



Studies toward the total synthesis of pentalenic acid
by Steven Michael Reister

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in
Chemistry

Montana State University

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Abstract:

The intent of the research contained herein was to synthesize the natural product pentalenic acid. Pentalenic acid is a small molecule with antibiotic properties. This molecule was chosen as a way to showcase ongoing synthetic methodologies of the Grieco research group. Unfortunately the complete synthesis of pentalenic acid was never realized, but the research proved to be both interesting and surprising. The original route proposed for a key intermediate was much more of a synthetic challenge than was anticipated. In fact it was eventually decided that the desired intermediate could not be obtained via this route and an alternative route was sought after. The alternative route proposed was successful and the desired intermediate was obtained in the same number of synthetic steps as the original. With this intermediate in hand, the key step in the synthesis was performed with rather surprising results. The major product obtained was not the desired one. In fact it was found that the reaction had proceeded in a manner which was thought to be very unlikely. Models and literature precedent predicted that the reaction would proceed the desired way, but in practice it did not. Regrettably the product obtained was not amenable to the synthesis of pentalenic acid, and synthetic efforts concluded. Although these results were unfortunate/they have proven interesting and may be of use to future scientists.

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by

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A thesis submitted in partial fulfillment
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Bozeman, Montana

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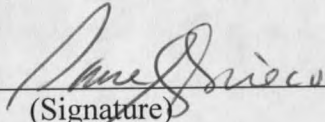
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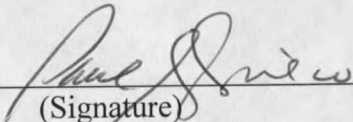
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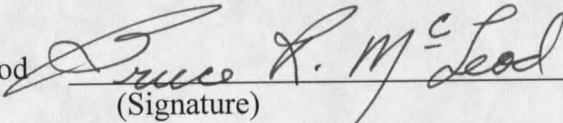
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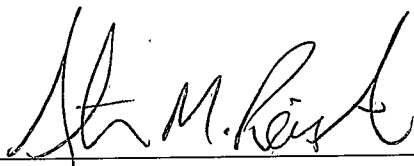
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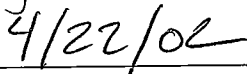


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ABSTRACT

The intent of the research contained herein was to synthesize the natural product pentalenic acid. Pentalenic acid is a small molecule with antibiotic properties. This molecule was chosen as a way to showcase ongoing synthetic methodologies of the Grieco research group. Unfortunately the complete synthesis of pentalenic acid was never realized, but the research proved to be both interesting and surprising. The original route proposed for a key intermediate was much more of a synthetic challenge than was anticipated. In fact it was eventually decided that the desired intermediate could not be obtained via this route and an alternative route was sought after. The alternative route proposed was successful and the desired intermediate was obtained in the same number of synthetic steps as the original. With this intermediate in hand, the key step in the synthesis was performed with rather surprising results. The major product obtained was not the desired one. In fact it was found that the reaction had proceeded in a manner which was thought to be very unlikely. Models and literature precedent predicted that the reaction would proceed the desired way, but in practice it did not. Regrettably the product obtained was not amenable to the synthesis of pentalenic acid, and synthetic efforts concluded. Although these results were unfortunate, they have proven interesting and may be of use to future scientists.

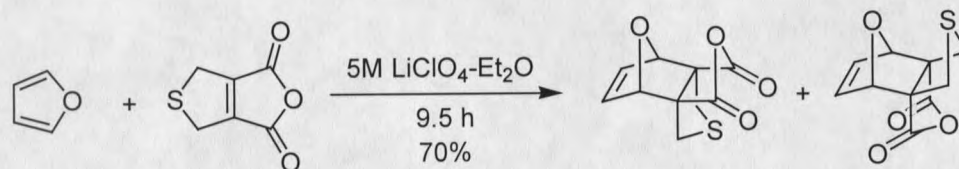
CHAPTER 1

INTRODUCTION

Diels-Alder Reaction

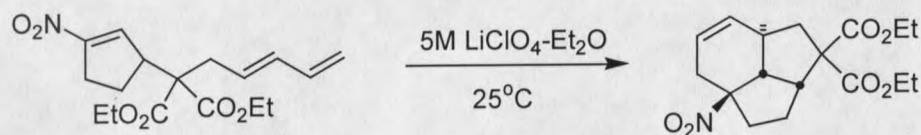
Since its discovery over 50 years ago, the Diels-Alder reaction has become one of the most useful tools in the synthetic organic chemist's arsenal. New variations and applications are continually being developed, allowing for the construction of a wide range of synthetic targets. In recent years, studies have shown that reaction medium can have a powerful influence upon these pericyclic reactions. In this study, we set out to investigate the applicability of these recent advances of the Diels-Alder reaction in the construction of spiro fused ring systems.

Grieco and coworkers have shown that the use of 5M LiClO₄-Et₂O as a medium greatly enhances the reaction rate and selectivity of classically difficult Diels-Alder transformations.¹ This exciting revelation showed that reactions which normally required elevated temperatures and pressures could now be performed at room temperature and ambient pressure. Dauben found that the following reaction required a 6 hour reaction time under 15 kbar of pressure in methylene chloride,² whereas Grieco found the same reaction proceeded in 9.5 hours at ambient temperature and pressure in 5M LiClO₄-Et₂O (Equation 1).



Equation 1. Grieco Diels-Alder

Guy and Serva found similar rate enhancements when moving from thermal conditions to 5M LiClO₄-Et₂O.³ The following reaction proceeded in only 22% yield after 65 hours at 80°C; however, after just 24 hours at room temperature in 5M LiClO₄-Et₂O, a 70% yield was obtained (Equation 2). It is interesting to note that only one stereoisomer was obtained in this reaction.



Equation 2. Guy Diels-Alder

It is apparent from these examples that the Diels-Alder reaction is extremely useful in allowing access into otherwise difficult ring systems. With that, we set out to attempt to apply this methodology to the angular fused triquinane nucleus.

Terpenes

Terpenes are an exciting class of natural products due to their wide array of carbocyclic ring systems and functional groups. As a result, these compounds have generated a significant amount of synthetic interest over the years. A relatively small subtype of these compounds is the polyquinanes, which are composed entirely of fused five-membered rings.⁴ These compounds represent a fairly recent discovery, in fact the structure of the first polyquinane natural product hirsutic acid-C was determined in only 1966.⁴ It is not surprising that a number of synthetic strategies have been developed around this unusual framework.

