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## Nickel Catalyzed Cyclizations of Alkynyl-Etones and Their Application to the Formal Synthesis of Pentalenic Acid

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CERTIFICATE OF ORAL EXAMINATION

Kevin Schlosser, having been admitted to the Carl and Winifred Lee Honors College in 1993, successfully presented the Lee Honors College Thesis on December 6, 1996.

The title of the paper is:

**"Nickel Catalyzed Cyclizations of Alkynyl-Enones and Their Application to the Formal Synthesis of Pantalenic Acid"**

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Chemistry

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Lee Honors College

**Nickel Catalyzed Cyclizations of Alkynyl-Enones and Their  
Application to the Formal Synthesis of Pentalenic Acid**

**Kevin Schlosser  
December 6, 1996**

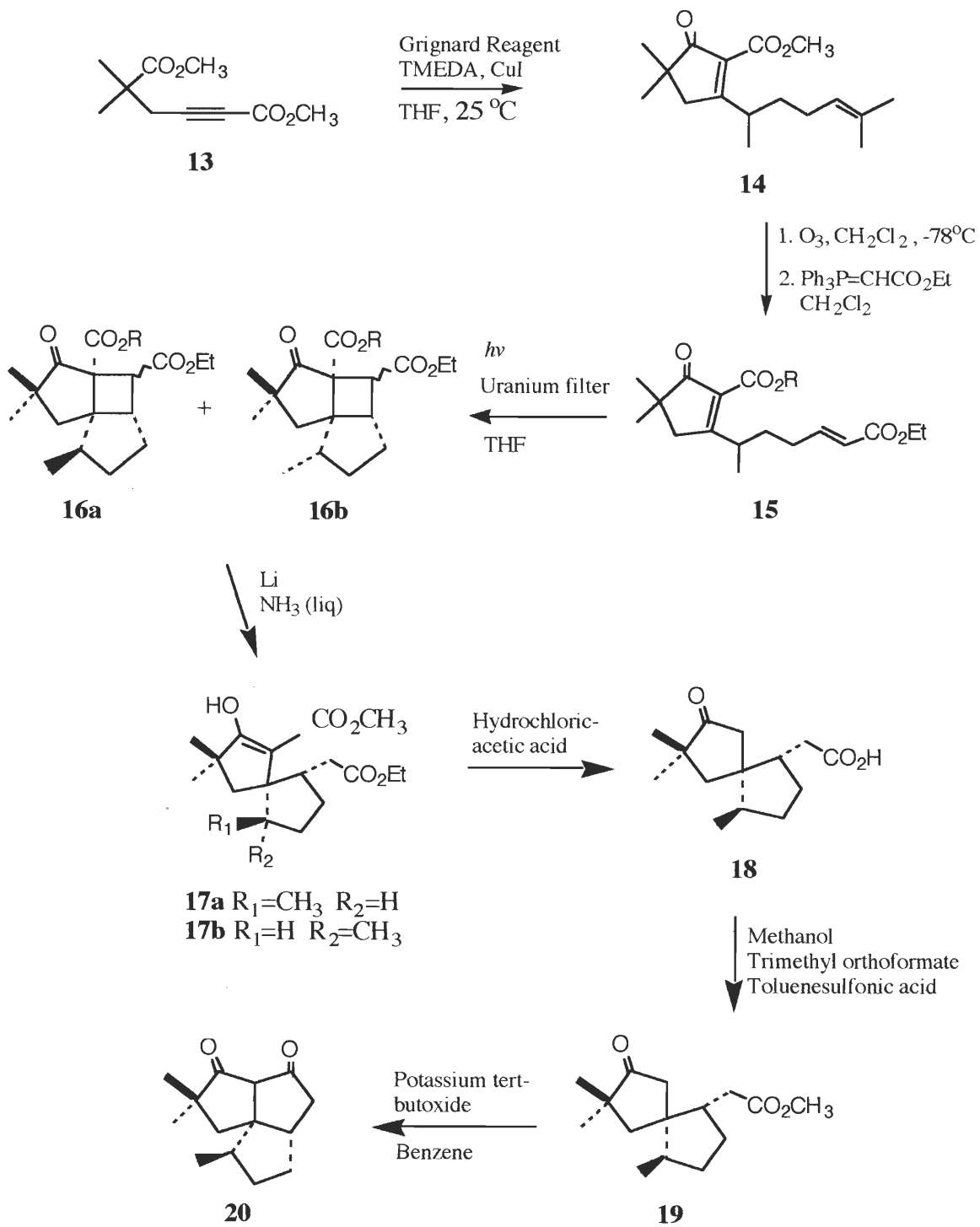
## Objective

Pentalenic acid is a very important molecule because it is a biosynthetic intermediate of pentalenolactone, which has antibiotic effects on Gram-positive/negative bacteria and pathogenic fungi. These effects are due to its ability to inhibit glyceraldehyde 3-phosphate dehydrogenase.<sup>1</sup> However, the total synthesis of pentalenic acid is very lengthy.<sup>2</sup> This project will begin the process of finding a more convenient route to pentalenic acid. Previously in this laboratory there have been experiments conducted in the cyclization of enones with nickel (0).<sup>3</sup> It is hypothesized that this method can be used to shorten the preparation of pentalenic acid.

