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Los Angeles

Progress Towards the Total Synthesis of Rugulosone

and

Methodologies of Alkene Isomerization and Formation of Substituted Adamantanones

A dissertation submitted in partial satisfaction of the
requirements for the degree of Doctor of Philosophy
in Chemistry

by

Gloria Shen Lee

2014

ABSTRACT OF THE DISSERTATION

Progress Towards the Total Synthesis of Rugulosone

and

Methodologies of Alkene Isomerization and Formation of Substituted Adamantanones

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Gloria Shen Lee

Doctor of Philosophy in Chemistry

University of California, Los Angeles

2014

Professor Michael E. Jung, Committee Chair

In Chapter 1, potential strategies toward the synthesis of rugulosone were investigated. Although initial efforts towards forming the bicyclo[3.3.1]nonane core via a Michael addition – Dieckmann condensation reaction sequence did not prove useful for our investigations, the synthesis of the core was accomplished via a highly efficient tetraalkylation of commercially available starting materials. Using our developed methodology, we were able to isomerize unactivated alkenes to form the C_2 symmetric core necessary for the natural product. Studies toward the addition of the northern side chain were conducted, and proved to be promising.

Synthesis of a protected southern side chain was accomplished, and may be used in the future to couple with the functionalized core to facilitate a highly divergent synthesis of the natural product.

For our work towards the synthesis of the core of rugulosone, we developed a methodology to isomerize exo-methylene groups to their corresponding tri-substituted internal alkenes. The exo-methylene groups of 2,6-disubstituted bicyclo[3.3.1]nonan-9-ones were readily isomerized over a palladium catalyst under an atmosphere of hydrogen to form predominantly the isomer with C_2 symmetry with very little formation of the analogous product with C_S symmetry. A hydrogen source was essential to effect the rearrangement.

The third and last chapter outlines formation of highly substituted adamantanones. Adamantane-based small molecules are useful in the treatment of a variety of conditions, ranging from neurodegenerative disorders such as Parkinson's and Alzheimer's disease, to viral infections such as HIV. We thus desired to efficiently construct substituted adamantanones, potential precursors to the corresponding adamantanes. Trifluoromethanesulfonic acid facilitated formation of the adamantanone core from 1,5-dialkyl-3,7-dimethylenebicyclo[3.3.1]nonan-2-one, which was easily obtained in one step from commercially available starting materials. The resulting adamantyl cation was trapped with a variety of nucleophiles to form tetrasubstituted adamantanones. Aromatic and heteroaromatic nucleophiles have proven to be successful, and oxygen and nitrogen nucleophiles provide access to a wide variety of functionality at the newly formed tertiary position.

The dissertation of Gloria Shen Lee is approved.

Kendall N. Houk

Jing Huang

Michael E. Jung, Committee Chair

University of California, Los Angeles

2014

To my loving parents, Mr. and Mrs. Philip and Teresa Lee.

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To my committee members, Dr. Kendall Houk, Dr. Steven Clarke, Dr. Jing Huang, and Dr. Benhur Lee, for their time to serve on my committee.

I would like to thank all previous and current Jung lab members, for their time and willingness to help me, their knowledge and expertise in chemistry, and their jokes and laughter through tough times. I will surely miss the good 'ol Jung lab!

A big thank you to my friends and colleagues in other labs at UCLA. Whether it was to grab lunch or to run out for a quick coffee, those breaks were much needed and appreciated.

And finally, I would like to thank my family for all their love and support through the years. No matter how crazy and seemingly out of control my world got, they assured me that with a little time, patience, and hard work, everything would be okay. Turns out, they were right.

VITA

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PUBLICATIONS AND PRESENTATIONS

M. E. Jung, G. S. Lee, H. V. Pham, and K. N. Houk. Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di(exo)methylenes to Endocyclic Dienes. *Org. Lett.* **2014**, *16*, 2382.

Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di(exo)methylenes to Endocyclic Dienes. 247th American Chemical Society National Meeting. Dallas, TX. Mar. 19, 2014. (Oral Presentation)

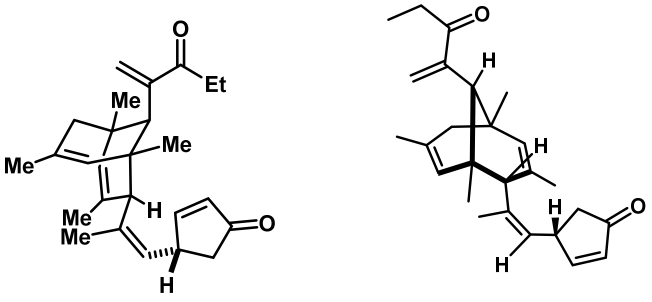
Efficient Syntheses of Highly Substituted Adamantanones. 248th American Chemical Society National Meeting. San Francisco, CA. Aug. 10, 2014. (Oral Presentation)

M. E. Jung, G. S. Lee. Efficient Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonanes. *J. Org. Chem.* **2014**, *79,* 10547.

CHAPTER 1

Progress Towards the Total Synthesis of Rugulosone

INTRODUCTION



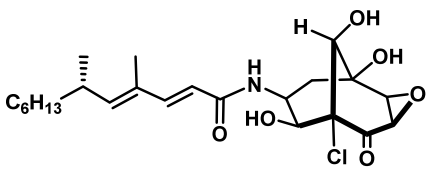
Rugulosone, 1 **Rugulosone, 1**

Figure 1-1. Structure of Rugulosone (**1**).

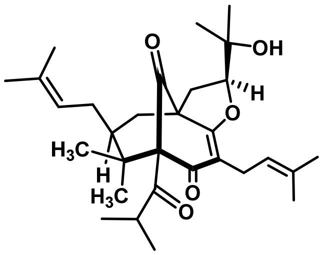
Rugulosone **1** (Figure 1-1) is a secondary metabolite which was first isolated by Moosophon and coworkers in 2009 from the fungal strain *Emericella rugulosa* in 2009.[1] Previous natural products isolated from the fungal genus have sparked much interest in the scientific community, possessing properties of being cytotoxic against cancer cell lines, sesterterpenes with unusual tricyclic and pentacyclic skeletons, and prenylated polyketides.

Rugulosone has shown significant biological activity, including *in vitro* antimalarial activity against *Plasmodium falciparum* with an IC_{50} value of 1.9 µg/mL, antimycobacterial activity against *Mycobacterium tuberculosis* with a MIC value of 12.5 µg/mL. In addition, rugulosone was also cytotoxic against the BC1, KB, and NCI-H187 cancer cell lines, with IC_{50} values of 1.3, 2.6, and 1.3 µg/mL, respectively.

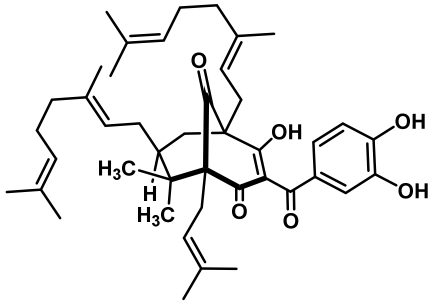
Rugulosone has a bicyclo[3.3.1]nonane core that is present in a number of natural products (Figure 1-2), most notably a class of polyprenylated acylphloroglucinols (PPAPs) that bear a highly substituted and oxygenated bicyclo[3.3.1]nonane-2,4,9-trione framework. A number of total syntheses of this class of molecules have been accomplished, including garsubellin A, hyperforin, and guttiferone A, to name a few.[2] Also, many groups have focused their efforts on developing stereocontrolled syntheses of the intriguing bicyclononane core.[3] A number of general reviews on the formation of the bicyclo[3.3.1]nonane core have been published.[4] However, the bicyclo[3.3.1]nona-2,6-diene core of rugulosone is the first derivative of its kind to be obtained from a natural source. The highly symmetric bicyclic framework presents a great challenge for synthetic organic chemists. No synthesis of rugulosone has been reported to date.



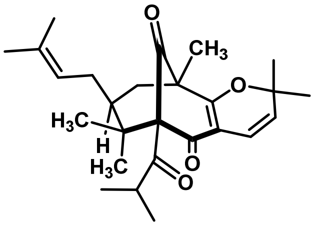
Gymnastatin G, 2



Garsubellin A, 3



Guttiferone B, 4



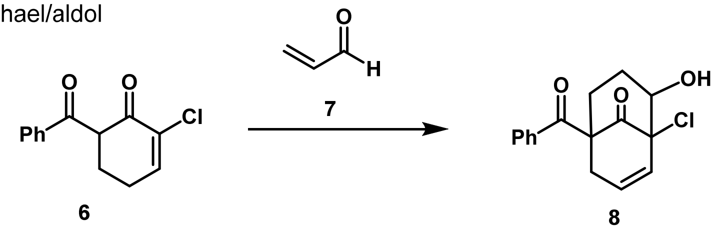
Papuaforin A, 5

Figure 1-2. Natural products bearing a bicyclo[3.3.1]nonane core.

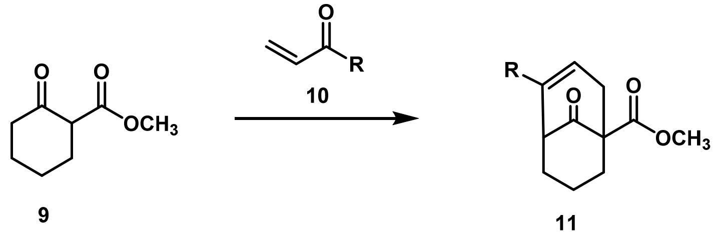
A number of routes are used to form the bicyclo[3.3.1]nonane core present in natural products (Scheme 1-1). The most commonly used methods are:

1. Michael addition – intramolecular aldol
2. Annulations of β-keto esters
3. Pd-catalyzed cyclization with acetyloxymethallyl acetate
4. Cycloalkylations

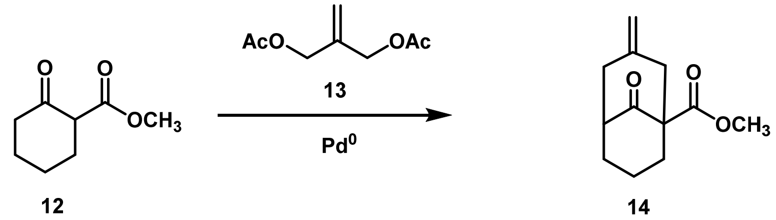
1. Michael/aldol



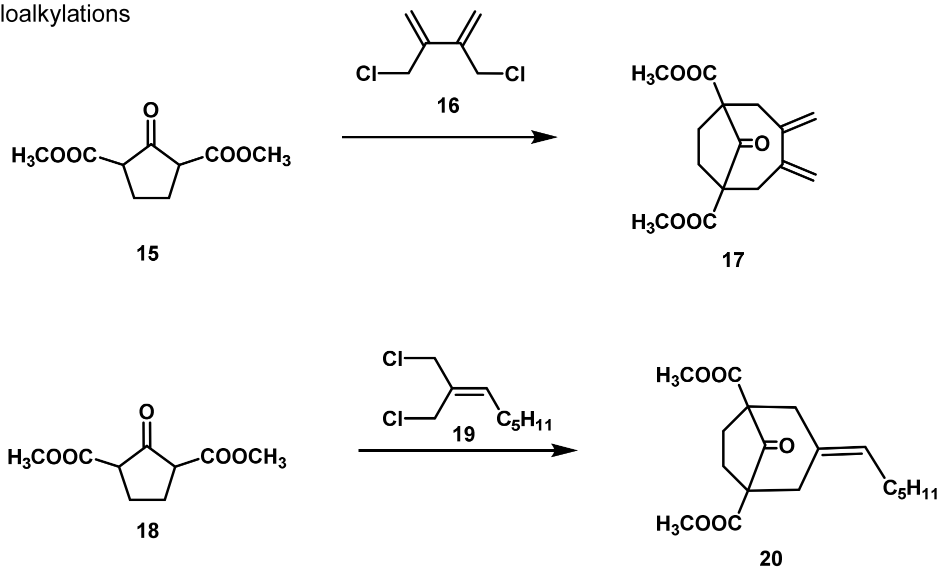
2. Annulation of ß-keto esters



3. Pd catalyzed cyclization with acetyloxymethallyl acetate



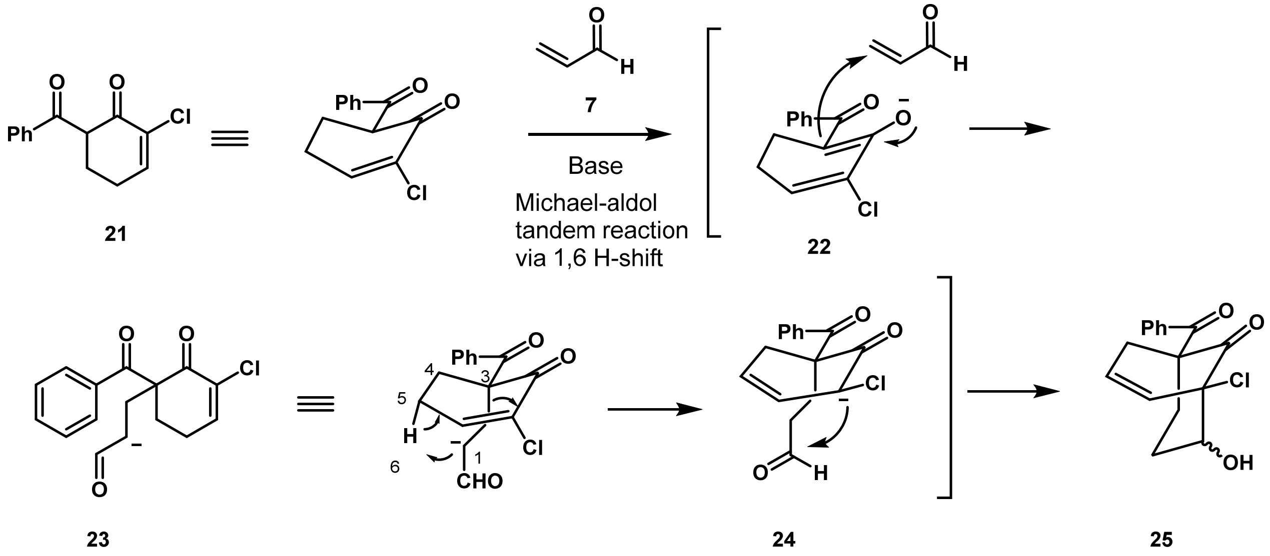
4. Cycloalkylations



Scheme 1-1. Selected methods of forming bicyclo[3.3.1]nonanone core.

5. Ring cleavage of adamantane derivatives
6. Ring closing metathesis
7. Annulations of cyclooctane derivatives

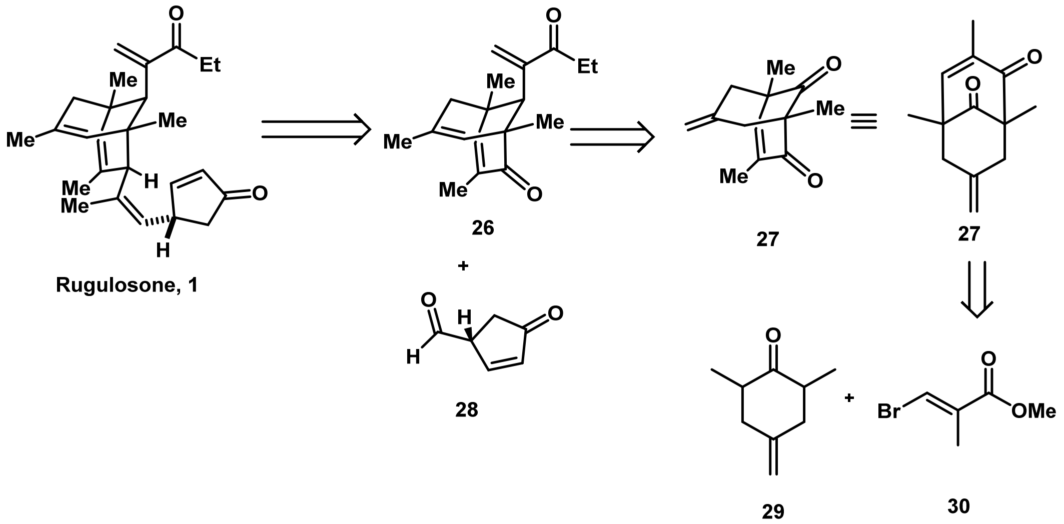
Previously in our lab, in a proposed synthesis of Gymnastatin G, one of the key steps of the synthesis was the formation of the bicyclo[3.3.1]nonane core, which relied on the tandem Michael-aldol reaction shown in Scheme 1-2. First, Michael addition of the chlorodiketone **21** to acrolein gave the intermediate **22**, which then underwent a 1,6-hydrogen shift, or a simple deprotonation/reprotonation, that was then perfectly set up for an intramolecular aldol reaction to close the second ring, giving a mixture of the alcohols **25**.



Scheme 1-2. Progress towards Gymnastatin G.

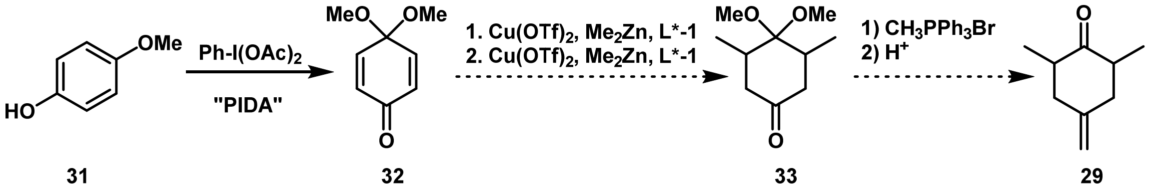
Our synthetic approach towards the synthesis of rugulosone relied on reported tandem reactions to form the bicyclic core, through reactions of either Michael addition – aldol condensation or Michael addition – Dieckmann condensation. We will now describe our efforts for the synthesis of the bicyclo[3.3.1]nonadienone core of rugulosone and its conversion to the natural product.

RESULTS AND DISCUSSION



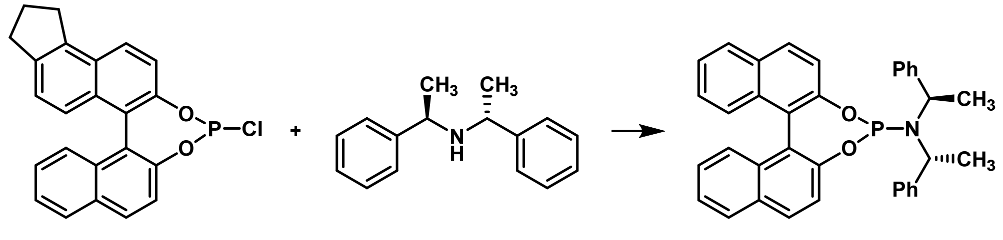
Scheme 1-3. Original retrosynthetic analysis for rugulosone **1**.

Our original retrosynthetic analysis of Rugulosone **1** is shown in Scheme 1-3. We envisioned completion of the natural product by appending the southern side chain **28** with the central fragment **26** in a highly convergent total synthesis. Fragment **26** would arise from the bicyclo[3.3.1]nonane core **27** that, in turn, would be formed from a tandem Michael addition – Dieckmann cyclization sequence starting with the cyclohexanone **29** and the methyl bromomethacrylate **30**.



Scheme. 1-4. Proposed forward synthesis to make cyclohexane **29**.

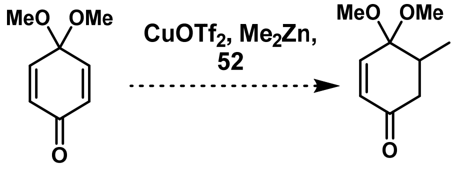
Our forward synthesis began with the formation of 2,6-dimethyl-4-methylene-cyclohexanone **29** (Scheme 1-4). The synthesis commenced with 4-hydroxyanisole **31**,



34 **35** **36**

Scheme 1-5. Formation of Feringa's ligand **36.**

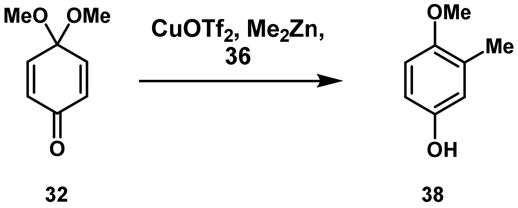
Table 1-1. Attempted 1,4-additions to cyclohexadienone **32**.