A subclass of the polyquinanes is the triquinanes. These compounds are distinguished by a carbocyclic framework which consists of three fused five membered rings. These ring systems can occur in one of three arrangements: angular, linear, or axial (Figure 1).⁴

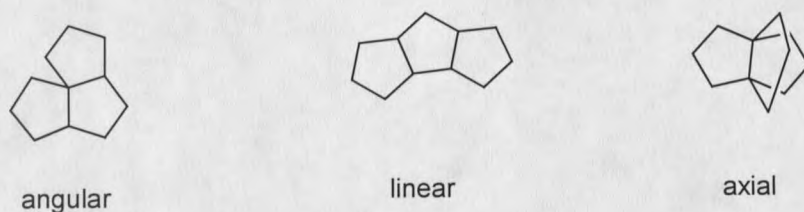


Figure 1. Possible Arrangements of Triquinane Nucleus

Each of these arrangements has been the subject of synthetic interest over the years, and as a result the synthesis of a number of representative natural products can be found in the literature.⁴

For the purpose of this study the angular fused analogues were of sole interest, and in particular the natural product pentalenic acid (Figure 2).

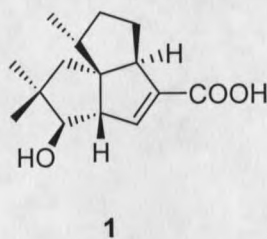
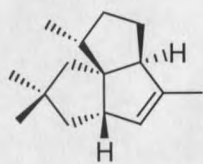
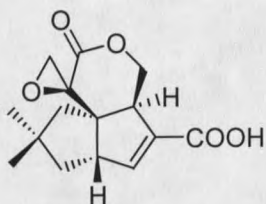


Figure 2. Pentalenic Acid

Pentalenic acid was isolated in 1978 from the fermentation broth of the fungus *Streptomyces Griseochromogenes* along with its counter parts pentalenene and pentalenolactone-H (Figure 3). It is a member of the pentalenolactone group of fungal metabolites which exhibit antibiotic activity.⁴



Pentalenene



Pentalenolactone-H

Figure 3. Analogues of Pentalenic Acid

CHAPTER 2

STATEMENT OF THE PROBLEM

Interest in this molecule was sparked by efforts to continue investigation of the Diels-Alder reaction. It was felt that the use of $\text{LiClO}_4\text{-Et}_2\text{O}$ could facilitate an intramolecular Diels-Alder reaction providing a facile entry into the needed angular ring system (Figure 4).

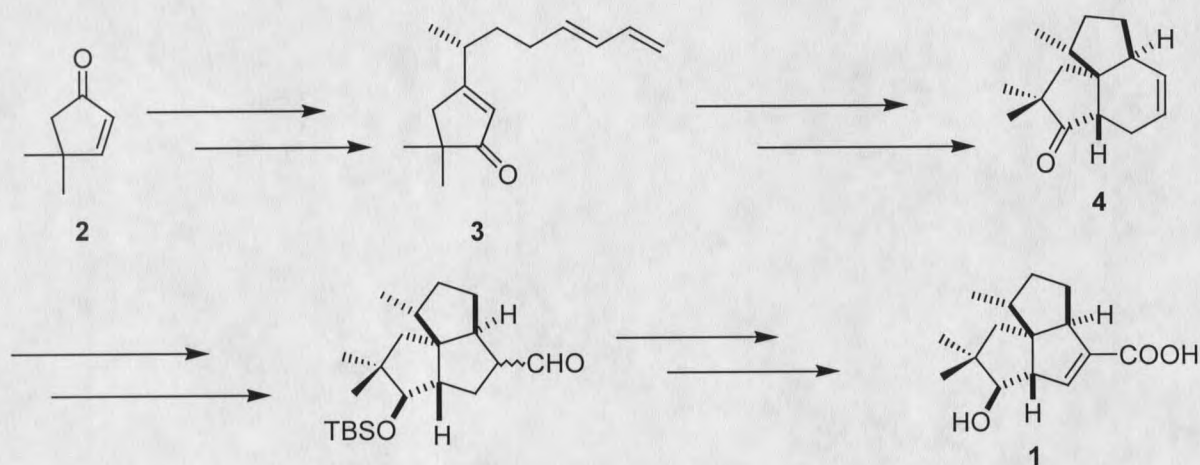


Figure 4. Retrosynthetic Analysis of Pentalenic Acid

It was originally felt that triene **3** could be obtained via a 1,2-addition of an appropriate Grignard reagent to enone **2** followed by an oxidative 1,3-allylic transposition of the resulting alcohol. With triene **3** in hand, the Diels-Alder could be completed to give tricyclic **4** resulting from an exo transition state. The olefin remaining in the six membered ring can then be used to effect a ring contraction providing the desired 5-5-5 angular fused triquinane nucleus. A few further manipulations could then provide the target pentalenic acid **1**.

CHAPTER 3

METHODS AND MATERIALS

General

Proton (^1H) and carbon (^{13}C) Nuclear Magnetic Resonance spectra were recorded on either a Bruker Avance DPX 300 or 500. Chemical shifts are reported in parts per million (δ). Infrared (IR) spectra were taken on a Bruker ISF 250. Signals are reported as strong (s), medium (m), or weak (w). High resolution mass spectra were obtained on a BG 70E-HF. Reactions were monitored using thin layer chromatography (TLC) using E. Merck silica gel 60 F-254 (0.25 mm thickness) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution and warming on a hot plate. Scientific Absorbents silica gel (40 micrometer particle size) was used for all flash chromatography. All reactions were performed under an atmosphere of argon, unless otherwise noted. All solvents are reagent grade unless stated otherwise. Anhydrous solvents were dried immediately before use. Dichloromethane and triethylamine were distilled from calcium hydride. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Lithium perchlorate was dried under high vacuum at 180°C for 48 hrs.

Synthetic Procedures**Octa-5,7-dien-2-ol (8).**

A solution of aldehyde 7 (2.0 g, 18.2 mmol) in 100 ml THF was treated at -78°C with a 1.4 M solution of methylolithium in pentane (15.6 ml, 21.8 mmol). After 15 min, the solution was quenched with a saturated aqueous ammonium chloride solution and

allowed to warm to room temperature. The aqueous fraction was washed several times with diethyl ether. The combined organic fractions were washed successively with brine and water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting crude oil was chromatographed on flash silica gel, eluting with pentane-diethyl ether (1:1) to afford alcohol **8** (1.86 g, 81%) as a clear colorless oil: ^1H NMR (CDCl_3 , 300 MHz) δ 6.37-6.24 (m, 1H), 6.12-6.04 (m, 1H), 5.76-5.66 (m, 1H), 5.06 (d, 1H, $J = 16.8$ Hz), 4.95 (d, 1H, $J = 9.9$ Hz), 3.84-3.78 (m, 1H), 2.23-2.14 (m, 2H), 1.59-1.52 (m, 2H), 1.18 (d, 3H, $J = 6.3$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 137.06, 134.55, 131.31, 115.06, 67.57, 38.49, 28.85, 23.48; IR (cm^{-1}) 3353 (s), 2969 (s), 1652 (m), 1603 (m); m/e (M^+) calcd. 126.1045, found 126.1045.