As illustrated by the procedure taken from Crimmins and Deloach, the total synthesis of pentalenic acid is very lengthy. Scheme 2 shows this process up to a key intermediate in the synthesis **20**. This is the compound the nickel chemistry will produce, and the remaining procedure will be identical to that of Crimmins and Deloach. The outline of the original synthesis along with the outline of the proposed nickel based synthesis included later will show a direct comparison of the difference in length of the two procedures.

### Crimmons's method

The method employed by Crimmins in preparation of pentalenic acid starts with diester **13**. This diester was treated with a grignard reagent of 6-chloro-2-methyl-2-heptene with tetramethylethylenediamine and copper iodide. This reaction yielded diene **14** through conjugate addition and then cyclization. Under an atmosphere of ozone in the presence of a phosphine compound, diene **14** was converted to diene ester **15**. This compound was then irradiated through a uranium glass filter to yield **16** in a 13:1 ratio of isomers. The cyclobutane ring was reductively cleaved by treatment with lithium in liquid ammonia. This gives  $\beta$ -keto ester **17** in two stereoisomeric forms in a 13:1 ratio. This shows that compounds **16a,b** each produce **17a,b**. It is possible to increase the ratio by increasing the size of the substituent on the cyclopentenone (ex.  $-\text{COCH}_2\text{CH}_3$  instead of  $-\text{COCH}_3$ ). **17** was then treated with hydrochloric-acetic acid, and the resulting hydrolysis-decarboxylation produced **18**. This carboxylic acid then underwent esterification by treatment with methanol and trimethyl orthoformate with p-toluenesulfonic acid serving as a catalyst to yield **19**. This compound was then cyclized using potassium tert-butoxide in benzene to form **20**.