32 **37**

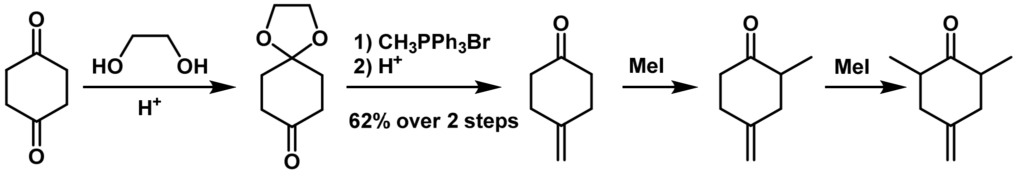
Entry	Conditions	Results
1	Me_2CuLi	Formed 4-methoxyphenol
2	Me_2Zn	No reaction
3	$ZnCl_2$, MeMgBr	No reaction
4	Me_2Zn, $Cu(OTf)_2$, *R*-BINOL, Et_3N	No reaction
5	MeLi, $CuBr{\cdot}Me_2S$, TMSCl, -78 ˚C	No reaction
6	$CuBr{\cdot}Me_2S$, HMPA, TMSCl	Formed 3-methyl-4-methoxyphenol **38**

which was oxidized with phenyliodine diacetate (PIDA) in methanol to give the enone **32**. Next, it was envisioned that one could perform two cuprate additions to the enone **32**. However, attempts to use Feringa's ligand[5] **36**, prepared as shown in Scheme 1-5, failed to give cuprate addition to the enone. Table 1-1 shows conditions attempted for the cuprate addition. Simple reaction with lithium dimethylcuprate reformed the previous starting material, 4-methoxyphenol (entry 1). No reaction was observed when enone **32** was treated with a solution of dimethylzinc. Similarly, treatment with dimethylzinc or a mixture of zinc chloride and methylmagnesium bromide gave no reaction. In addition, treatment of zincate reagents with a copper source, as in entries 4 and 5, gave no reaction. Although treatment of the enone **32** with copper bromide dimethyl sulfide complex in HMPA as an additive did not return starting material, we instead isolated 3-methyl-4-methoxyphenol **38**, the rearomatized product after addition of methyl cuprate.



Scheme 1-6. Formation of 3-methyl-4-methoxyphenol **38**.

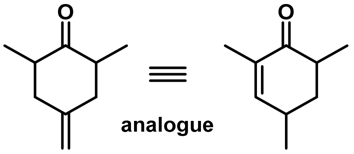
Subsequently, we turned our attention to an alternative proposed forward synthesis (Scheme 1-7). Starting with cyclohexane-1,4-dione **39**, monoprotection with ethylene glycol then subsequent Wittig reaction formed the methylene ketal which could then be deprotected to give the ketone **41**.[6] However, treatment with methyl iodide under a variety of basic conditions gave mixtures of mono-, di-, and trimethylated products. Thus, we were unable to prepare 2,6-dimethyl-4-methylenecyclohexanone **29** selectively.



39 **40** **41** **42** **29**

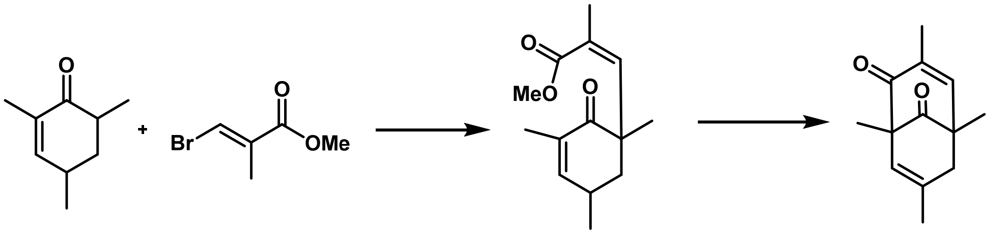
Scheme 1-7. Alternative proposed synthesis of **29**.

Since we were unable to synthesize the ketone **29**, we set out to make the constitutional isomer ketone **43** (Figure 1-3), which should be able to undergo our desired Michael addition – Dieckmann condensation sequence (Scheme 1-8).[7]



29 **43**

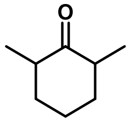
Figure 1-3. Constitutional isomer and analogue **43**.



43 **30** **44** **45**

Scheme 1-8. Michael addition – Dieckmann condensation to give bicyclo[3.3.1]nonadienone **45**.

Before attempting to perform the Michael addition – Dieckmann condensation reaction sequence on the enone **43**, a model system was used first. Thus, a mixture of 2,6-dimethylcyclohexanone diastereomers **46** was selected as the model substrate. Treatment of 2,6-

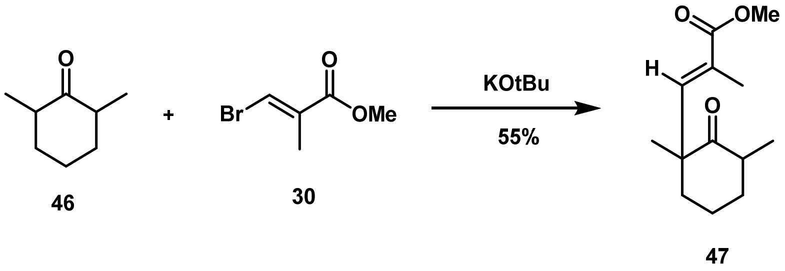


46

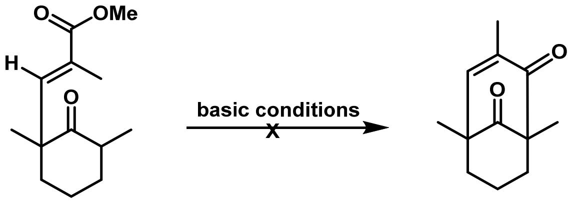
model substrate

Figure 1-4. Model substrate for Michael addition – Dieckmann condensation.

dimethylcyclohexanone **46** with methyl bromomethacrylate **30** under basic conditions using potassium tert-butoxide furnished the Michael adduct **47** in an unoptimized yield of 55% (Scheme 1-9). No formation of the Michael addition – Dieckmann condensation product was observed when this reaction was carried out. Further treatment of the ketoester **47** with base did not result in ring closure to form the bicyclic compound **48** (Scheme 1-10). However, upon closer inspection, the alkene that was formed was the *E*-isomer, and therefore it would be impossible to form a 6-membered ring with this geometry. Thus, we had to first isomerize the double bond to the *Z*-isomer.

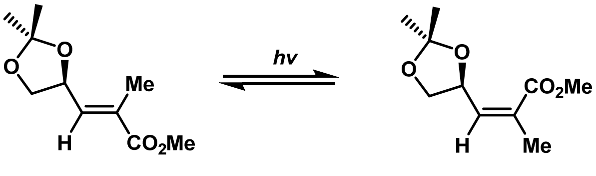


Scheme 1-9. Michael addition of **46** to methyl bromomethacrylate **30** to form ketoester **47**.



47 **48**

Scheme 1-10. Attempted formation of Dieckmann condensation to form dione **48**.



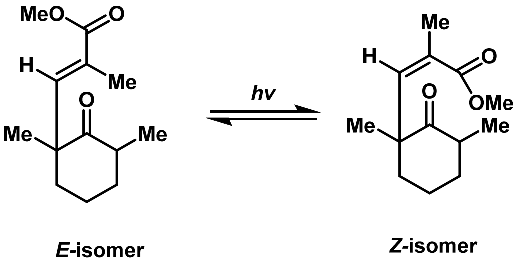
49 **50**

Scheme 1-11. Reported example of light activated *E/Z* isomerization of alkenes.

There are a number of literature procedures reported for the *E/Z* isomerization of alkenes.[8] One example by Garcia-Exposito and coworkers is shown in Scheme 1-11, where the alkene is trisubstituted, a methyl group and ester group are on one carbon, and a large bulky substituent and hydrogen are on the other side. Under activation with ultraviolet light, an equilibrium could be effected between the two isomers. In this case, after 60 minutes in acetone, a 1:1 ratio of *E*- and *Z*-isomers was observed. Thus, we set out to isomerize our *E* isomer as the presumably thermodynamic isomer to the less stable *Z*-isomer. A number of conditions were attempted, with mixed results (Table 1-2).

A number of entries used deuterated solvent in an NMR tube for easy analysis by NMR spectroscopy. Thus, under a handheld UV lamp, a new vinyl proton appeared, but was slow to convert to product, even under prolonged reaction time. Using a strong ultraviolet lamp in acetonitrile, slow conversion was again observed. After 6 hours at very dilute concentration in a quartz reaction flask, only 20% conversion was observed.

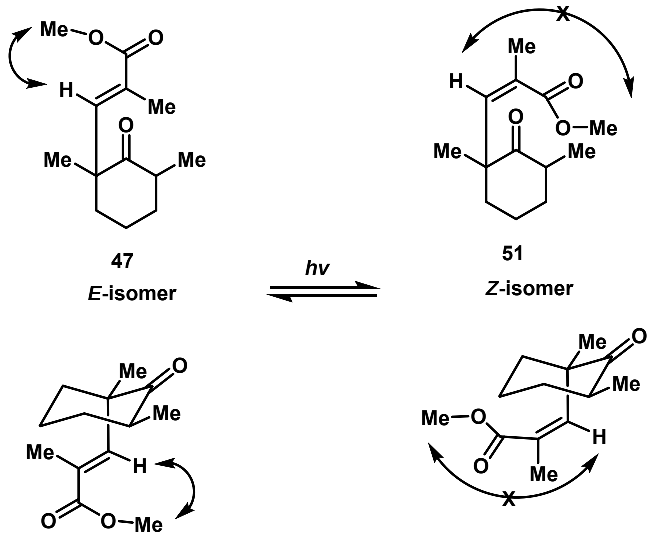
Table 1-2. *E/Z* isomerization of alkene **47**.



47 **51**

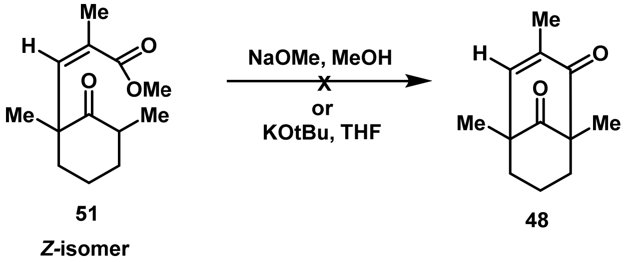
Entry	Conditions	Solvent	Time	Molarity	Results
1	Handheld UV lamp, NMR tube	Acetone-d6	1 h	0.63 M	See new vinyl proton
2	Handheld UV lamp, NMR tube	Acetone-d6	12 h	0.63 M	See *Z*-isomer formation
3	Handheld UV lamp, NMR tube	Acetone-d6	12 h	0.05 M	Slow conversion
4	450W lamp, NMR tube	Acetonitrile-d3	0.5 h	0.05 M	See new vinyl proton
5	450W lamp, Quartz reaction flask	Acetone	6 h	0.05 M	Only 20% conversion

We were able to distinguish the two isomers in the 2D-NMR using nOE correlation (Scheme 1-12).[9] The methyl ester of the *E*-isomer showed an nOE with the vinyl proton, while in the *Z*-isomer, the methyl ester is now flipped and thus there is no nOE with the vinyl proton.



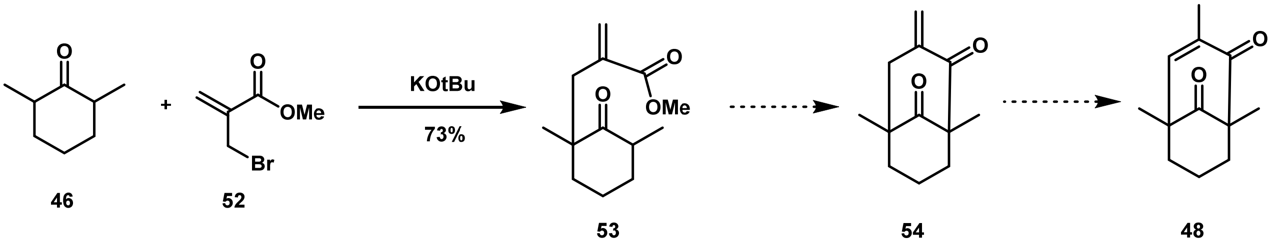
Scheme 1-12. nOE correlation of *E*-isomer **47** and *Z*-isomer **51**.

The small amount of *Z*-isomer **51** that was isolated was used in an attempt to effect a Dieckman condensation (Scheme 1-13). However, treatment with mild basic conditions of sodium methoxide and potassium tert-butoxide gave unidentifiable products.

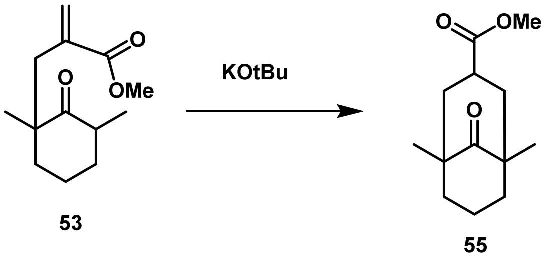


Scheme 1-13. Attempts to perform Dieckmann condensation to form bicyclic dione **48**.

Another possible method to form the bicyclo[3.3.1]nonane ring system is shown in Scheme 1-14. Treatment of 2,6-dimethylcyclohexanone **46** with methyl 2-(bromomethyl)acrylate **52** would undergo either an SN2 or SN2' reaction to give **53**. Ring closure to give the bicyclo[3.3.1]nonane **54**, followed by final isomerization of the resulting methylene would provice access to our unsaturated natural product core. However, after the first alkylation to give **53**, treatment with potassium tert-butoxide did not result in a Dieckman condensation but rather an intramolecular Michael addition to form the bicyclo[3.3.1]nonane ester **55** (Scheme 1-15).

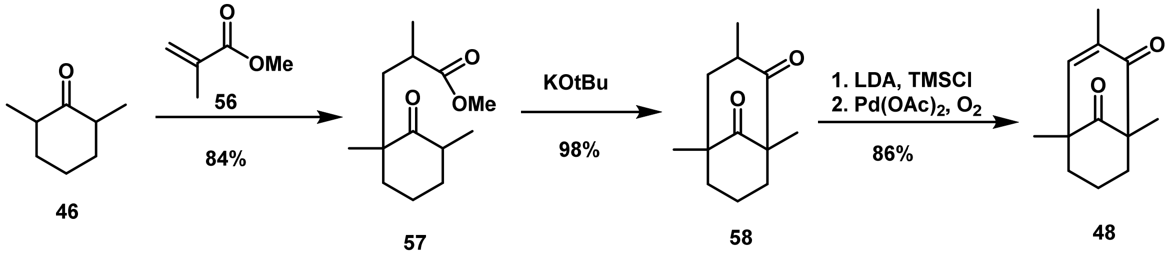


Scheme 1-14. Attempt to perform Michael addition – Dieckmann condensation to form the bicyclicdione **54**.



Scheme 1-15. Michael addition of **53** with potassium tertbutoxide to form bicyclodione **55**.

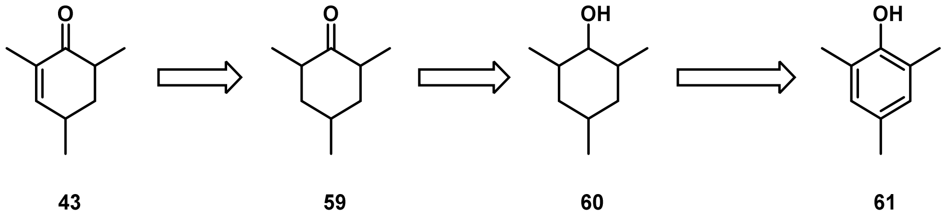
We then set out to perform a Michael addition – aldol condensation sequence with methyl methacrylate **56** instead of either methyl bromomethacrylate **30** or methyl 2-(bromomethyl)acrylate **52** to avoid the formation of the resulting *E*-alkene or the unexpected bicyclononane ester. Via this method, after the first Michael addition to form **57**, there is free rotation around the C-C single bond so that the subsequent aldol reaction can occur to form the bicycle **58** (Scheme 1-16). To make our desired bicyclo[3.3.1]nonane core, we would then oxidize bicycle **58** to afford the desired unsaturation of intermediate **48**. This annulation/oxidation reaction sequence was used previously in efforts towards the total synthesis of hyperforin, a bicyclo[3.3.1]nonane containing natural product.[10]



Scheme 1-16. Application to our system.

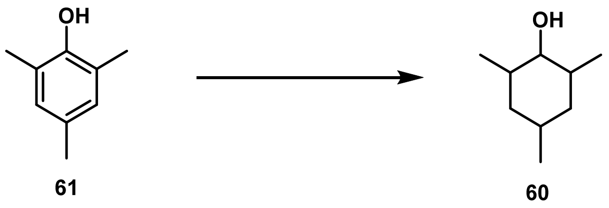
Thus, we set out to follow Scheme 1-16 as a model system for the annulation and oxidation sequence. Since 2,6-dimethylcyclohexanone **46** was commercially available and we could quickly test this annulation-oxidation concept sequence, we started with the Michael addition with methyl methacrylate to form the ketoester **57** in 84% yield. Then, gratifyingly, treatment of **57** with potassium tert-butoxide yielded bicyclo[3.3.1]nonane **58** in 98% yield. Then, oxidation under Saegusa-Ito conditions with trimethylsilyl chloride followed by palladium acetate and oxygen then gave the dione **48** in 86% yield over two steps. Thus, we were able to prove the concept of performing this multi-step Michael – aldol sequence. With the dione **48** in hand, we had established in this model system that it was possible to do the Michael – aldol sequence. Now, we needed to carry out this sequence on a trimethylated cyclohexenone substrate.

Retrosynthetic analysis of the 2,4,6-trimethylyclohexenone **43** is shown in Scheme 1-17. We envisioned the formation of the enone **43** via oxidation of the trimethylcyclohexanone **59** which, in turn, would come from the corresponding alcohol. The alcohol would come from complete hydrogenation of the aromatic precursor, 1,3,5-trimethylphenol **61**.



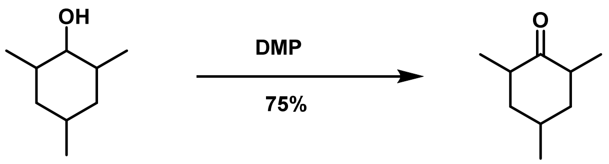
Scheme 1-17. Retrosynthesis to make trimethyl cyclohexenone **43**.

Table 1-3. Reduction of 1,3,5-trimethylphenol **61**.



Entry	Conditions	Result
1	Raney Ni-Al, KOH, H_2O, 90 ºC, 12 h	No reaction
2	Raney Ni-Al, H_2, 80 ºC, 65atm, 2 d	No reaction
3	Raney Ni-Al, H_2, 135 ºC, 110atm, 2 d	No reaction
4	Rh/Al_2O_3, H_2, 40 bar, 4 d	Quantitative yield

Thus, hydrogenation of the aromatic ring of **61** with Raney Ni-Al[11] was attempted (Table 1-3). However, no reaction was observed under basic conditions with potassium hydroxide, elevated temperature, or increased pressure for long periods of time under an atmosphere of hydrogen (entries 1-3). It was then found that the conditions of rhodium on alumina and high pressure of hydrogen for 4 days[12] produced the desired secondary alcohol in quantitative yield.

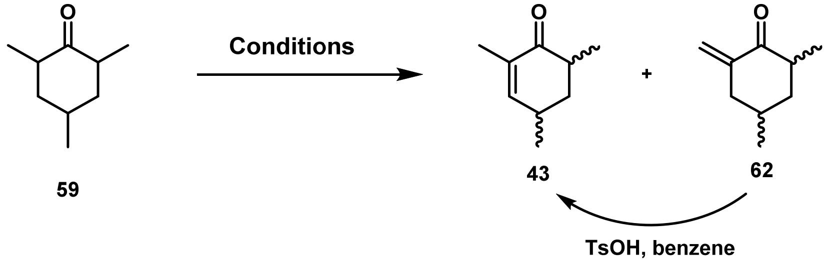


60 **59**

Scheme 1-18. Oxidation to ketone **59**.

