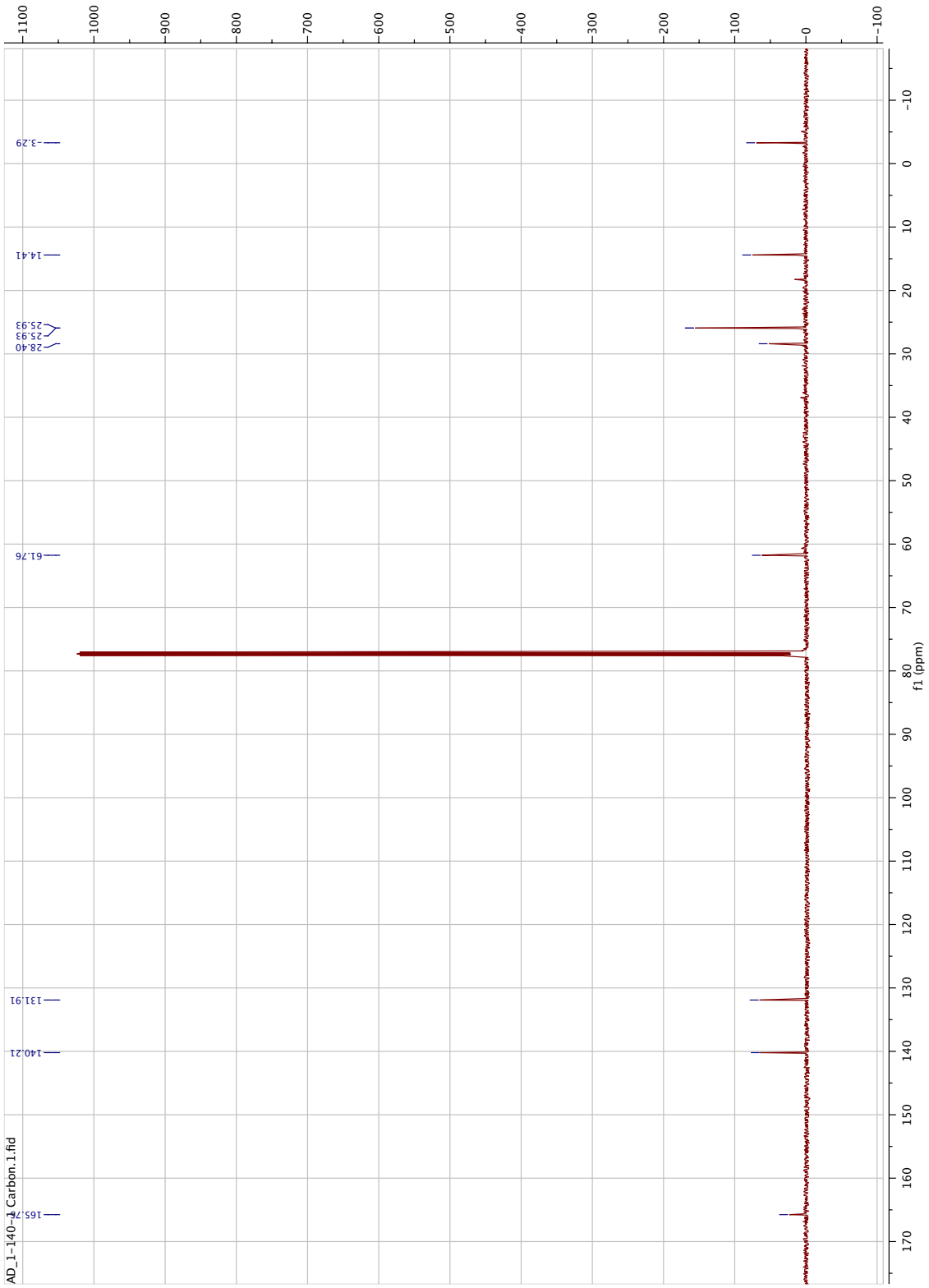

Figure A.2 ^{13}C-NMR spectrum of compound **25** in $CDCl_3$ (500 MHz).

Figure A.3 ^{1}H-NMR spectrum of compound **27** in $CDCl_3$ (300 MHz).