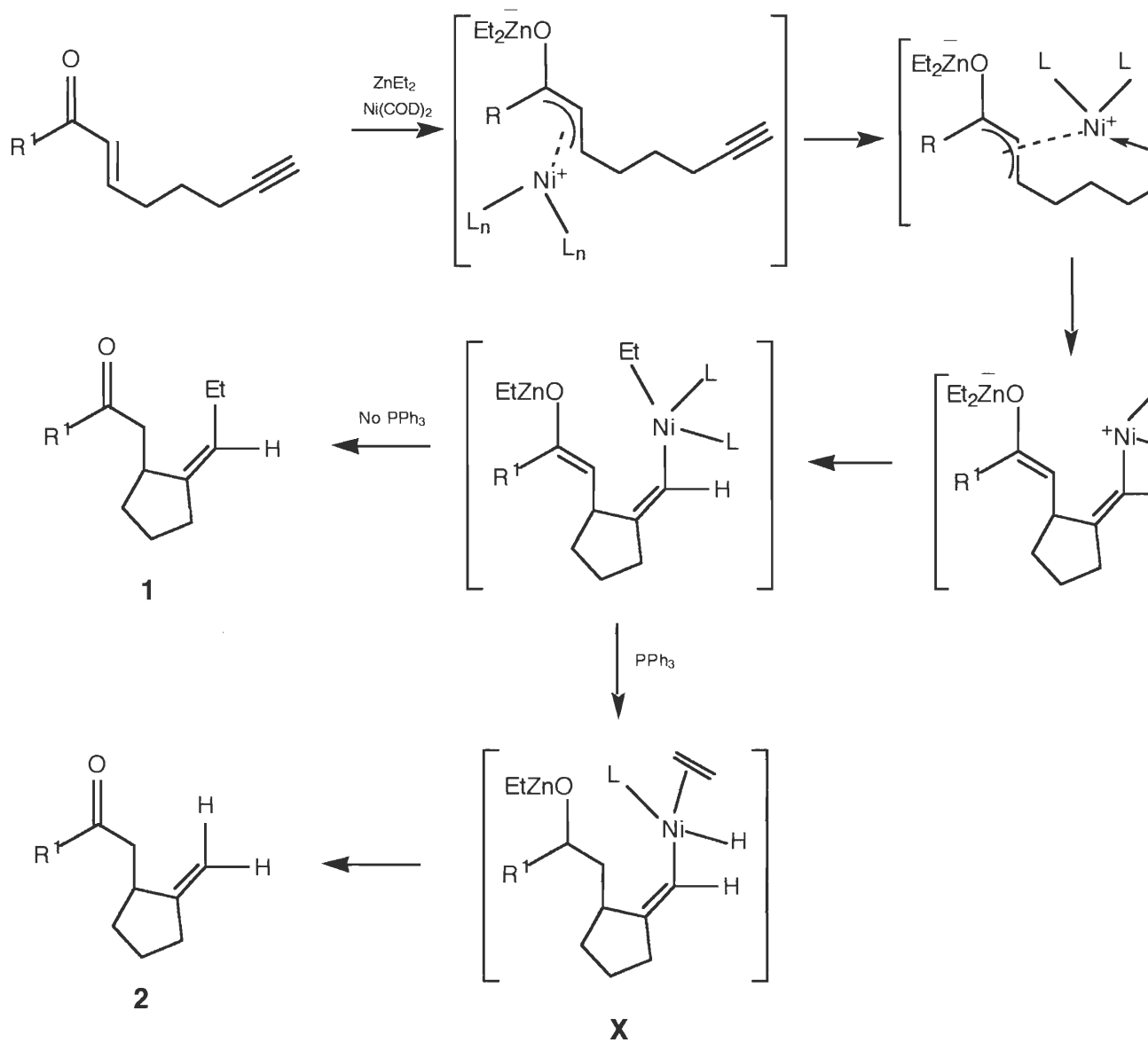


## Background

Previously in this laboratory it has been found that using nickel (0) as a catalyst along with organozincs can induce cyclizations of enones. An example of this type of chemistry that has been conducted is illustrated in scheme 1. The result of these reactions is either alkylation or reduction. The result is dependent on the addition of a nucleophilic ligand such as triphenyl phosphine. If no ligand is added, cyclization occurs and the R group on the zinc alkylates at the site of the nickel. The alkyl group takes the place of the nickel complex by reductive elimination to give **1**.

However, if a phosphine ligand is added, that ligand causes  $\beta$ -H elimination.  $\beta$ -H elimination is a process in which a hydrogen atom is transferred to the metal from the second carbon away from the metal. The resulting metal hydride species **X** then undergoes reductive elimination to produce **2**.

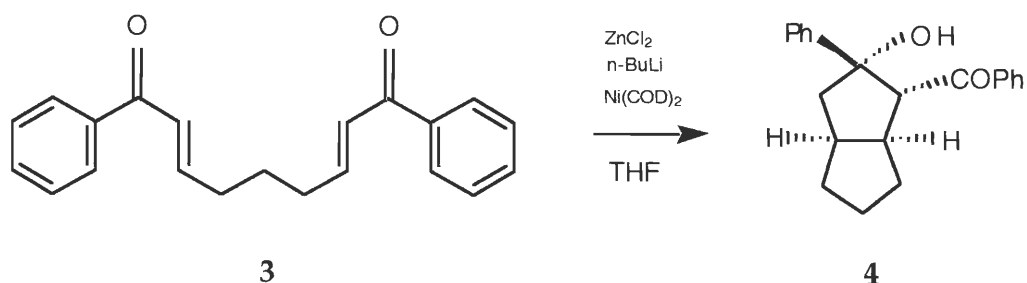
Scheme 1.4





Another example of this specific nickel chemistry can be seen in the cyclization of bis-enone **3** to give a bicyclo-octane **4** (scheme 2). This reaction was conducted to test the experimental conditions to be used in the main experiment. The experimental procedure of this reaction is described in the experimental section.