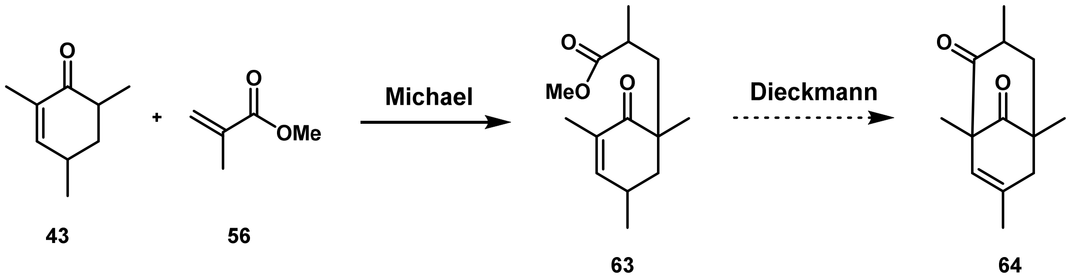
Subsequent oxidation with DMP gave the corresponding ketone **59** in 75% yield (Scheme 1-18). Oxidation of the ketone **59** to the isomeric enones **43** and **62** is shown in Table 1-4. Under Saegusa-Ito conditions, the desired product **43** was isolated in 20% yield, whereas first making the phenylselenide then oxidation with hydrogen peroxide gave the desired enone **43** in 33% (entries 1-2). It was then found that instead of forming phenylselenium bromide *in situ*, using the commercially available PhSeBr reagent followed by oxidative elimination gave a mixture of the two enones **43** and **62** in a combined yield of 70%, which can be subjected to toluenesulfonic acid in refluxing benzene to obtain only enone **43**.

Table 1-4. Oxidation to enone **43**.



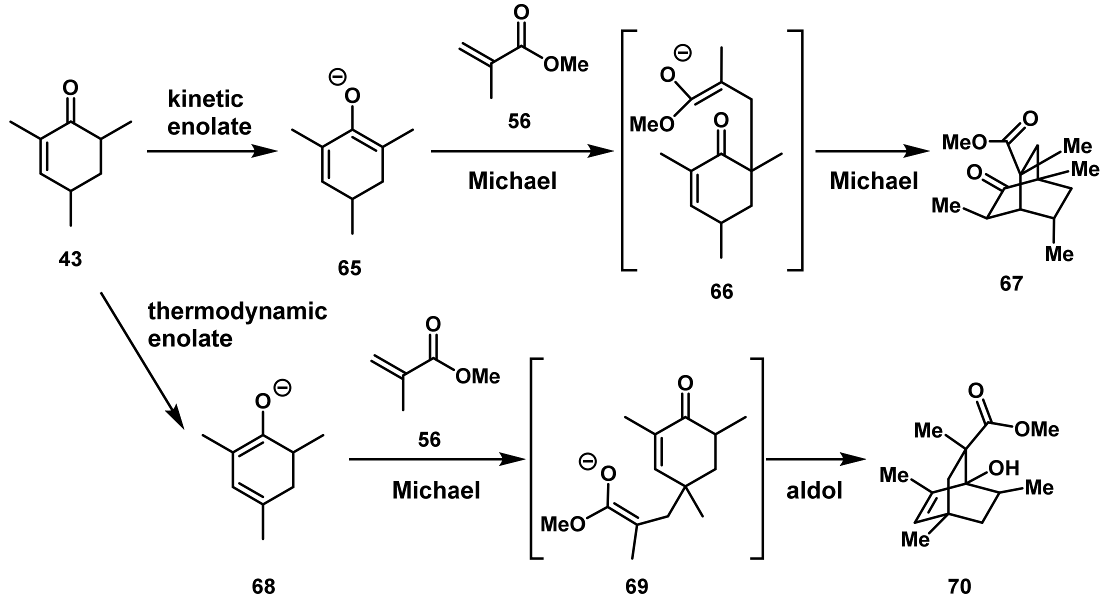
59 **43** **62**

Entry	Conditions	Combined Yield (%)
1	LDA, TMSCl; $Pd(OAc)_2$, O_2	20
2	LDA, HMPA, PhSeSePh, Br_2; H_2O_2	33
3	LDA, HMPA, PhSeBr; H_2O_2	70



Scheme 1-19. Desired Dieckmann condensation of enone **43** and methylmethacrylate **56**.

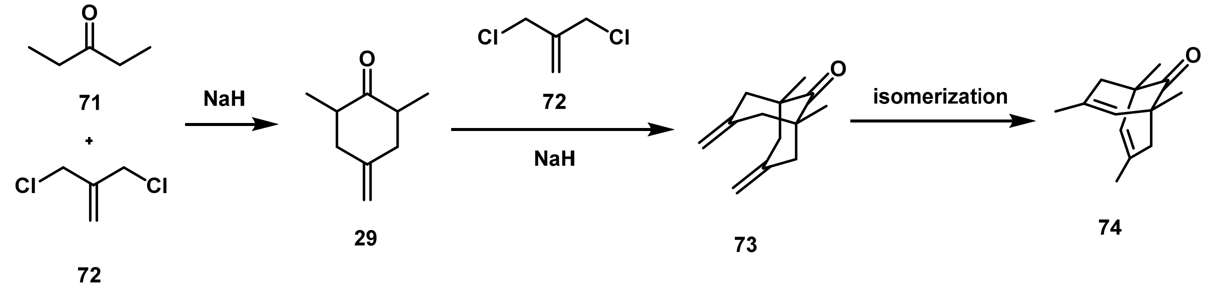
With enone **43** in hand, we were ready to attempt the Michael – Dieckmann sequence (Scheme 1-19). When we reacted the trimethylcyclohexenone **43** with methyl methacrylate **56**, we obtained very little of our desired Michael product **63**. However, resubjecting the Michael product **63** to potassium tert-butoxide did not afford the expected Michael – Dieckmann product **64**, but we instead observed formation of another bicyclic compound, namely, a bicyclo[2.2.2]octanone product. This was determined to be a result of a Michael reaction. The proposed formation of the



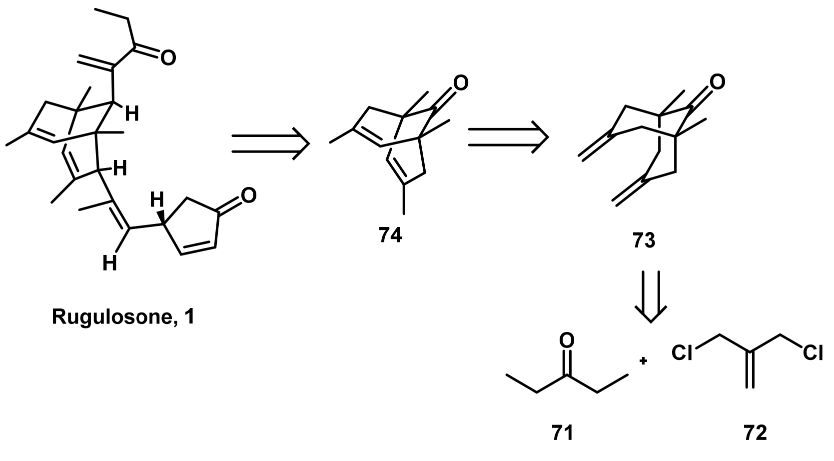
Scheme 1-20. Formation of bicyclo[2.2.2]octanes **67** and **70**.

two bicyclo[2.2.2]octanones **67** and **70** are shown in Scheme 1-20. Instead of the desired Michael – Dieckmann sequence, we observed a double Michael and/or a Michael – aldol reaction sequence to produce the bicyclooctanones **67** and **70**. This double Michael reaction sequence has been reported previously.[13] Other compounds were also formed but their structures were not identified at this time.

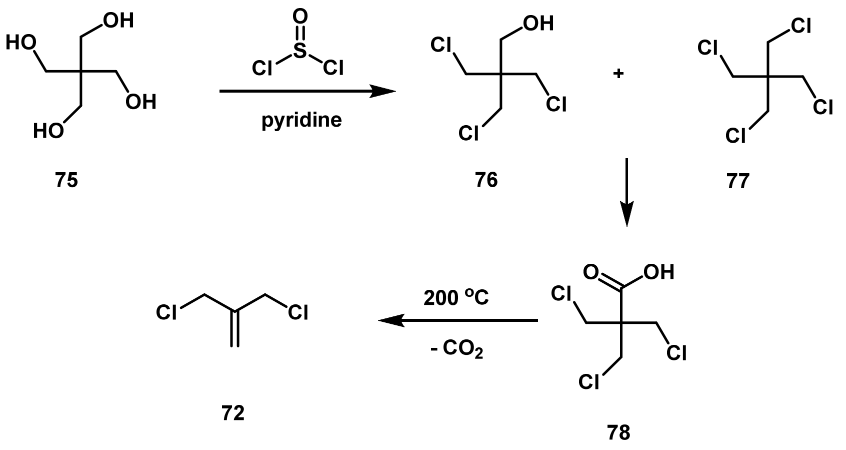
Because of this result, we decided to revisit our retrosynthetic analysis to make the bicyclononane core. We recognized the symmetry present in the bicyclo[3.3.1]nona-2,6-diene core. Thus, we came up with a new approach, namely, could we effect the tetraalkylation of 3-pentanone **71** with two equivalents of the readily available 3-chloro-2-(chloromethyl)prop-1-ene **72** to give the bicycle **73** (Scheme 1-21).[14] Our revised retrosynthesis is shown in Scheme 1-22.



Scheme 1-21. New approach to form bicyclo[3.3.1]nonane core **74**.

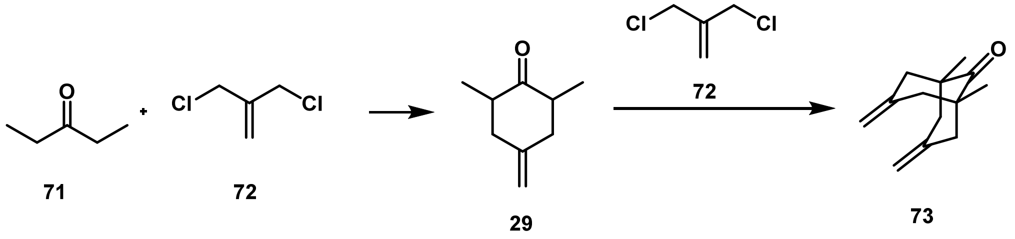


Scheme 1-22. Revised retrosynthesis.



Scheme 1-23. Formation of allyl dichloride **72**.

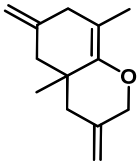
Table 1-5. Formation of cyclohexanone **29** and bicycle **73**.



Entry	Condition	Result
1	K_2CO_3, rt, 3d	No reaction
2	LDA, rt, 3d	No reaction
3	LHMDS, rt, 3d	No reaction
4	NaH, 90 – 100 ˚C, 3d	Multiple products
5	NaH, 110 ˚C, 12 h	90% yield of **73**

First, the allyl dichloride **72** was synthesized from pentaerythritol **75** according to the literature procedure (Scheme 1-23).[15] Then, treatment of 3-pentanone **71** with the allyl dichloride **72** with excess base of potassium carbonate, LDA, and LHMDS gave no reaction (Table 1-5).

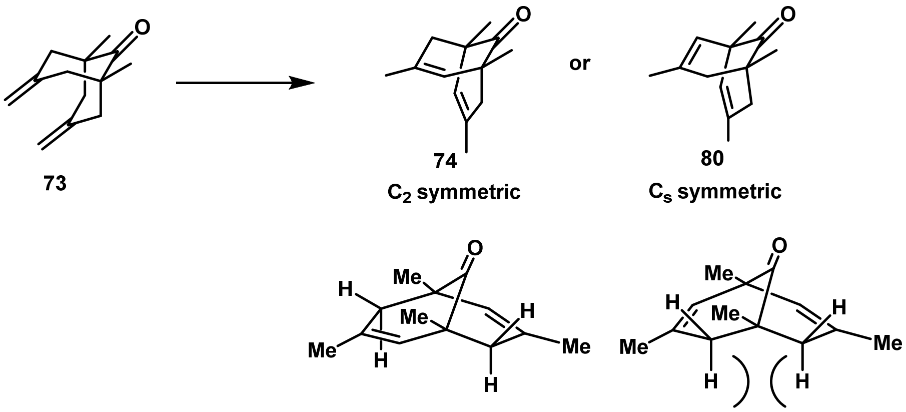
Presumably, the conditions were either not strongly basic enough or due to steric hindrance, the quaternary centers were unable to be formed effectively. In toluene at 90 – 100 ˚C using four equivalents of sodium hydride, a multitude of products were formed. One of the byproducts that we observed was the O-alkylated product **79**. At the higher temperature of refluxing toluene, we were able to effect the highly efficient tetraalkylation to form the bicycle **73** in 90% isolated yield.



79

Figure 1-5. Side product **79**.

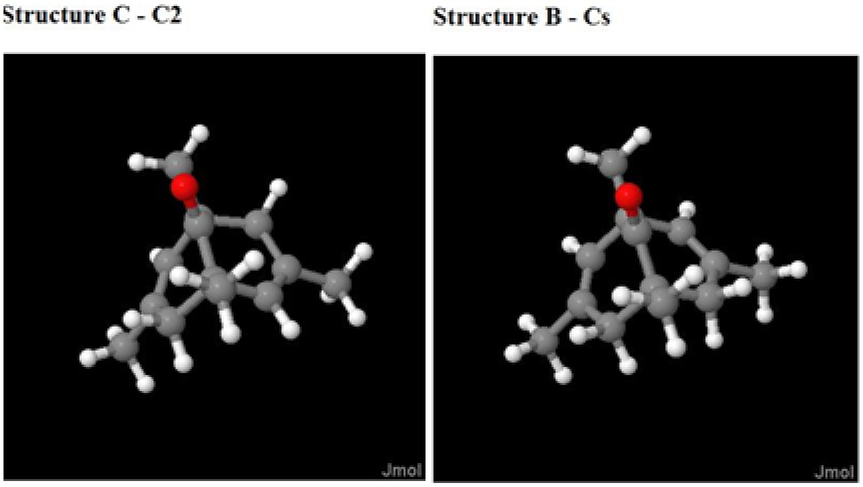
With the bicyclo[3.3.1]nonane **73** in hand, we then turned our attention to the isomerization of the exo-methylenes to the internal, trisubstituted alkenes. However, upon closer inspection, one realizes there are two possible isomers that can form, namely, the C_2 isomer **74**, with an axis of symmetry going through the carbonyl, or the C_S isomer **80**, with a plane of symmetry again going



Scheme 1-24. Isomerization of bicycle **73** to give two isomers, **74** and **80**.

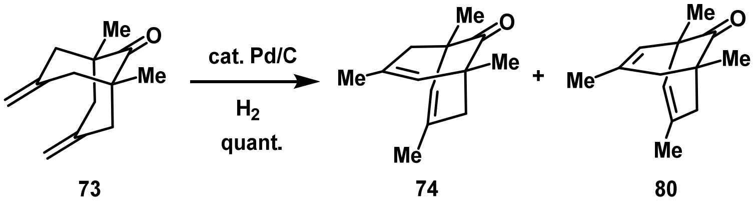
through the carbonyl. Our initial inspection using Dreiding models led us to the prediction that the C_2 isomer would be favored, as the C_S isomer has two interacting allylic protons (Scheme 1-24). We decided to investigate the stability of the two structures computationally.

The initial calculations were done by Max Koepelevich, using B3LYP/6-31G calculations (Figure 1-6). He found that the C_2 isomer was more stable than the C_S isomer by 3.3 kcal/mol. We then collaborated with Hung Pham in the laboratory of Professor Ken Houk and developed a methodology of palladium hydride promoted stereoselective isomerization of unactivated di(exo)methylenes to endocyclic dienes (Scheme 1-25; also, see Chapter 2 of this dissertation).


Structure C - C2

Structure B - Cs

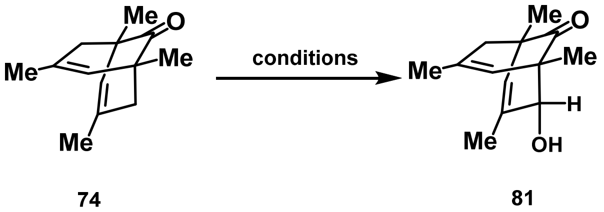
Figure 1-6. 3D structures of isomers **74** and **80** by Max Kopelevich.



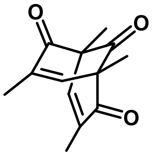
Scheme 1-25. Isomerization of bicycloketone **73** with catalytic palladium on charcoal.

With the bicyclo[3.3.1]nonane C_2 isomer **74** in hand, we then set out to functionalize the symmetric bicycle with a functional handle in order to attached our southern side chain. Allylic oxidation conditions were tried to effect a mono-allylic oxidation of the completely symmetric compound. Thus, only slightly more than one equivalent of reagent was used in all the cases (Table 1-6). Manganese oxide and palladium acetate under acetic acid conditions returned predominantely starting material. Treatment with selenium oxide under a variety of conditions gave starting material and possibly traces of other product. In one case, under tert-butanol conditions, we observed via GCMS the possible formation of the overoxidized trione **82** but could not confirm the structure via NMR. Attempts to form the allylic bromide were made using reagents such as NBS and bromine, but a mixture of compounds were formed.

Table 1-6. Attempted allylic oxidation of bicycle **74**.



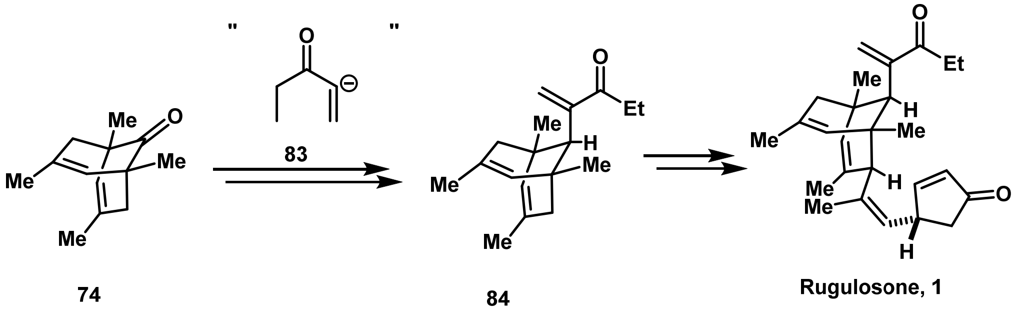
Entry	Conditions	Result
1	$Pd(OAc)_2$, MnO_2, AcOH	No reaction
2	SeO_2, DMSO	Mixture
3	SeO_2, tBuOOH	Mixture
4	SeO_2, tBuOH	Product + trione **82**
5	SeO_2, DMSO	Mixture
6	NBS or Br_2	Mixture



82

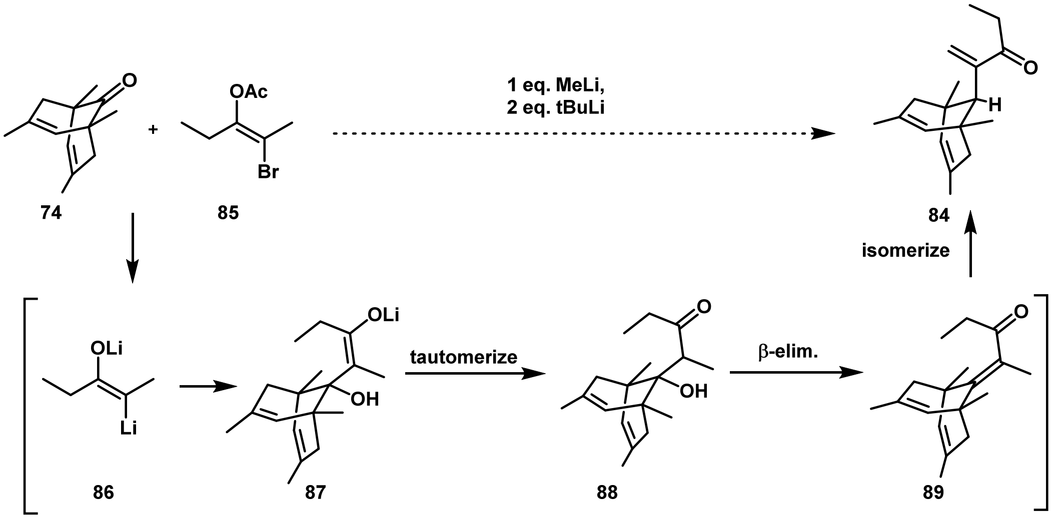
Figure 1-7. Overoxidized trione **82**.

We then turned our attention to installing the northern side chain first. We thought of a way to make an “aldol equivalent” as shown in Scheme 1-26. The addition of dianions to sterically congested carbonyls has been reported by Kowalski and coworkers[16] and it seemed applicable to our neopentyl ketone system to install the northern side chain in a single step.