Methanesulfonic acid 1-methyl-hepta-4,6-dienyl ester (9).

A solution of alcohol **8** (1.1 g, 7.92 mmol) in 75 ml of dichloromethane was successively treated with triethylamine (1.8 ml, 11.9 mmol) and methanesulfonyl chloride (0.75 ml, 8.72 mmol) at 0°C . The resulting solution was allowed to warm to room temperature over 4 h. The reaction mixture was then washed with a saturated aqueous ammonium chloride solution and water. The organic fraction was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting crude mesylate **9** (1.55 g, 97%) was used in the next reaction without purification. ^1H NMR (CDCl_3 , 300 MHz) δ 6.32-6.23 (m, 1H), 6.13-6.04 (m, 1H), 5.71-5.64 (m, 1H), 5.08 (d, 1H, $J = 17.1$ Hz), 4.97 (d, 1H, $J = 9.9$ Hz), 4.83-4.77 (m, 1H), 2.99 (s, 3H), 2.19 (bd, 2H, $J = 6.0$ Hz), 1.87-1.68 (m, 2H), 1.41 (d, 1H, $J = 6.3$ Hz); ^{13}C NMR (CDCl_3 , 75

MHz) δ 136.77, 132.83, 131.99, 115.64, 79.41, 38.64, 36.01, 28.06, 21.13; IR (cm^{-1}) 2939 (m), 1352 (s); m/e ($M + \text{NH}_4^+$) calcd. 222.1164, found 222.1171.

7-Bromo-octa-1,3-diene (10).

A solution of mesylate **9** (1.55 g, 7.59 mmol) in 75 ml of THF was treated with lithium bromide (1.0 g, 11.38 mmol) at room temperature. The resulting solution was then heated to reflux for 12 h. The reaction mixture was filtered through a plug of silica gel and concentrated *in vacuo*. The resulting crude oil was chromatographed using flash silica gel, eluting with pentane-diethyl ether (10:1) to afford diene **10** (1.41 g, 98%) as a clear colorless oil: ^1H NMR (CDCl_3 , 300 MHz) δ 6.37-6.24 (m, 1H), 6.15-6.06 (m, 1H), 5.71-5.61 (m, 1H), 5.09 (d, 1H, $J = 16.5$ Hz), 4.97 (d, 1H, $J = 10.2$ Hz), 4.15-4.10 (m, 1H), 2.33-2.19 (m, 2H), 2.00-1.77 (m, 2H), 1.71 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 136.91, 133.03, 132.03, 115.46, 50.82, 40.35, 30.66, 26.40; IR (cm^{-1}) 2923 (m), 1652 (w), 1603 (w); m/e (M^+) calcd. 188.0201, found 188.0200.

4-(4,4-Dimethyl-3-oxo-cyclopent-1-enyl)-pentanal (15).

Sodium Bicarbonate (2.2 g, 26.4 mmol) was added to 80 ml of CH_2Cl_2 and cooled to -78°C . O_3 was bubbled through the suspension until it turned deep blue color persists, approximately 15 min. **14** (508 mg, 2.64 mmol) was added in 26 ml of MeOH, allowed to stir 1 min then quenched with Me_2S (2.0 ml, 26.4 mmol). The resulting suspension was allowed to warm to room temperature over 4 hours and concentrated *in vacuo*. The resulting crude oil was chromatographed on flash silica gel, eluting with hexanes-ethyl

acetate (1:1) to afford aldehyde **15** (411mg, 80%) as a clear colorless oil: ^1H NMR (CDCl_3 , 300 MHz) δ 9.77 (s, 1H), 5.85 (s, 1H), 2.60-2.54 (m, 1H), 2.47-2.37 (m, 1H), 1.91-1.71 (m, 2H), 1.14 (d, 3H, $J = 6.9$ Hz), 1.09 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 214.13, 201.21, 182.17, 126.51, 45.49, 43.88, 41.37, 36.47, 26.67, 25.05, 18.61; IR (cm^{-1}) 2965 (m), 1724 (m), 1702 (s), 1611 (m); m/e (M^+) calcd. 194.1307, found 194.1310.

5,5-Dimethyl-3-(1-methyl-hepta-4,6-dienyl)-cyclopent-2-enone (3).

To a suspension of bis(cyclopentadienyl)zirconium chloride hydride (79 mg, 0.308 mmol) in CH_2Cl_2 (1.0 ml) was added 3-trimethylsilyl-1-propyne (48 μl , 0.324 mmol), and the mixture was stirred at room temperature for 10 min. To this solution was sequentially added **15** (30 mg, 0.154 mmol) in CH_2Cl_2 (0.3 ml) and silver perchlorate (2 mg, 0.0077 mmol). The solution was stirred at rt for 1 h then heated to reflux for 4 h. The reaction mixture was then poured into ca 20 ml of a saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3x 20ml). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The resulting crude oil was chromatographed on flash silica gel, eluting with pentane-diethyl ether (1:1) to afford triene **3** (25 mg, 74%) as a clear colorless oil: ^1H NMR (CDCl_3 , 300 MHz) δ 6.36-6.23 (m, 1H), 6.09-6.00 (m, 1H), 5.86 (s, 1H), 5.70-5.61 (m, 1H), 5.08 (d, 1H, $J = 16.5$ Hz), 4.97 (d, 1H, $J = 10.2$ Hz), 2.60-2.53 (m, 1H), 2.43 (s, 2H), 2.11-2.04 (m, 2H), 1.71-1.47 (m, 2H), 1.13 (d, 3H, $J = 6.9$ Hz), 1.11 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 214.40, 183.52, 136.91, 133.90, 131.66, 126.24, 115.40, 45.59, 43.84, 36.62

34.27, 30.06, 25.16, 18.72; IR (cm^{-1}) 2963 (m), 1705 (s), 1612 (m); m/e (M^+) calcd. 218.1671, found 218.1662.

2,2,9-Trimethyl-2,3,3a,4,6a,7,8,9-octhydro-1 *H*-cyclopenta[*d*]indene (16).