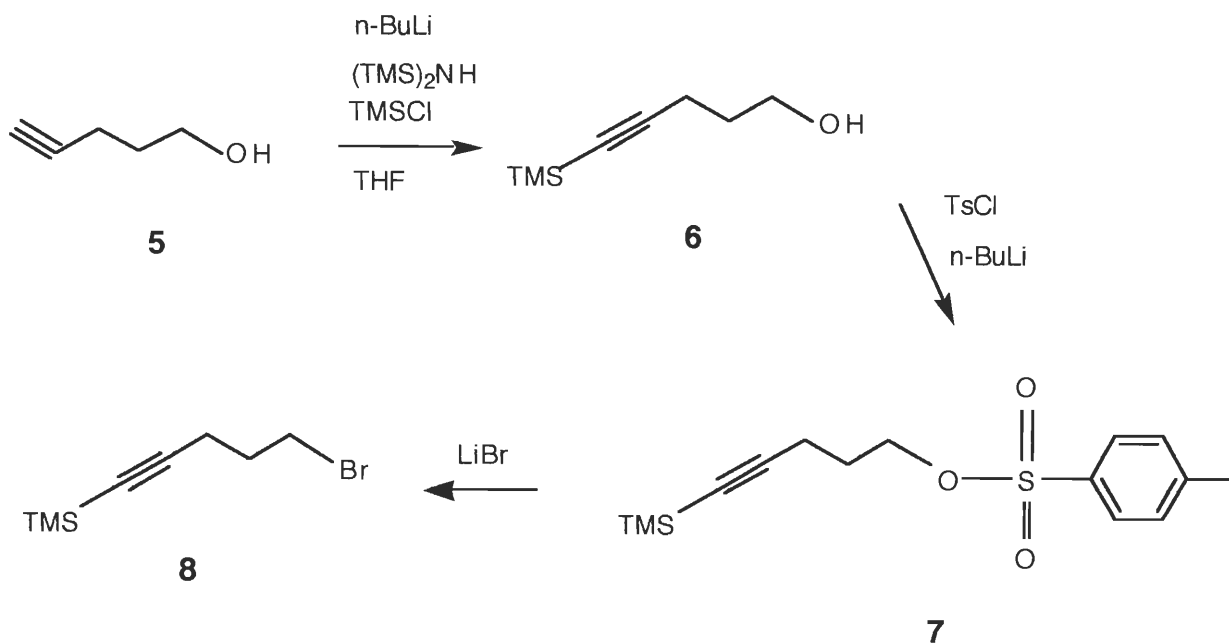
**Scheme 2**



### Results and Discussion

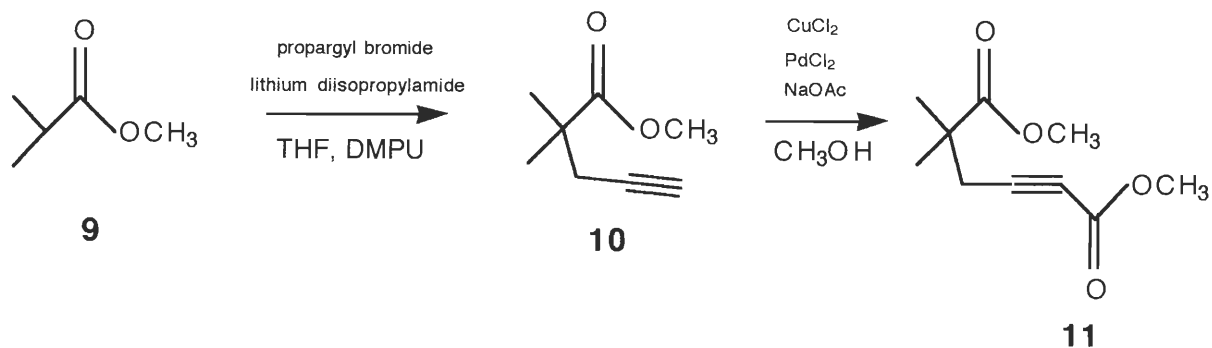
The goal of this project was to synthesize an intermediate in the synthesis of pentalenic acid that could be cyclized via the nickel catalyzed reactions. This project started with the preparation of the starting materials needed for the eventual nickel catalyzed cyclization into pentalenic acid. The procedure for this synthesis is taken directly from Crimmins and DeLoach<sup>2</sup>. There were two starting materials, an alkyl bromide and a diester, that were necessary to begin the synthesis. The alkyl bromide was prepared starting with **5**, adding a trimethyl silane group, giving **6**. A tosylate group was added and then that compound **7** was brominated by treatment with lithium bromide yielding alkyl bromide **8** (Scheme 3)<sup>5</sup>.

Scheme 3



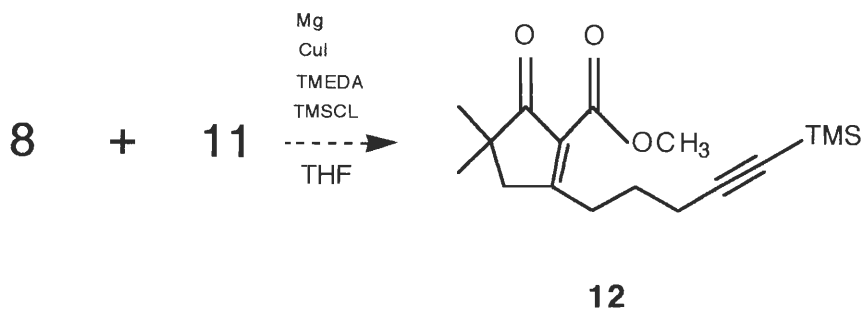
Preparation of the diester **11** began with methyl isobutyrate **9**. Treatment with butyl lithium, diisopropylamine, and propargyl bromide afforded **10**. The addition of butyl lithium and diisopropylamine results in lithium diisopropylamide (LDA), which is used to convert ketones to the corresponding lithium enolate. The lithium and hydrogen interchange because LDA is less basic than butyl lithium. The enolate then works as a nucleophile, attacking the bromide. **10** was then treated with copper (II) chloride, sodium acetate and a palladium (II) catalyst to afford diester **11** which is the other starting substrate (Scheme 4)<sup>2</sup>.