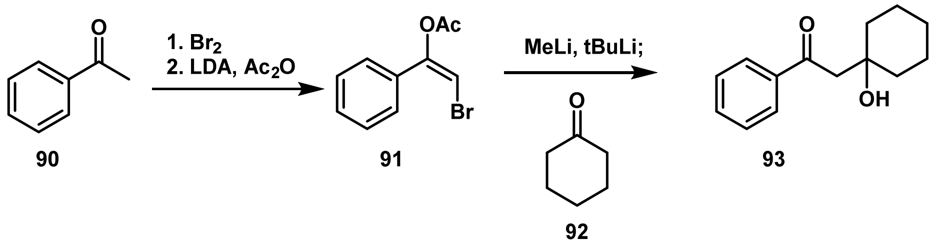
Scheme 1-26. Approach to install the northern side chain.

Application of the dianion concept to our system is shown in Scheme 1-27. First, the bromo enol acetate **85** was treated with methyllithium and two equivalents of tert-butyllithium to form the dilithiate **86**, which could then add to the bicyclic ketone **74** to form intermediate **87**. Tautomerization to **88** and β-elimination would form **89**. Either **89** could have been isolated and later isomerized, or the compound might have isomerized *in situ* to the more stable isomer **84**.



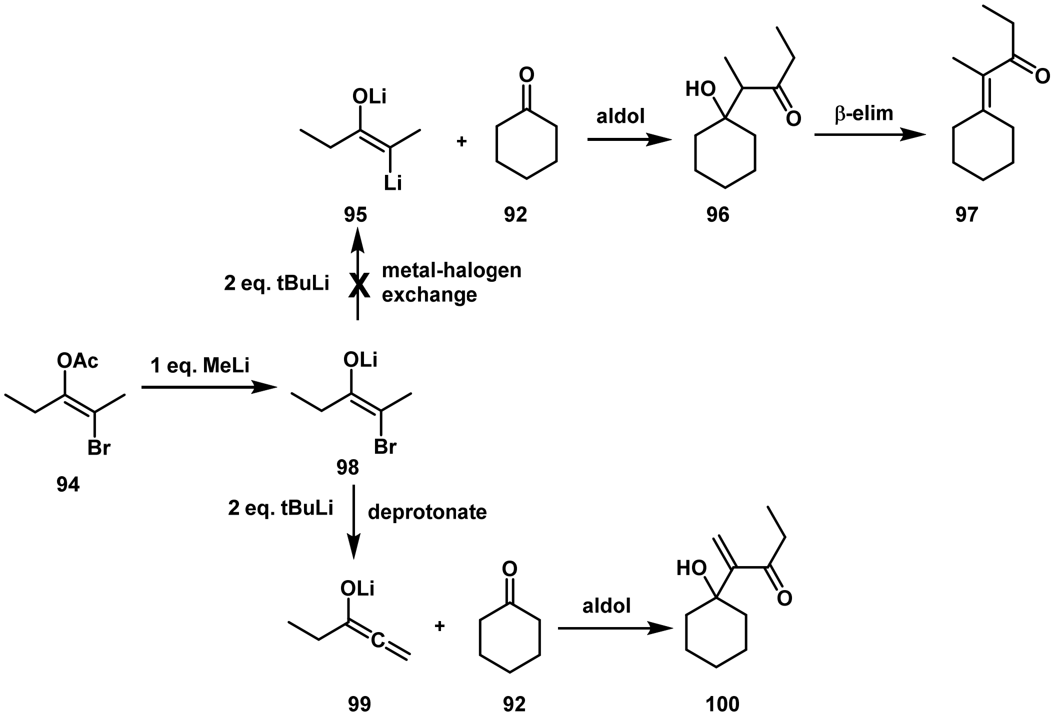
Scheme 1-27. Application of dianion chemistry to our system.

Before applying this idea to the real system, a few preliminary reactions were carried out (Scheme 1-28). First, to reproduce the literature results, acetophenone **90** was treated with bromine, followed by LDA and acetic anhydride to form the bromo enol acetate (Scheme 1-28). Treatment of this intermediate with methyllithium and tert-butyllithium formed the dianion *in situ*,



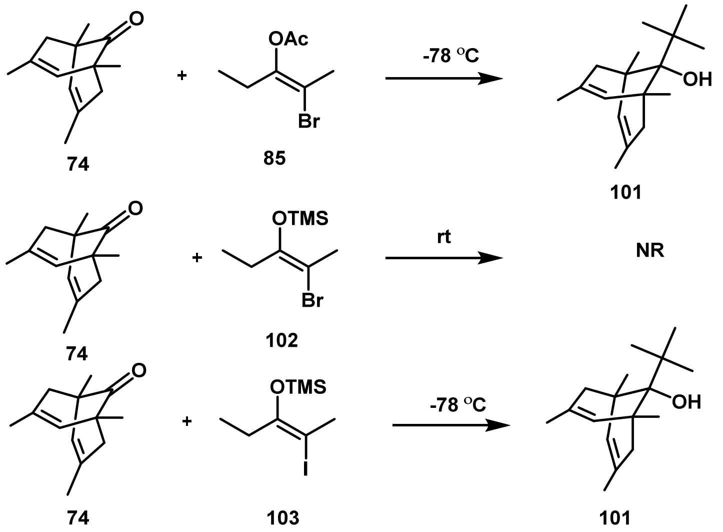
Scheme 1-28. Dianion addition control experiment.

and it was able to add to cyclohexanone **92** to form the ketoalcohol **93**, as reported. Next, another control experiment was carried out using our real dianion nucleophile that has an additional methyl group with cyclohexanone. However, the bromo enol acetate **94** and cyclohexanone gave a product that had a molecular weight two less than the expected product. We believe what occurred is shown in Scheme 1-29. After forming the first lithiate, instead of undergoing a metal-halogen exchange, tert-butyllithium instead deprotonated the terminal proton to form the allenoate **99**, which then added to cyclohexanone to form the ketoalcohol **100**, which has a molecular weight two less than the desired and expected product **96**.

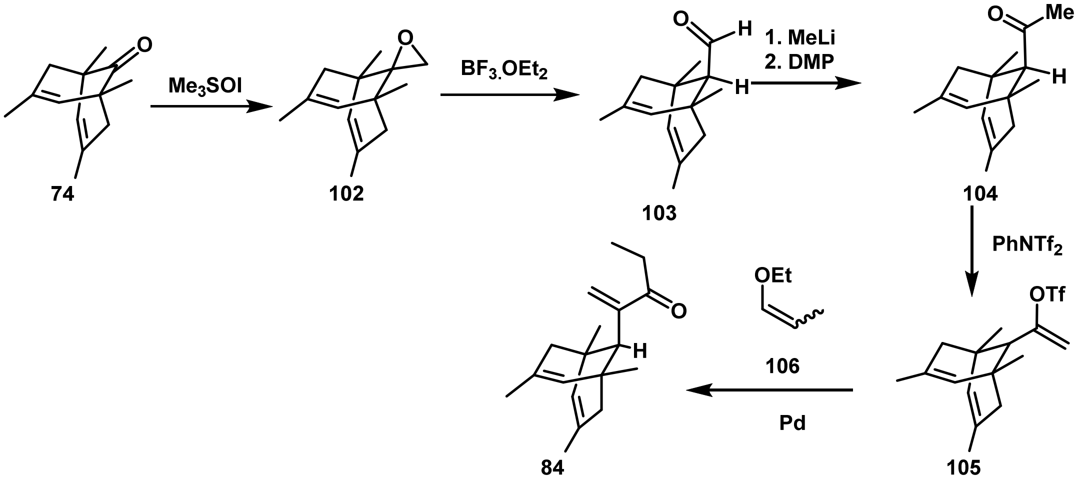


Scheme 1-29. Reaction of **94** with cyclohexanone.

Even though this was the case, we decided to try this method on our system. However, using the bromo enol acetate **94** with our bicyclo[3.3.1]nonanone **74**, only formation of the tert-butyllithium adduct of the ketone, namely the alcohol **101**, was observed (Scheme 1-30). This is surprising in that not only did neither the dianion nor the allenoate add to the ketone, but instead tert-butyllithium added as a very hindered nucleophile to the very hindered ketone. This result might be because of the steric hindrance of our substrate, and thus only a very harsh nucleophile such as tert-butyllithium was able to add, even though it is extremely hindered. When the bromo trimethylsilyl enol **102** was used, no reaction was observed. When we used the iodo analogue **103**, again we saw only addition of the tert-butyl group to give the alcohol **101**.



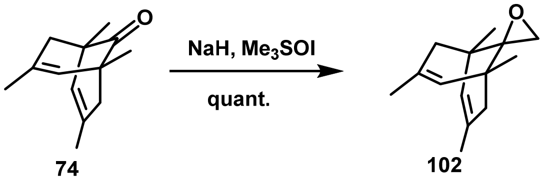
Scheme 1-30. Reaction of dianion substrates with bicycle **74**.



°

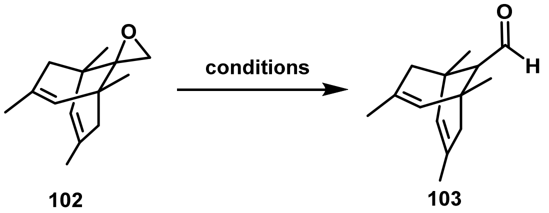
Scheme 1-31. Forward synthesis of northern side chain.

We decided next to adopt a stepwise approach to forming the northern side chain. Thus, the epoxide **102** would be formed, followed by ring opening to form the aldehyde **103**, addition of methyllithium and oxidation to form the ketone **104**. Treatment with phenyl triflate to form the enol triflate **105**, and then a final Heck coupling would form the northern side chain (Scheme 1-31).



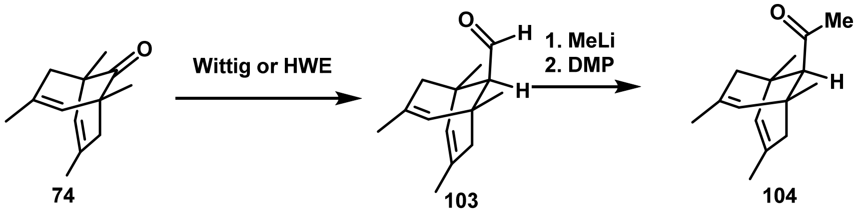
Scheme 1-32. Formation of epoxide **102** from diene **74**.

Table 1-7. Opening of epoxide **102**.



Entry	Acid	Yield (%)
1	TsOH	No reaction
2	H_3PO_4: DMSO	No reaction
3	Ti(OiPr)$_4$	No reaction
4	Ti(OiPr)$_4$, Mg, TMSCl	No reaction
5	$CHCl_3$, reflux	No reaction
6	$SnCl_4$	Decomposition
7	Et_2AlCl	Decomposition
8	$BF_3.OEt_2$	13 spots!

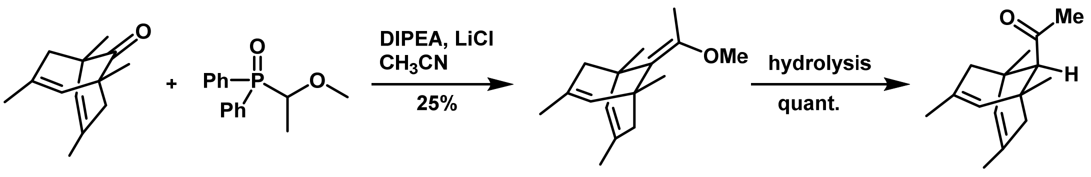
The forward synthesis started with the epoxidation of the bicycle **74** with Corey's reagent which afforded the epoxide **102** in quantitative yield (along with grease from the sodium hydride). However, a variety of conditions were tried to effect epoxide rearrangement, all to no avail (Table 1-7). Acids such as tosic acid and phosphoric acid gave no reaction (entries 1-2). Milder Lewis acidic conditions such as treatment with titanium isopropoxide, chloroform, diethylaluminum chloride or tin tetrachloride also gave no conversion to product. Treatment with boron trifluoride etherate gave a multitude of spots.



Scheme 1-33. Revised synthesis of methyl ketone **104**.

At this point, a different approach was considered, namely using a Wittig olefination or a Horner reaction to form the methyl ketone **104** (Scheme 1-33). There were only two examples of a highly substituted Horner reaction using substituted diphenylphosphine oxide **107** in the literature.[17] Since the additional methyl substituent is already there, this sequence would only require two steps from the ketone to make the methyl ketone functionality of **104**. However, under a variety of conditions, the hindered Horner reaction did not produce high yields, with the best conditions producing only a 25% conversion to the enol ether **108** by GCMS (Scheme 1-34). Hydrolysis of the enol ether **108** gave a quantitative yield of the methyl ketone **104**.

Thus, a longer, four-step sequence was used instead to introduce the methyl ketone to the bicyclononane ketone from which the northern side chain could be built (Table 1-8).[18] Using methoxymethyltriphenylphosphonium chloride with phenyllithium or sodium hydride, we observed a complicated mixture of products. No reaction was observed when we attempted a Peterson olefination using the trimethylsilyl analogue. Finally, after making the methoxymethylphosphine

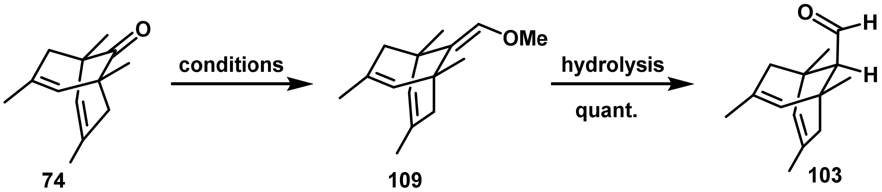


74 **107** **108** **104**

Scheme 1-34. Hindered Horner reaction to the form methyl ketone **104**.

oxide from the corresponding methoxymethyltriphenylphosphonium chloride, treatment of the phosphine oxide with LDA in the presence of the ketone **74** gave 40% yield of the methyl enol ether **109**. Hydrolysis gave the aldehyde **103** in quantitative yield.

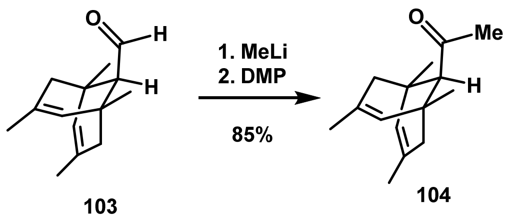
Table 1-8. Horner reaction for formation of aldehyde **103**.



74 **109** **103**

Entry	Conditions	Results
1	$Ph_3PCH_2OCH_3Cl$, PhLi	Mixture (works well with cyclohexanone)
2	$Ph_3PCH_2OCH_3Cl$, NaH, DMSO	Mixture
3	$TMSCH_2OMe$, sBuLi	No reaction
4	$Ph_2POCH_2OCH_3$, LDA	40%

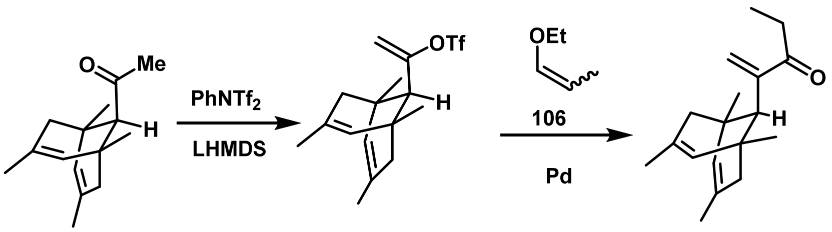
Conversion of the aldehyde **103** to the methyl ketone **104** was uneventful. Treatment with methyllithium and subsequent Dess-Martin oxidation proceeded in 85% over two steps to give methyl ketone **104** (Scheme 1-35).



103

104

Scheme 1-35. Conversion of aldehyde **103** to methyl ketone **104**.



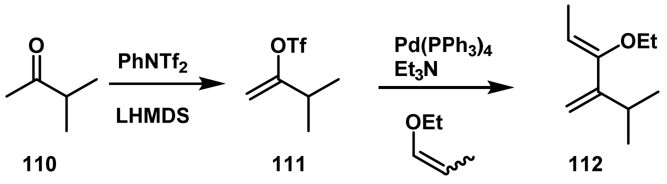
104

105

84

Scheme 1-36. Heck coupling to install northern side chain.

With the methyl ketone **104** in hand, we then attempted to install the northern side chain via a Heck coupling, as shown in Scheme 1-36. Formation of the enol triflate **105** and treatment with ethoxypropene **106** with palladium would furnish ketone **84**.



110

111

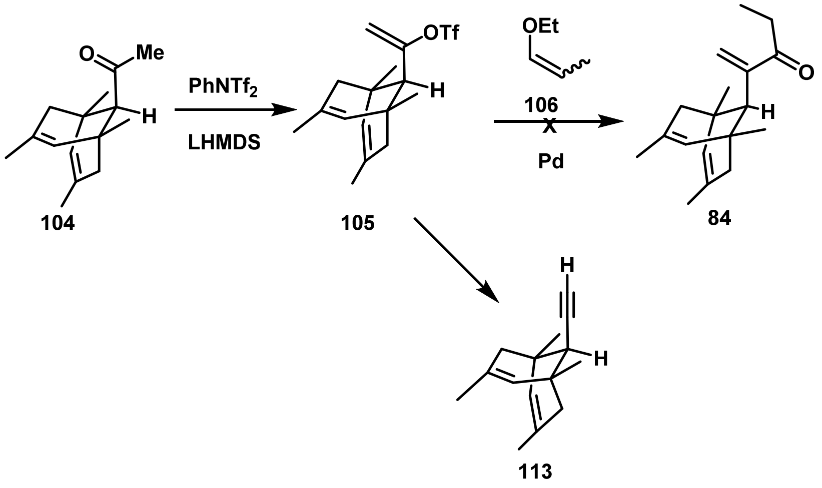
106

112

Scheme 1-37. Model system for Heck coupling.

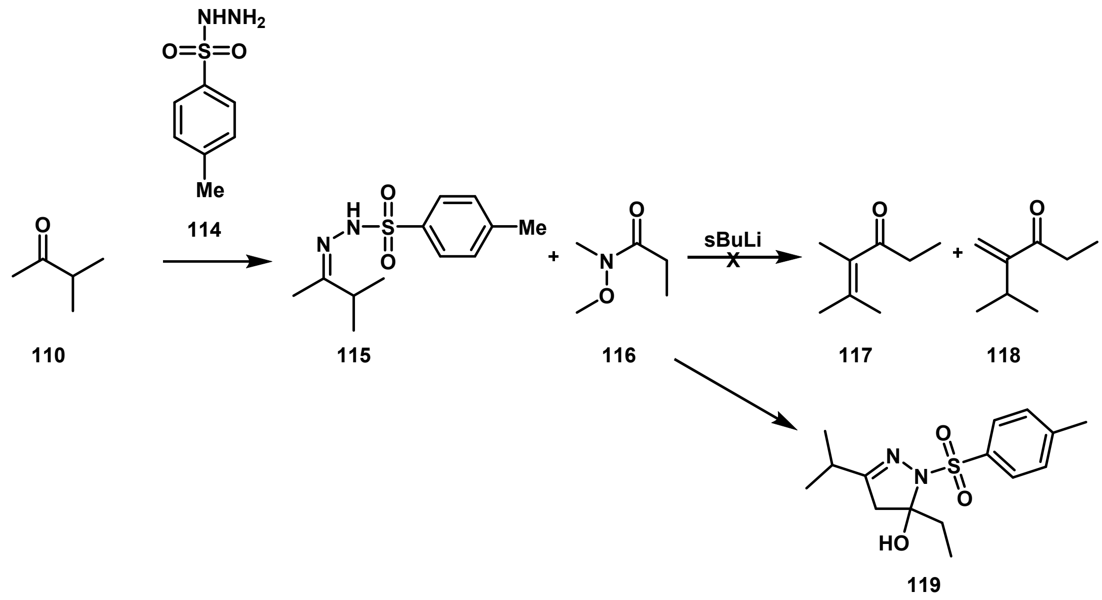
First, we performed the reaction sequence on a model system, as shown in Scheme 1-37.[19] Treatment of methyl isopropyl ketone **110** with lithium bis(trimethylsilyl)amide and *N*-phenyltriflimide selectively formed the less substituted enol triflate **111**. Addition of ethoxypropene **106** and tetrakis- (triphenylphosphine)palladium and triethylamine furnished the Heck coupling product **112** in trace amounts.

With this proof-of-concept reaction in hand, we then applied the approach to our system (Scheme 1-38). However, treatment of the enol triflate **105** with ethoxypropene **106** under identical conditions to those previously used in our model system did not furnish any desired product and instead gave a multitude of products. One of the side products isolated was the alkyne **113**, the result of the β-elimination of the highly reactive enol triflate.