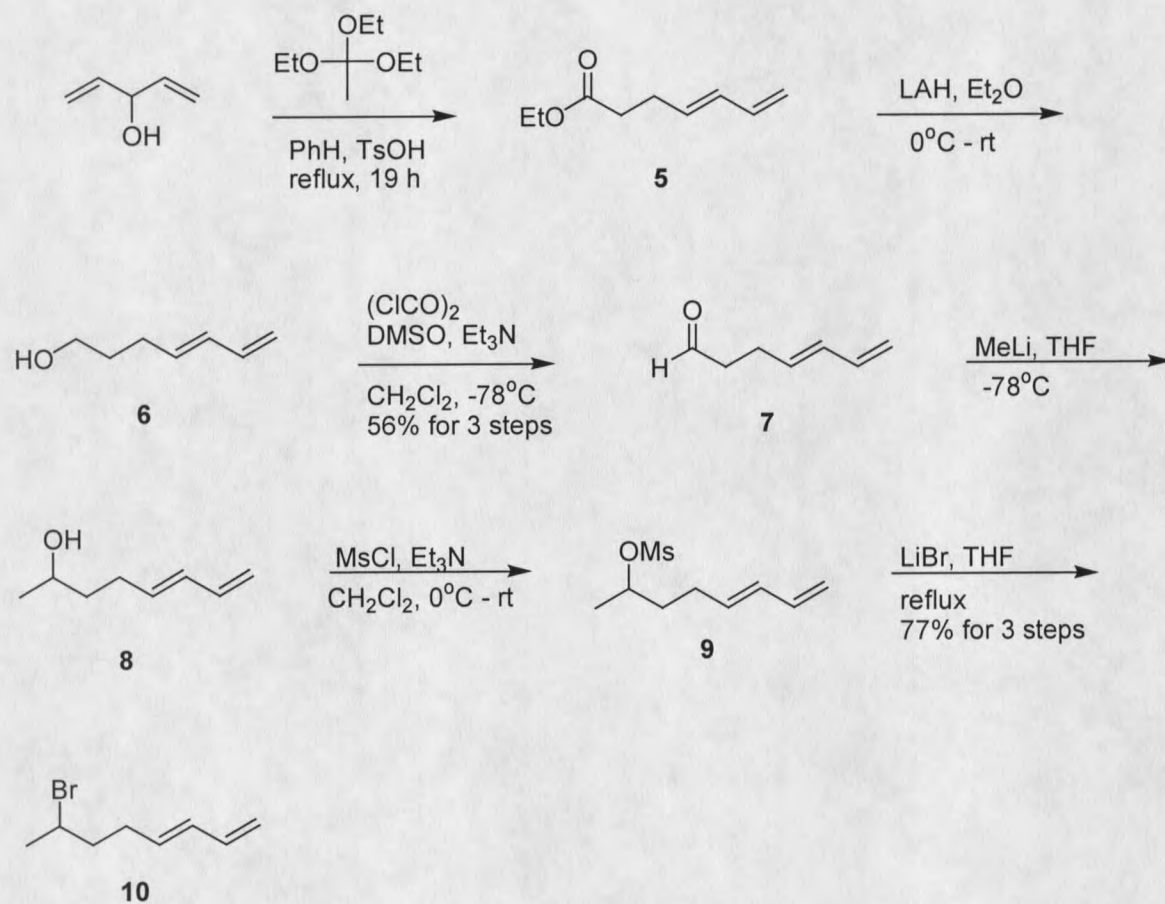
A solution of triene **3** (600 mg, 2.748 mmol) and *N,N*-diethylaniline (0.44 ml, 2.748 mmol) in 69 ml of *o*-dichlorobenzene was placed in a sealed tube and heated to 200°C. After 48 h the resulting solution was cooled to room temperature and applied directly to a chromatography column containing flash silica gel. Elution with hexanes until all *o*-dichlorobenzene came through followed by hexanes-diethyl ether (20:1) afforded ketones **17**, **18**, and **19** (204 mg, 34%) as a complex mixture. Further elution afforded ketone **16** (162 mg, 27%) as a clear colorless oil: ^1H NMR (C_6D_6 , 500 MHz) δ 5.85-5.82 (dt, 1H, $J = 9.0, 3.5$ Hz), 5.74-5.70 (m, 1H), 2.45-2.40 (dd, 1H, $J = 15.5, 7.0$ Hz), 2.22 (d, 1H, $J = 10.5$ Hz), 1.97-1.91 (m, 1H), 1.81-1.77 (m, 1H), 1.69-1.61 (m, 1H), 1.45-1.40 (m, 1H), 1.28-1.21 (m, 1H), 1.23 (ab, 2H, $J = 14.5$ Hz), 1.13-1.08 (m, 1H), 1.01 (s, 3H), 0.99 (s, 3H), 0.73 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (C_6D_6 , 75 MHz) δ 226.14, 134.34, 128.56, 52.00, 51.57, 47.39, 44.27, 43.08, 39.78, 30.44, 28.70, 26.38, 25.62, 24.27, 15.74; IR (cm^{-1}) 2958 (s), 1735 (s); m/e (M^+) calcd. 218.1671, found 218.1657.

CHAPTER 4

RESULTS

Synthesis of 7-Bromo-octa-1,3-diene

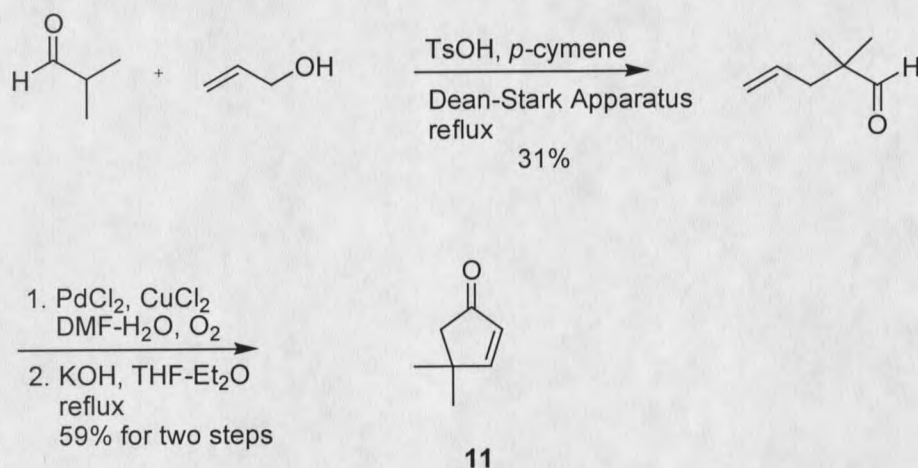
With that, the synthesis of Diels-Alder precursor triene **3** was initiated by first synthesizing bromide **10** (Scheme 1).



Scheme 1. Synthesis of 7-Bromo-octa-1,3-diene

Aldehyde **7** was synthesized via the procedure of Spino.⁵ 1,4-Pentadiene-3-ol was subjected to Johnson ortho ester Claisen conditions to provide ethyl ester **5**. The ester

was reduced using lithium aluminum hydride to alcohol **6**, followed by oxidation to the aldehyde via Swern oxidation conditions. Conversion to the bromide was accomplished by the addition of MeLi to the aldehyde followed by conversion of the resulting alcohol first to the mesylate then to the bromide. With the bromide in hand, preparation of triene **3** was initiated via the 1,2 addition of bromide **10** into 4,4-dimethyl-2-cyclopenten-1-one (**11**), readily available in three steps by the method of Magnus⁶ (Scheme 2).