## Scheme 4



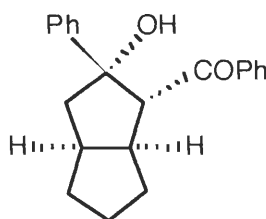
A Grignard reagent of the alkyl bromide **8** was formed in situ and together with substrate **11** were treated with copper (I) iodide and TMEDA (Scheme 5)<sup>2</sup>. Attempts to effect their coupling to produce **12** were not successful. It is hypothesized that the Grignard reagent of the bromide and magnesium was never formed. Each of the substrates were tested for purity to be sure it was not due to a substrate, however, no problem was ever isolated.

## Scheme 5



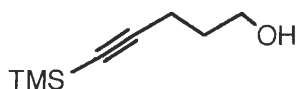
## Experimental

Tetrahydrofuran was freshly distilled before use. All reaction were maintained under argon gas. Measurements of Ni(COD)<sub>2</sub> and ZnCl<sub>2</sub> were conducted in the glove box. All spectral data were identical to that previously reported.



### **1-S\*-2-R\*-3-S\*-5-S\*-2-Benzoyl-3-hydroxy-3-phenylbicyclo[3.3.0] octane.**

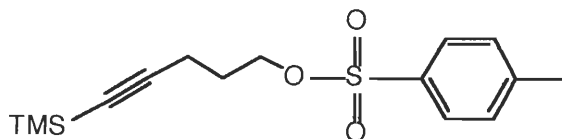
To a solution of ZnCl<sub>2</sub> (171 mg, 1.25 mmol) in 11 mL THF cooled to 0 °C was added n-BuLi (740mL of a 2.4 M solution in hexane, 1.79 mmol). The solution was stirred at 0 °C for 30 minutes. To the solution was added by cannula transfer a solution of Ni(COD)<sub>2</sub> (5.4 mg, 0.02 mmol) in 6 mL THF. That solution was immediately transferred to a solution of **1** (163 mg, 0.54 mmol) cooled to 0 °C in 6 mL THF. The reaction was stirred at 0 °C for 1 h. It was then quenched with a saturated NaHCO<sub>3</sub> solution (25 mL), extracted with EtOAc (4x25 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The oil was chromatographed with silica gel and petroleum ether/diethyl ether 85:15 to yield 47 mg of **4** in white crystalline form.



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### 1-(trimethylsilyl)-1-pentyn-5-ol

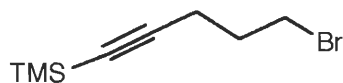
A solution of n-BuLi in hexane (2.3 N, 12.9 mL, 28.6 mmol) was added to a solution of 5-pentyn-1-ol (1.00 g, 14.3 mmol) in THF (28.6 mL) at  $-78^{\circ}\text{C}$ . The reaction was allowed to react for 1 hr, and then was treated with TMSCl (3.8 mL, 3.26 g, 30 mmol), warmed to  $25^{\circ}\text{C}$  for 1 hr, quenched with water, extracted with ether, and finally concentrated. This concentrate was then treated with 3 N HCl (10 mL), extracted with ether (3x), washed with aqueous solutions of  $\text{NaHCO}_3$  and  $\text{NaCl}$  (3x), dried with  $\text{MgSO}_4$ , and finally concentrated<sup>5</sup>.



7

### 5-(trimethylsilyl)-4-pentynyl p-Toluenesulfonate

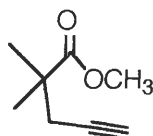
The concentrate of 1-(trimethylsilyl)-1-pentyn-5-ol was diluted in THF (14.3 mL) and treated with 2.3 N n-BuLi in hexane (6.2 mL, 14.3 mmol) at  $-78^{\circ}\text{C}$  for 1 hr, and then p-toluenesulfonyl chloride (3 g, 15.7 mmol) in THF (7.1 mL) at room temperature for 6 hr. The mixture was then quenched with water and extracted with ether. The organic layer was then washed with aqueous solutions of  $\text{NaHCO}_3$  and  $\text{NaCl}$  (3x), dried with  $\text{MgSO}_4$ , and concentrated<sup>5</sup>.