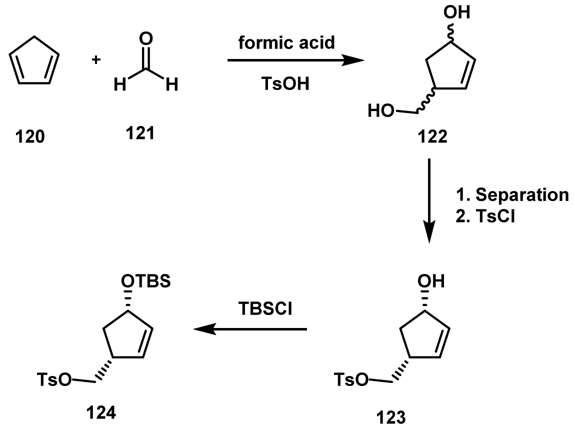
Scheme 1-38. Attempted Heck coupling to form northern side chain.

Our next approach to installing the northern side chain was to perform a Shapiro reaction, and the application to the same model system is shown in Scheme 1-39. Hydrazone **115** was first synthesized from the corresponsing ketone **110** and *p*-toluenesulfonyl hydrazine **114**. However, reaction with the Weinreb amide **116** did not furnish the expected alkene products **117** or **118**. Instead, a cyclization occurred and the hydroxyl dihydropyrazole **119** was isolated.



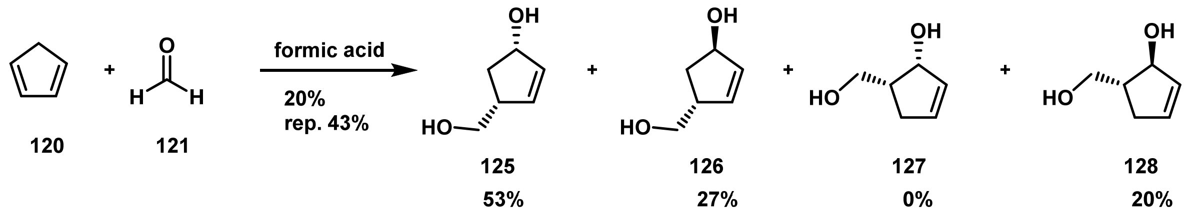
Scheme 1-39. Attempted Shapiro reaction.

With the failure to install the northern side chain, we then turned our attention to forming the southern side chain by making the selectively protected diol **124** (Scheme 1-40). Synthesis of the southern side chain was based on literature precedent,[20] starting with the Prins reaction of cyclopentadiene and formaldehyde to form the diol **122**. Selective primary tosylation would give intermediate **123**, then TBS protection would furnish the protected diol **124**.



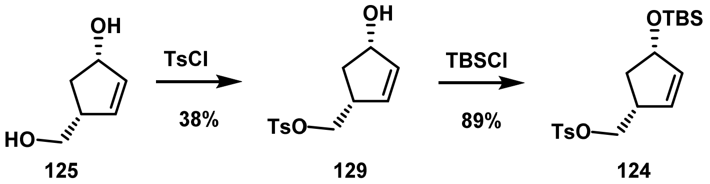
Scheme 1-40. Proposed synthesis of the southern side chain.

The Prins reaction of cyclopentadiene and formic acid gave a mixture of all four stereoisomers (Scheme 1-41). Although all four products **125**, **126**, **127**, and **128** are very close stereoisomers, we were able to separate the compounds on silica gel chromatography, using a 1:100 product: silica gel ratio in a 19:1 dichloromethane:methanol solvent system.



Scheme 1-41. Formation of diols **125**, **126**, **127**, and **128.**

Thus, we decided to protect the diol diastereomer necessary for our natural product, **125**, with silyl protecting groups. Selective tosylation of the diol **125** was achieved in a moderate yield of 38% to give the alcohol **129** (Scheme 1-42). Secondary alcohol protection with TBSCl gave **124** in 89% yield.



Scheme 1-42. Selective protections of diol **125** to give compound **124**.

Even though we were able to prepare the protected tosylate **124**, we did not pursue the attachment of the southern side chain due to time constraints.

CONCLUSION

A potential strategy toward the synthesis of rugulosone has been investigated. Although initial efforts towards forming the bicyclo[3.3.1]nonane core via a Michael addition – Dieckmann condensation reaction sequence did not prove successful, the synthesis of the core was accomplished via a highly efficient tetraalkylation of commercially available starting materials. This methodology of isomerization of unactivated alkenes produced the C_2 symmetric core. Studies toward the addition of the northern side chain have been conducted, and look promising. Synthesis of southern side chain has been accomplished, and is ready to be coupled with the functionalized core to facilitate a highly divergent synthesis of the natural product.

EXPERIMENTAL

General

All reactions were carried out under an argon atmosphere unless otherwise specified. Methylene chloride was distilled from calcium hydride under an argon atmosphere. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), integration, multiplicity and coupling constant (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). HPLC purification was conducted on a Shimadzu HPLC system with a refractive index detector RID-10A and one Luna 5 µm C18(2) column with acetonitrile and water as an eluent. High resolution mass spectrometry was taken on a Thermo Fisher Scientific Exactive Plus mass spectrometer equipped with an IonSense ID-CUBE DART ion source.

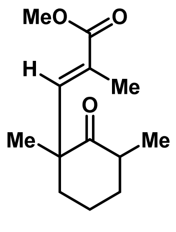
Methyl (*E*)-3-(1,3-dimethyl-2-oxocyclohexyl)-2-methylpropenoate, 47.

To a suspension of potassium tert-butoxide (2.02 g, 18.0 mmol) in THF (15 mL) was added 2,6-dimethylcyclohexanone (0.822 mL, 6.0 mmol) in THF (20 mL) at -78 ˚C. The reaction was stirred for 1.5 h. A solution of methyl bromomethacrylate (1.45 mL, 12.0 mmol) in THF (10 mL) was added and the reaction continued to stir at -78 ˚C for 3 h. The solution was then quenched with a saturated solution of NH_4Cl (30 mL), extracted with diethyl ether (3 X 30 mL), washed with brine (30 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester **47** (0.74 g, 3.29 mmol, 55%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.91 (s, 1H)

3.71 (s, 3H)



***E*-isomer**

47

2.59 (ddq, *J* = 17.8, 6.4, 6.4 Hz, 1H)

2.04 (dq, *J* = 14.0, 3.2 Hz, 1H)

1.99 (m, 1H)

1.81 (ddddd, *J* = 13.5, 13.5, 13.5, 13.5, 3.5 Hz, 1H)

1.64 (m, 1H)

1.59 (s, 3H)

1.48 (ddd, *J* = 13.6, 13.6, 3.6 Hz, 1H)

1.29 (dddd, *J* = 12.8, 12.8, 12.8, 3.6 Hz, 1H)

1.12 (s, 3H)

0.95 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 168.4, 146.3, 129.5, 51.9, 51.6, 44.5, 42.9, 38.0, 22.4, 21.8, 14.7, 12.4.

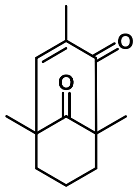
GCMS (*m/z*): 224.2.

1,3,5-Trimethylbicyclo[3.3.1]non-3-ene-2,9-dione, 48.

To a solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (5 mL) was added *n*-butyllithium (2.5 M in hexanes, 1.0 mL, 2.5 mmol) at -78 ˚C. The reaction flask was warmed to 0 ˚C for 30 min, and a solution of dione **58** (0.194 g, 1.0 mmol) in THF (3 mL) was added. The flask was cooled to -78 ˚C, a solution of TMSCl (0.50 mL, 4.0 mmol) in THF (1 mL) was added, then warmed to 0 ˚C and let stir for 2 h. The reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (3 X 10 mL), washed with brine (30 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. The crude mixture was then dissolved in DMSO (3 mL). Palladium acetate was added (0.112 g, 5.0 mmol) and the reaction mixture was left to stir overnight under an atmosphere of oxygen. The reaction was quenched with water (5 mL), and extracted with ethyl acetate (3 X 10 mL), washed with brine (30 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dione **48** (0.167 g, 0.86 mmol, 86%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

6.50 (bq, *J* = 1.5 Hz, 1H)



48

1.97 (m, 1H)

1.90 (s, 3H)

1.79 (bd, *J* = 12.5 Hz, 1H)

1.69 (m, 2H)

1.57 (m, 2H)

1.27 (s, 3H)

1.23 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 200.9, 148.0, 138.4, 61.7, 49.5, 41.8, 38.4, 21.4, 18.9, 16.2, 15.6.

GCMS (*m/z*): 192.0.

Methyl (*Z*)-3-(1,3-dimethyl-2-oxocyclohexyl)-2-methylpropenoate, 51.

A solution of ketoester **47** (0.100 g, 4.46 mmol) in acetone (9 mL) was added to a quartz reaction flask, then subjected to a 450W mercury UV lamp for 6 h. The solution was then concentrated *in vacuo*. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester **51** (0.020 g, 0.892 mmol, 20%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.01 (q, *J* = 1.6 Hz, 1H)

3.61 (s, 3H)

2.75 (ddq, J = 12.8, 6.4, 6.4 Hz, 1H)

2.00 – 1.90 (m, 1H)

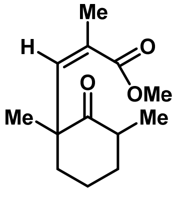
1.97 (d, *J* = 1.6 Hz, 3H)

1.75 (ddddd, *J* = 13.6, 13.6, 13.6, 3.6, 3.6 Hz, 1H)

1.61 (m, 2H)

1.50 (td, *J* = 13.6, 4.0 Hz, 1H)

1.35 – 1.25 (m, 1H)



***Z*-isomer**

51

1.15 (s, 3H)

0.95 (d, *J* = 6.4 Hz, 3H).

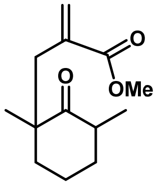
Methyl 2-((1,3-dimethyl-2-oxocyclohexyl)methyl)acrylate, 53.

To a suspension of potassium tert-butoxide (0.067 g, 0.60 mmol) in THF (3 mL) was added 2,6-dimethylcyclohexanone (0.068 mL, 0.50 mmol) in THF (2 mL). The reaction was cooled to -78 ˚C, then a solution of methyl bromomethylacrylate **52** (0.09 mL, 0.50 mmol) in THF (2 mL) was added dropwise. The reaction was stirred for 1.5 h, then quenched with a saturated solution of NH_4Cl (10 mL), extracted with ethyl acetate (3 X 15 mL), washed with brine (15 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester **53** (0.082 g, 0.44 mmol, 73%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

6.18 (d, *J* = 1.0 Hz, 1H)

5.47 (bs, 1H)



53

3.69 (s, 3H)

3.04 (d, *J* = 14.0 Hz, 1H)

2.91 (ddq, *J* = 13.0, 6.5, 6.5 Hz, 1H)

2.36 (d, *J* = 14.0 Hz, 1H)

2.05 (m, 1H)

1.97 (qt, *J* = 13.5, 3.7 Hz, 1H)

1.86 (dq, *J* = 13.7, 3.0 Hz, 1H)

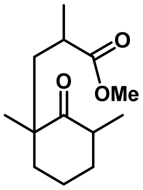
1.63 (bd, *J* = 13.6 Hz, 1H)
1.54 (td, *J* = 13.5, 4.0 Hz, 1H)
1.32 (qd, *J* = 13.0, 4.0 Hz, 1H)
0.99 (d, *J* = 6.5 Hz, 3H)
0.93 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 167.7, 136.8, 128.2, 51.9, 48.6, 41.7, 41.4, 39.5, 36.6, 22.5, 21.2, 15.0.

GCMS (*m/z*): 224.1.

Methyl 3-(1,3-dimethyl-2-oxocyclohexyl)-2-methylpropanoate, 57.

To a suspension of potassium tert-butoxide (3.36 g, 30.0 mmol) in THF (30 mL) was added 2,6-dimethylcyclohexanone (1.37 mL, 10.0 mmol) in THF (10 mL) at -78 ˚C and stirred for 0.5 h. A solution of methylmethacrylate (1.60 mL, 15.0 mmol) in THF (20 mL) was added and the reaction continued to stir at -78 ˚C for 4 h. The solution was then quenched with a saturated solution of NH_4Cl (30 mL), extracted with diethyl ether (3 X 30 mL), washed with brine (30 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester **57** (1.90 g, 8.4 mmol, 84%) as a light yellow oil. The product is a mixture of at least diastereomers. The proton NMR is of the major diastereomer.



57

^{1}H NMR (500 MHz, CDCl$_3$) δ:

3.65 (s, 3H)

2.57 (m, 1H)

2.42 (m, 1H)

1.99 (m, 2H)

1.84 (m, 1H)

1.75 – 1.47 (m, 4H)

1.38 – 1.24 (m, 1H)

1.19 (d, *J* = 6.9 Hz, 3H)

1.14 (d, *J* = 4.8 Hz, 3H)

0.97 (d, *J* = 6.6 Hz, 3H).

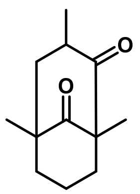
The ^{13}C data is for the mixture of diastereomers.

^{13}C NMR (75 MHz, CDCl$_3$) δ 216.7, 216.6, 216.4, 178.4, 178.3, 176.9, 51.7, 51.6, 51.5, 48.6, 43.0, 42.5, 41.2, 40.9, 40.8, 39.4, 37.9, 36.8, 36.6, 36.3, 36.2, 35.9, 35.4, 24.1.

1,3,5-Trimethylbicyclo[3.3.1]nonane-2,9-dione, 58.

To a suspension of potassium tert-butoxide (1.50 g, 13.3 mmol) in THF (20 mL) was added ketoester **57** (2.0 g, 4.4 mmol) in THF (10 mL) at -78 ˚C and slowly warmed to 21 ˚C and stirred for 1 h. The solution was then cooled to -78 ˚C, quenched with a saturated solution of NH$_4$Cl (30 mL), extracted with diethyl ether (3 X 30 mL), washed with brine (30 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give a crude oil.

Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dione **58** (0.83 g, 4.3 mmol, 98%) as a light yellow oil.



58

^{1}H NMR (300 MHz, CDCl$_3$) δ:

2.34 (bd, *J* = 11.0 Hz, 1H)

2.19 (m, 1H)

1.89 – 1.87 (m, 2H)

1.62 (dd, *J* = 15.5, 4.0 Hz, 1H)

1.57 (tdd, *J* = 13.0, 13.0 Hz, 1H)

1.50 (bd, *J* = 12.5 Hz, 2H)

1.43 (m, 1H)

1.21 (s, 3H)

1.11 (s, 3H)

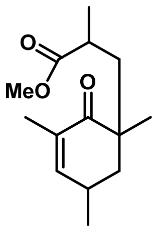
1.08 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 214.7, 214.1, 60.8, 46.2, 44.6, 43.9, 42.7, 38.2, 24.8, 19.7, 17.9, 13.2.

GCMS (*m/z*): 194.1.

Methyl 2-methyl-3-(1,3,5-trimethyl-2-oxocyclohex-3-en-1-yl)propanoate, 63.

To a suspension of potassium tert-butoxide (0.17 g, 1.52 mmol) in THF (5 mL) was added 2,4,6-trimethylcyclohex-2-en-1-one **43** (0.07 g , 0.51 mmol) in THF (2 mL) at -78 ˚C and stirred for 0.5 h. A solution of methyl methacrylate (0.08 mL, 0.76 mmol) in THF (2 mL) was added and the reaction continued to stir at -78 ˚C for 3 h. The solution was then quenched with a saturated solution of NH_4Cl (20 mL), extracted with ethyl acetate (3 X 20 mL), washed with brine (20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester **63** (0.004 g, 0.017 mmol, 6%) as a light yellow oil as a mixture of mostly two diastereomers. The NMR data is for the mixture of diasteromers.



63

^1H NMR (500 MHz, $CDCl_3$) δ:
6.78 (s, 1H)
3.69 (s, 1.8H)
3.65 (s, 1.2H)
2.52 (m, 1H)
2.40 (m, 1H)
2.21 (s, 3H)
2.07 (m, 2H)
1.92 – 1.77 (m, 2H)
1.38 (d, $J = 4.4$ Hz, 3H)
1.25 (d, $J = 7.2$ Hz, 3H)
1.08 (d, $J = 7.2$ Hz, 3H)
0.98 (d, $J = 7.2$ Hz, 3H).

(±)(1*R*,3*R*,4*R*,5*R*,8*S*)-5-Acetyl-1,3,5,8-tetramethylbicyclo[2.2.2]octan-2-one, 67.

To a suspension of potassium tert-butoxide (0.17 g, 1.52 mmol) in THF (5 mL) was added 2,4,6-trimethylcyclohex-2-en-1-one **63** (0.07 g , 0.51 mmol) in THF (2 mL) at -78 ˚C and stirred for 0.5 h. A solution of methyl methacrylate (0.08 mL, 0.76 mmol) in THF (2 mL) was added and the reaction continued to stir at -78 ˚C for 3 h. The solution was then quenched with a saturated solution of NH_4Cl (20 mL), extracted with ethyl acetate (3 X 20 mL), washed with brine (20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the bicyclo[2.2.2]octane **67** (0.019 g, 0.085 mmol, 27%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

3.64 (s, 3H)

2.55 (m, 2H)

2.51 (m, 1H)

2.01 (bs, 1H)

1.81 (dd, *J* = 17.0, 13.0 Hz, 1H)

1.37 (s, 3H)

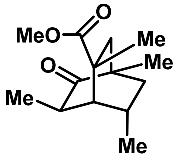
1.25 (d, *J* = 18.0 Hz, 1H)

1.08 (ddd, *J* = 15.5, 7.5, 3.5 Hz, 1H)

1.04 (d, *J* = 9.0 Hz, 3H)

0.97 (d, *J* = 9.5 Hz, 3H)

0.95 (s, 3H).



67

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one, 73.

To a suspension of 60% NaH in mineral oil (0.176g, 4.40 mmol) (washed three times with hexanes) in toluene (5 mL) was added dropwise 3-pentanone (0.086g, 1.00 mmol) in toluene (2 mL). A solution of 1-chloro-2-(chloromethyl)-2-propene (0.254 g, 2.20 mmol) in toluene (2 mL) was added dropwise and the reaction was refluxed overnight. The solution was then cooled to room temperature and quenched with a saturated solution of NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (3 X 20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the bicyclononanone **73** (0.171 g, 0.90 mmol, 90%) as a light yellow oil.

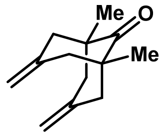
^{1}H NMR (500 MHz, $CDCl_3$) δ

4.73 (s, 4H)

2.57 (d, *J* = 15.0 Hz, 4H)

2.42 (d, *J* = 15.0 Hz, 4H)

1.03 (s, 6H).



73

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5, 141.8, 112.7, 49.7, 45.3, 23.5.

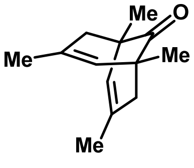
HRMS (ESI, *m/z*): 191.1424, calculated for [$C_{13}H_{19}O$] 191.1436.

(±) (1*R*,5*R*)-1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-dien-9-one, 74.

To a solution of the bicyclononanone **73** (0.050 g, 2.63 mmol) in ethyl acetate (5 mL) was added palladium (10 wt. % on activated carbon) (0.011 g, 0.11 mmol). The reaction vessel was then purged with a hydrogen balloon for 5 min, then allowed to stir at ambient temperature and pressure for 1 h. The mixture was then filtered over Celite, washed with ethyl acetate (15 mL), then concentrated in vacuo to give diene **74** and other products (0.50 g, 2.63 mmol, 100%) as a light yellow oil. The crude mixture was then purified via HPLC.

^{1}H NMR (500 MHz, CDCl$_3$) δ

5.14 (2H, s)



74

2.27 (2H, d, *J* = 17.0 Hz)

2.22 (2H, d, *J* = 17.0 Hz)

1.65 (6H, s)

1.07 (6H, s).

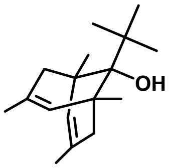
^{13}C NMR (125 MHz, CDCl$_3$) δ 216.6, 132.8, 130.9, 48.5, 45.5, 22.3, 21.1.

HRMS (ESI, *m/z*): 191.1425, calculated for [$C_{13}H_{19}O$] 191.1436.

(±)(1*R*,5*R*)-9-[(1,1-Dimethylethyl)-1,3,5,7-tetramethylbicyclo[3.3.1]nona-2,6-dien-9-ol, 101.