Scheme 2. Synthesis of 4,4-Dimethyl-2-cyclopenten-1-one

Unfortunately, all attempts to accomplish this reaction failed (Figure 5). Initially an attempt was made to perform a lithium-halogen exchange on bromide **10** using *t*-butyl lithium, followed by addition of the resulting alkyl lithium to enone **11**. However, all that was recovered was the addition of *t*-butyl anion into the enone. Next a simple Grignard type addition was attempted. This gave only enone **11** without formation of the Grignard reagent. It was later found that additions of this type sometimes require formation of the anion by reaction of the bromide with lithium metal under sonication conditions.⁷

However, when this reaction was attempted again all that was recovered was starting material. This reaction was finally tried using lithium with a 2% sodium content, as it was found that a high sodium content is necessary to promote metal-halogen exchange.⁸ This reaction again gave only recovered starting material.

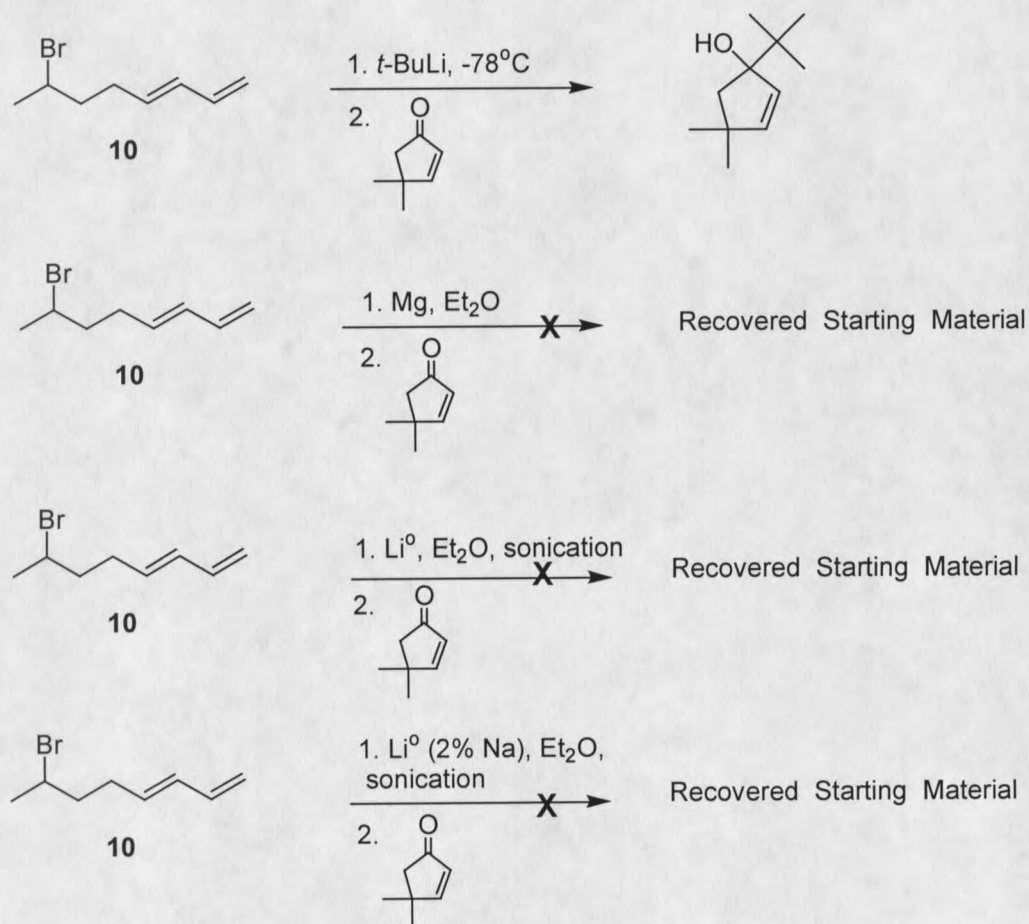


Figure 5. Results of Attempted 1,2-Addition

The reason behind this failure remains unclear; however, after some investigation the following conjecture is put forth. It has been shown that alkenyl Grignard reagents can undergo intramolecular cyclizations as shown in Figure 6.⁹

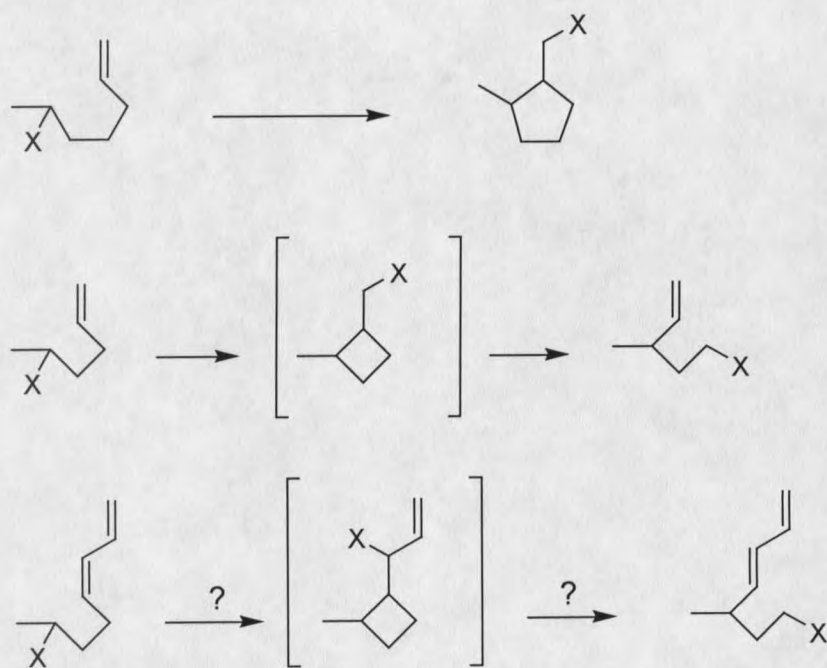
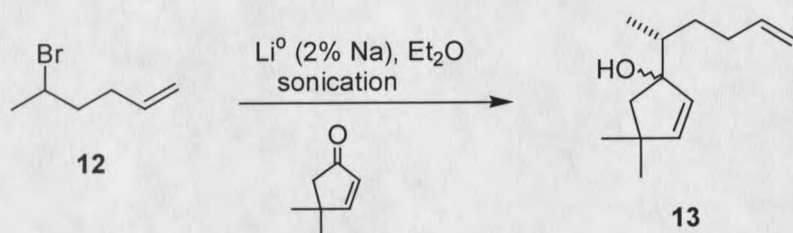


Figure 6. Possible Explanation of 1,2-Addition Failure

Kossa reported that the rate of cyclization was dependent upon whether the Grignard was primary, secondary, or tertiary. He found that the rate of cyclization was highest for 2° anions, and five membered rings formed faster than both four and six. Although studies were completed, as expected, only on isolated olefins and not on dienes, one could surmise that given the added stability of an allylic anion, the same sort of mechanism could apply in the reactions above. However, no cyclized or rearranged products were isolated from the above reactions. With these unfortunate results, the synthesis of triene **3** had to be performed in a different manner.