8

### 5-Bromo-1-(trimethylsilyl)-1-pentyne

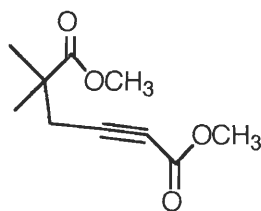
The purified tosylate from above was treated with LiBr (2.49 g, 28.6 mmol) in acetone (28.6 mL) at room temperature for 12 hr. The mixture was quenched with water (115 mL), extracted with pentane (4x), washed with aqueous solutions of NaHCO<sub>3</sub> and NaCl (1x), dried with MgSO<sub>4</sub>, and concentrated. The crude mixture was then purified through distillation<sup>5</sup>.



10

### Methyl 5,5-dimethylhex-1-yne-6-oate

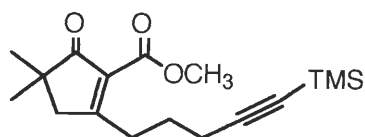
A solution of diisopropylamine (1.5 mL, 10.8 mmol) in THF (10 mL) was cooled to 0 °C. To this solution was added a solution of n-butyl-lithium in hexane (4.2 mL, 10.8 mmol). The solution was cooled to -78°C with stirring over 10 min. A solution of methyl isobutyrate (1 g, 9.8 mmol) in THF (1 mL) was added dropwise. After stirring for 1 hr at -78°C, a solution of propargyl bromide (1.2 mL, 80% by weight, 10.8 mmol) in freshly distilled HMPA (1.9 mL) was added dropwise. This mixture was stirred for 1 hr at -78°C. It was then quenched with a saturated solution of ammonium chloride and warmed to room temperature. The solvent was removed in vacuo and the concentrate was dissolved in ether. The solution was washed with water (4x), dried with MgSO<sub>4</sub>, concentrated, and distilled<sup>2</sup>.



11

### Dimethyl 5,5-dimethylhex-2-ynoate

The above acetylene (1 g, 7.2 mmol) was combined with palladium chloride (9.2 mg, 0.06 mmol), copper (II) chloride (1.93 g, 14.3 mmol), and sodium acetate (1.18 g, 14.3 mmol) in 30 mL of absolute methanol. This mixture was stirred under an atmosphere of carbon monoxide for 3 hr. The solvent was removed in vacuo and the concentrate was dissolved in ether. This solution was washed with water, 50% aqueous solution of ammonium hydroxide, and brine. The solution was then dried with  $\text{MgSO}_4$  and concentrated. It was then purified through distillation<sup>2</sup>.



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**2-Carbomethoxy-5,5-dimethyl-3-(2-methyl-2-hepten-6-yl)cyclopent-2-en-1-one**  
 5-Bromo-1-(trimethylsilyl)-1-pentyne (1 g, 6.8 mmol) was combined with magnesium (0.22 g, 9.2 mmol) in THF (10 mL) to form a grignard reagent. This solution was added to a mixture of copper (I) iodide (0.88g, 4.6 mmol) and freshly distilled tetramethylethylenediamine (1.0 mL, 6.8 mmol) in THF (30 mL) at  $-78^\circ\text{C}$ . This mixture was stirred for 1 hr at  $-78^\circ\text{C}$ . A solution of diester **11** (0.90 g, 4.6 mmol) in THF (2 mL) was added dropwise to the mixture. This mixture was stirred at  $-78^\circ\text{C}$  for 1 hr, and then warmed to room temperature

(about 2 hr). The mixture was quenched with 10% HCl and then extracted with ether. Preliminary thin layer chromatography tests showed that no desired product was produced<sup>2</sup>.

### **Future Work**

The primary focus of this laboratory is the study of metal catalyzed organic reactions. This project will be continued to actually prepare pentalenic acid from starting material **11** using nickel (0) as a catalyst. Using the product that was prepared via the method of Crimmins and DeLoach as the starting material, the plan of synthesis of pentalenic acid is as follows (scheme 6). Using diethyl zinc, triphenyl phosphine and Ni(COD)<sub>2</sub> induces oxidative addition of the nickel across the double bond. The oxidation state of the nickel changes from zero to two. Oxidative addition occurs when the oxidation state of a metal in the reaction is increased by two by adding it onto another compound.

This compound then undergoes ligand coordination in which the nickel coordinates with the triple bond. It forms a pi-complex with the pi-electrons of the double and triple bonds.

The nickel then undergoes migratory insertion by forming a ring, and migrating to the triple bond. In this process a ligand is inserted from the metal onto another atom. A donor bond and a  $\sigma$ -bond form a new  $\sigma$ -bond. This causes the triple bond to reduce to a double bond.