To 2,2'-bipyridyl (0.010 g, 0.64 mmol) was added methyllithium (1.4M in diethyl ether, 0.36 mL, 0.52 mmol) at -78 ˚C. The solution was warmed to room temperature to remove the diethyl ether. Dimethoxyethane (2 mL) was added at 0 ˚C, warmed to room temperature for 6 min, then cooled to -78 ˚C. Tert-butyllithium (1.7 M solution in pentane, 0.34 mL, 0.2 mmol) was added and stirred for 10 min. The bicycle **74** (0.05 g, 0.26 mmol) was then added to the mixture and stirred for 2 h. The reaction was then quenched with 1M HCl (10 mL), extracted with ethyl ether (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the bicycle **101** (0.006 g, 0.023 mmol, 9%) as a light yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ:



101

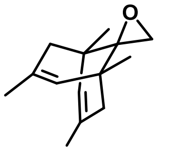
4.97 (s, 1H)
4.75 (s, 1H)
2.25 (d, *J* = 17.0 Hz, 1H)
2.20 (d, *J* = 17.5 Hz, 1H)
1.80 (d, *J* = 18.0 Hz, 1H)
1.59 (s, 3H)
1.57 (s, 3H)
1.42 (d, *J* = 17.5 Hz, 1H)
1.26 (s, 3H),
1.21 (s, 3H),
1.15 (s, 9H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 136.0, 132.9, 131.9, 131.8, 45.5, 44.9, 43.8, 43.0, 41.3, 32.0, 31.5, 27.2, 26.9, 22.7, 22.4.

(±)(1R,5R)-1,3,5,7-Tetramethylspiro[bicyclo[3.3.1]nonane-9,2'-oxirane]-2,6-diene

To a solution of the bicycle **74** (1.0 g, 5.3 mmol) in THF (20 mL) was added a solution of NaH (0.32 g, 7.8 mmol) and trimethylsulfoxonium iodide (1.7 g, 7.8 mmol) in DMSO (10 mL). The reaction was stirred overnight. The reaction was then quenched with water (20 mL), extracted with ethyl acetate (5 X 20 mL), washed with brine (20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give epoxide **102** (1.1 g, 5.5 mmol, 100%) as a crude yellow oil that was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ:


102

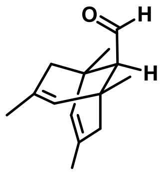
5.12 (s, 1H)
5.05 (s, 1H)
2.77 (s, 2H)
2.17 – 2.05 (m, 4H)
1.65 (s, 3H)
1.63 (s, 3H)
0.85 (s, 3H)
0.80 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 131.9, 130.7, 129.6, 64.2, 46.3, 45.4, 42.5, 36.1, 35.4, 23.0, 22.8, 21.4, 20.8.

GCMS (m/z): 204.2.

1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-diene-9-carbaldehyde, 103.

To a solution of the enol ether **109** (0.44 g, 2.0 mmol) in THF (20 mL) was added a solution of 2M HCl (10 mL). The reaction was stirred at 21 ˚C for 3 h. The reaction was then extracted with ethyl acetate (3 X 40 mL), washed with brine (50 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the aldehyde **103** (0.41 g, 2.0 mmol, 99%) as a light yellow oil.



103

^{1}H NMR (500 MHz, $CDCl_3$) δ:

9.55 (d, *J* = 6.5 Hz, 1H)

5.18 (s, 1H)

5.07 (s, 1H)

1.96 (d, *J* = 18.5 Hz, 1H)

1.86 (d, *J* = 6.5 Hz, 1H)

1.85 (d, *J* = 16.5 Hz, 1H)

1.77 (d, *J* = 18.0 Hz, 1H)

1.68 (d, *J* = 17.0 Hz, 1H)

1.67 (s, 3H)

1.60 (s, 3H)

1.03 (s, 3H)

1.01 (s, 3H).

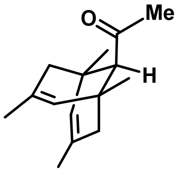
^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 132.5, 131.7, 131.5, 128.3, 81.1, 44.8, 40.4, 35.6, 34.6, 26.8, 26.4, 23.0, 22.8.

HRMS (ESI, *m/z*): 204.1590, calculated for $C_{14}H_{21}O$ $(M+H)^+$ 204.1514.

1-(1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-dien-9-yl)ethan-1-one, 104.

To a solution of the aldehyde **109** (0.2 g, 0.979 mmol) in THF (2 mL) was added methylmagnesium bromide (3M solution in diethyl ether, 4.4 mL, 1.47 mmol) at 0 ˚C. The reaction was stirred for 3 h, then quenched with a solution of $Na_2S_2O_3$ (5 mL), extracted with ethyl acetate (3 X 10 mL), washed with brine (50 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. The crude oil was the redissolved in dry ethyl acetate (5 mL) and IBX was added (0.82 g, 2.9 mmol). The solution was heated to 80 ˚C for 2 h. The solution was cooled to room temperature, excess IBX was filtered off, then concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the methyl ketone **104** (0.18 g, 0.83 mmol, 85%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:



104

5.07 (s, 1H)

4.94 (s, 1H)

2.54 (s, 1H)

2.15 (s, 3H)

2.09 (d, *J* = 17.5 Hz, 1H)

1.93 (d, *J* = 17.5 Hz, 1H)

1.69 (d, *J* = 17.5 Hz, 1H)

1.65 (s, 3H)

1.57 (s, 3H)

1.53 (d, *J* = 17.0 Hz, 1H)

1.00 (s, 3H)

0.99 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 133.3, 132.7, 131.2, 126.3, 61.1, 46.4, 39.8, 35.8, 35.7, 34.8, 26.8, 25.5, 23.1, 22.8.

HRMS (ESI, *m/z*): 219.1739, calculated for $C_{15}H_{23}O$ $(M+H)^+$ 219.1749.

9-(Methoxymethylene)-1,3,5,7-tetramethylbicyclo[3.3.1]nona-2,6-diene, 109.

To a solution of diisopropylamine (2.43 mL, 17.0 mmol) in THF (30 mL) was added *n*-butyllithium (2.0 M in hexanes, 8.31 mL, 16.8 mmol) at -78 ˚C. The reaction flask was warmed to 0 ˚C for 30 min then cooled back to -78 ˚C. Diphenyl(methoxymethyl)phosphine oxide (4.53 g, 18.4 mmol) was added, followed by a solution of the bicycle **74** (1.0 g, 5.3 mmol) in THF (10 mL). The reaction mixture was stirred for 4 h. After disappearance of all starting material by TLC, the reaction was quenched with water (20 mL), extracted with ethyl acetate (3 X 50 mL), washed with brine (50 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. The crude oil in THF (10 mL) was then added to a solution of washed NaH (2.1 g, 52.6 mmol) in THF (30 mL) and let stir for 16 h. The solution was then cooled to 0 ˚C, quenched with water (30 mL), extracted with ethyl acetate (3 X 50 mL), washed with brine (50 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dione **109** (0.45 g, 2.1 mmol, 40%) as a light yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

5.69 (s, 1H)

5.07 (s, 1H)

4.97 (s, 1H)

3.48 (s, 3H)

2.13 (bd, *J* = 17.0 Hz, 1H)

1.92 (bd, *J* = 17.0 Hz, 1H)

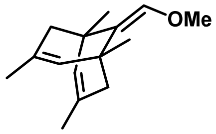
1.79 (bd, *J* = 17.0 Hz, 1H)

1.70 (bd, *J* = 17.0 Hz, 1H)

1.58 (s, 6H)

1.42 (s, 3H)

1.10 (s, 3H).



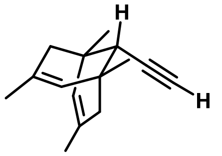
109

(±)(1*R*,5*R*)-9-Ethynyl-1,3,5,7-tetramethylbicyclo[3.3.1]nona-2,6-diene, 113.

To a solution of the methyl ketone **104** (0.16 g, 0.73 mmol) in THF (2 mL) was added lithium bis(trimethylsilyl)amide (LHMDS, 0.9 M solution in THF, 0.9 mL, 0.81 mmol) at -78 ˚C. The reaction was warmed to 0 ˚C for 0.25 h, then cooled to -78 ˚C. *N*-Phenyl-bis(trifluoromethanesulfonimide) (0.29 g, 0.81 mmol) in THF (1 mL) was added slowly, then the reaction was warmed to 0 ˚C and continued to stir for 2 h. The solution was quenched with a saturated solution of NaHCO$_3$ (10 mL), extracted with diethyl ether (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give the crude enol triflate **105** as a light yellow oil. The crude enol triflate **105** was then dissolved in DMSO (1.6 mL) in a screw cap flask, to which the ethoxy propene **106** (0.32 g, 3.6 mmol), palladium (II) acetate (0.005 g, 0.022 mmol), and triethylamine (0.15 mL, 1.1 mmol) were added. The reaction mixture was heated to 60 ˚C for 3 h. The reaction was then quenched with dropwise addition of water (5 mL), extracted with hexanes (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give the alkyne **113** in trace amounts as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.09 (bs, 1H)



113

4.97 (bs, 1H)

2.17 (d, *J* = 3.5 Hz, 1H)

1.89 (bd, *J* = 21.0 Hz, 1H)

1.70 (d, *J* = 21.0 Hz, 1H)

1.64 (d, *J* = 23.0 Hz, 1H)

1.63 (s, 3H)

1.59 (s, 3H)

1.50 (d, *J* = 21.5 Hz, 1H)

1.19 (s, 3H)

1.14 (s, 3H)

1.00 (d, *J* = 3.5 Hz, 1H).

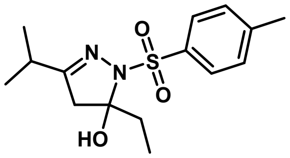
^{13}C NMR (100 MHz, CDCl$_3$) δ 132.6, 131.2, 130.5, 127.5, 84.2, 70.8, 44.4, 43.6, 39.7, 35.8, 35.5, 27.2, 26.9, 23.2, 22.9.

HRMS (ESI, *m/z*): 201.1628, calculated for $C_{15}H_{21}$ $(M+H)^+$ 201.1643.

5-Ethyl-3-isopropyl-1-(4-methylphenylsulfonyl)-4,5-dihydro-1*H*-pyrazol-5-ol, 119.

To a solution of hydrazone **115** (0.20 g, 0.78 mmol) in hexane (2 mL) and TMEDA (2 mL) was added sec-butyllithium (0.87 M solution in cyclohexane, 2.0 mL, 1.7 mmol) at -55 ˚C. The solution was stirred at this temperature for 2 h, then at 0 ˚C for 0.5 h. A solution of the Weinreb amide **116** (0.11 g, 0.94 mmol) in hexane (2 mL) was added and the reaction mixture was allow to warm to 21 ˚C and stirred overnight. The reaction was quenched with a saturated solution of NaHCO$_3$ (5 mL), extracted with hexane (3 X 10 mL), washed with water (5 X 10 mL) and 1M HCl (1 X 10 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dihydropyrazole **119** in trace amounts.

^{1}H NMR (500 MHz, CDCl$_3$) δ:



119

7.83 (bd, J = 7.0 Hz, 2H)

7.26 (bd, J = 8.0 Hz, 2H)

2.83 (d, J = 17.5 Hz, 1H)

2.67 (d, J = 18.0 Hz, 1H)

2.57 (sep, J = 7.0 Hz, 1H)

2.39 (s, 3H)

2.26 (dq, *J* = 14.4, 7.2 Hz, 1H)

2.23 (s, 1H)

2.15 (dq, *J* = 14.4, 7.2 Hz, 1H)

1.08 (d, *J* = 7.0 Hz, 3H)

1.06 (d, *J* = 7.0 Hz, 3H)

0.97 (t, *J* = 7.5 Hz, 3H).

(±)((1*S*,4*R*)-4-Hydroxycyclopent-2-en-1-yl)methyl 4-methylbenzenesulfonate, 129.

To a solution of diol **125** (0.12 g, 0.45 mmol) in dichloromethane (2 mL) and pyridine (2 mL) was added *p*-toluenesulfonyl chloride (0.10 g, 0.53 mmol) at 21 ˚C and the reaction was stirred overnight. The reaction was then extracted with dichloromethane (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the alcohol **129** (0.045 g, 0.17 mmol, 38%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.78 (d, *J* = 8.0 Hz, 2H)

7.34 (d, *J* = 8.0 Hz, 2H)

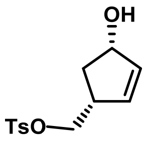
5.91 (m, 1H)

5.75 (bd, *J* = 5.0 Hz, 1H)

4.76 (bs, 1H)

3.99 (m, 2H)

2.91 (m, 1H)



129

2.45 (s, 3H)

2.40 (dt, *J* = 14.2, 7.8 Hz, 1H)

1.65 (bs, 1H)

1.36 (dt, *J* = 14.0, 4.0 Hz, 1H).

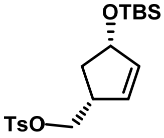
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 136.3, 133.3, 132.8, 129.9. 127.9, 76.5, 72.7, 43.8, 36.4, 21.6.

(±)((1*S*,4*R*)-4-((1,1-Dimethylethyldimethylsilyl)oxy)cyclopent-2-en-1-yl)methyl 4-methylbenzenesulfonate, 130.

To a solution of the alcohol **129** (0.10 g, 0.37 mmol) in dimethylformamide (DMF, 2 mL) and pyridine (0.014 mL, 0.66 mmol) was added tert-butyldimethylsilyl triflate (0.10 mL, 0.44 mmol) at room temperature and the reaction was stirred overnight. The reaction was then extracted with dichloromethane (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the cyclopentene **xx** (0.126g, 3.31 mmol, 89%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.75 (d, *J* = 8.5 Hz, 2H)



130

7.31 (d, *J* = 8.0 Hz, 2H)

5.75 (bd, *J* = 6.0 Hz, 1H)

5.67 (bd, *J* = 5.5 Hz, 1H)

4.75 (m, 1H)

3.93 (dd, *J* = 9.0, 7.0 Hz, 1H)

3.87 (dd, *J* = 9.0, 7.5 Hz, 1H)

2.41 (s, 3H)

2.26 (ddd, *J* = 13.5, 6.0, 6.0 Hz, 1H)

1.24 (m, 2H)

0.89 (s, 9H)

0.06 (s, 6H).

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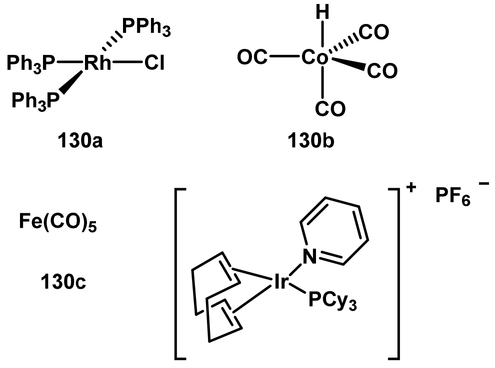
CHAPTER 2

Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di-(exo)methylenes to Endocyclic Dienes

INTRODUCTION

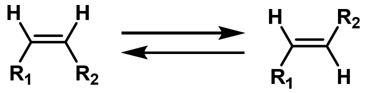
Isomerization of alkenes with transition metals and their complexes under catalytic conditions has been well studied.[1] A range of metals has been used, including Ir, Ni, Rh, Pd, and Co, to make catalysts used for the isomerization of a range of functional groups (Figure 2-1).



130a **130b** **130c** **130d**

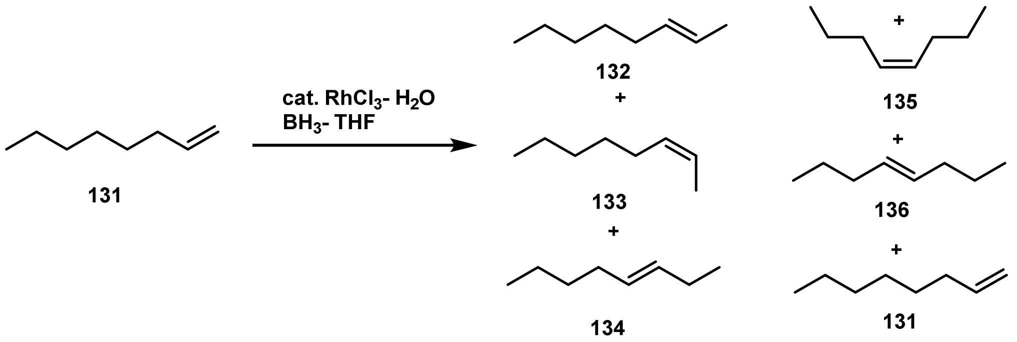
Figure 2-1. Examples of common transition metal isomerization catalysts, **130a-d**.

Allyl arenes can be converted into the alkyl styrene isomers, and allyl alcohols can be converted into the corresponding ketone after tautomerization.[2] In addition, an equilibrium can be effected between *E* and *Z* alkene isomers.[3]



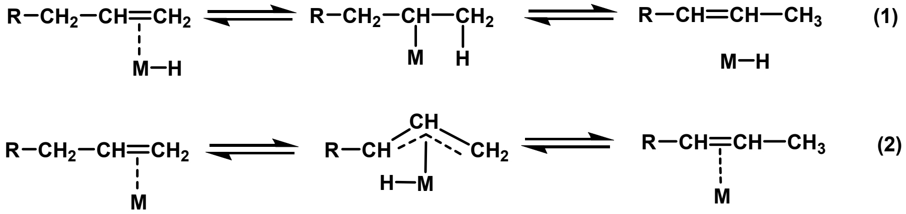
Scheme 2-1. *E/Z* isomerization of alkenes.

However, there has been little research on the isomerization of unfunctionalized alkenes. Of the few accounts reported, many use large transition metal complexes, numerous additives, high temperatures and long reaction times.[4]



Scheme 2-2. Isomerization of oct-1-ene **131** to isomers **132-136.**

One example is the isomerization of straight chain olefinic hydrocarbons with rhodium (Scheme 2-2).[5] Morrill and coworkers found that treatment of oct-1-ene **131** with rhodium trichloride and borane-THF complex gave a mixture of the isomers **132-136** as well as recovered starting material. Two pathways were possible to produce the products (Scheme 2-3): addition/elimination reactions of metal hydride complexes (eq. 1) or a rearrangement through a π-allyl complex, consisting of coordination of the metal with alkene, followed by a reversible hydrogen transfer to generate the π-allyl M-H complex (eq. 2). In this report, deuterium labeling studies were conducted and it was determined that the isomerization pathway most likely goes through the metal hydride addition/elimination mechanism, instead of the π-allyl complex.

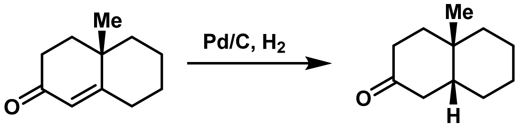


$$\mathrm{R{-}CH_2{-}\underset{\substack{\vdots\\ M-H}}{CH{=}}CH_2} \rightleftharpoons \mathrm{R{-}CH_2{-}\underset{M}{CH}{-}\underset{H}{CH_2}} \rightleftharpoons \mathrm{R{-}CH{=}CH{-}CH_3}\ \ \underset{\mathrm{M{-}H}}{} \qquad (1)$$

$$\mathrm{R{-}CH_2{-}\underset{\substack{\vdots\\ M}}{CH{=}}CH_2} \rightleftharpoons \mathrm{R{-}CH\overset{CH}{\cdots}CH_2}\ \underset{\mathrm{H{-}M}}{} \rightleftharpoons \mathrm{R{-}\underset{\substack{\vdots\\ M}}{CH{=}}CH{-}CH_3} \qquad (2)$$

Scheme 2-3. Two potential mechanistic pathways of alkene isomerization.

In general, palladium on charcoal, written as Pd/C, is used to hydrogenate alkenes[6] with, in many cases, high facial selectivity (Scheme 2-4).[7]

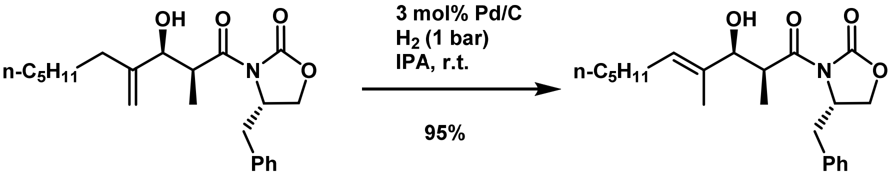


137

138

Scheme 2-4. Hydrogenation conditions with palladium on charcoal.

An unexpected report showed that using 3 mol% Pd/C and hydrogen (1 bar) in isopropyl alcohol as solvent gave predominantly the isomerized product instead of the expected hydrogenated product. Fordred, *et al.,* then developed a methodology with $Pd(OH)_2/C$ and hydrogen in acetonitrile to isomerize alkenes.[8] However, this methodology was only used for allylic alcohols, not unactivated alkenes (Scheme 2-5).