Synthesis of Diels-Alder Substrate

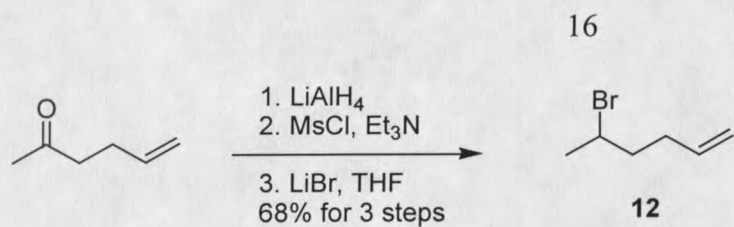
It was felt that if a 1,2-addition, with a molecule with some sort of synthetic handle, was able to be accomplished, the diene unit would be able to be installed last. With this, it was found that Fukumoto had accomplished the 1,2-addition of 2-bromo-5-hexene into 4,4-dimethyl-2-cyclopenten-1-one using lithium metal to facilitate halogen exchange (Equation 3).¹⁰



Equation 3. Fukumoto 1,2-Addition

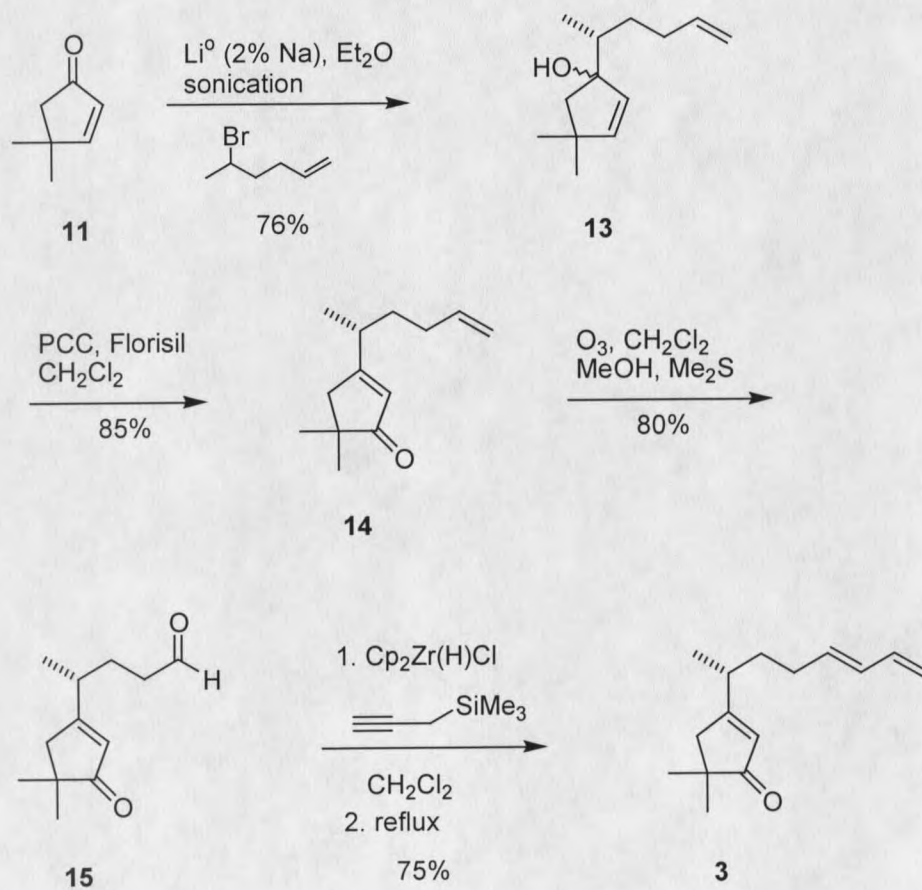
Interestingly, this seems to be the solution to the aforementioned problem with these types of Grignard additions. However when this method was employed using bromide **10** all that was recovered was starting material. The reaction in eq **3** was found to be scale dependent. That is, when the reaction was performed on small scale (0.1 mmol), starting material was recovered, but on large scale (5 mmol) the reaction proceeded without incident. It is believed that the reaction with diene **10** would have worked if it had been attempted on larger scale. However, as soon as this alternative route presented itself it was undertaken without question and the previous one abandoned.

Toward this end, bromide **12** was synthesized in three steps from commercially available starting material 5-hexen-2-one (Equation 4).



Equation 4. Synthesis of 5-Bromo-1-hexene

With this bromide in hand, the synthesis to afford triene **3** proceeded smoothly as shown in Scheme 3.



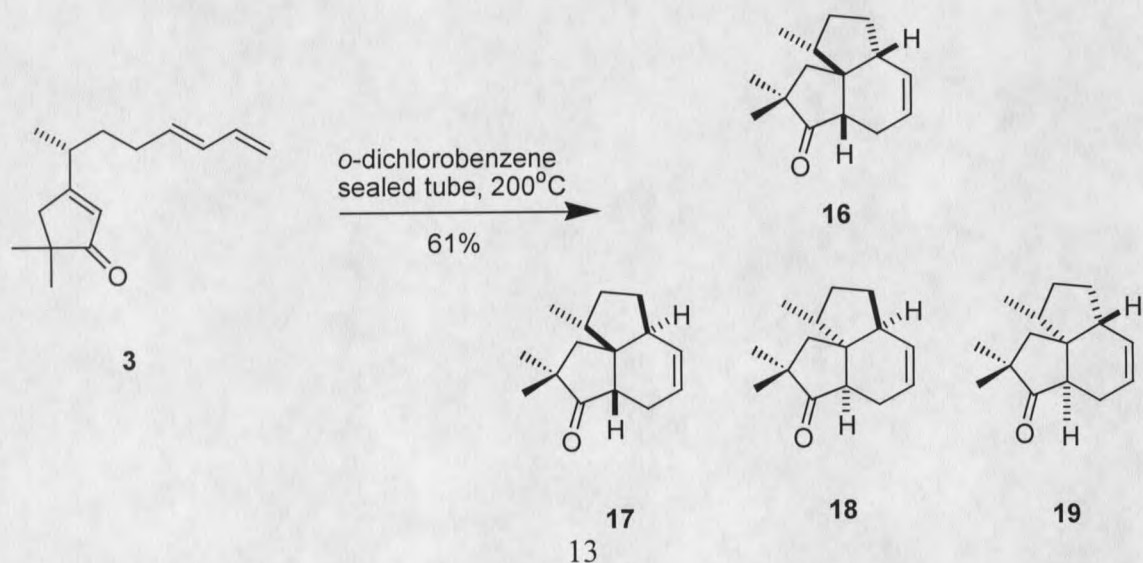
Scheme 3. Synthesis of Diels-Alder Substrate