This compound undergoes transmetallation, in which the ethyl groups on the zinc compound transfer to the nickel, leaving both sides of the molecule neutral. In this instance transmetallation describes the transfer of an ethyl group from one metal, zinc, to another metal, nickel.



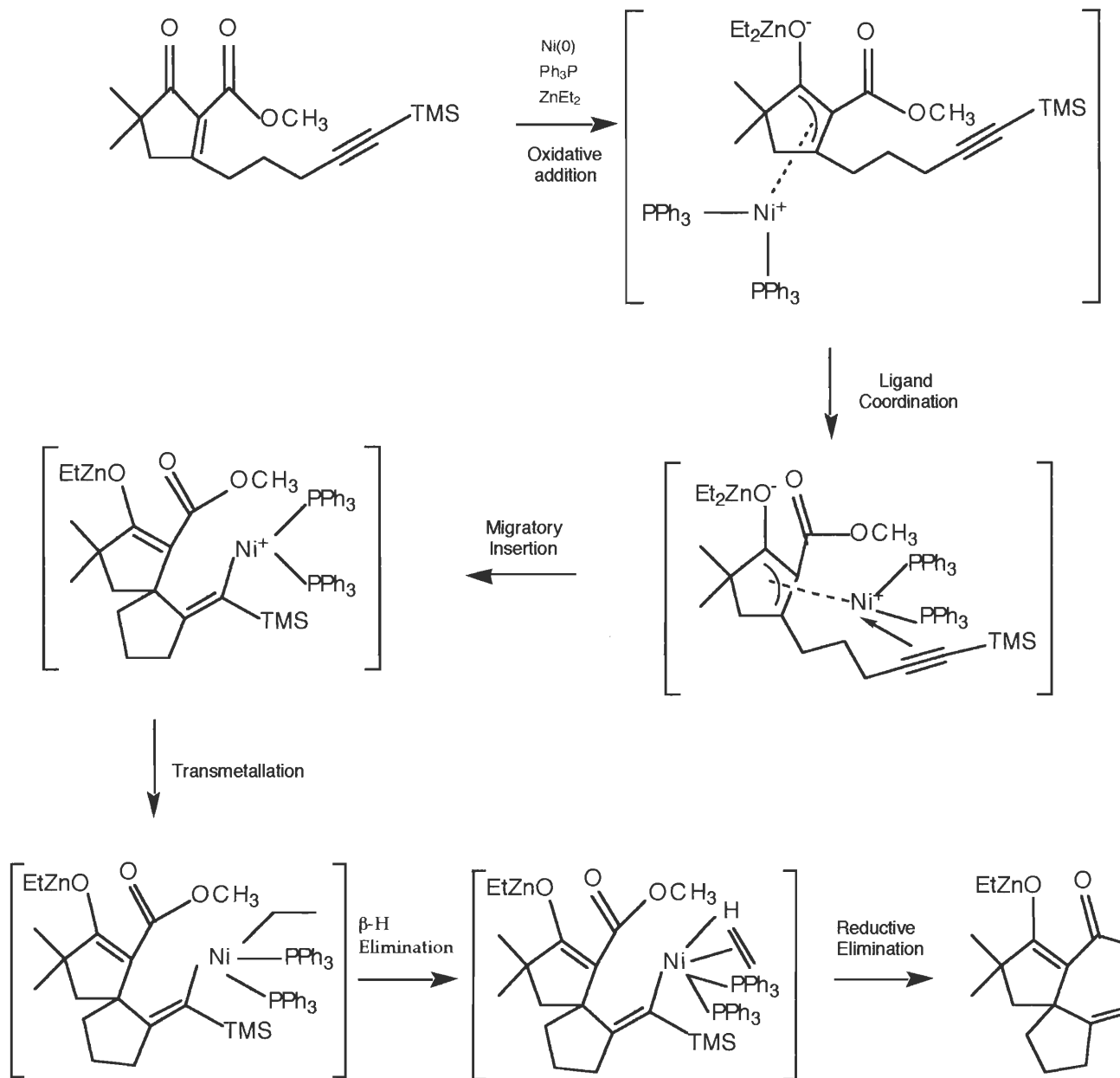
This molecule then undergoes  $\beta$ -H elimination. This occurs because the ligands, triphenyl phosphine, on the nickel provide a high electron density. The hydrogen on the ethyl group moves to the nickel, leaving a pi-electron complex of nickel to the ethyl group.

It then undergoes reductive elimination where the nickel is removed and the proton that was bonded to the nickel takes its place. Reductive elimination is the opposite of oxidative addition. The total electron count of the metal involved is reduced by two.

If there was no triphenyl phosphine added to the reaction, the nickel would not have a rich electron density and B-H elimination would not occur. Instead the ethyl group would alkylate the place where the nickel left.