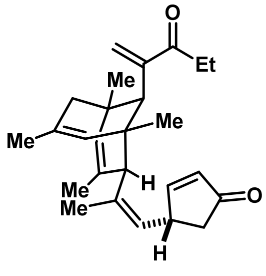
139

140

Scheme 2-5. Reported isomerization of allylic alcohol **139**.

In this chapter, we describe the study of the isomerization of a novel bicyclic di-(exo)methylene system to the internal dienes.

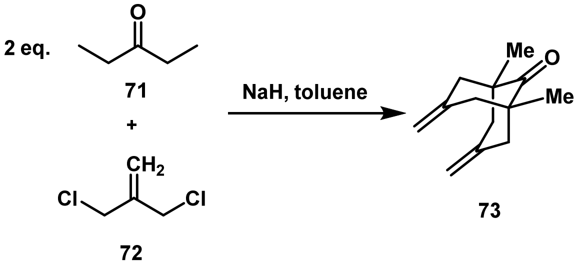
RESULTS AND DISCUSSION



Rugulosone, 1

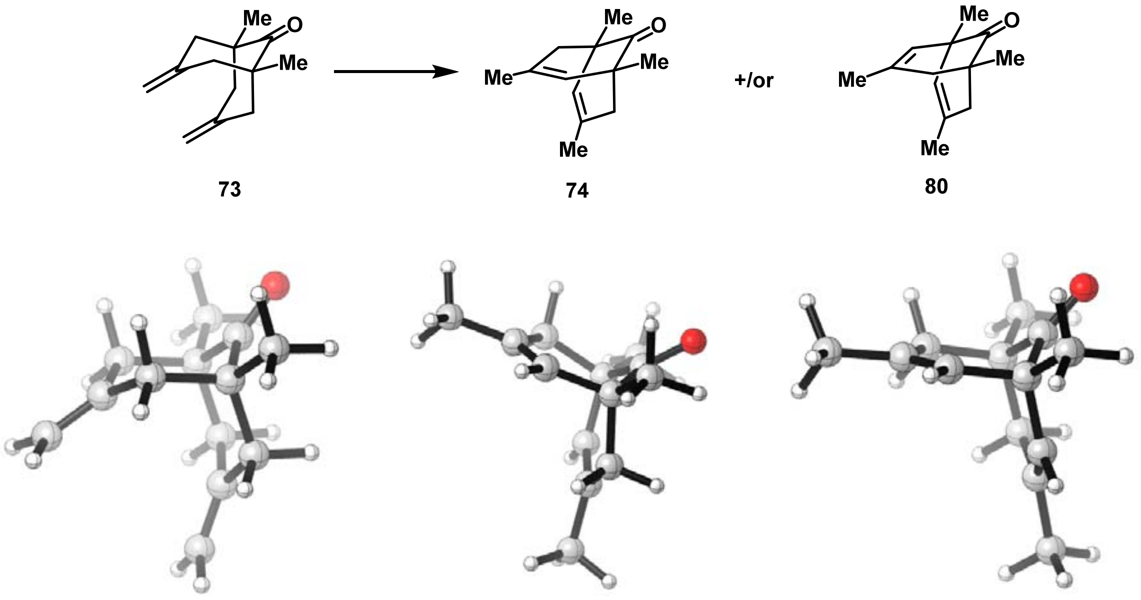
Figure 2-2. Rugulosone **1**.

For our efforts towards the total synthesis of the natural product rugulosone, **1**,[9] we needed a simple and efficient way to construct the bicyclo[3.3.1]nona-2,6-diene core. Our approach began by first obtaining the simple analogue 1,5-dimethyl-3,7-bis(methylene)bicyclo[3.3.1]nonan-9-one **73** in one step by the tetraalkyation of 3-pentanone **71** with 1-chloro-2-(chloromethyl)-2-propene **72** (Scheme 2-6). We then needed to isomerize the di-(exo)methylenes of the diene **73** to the internal, trisubstitued alkenes.



Scheme 2-6. Formation of dienone **73**.

Before attempting any experiments, a closer examination proved that the transformation might not have been as simple as it appears. Two possible isomers could form from the rearrangement of the diene **73**. Namely, the C_2 isomer **74**, with an axis of symmetry going through the carbonyl, and/or the C_S isomer **80**, with a place of symmetry going through the carbonyl, could be formed (Scheme 2-7). The C_2 isomer **74** was the one required for the synthesis of the natural product rugulosone.



Exocylic **C_2** **C_S**

Scheme 2-7. Chemdraw representation and molecular ball-and-stick models of isomerization of **73** to give **74** and/or **80.**

In addition, we believed that the C_2 isomer **74** would be more stable than C_S isomer **80** due to the steric non-bonded interaction of the indicated allylic hydrogens present in **80** but not in the C_2 isomer **74** (Figure 2-3).

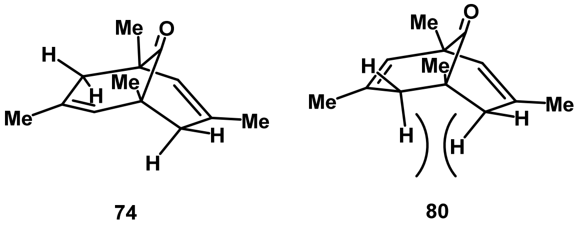
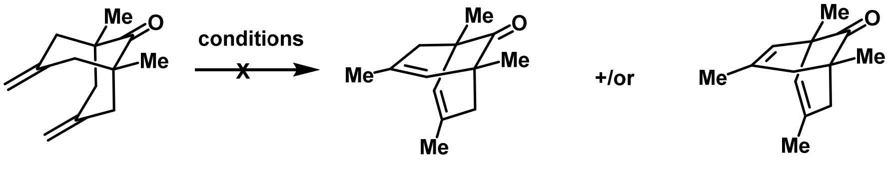


Figure 2-3. Structures of the C_2 and C_S dienes **74** and **80**.

Initial attempts to directly isomerize the diene **73** with transition metal catalysts such as Wilkinson's or Crabtree's catalyst failed to yield either **74** or **80**; only starting material was recovered.[10] Similarly, reaction with palladium (II) acetate or palladium (II) chloride gave no reaction. Under either basic 4-dimethylaminopyridine (DMAP) or slightly acidic (silver perchlorate) or microwave conditions with or without silica gel, again no reaction was observed. The uniquely strained and/or hindered structure of the bicyclononane core may cause this lack of reactivity.

Table 2-1. Attempts to isomerize bicyclodiene **73**.

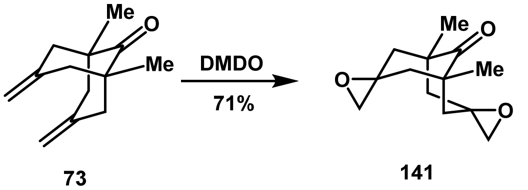


73 **74** **80**

Entry	Conditions	Results
1	Wilkinson's catalyst ($RhCl(PPh_3)_3$)	No reaction
2	H_2, Crabtree's catalyst $[Ir(cod)(PCy_3)(py)]PF_6$	No reaction
3	$Pd(OAc)_2$, benzene reflux	No reaction
4	DMAP	No reaction
5	$PdCl_2$	Completely saturated product
6	$AgClO_4$	No reaction
7	MW, various temperatures, times, w/ or w/o silica gel	No reaction

Since we were unable to directly isomerize the olefins, we decided upon a longer and more complicated process. After the initial formation of the diepoxide, if it could be opened to either the tertiary alcohol or the allylic alcohol, then cleavage of either alcohol would form the desired internal olefins.

Epoxidation of **73** with *meta*-chloroperoxybenzoic acid (*m*CPBA) or oxone gave a mixture of products. Treatment of **73** with dimethyldioxirane (DMDO) at room temperature for three hours afforded the single diepoxide **141** in 71% yield. We have assigned the structure as the bis(exo)epoxide **141** due to steric hinderance.

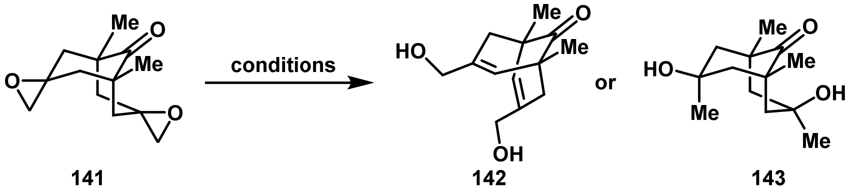


Scheme 2-8. Epoxidation of bicycle **73** to give diepoxide **141**.

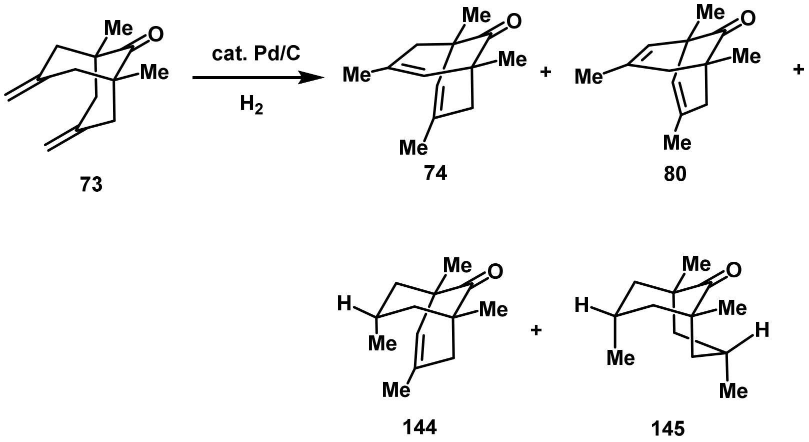
Many conditions were used in an attempt to promote ring opening of the diepoxide to either the allylic alcohol or the tertiary alcohol (Table 2-2). Conditions such as Super Hydride, $LiEt_3BH$,[11] $LiEt_2N$,[12] chloroform,[13] and magnesium isopropylcyclohexylamine (MICA)[14] either only returned starting material or gave a complex mixture of products. It is presumed that the lack of activity is due to the uniquely structured bicyclononane ring system.

The desired isomerization of the diene **73** was, however, effected by the use of an activated palladium catalyst mixed with hydrogen gas. Thus, treatment of **73** in methanol with 4 mol% Pd/C under a balloon of hydrogen afforded the desired C_2 isomer **74** along with the monoreduced and direduced products **144** and **145** (Scheme 2-9).

Table 2-2. Attempts to open diepoxide **141**.



Entry	Conditions	Results
1	LAH, reflux, 1 day	No reaction
2	LAH, Fieser workup	No reaction
3	$NaBH_4$, LiCl	Complex mixture
4	$LiEt_3BH$	Complex mixture
5	$LiNEt_2$	Complex mixture
6	TMSOTf, DBU	No reaction
7	$Al(OiPr)_3$	Complex mixture
8	LDA	Complex mixture
9	TsOH, $CHCl_3$	Complex mixture
10	nBu_3SnH, AIBN, NaI	Complex mixture
11	MICA	Complex mixture



Scheme 2-9. Isomerization of **73** to give **74** and other products.

It was surprising to us that under these conditions, the predominant products were the C_2 and C_S isomers **74** and **80**, respectively, and not the hydrogenated products as one typically expects from these hydrogenation conditions. Thus, a number of control experiments were conducted to demonstrate that hydrogen was required for this isomerization (Table 2-3). Although there initially appeared to be a temperature effect on the ratios of C_2 and C_S isomers, multiple runs later proved it was within experimental error (entry 2). Under an argon atmosphere, instead of hydrogen, no reaction was observed. To eliminate the possibility of hydrogen being needed to reduce potential palladium oxide that formed on the surface and to regenerate active palladium (0), the catalyst was pretreated with hydrogen gas and then the flask was purged with argon. This procedure also gave no isomerization. The addition of excess cyclohexene (to remove all the hydrogen gas) before the addition of **73** was also unsuccessful. However, the use of ammonium formate, which generates hydrogen gas *in situ* for transfer hydrogenation, also produced the expected isomerization. Therefore, it seems that the reaction requires a small amount of hydrogen to initiate the isomerization.

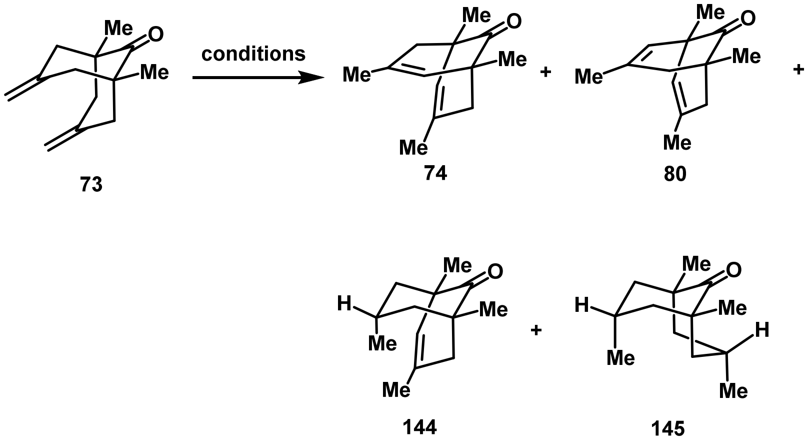


Table 2-3. Control experiments to demonstrate need for hydrogen gas.

Entry	Conditions	Results
1	H_2, Pd/C, 25 ºC	70% yield, mixture of C_2, C_s, mono-, and di- reduced products
2	H_2, Pd/C at 0 and 35 ºC	Slightly different ratio of C_2 and C_s
3	Pd/C, argon	No reaction
4	"activated" Pd/C, then flush with argon	No reaction
5	Pd/C, HCO_2NH_4, argon	Product formation
6	H_2, Pd/C	90% (1g scale)

Being able to obtain the desired C_2 isomer **74**, we then sought to increase the relative yields of the isomeric products. It is known that solvent effects can play a large role in hydrogenation rates.[15] Therefore, we believed that if we could slow down the hydrogenation pathway via a change of solvent, then the alkene isomerization pathway might be favored. Table 2-4 shows a variety of solvent systems there were screened to see if solvent effects could improve the yield of the isomerization.

It was found that polar, protic solvents such as methanol and isopropanol gave large amounts of the monoreduced product **144** and some of the fully reduced material **145**. Reaction in ethyl acetate gave the desired C_2 product **74** in high yield (87%), along with the first observation of the formation of the C_S isomer **80** and the monoreduced product **144.** This was our first observation of a lack of formation of the di-reduced product **145**. Other polar, aprotic solvents, such as acetone, dioxane and THF, also produced predominantely the desired C_2 product **74** along with small amounts of the C_S isomer **80** and the monoreduced compound **144**. Again, no fully

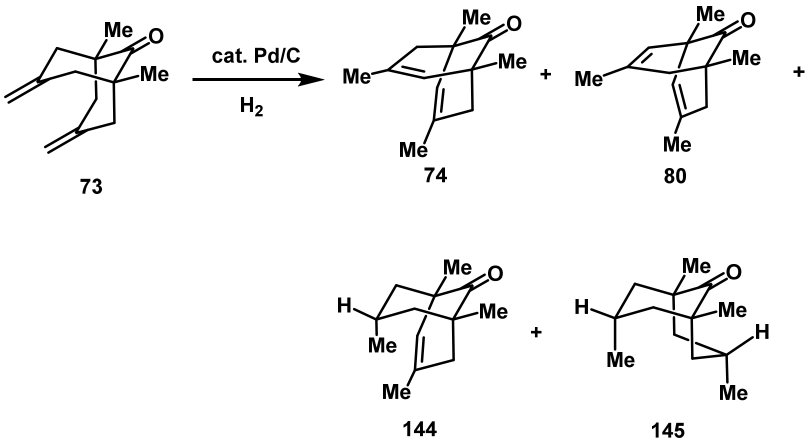
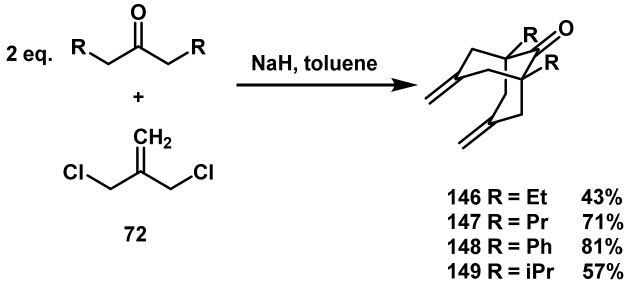


Table 2-4. Solvent effects on conversion of **73** to **74, 80, 144**, and **145**.

entry	solvent	time	74	80	144	145	SM
1	MeOH	1h	68	0	28	4	0
2	iPrOH	1h	68	0	26	6	0
3	EtOAc	1h	87	9	4	0	0
4	Hexane	1h	81	7	12	0	0
5	Acetone	1h	79	6	14	0	0
6	Dioxane	1h	64	6	11	0	19
7	THF	1h	77	9	13	0	1

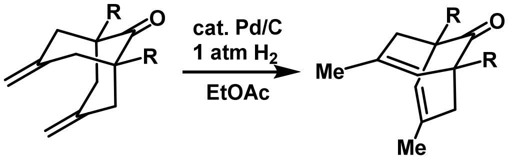
reduced product **148** was observed. Using a non-polar solvent such as hexane afforded isomerization with similar results. Thus, we were able to obtain a more desirable ratio between the C_2 isomer, the C_S isomer, the mono-reduced, and the di-reduced products by a change in solvent.

We then explored whether the isomerization to the C_2 isomer in great preference to the C_s isomer was general. Thus, the additional bis(exo-methylene) compounds, **146-149**, were prepared from the corresponding substituted ketones and the bis(chloromethyl)ethylene **72**. The structures and yields are given in Scheme 2-10.



Scheme 2-10. Formation of bicyclo[3.3.1]nonane analogues.

Treatment of both **146** and **147** under the conditions described above, namely Pd/C under an atmosphere of hydrogen gas, afforded predominately the C_2 products **150** and **151** in preference to the possible C_s product (Scheme 2-11). However, the diphenyl-substituted analogue **148** gave only starting material under these conditions with no production of any isomeric or reduction products. It is postulated that although palladium can certainly coordinate to the exo-methylene of the starting material, after hydride addition, it is difficult to eliminate the β-hydride to effect the isomerization, presumably because of the steric interaction with the large diphenyl substituents. Thus, we decided to synthesize the diisopropyl-substituted analogue **149** since phenyl and isopropyl groups are comparable in size. If isomerization could be effected, then we would conclude that there must be another reason other than steric hinderance that is causing the diphenyl to give no reaction. However, under our normal conditions, the diisopropyl analogue **149** gave a bad mixture of products. Thus, this preference for the C_2 product rather than the C_s product occurs for most alkyl substituents at the bridgehead carbons.

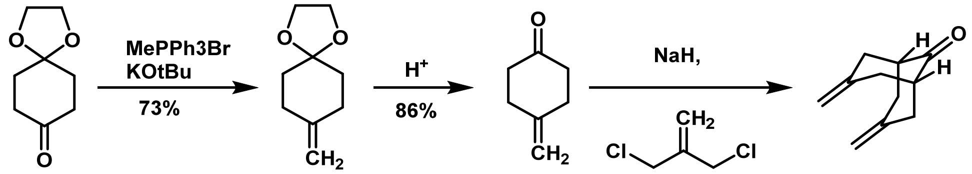


146 R = Et
147 R = Pr

150 R = Et
151 R = Pr

Scheme 2-11. Isomerization of alkenes **150** and **151.**

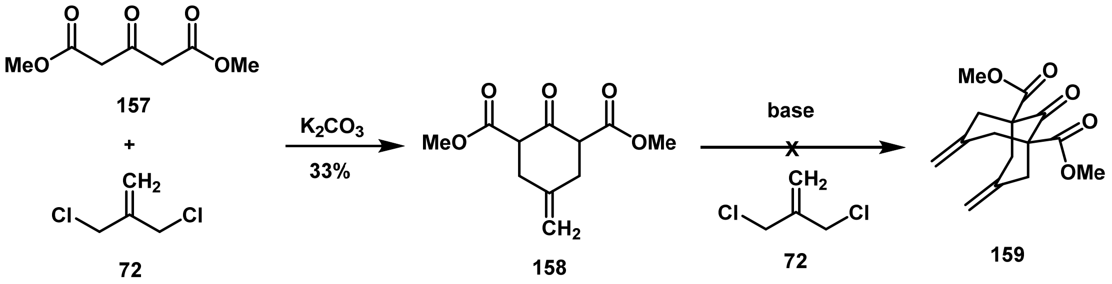
We attempted to make the parent compound, **156**, where R = H in **146**, but simple reaction of acetone with the allyl dichloride **72** failed to give any of the desired product. A longer route was attempted (Scheme 2-12), beginning with 1,4-cyclohexanedione monoketal **152**, followed by Wittig reaction to produce the exo-methelene group of intermediate **153** and then deprotection to form the ketone **154**. Under various basic conditions, reaction of the ketone **154** with the allyl dichloride **72** gave only trace amounts of the parent bicyclo[3.3.1]nonanone **156**.