The 1,2-addition of 4,4-dimethyl-2-cyclopenten-1-one gave a 76% yield of allylic alcohol **13**. In the presence of PCC, this material underwent an allylic 1,3-transposition to give an 85% yield of enone **14**.¹¹ Ozonolysis of the terminal olefin gave an 80% yield of aldehyde **15**. As expected ozonolysis occurred chemoselectively at the more electron rich terminal olefin rather than the electron deficient olefin of the enone. At this point in the synthesis some question came as to how the diene unit would be introduced. An approach employing a Wittig reaction for diene installation was expected to yield both *cis* and *trans* isomers. Upon inspection of Dreiding models, though, it was determined that the *cis* diene would be unreactive towards the Diels-Alder cyclization. Suzuki had demonstrated, however, a *trans* selective terminal 1,3-diene synthesis employing propargyl trimethylsilane and Schwartz reagent, and application of this procedure proceeded without incident to give a 75% yield of the desired triene **3**.¹²

CHAPTER 5

DISCUSSION

With triene **3** in hand, an attempt at the Diels-Alder was ready to be made. It was decided that this reaction initially be attempted using thermal conditions. Triene **3** was heated for 48 h at 200°C in a sealed tube in *o*-dichlorobenzene with one equivalent of *N,N*-diethylaniline added as a proton scavenger. The reaction proceeded to give what appeared to be two separable products by thin layer chromatography. However, upon separation and characterization, the first spot was surmised to consist of an inseparable mixture of three products (**17**, **18**, **19**), comprising 34% of the yield. The second was one distinct product **16**, comprising 27% of the yield (Equation 5).



Equation 5. Diels-Alder Results

Determination of the structure of cycloadduct **16** was undertaken. Initial ^1H NMR experiments showed cyclic material, and nOe experiments were employed to determine the relative configuration. As shown in Figure 7, the nOe experiments suggested the configuration of the distinct product as that of the endo cycloadduct.

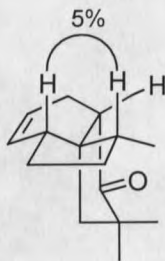


Figure 7. nOe Studies of Diels-Alder Product

The 5% nOe enhancement seen between the two pseudo axial hydrogens suggest that the major product is in the configuration in Equation 5. It should be noted that characterization of the inseparable mixture was not completed and the products were assumed to be the three other possible cycloadducts of the reaction.

These results were both unfortunate and unexpected. Cycloadduct **16** must arise from the endo transition state in Figure 8. It was felt that this would be a less favored transition state because of the boat like conformation adopted and also the steric interactions between the approaching diene and the geminal dimethyl group on the cyclopentenone ring. The exo transition state leading to **17** was thought to be favored. This was because of the more chair like conformation and lack of interactions between the diene and the ring. However, intuition proved to be incorrect, and under thermal conditions the endo cycloadduct is formed preferentially.

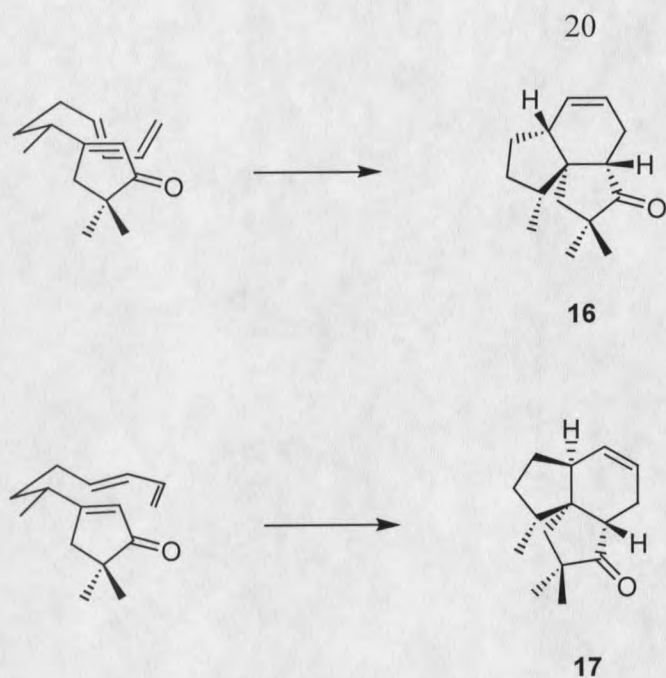
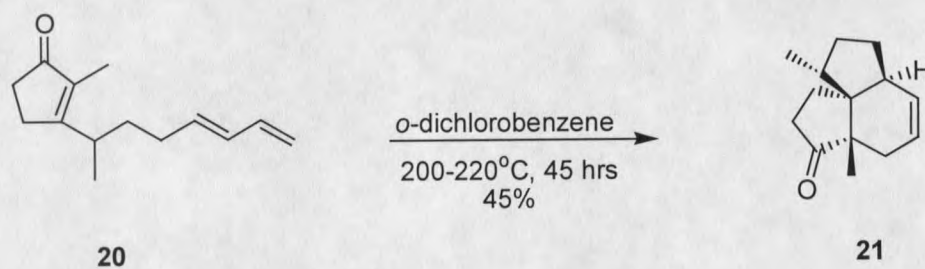


Figure 8. Transition States of Diels-Alder

It should be noted that the observed endo selectivity is in contrast to the reported results of Fukumoto.¹³ In the synthesis of silphinene, exclusive formation of the exo cycloadduct **21** in the thermal Diels Alder reaction of **20** was reported (Equation 6).