The ethyl zinc and ester groups then break off leaving the acyl ketene. (Scheme 6).

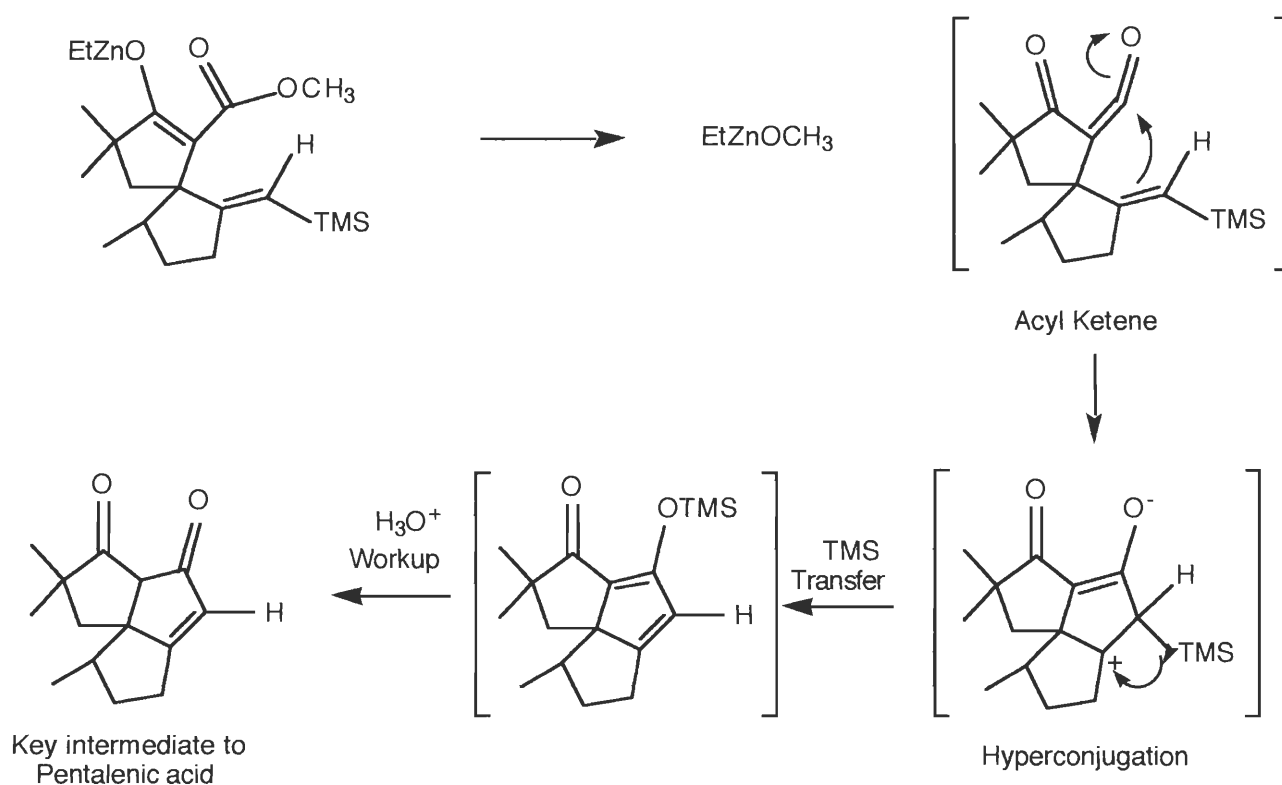
Scheme 6



The third ring forms and hyperconjugation occurs with the trimethylsilane group. Hyperconjugation adds to the stability of the compound because there is some overlap between the bond of the TMS group and the empty orbital of the adjacent carbon. This stabilizes the compound because the electron density can also occupy the empty orbital.

The trimethylsilane group transfers to the carbonyl oxygen and then acid workup removes the trimethylsilane group leaving the final product. This significantly reduces the number of steps to get to the final product, pentalenic acid (Scheme 7).

**Scheme 7**



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- <sup>1</sup>Paquett, L. A.;Annis, G.D. *J. Am. Chem. Soc.* **1982**, 104, 4504.
  - <sup>2</sup>Crimmins, M. T.;DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, 108, 799.
  - <sup>3</sup>Savchenko, A. V.; Montgomery, J. W. *J. Org. Chem.* **1996**, 61, 1562.
  - <sup>4</sup>Savchenko, A. V.; Montgomery, J. W. *J. Am. Chem. Soc.* **1996**, 118, 2099.
  - <sup>5</sup>Negishi, et al. *J. Am. Chem. Soc.* **1988**, 110, 5389.