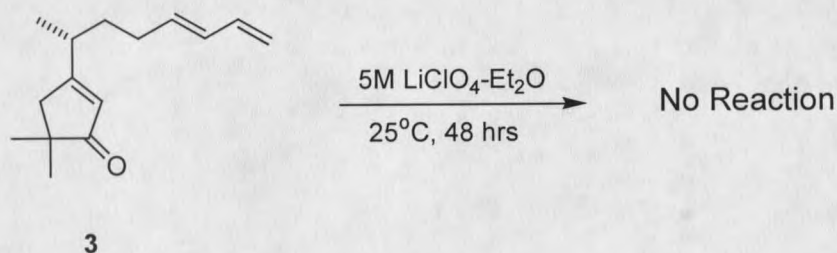


Equation 6. Fukumoto Diels-Alder

Fukumoto and coworkers claim that steric interactions between the cyclopentenone ring and the approaching diene make the endo transition state less favorable, leading to the

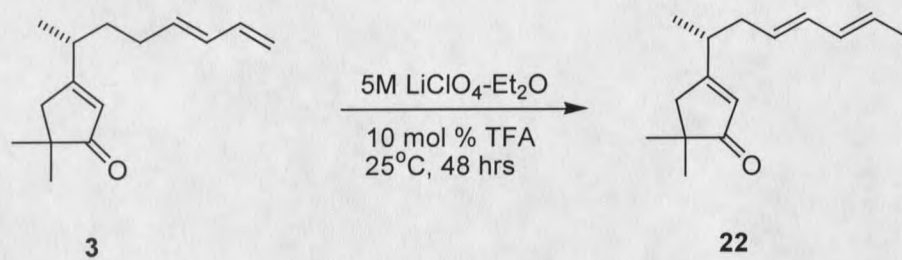
observed exo cycloadduct. However these interactions should be more pronounced in **3** due to the geminal dimethyl group on the ring. The observed endo selectivity leading to **16** is indeed surprising.

With these results in hand, an attempt at the Diels Alder using 5M LiClO₄-Et₂O was undertaken. Triene **3** was taken up in a freshly prepared solution of 5M LiClO₄-Et₂O and stirred at room temperature for 48 hours (Equation 7). After two days all that was recovered was starting material.



Equation 7. 5M LiClO₄-Et₂O Diels-Alder

This reaction was again attempted using the highly polar medium, but with the addition of trifluoroacetic acid (Equation 8). An acid catalyst is sometimes necessary to promote these reactions by generating an oxonium ion, which stabilizes the transition state. However, after two days at room temperature, crude NMR showed no cyclized product. All that was recovered was what appeared to be internalization of the diene by the acid catalyst.

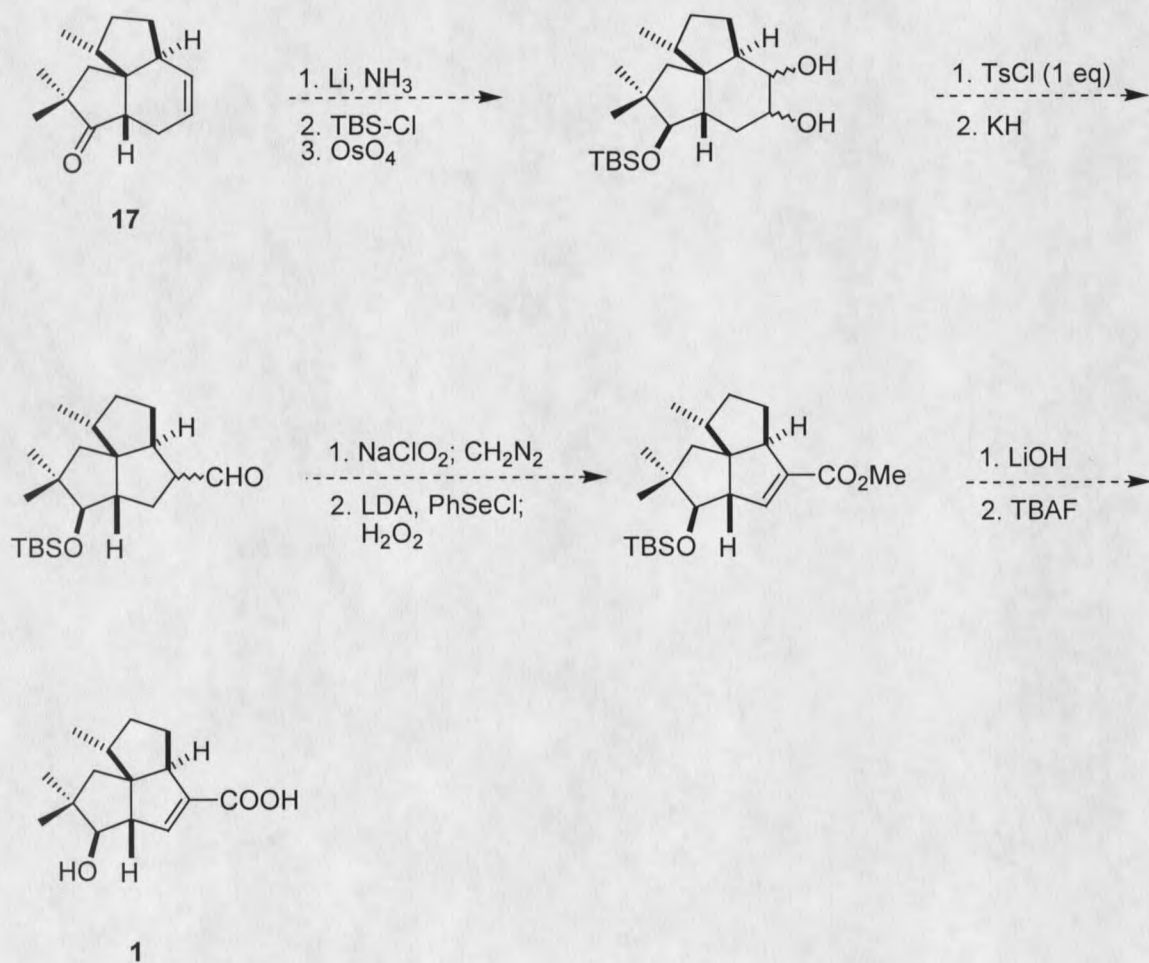


Equation 8. 5M LiClO₄-Et₂O + TFA Diels-Alder

CHAPTER 6

CONCLUSIONS

At this time a synthesis of pentalenic acid has not been realized. Bearing in mind that the intent of this research was to synthesize pentalenic acid, this could be considered a failure. However, if tricyclic ketone **17** can be achieved, the synthesis could be completed via the proposed route shown in Scheme 4.



Scheme 4. End of Synthesis

Most notable about this proposed route is the ring contraction employing a Pinnacol rearrangement. Both the facial selectivity of the dihydroxylation and the chemoselectivity of the conversion to the monotosylate are irrelevant since all possible products would undergo rearrangement to give either epimer of the same aldehyde. Furthermore, the resulting stereocenter would be destroyed prior to completion of the synthesis.

Unfortunately no known angular triquinanes contain the stereochemistry as seen in the major product **16** of the Diels-Alder reaction. However, new natural products are being isolated everyday, and perhaps in the future this chemistry could prove useful in the synthesis of another natural product.

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