152 153 154 72 156

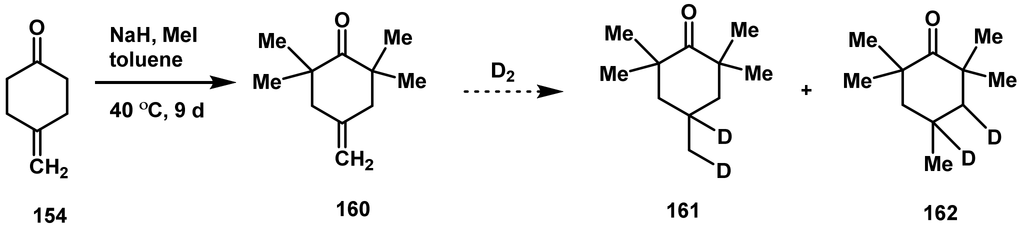
Scheme 2-12. Attempt to make bicycle **156**.

In addition, attempts were made to synthesize the ketodiester **159** (Scheme 2-13). Simple reaction of dimethyl 1,3-acetonedicarboxylate **157** with the allyl dichloride **72** furnished very little of the desired bicycle. And although we were able to form the cyclohexanone **158** via the dialkylation, all attempts to form the bicyclononane **159** were unsuccessful.



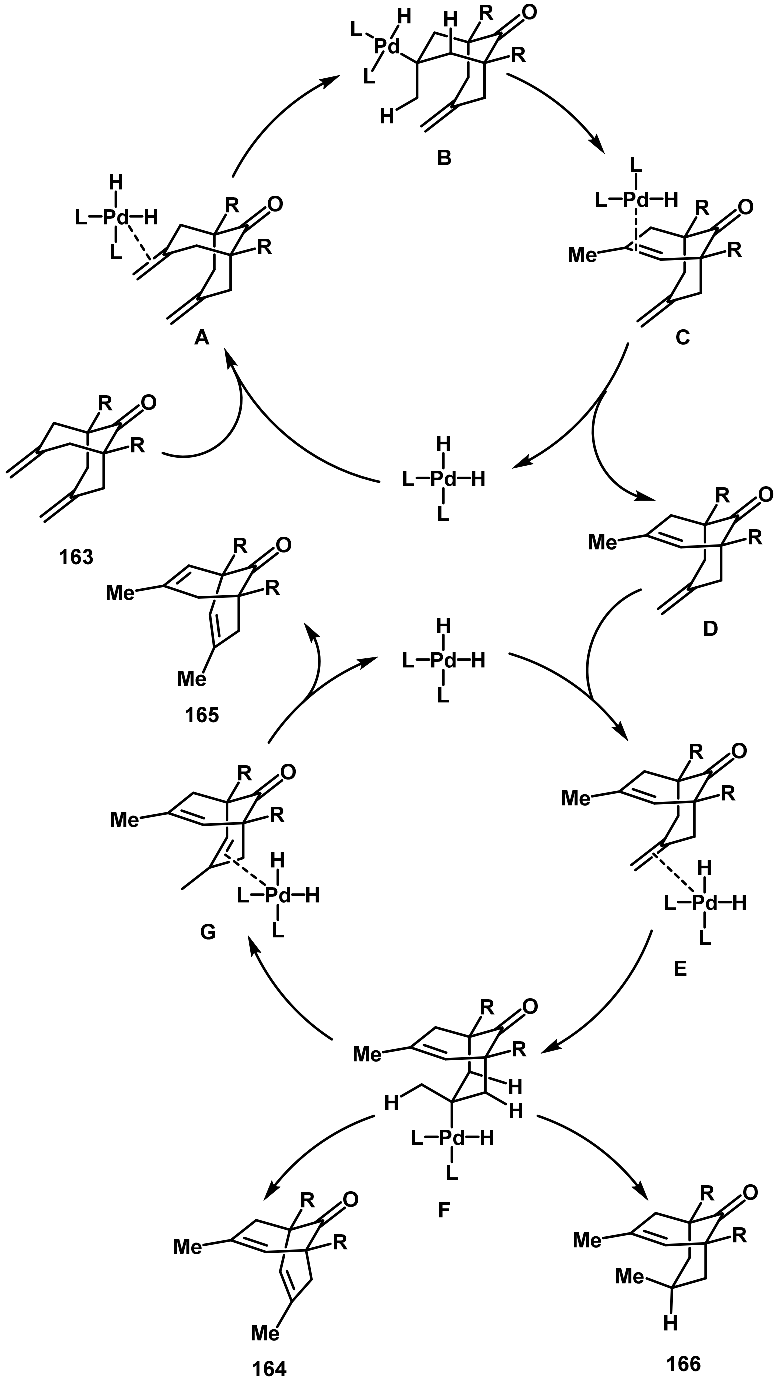
Scheme 2-13. Attempt to make ketodiester **159**.

We also attempted to make 2,2,6,6-tetramethyl-4-methylenecyclohexanone **162** for deuterium studies. We wanted to see if the orientation of the bicycle had any influence on the slow hydrogenation pathway over the isomerization pathway. Thus, in this monocyclic model, we could probe to see which of the two pathways are favored without the steric influence. Simple inspection of the NMR would be able to distinguish between the two possible deuterated products **161** and **162**. Attempted polyalkylation of 4-methylenecyclohexan-1-one **154** with methyl iodide gave many products. We obtained very little of the desired cyclohexanone **160** after 9 days at 40˚ C in benzene (Scheme 2-14). With only a small amount of cyclohexanone **160** in hand, experiments using deuterium gas were inconclusive.



Scheme 2-14. Treatment of **160** with deuterium gas.

The proposed mechanism for the isomerization is shown in Scheme 2-15. We believe the isomerization proceeds via a metal hydride addition/elimination sequence, instead of proceeding



Scheme 2-15. Proposed mechanism for the isomerization of **163.**

through a π-allyl complex.[10] Thus, coordination of the bis(exo-methylene) **163** with palladium would give **A**, followed by hydride addition to form **B**, subsequent β-hydride elimination to afford

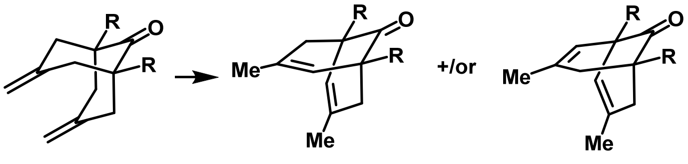
C, and then decomplexation to give the monoisomerized product **D**, which has never been observed. The same type of process can convert **D**, via the intermediates **E**–**G**, to either the C_2 isomer **164** or the C_S isomer **165** and can interconvert between these intermediates as well.

It is important to note that all these processes are reversible and the product ratio is most likely determined by thermodynamic stabilities. It is presumed that the thermodynamic equilibrium lies completely on the side of the C_2 isomer. Using our conditions, however, it is difficult to arrive at the thermodynamic equilibrium because although most processes are reversible, the process of an alkene being hydrogenated is probably not reversible.

In collaboration with the Houk laboratories, Hung Pham determined the energies of each of the isomers by calculating the structure and energies of reactants, the mono-isomerized species and the isomeric di-isomerized species with density functional theory. Using Gaussian 09,[16] optimizations were performed using B3LYP/6-31G(d),[17] followed by M06-2X/6-311+G(d,p) single point calculations to account properly for dispersion effects.[18] The results are shown in Table 2-5. The parent unsubstituted system **163** (R = H) shows a 2.9 kcal/mol preference for the C_2 diene isomer over the C_S diene. All of the trisubstituted alkenes were significantly more stable, e.g., 7-9 kcal/mol, than the disubstituted alkene starting materials. Methyl and larger alkyl substituents at the bridgehead carbons led to a greater preference for the C_2 isomer. This is in good agreement with the fact that under all conditions the C_2 diene **164** is the predominant product.

We set out to investigate the source of the preference for the C_2 isomer. As mentioned before, the examination of molecular models revealed a possible unfavorable steric interaction involving the two allylic hydrogen atoms in **165** as shown in Figure 2-3. Inspection of the optimized geometries

Table 2-5. Free energy calculations for C_2 and C_S isomers[a]



163

164

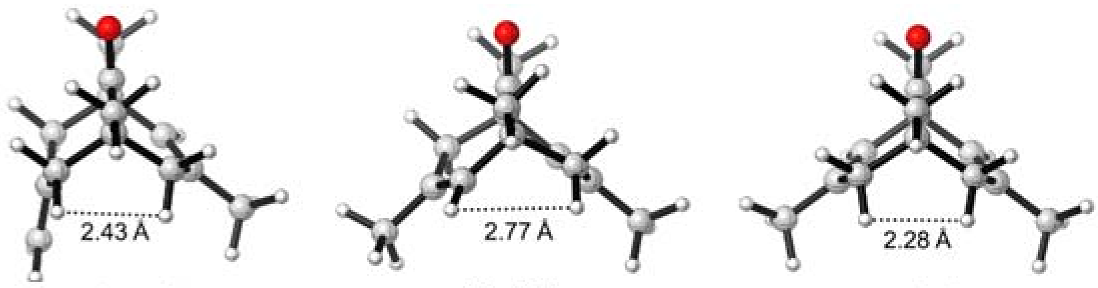
C_2

165

C_S

R	Exo (SM)	C_2	C_S	Difference
H	0.0	-8.0	-5.1	2.9
Me	0.0	-7.1	-3.8	3.3
Et	0.0	-9.0	-5.2	3.8
Pr	0.0	-8.7	-4.6	4.1
Ph	0.0	-9.2	-6.4	2.8

[a]Gas phase calculations were carried out using M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) and are quoted in kcal/mol.



144 (mono) -4.2 kcal/mol

74 (C_2) -7.1 kcal/mol

80 (C_S) -3.8 kcal/mol

Figure 2-4. The monoisomerized and C_2 and C_S bis-isomerized optimized structures.

Free energies calculated using M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) are relative to **73**.

reveals that, although the decrease in H---H distance correlates well with an increase in stability across the isomers (Figure 2-4), a 2.28 Å distance is not sufficient to conclude that the 3-4 kcal/mol thermodynamic preference is dominated by steric repulsion. Interestingly, a twisting of the bicyclo[3.3.1]nonadienone core in **74**, which is not observed in the less stable **80**, points towards ring strain induced by non-bonding interactions as being another component of the energy difference. This slight rotation relieves some of the unfavorable eclipsing interactions and translates to an increase in the endo hydrogen distance.

CONCLUSION

In summary, the facile isomerization of the bis(exo)-methylene bicyclo[3.1.1]nonane systems gives rise predominantly to the C_2 products rather than the possible C_S products. Theoretical calculations reveal that the origin of this preference stems from thermodynamic effects, involving transannular hydrogen-hydrogen interactions and ring strain induced by these interactions. Many of these results have been published recently.[19]

EXPERIMENTAL

General

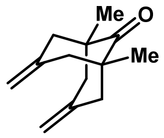
All reactions were carried out under an argon atmosphere unless otherwise specified. Dichloromethane was distilled from calcium hydride under an argon atmosphere. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), integration, multiplicity and coupling constant (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). HPLC purification was conducted on a Shimadzu HPLC system with a refractive index detector RID-10A and one Luna 5 µm C18(2) column with acetonitrile and water as an eluent. High resolution mass spectrometry was taken on a Thermo Fisher Scientific Exactive Plus mass spectrometer equipped with an IonSense ID-CUBE DART ion source.

General procedure for formation of di-(exo)methylenes

To a suspension of 60% sodium hydride in mineral oil (0.176 g, 4.40 mmol) (washed three times with hexanes) in toluene (5 mL) was added dropwise 3-pentanone (0.086g, 1.00 mmol) in toluene (2 mL). A solution of 1-chloro-2-(chloromethyl)-2-propene (0.254 g, 2.20 mmol) in toluene (2 mL) was added dropwise and the reaction was refluxed overnight. The solution was then cooled to room temperature and quenched with a saturated solution of NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (3 X 20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the bicyclononanone **73** (0.171 g, 0.90 mmol, 90%) as a light yellow oil.

Compounds **146** and **147** were prepared in an analogous manner.

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one, 73.



73

^{1}H NMR (500 MHz, $CDCl_3$) δ

4.73 (s, 4H)

2.57 (d, *J* = 15.0 Hz, 4H)

2.42 (d, *J* = 15.0 Hz, 4H)

1.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5, 141.8, 112.7, 49.7, 45.3, 23.5.

HRMS (ESI, *m/z*): 191.1424, calculated for [$C_{13}H_{19}O$] 191.1436.

General procedure for the palladium hydride promoted isomerization

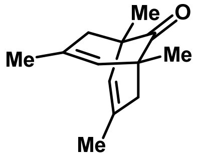
To a solution of the bicyclononanone **73** (0.050 g, 2.63 mmol) in ethyl acetate (5 mL) was added palladium (10 wt. % on activated carbon) (0.011 g, 0.11 mmol). The reaction vessel was then purged with a hydrogen balloon for 5 min, then allowed to stir at ambient temperature and pressure for 1 h. The mixture was then filtered over Celite, washed with ethyl acetate (15 mL), then concentrated in vacuo to give diene **74** and other products (0.50 g, 2.63 mmol, 100%) as a light yellow oil. The crude mixture was then purified via HPLC.

Compounds **150** and **151** were prepared and purified in an analogous manner.

(±) (1*R*,5*R*)-1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-dien-9-one, 74.

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.14 (s, 2H)



74

2.27 (d, *J* = 17.0 Hz, 2H)

2.22 (d, *J* = 17.0 Hz, 2H)

1.65 (s, 6H)

1.07 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 132.8, 130.9, 48.5, 45.5, 22.3, 21.1.

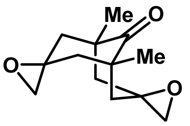
HRMS (ESI, *m/z*): 191.1425, calculated for [$C_{13}H_{19}O$] 191.1436.

1',5'-Dimethyldispiro[oxirane-2,3'-bicyclo[3.3.1]nonane-7',2''-oxiran]-9'-one, 141.

To a solution of freshly prepared dimethyldioxirane (DMDO) in acetone (9.26 mL, 0.78 mmol) was added the bicyclononanone **73** (0.050 g, 2.63 mmol) in acetone (2 mL). The reaction was allowed to stir at 21 ˚C for 1 h, then dried with $MgSO_4$ and concentrated in vacuo to give the diepoxide **141** (0.052 g, 89%) as white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ

2.95 (s, 4H)



141

2.31 (d, *J* = 14.5 Hz, 4H)

1.64 (d, *J* = 14.5 Hz, 4H)

1.08 (s, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 215.1, 59.7, 54.7, 47.1, 45.5, 23.8.

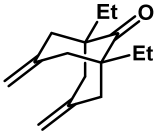
HRMS (ESI, *m/z*): 223.1324, calculated for [$C_{13}H_{19}O_3$] 223.1334.

1,5-Diethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one, 146.

^{1}H NMR (500 MHz, CDCl$_3$) δ

4.74 (t, *J* = 2 Hz, 4H)

2.57 (d, *J* = 14.8 Hz, 4H)



146

2.33 (d, *J* = 14.8 Hz, 4H)

1.50 (q, *J* = 7.6 Hz, 4H)

0.86 (t, *J* = 7.6 Hz, 6H).

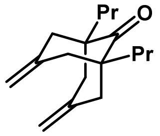
^{13}C NMR (125 MHz, CDCl$_3$) δ 218.5, 142.0, 113.1, 47.8, 46.6, 29.2, 8.0.

HRMS (ESI, *m/z*): 219.1738, calculated for [$C_{15}H_{23}O$] 219.1749.

3,7-Dimethylene-1,5-dipropylbicyclo[3.3.1]nonan-9-one, 147.

^{1}H NMR (500 MHz, CDCl$_3$) δ

4.73 (t, *J* = 2 Hz, 4H)



147

2.58 (d, *J* = 15.0 Hz, 4H)

2.39 (d, *J* = 15.0 Hz, 4H)

1.44 – 1.40 (m, 2H)

1.29-1.25 (m, 6H)

0.93 (t, *J* = 7.5 Hz, 6H).

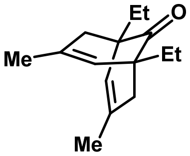
^{13}C NMR (125 MHz, $CDCl_3$) δ 218.4, 142.0, 112.8, 47.8, 47.1, 39.0, 16.8, 14.9.

HRMS (ESI, *m/z*): 247.2050, calculated for [$C_{17}H_{27}O$] 247.2062.

± (1*R*,5*R*)-1,5-Diethyl-3,7-dimethylbicyclo[3.3.1]nona-2,6-dien-9-one, 150.

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.17 (s, 2H)



150

2.24 (d, *J* = 17.0 Hz, 2H)

2.15 (d, *J* = 17.0 Hz, 2H)

1.73-1.66 (m, 2H)

1.67 (s, 6H)

1.35 (q, *J* = 7.0 Hz, 1H)

1.32 (q, *J* = 7.0 Hz, 1H)

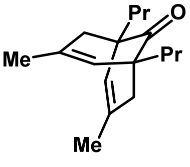
0.85 (t, *J* = 7 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.9, 133.5, 128.7, 49.1, 46.6, 27.2, 22.6, 8.5.

HRMS (ESI, *m/z*): 219.1737, calculated for [$C_{15}H_{23}O$] 219.1749.

(±) (1*R*,5*R*)-3,7-Dimethyl-1,5-dipropylbicyclo[3.3.1]nona-2,6-dien-9-one, 151.

^{1}H NMR (500 MHz, $CDCl_3$) δ



151

5.17 (s, 2H)

2.24 (d, *J* = 17.0 Hz, 2H)

2.14 (d, *J* = 17.0 Hz, 2H)

1.66 (s, 6H)

1.65-1.60 (m, 2H)

1.38-1.29 (m, 2H)

1.29-1.18 (m, 4H)

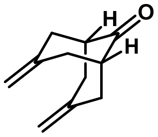
0.90 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.9, 133.1, 129.0, 48.9, 46.9, 37.1, 22.5, 17.4, 14.9.

HRMS (ESI, *m/z*): 247.0877, calculated for [$C_{17}H_{27}O$] 247.2062.

3,7-Dimethylenebicyclo[3.3.1]nonan-9-one, 156.

To a solution of sodium hydride (0.18 g, 4.5 mmol) in benzene (5 mL) was added 4-methylenecyclohexan-1-one **154** (0.2 g, 1.82 mmol) in benzene (5 ml) followed by a solution of allyl chloride **72** (0.25 g, 2.0 mmol) in benzene (2 mL). The reaction mixture was refluxed overnight, then quenched with dropwise addition of aqueous NH_4Cl (10 mL), extracted with ethyl acetate (3 X 10 mL), and washed with brine (10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the bicyclic dienone **156** (0.010 g, 0.06 mmol, 3%) as a light yellow oil.



156

^1H NMR (500 MHz, $CDCl_3$) δ:

4.78 (t, *J* = 2.0 Hz, 4H)

2.72 (bd, *J* = 14.0 Hz, 4H)

2.67 (bd, *J* = 15.0 Hz, 4H)

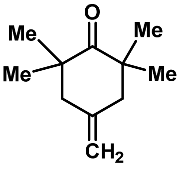
2.47 (bs, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9, 141.4, 113.7, 47.3, 42.1.

2,2,6,6-Tetramethyl-4-methylenecyclohexan-1-one, 160.

To a solution of 4-methylenecyclohexan-1-one **154** (0.1 g, 0.91 mmol) in toluene (5 ml) was added sodium hydride (0.43 g, 10.8 mmol) and methyl iodide (0.57 mL, 0.91 mmol). The solution was stirred at 40 ˚C for 9 d. The reaction mixture was quenched by the dropwise addition of water (5 mL), extracted with ethyl acetate (3 X 10 mL) and washed with brine (10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the cyclohexanone **160** (0.015 g, 0.09 mmol, 10%) as a light yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ:



160

4.90 (pentet, *J* = 1.2 Hz, 2H)

2.36 (t, *J* = 1.2 Hz, 4H)

1.11 (s, 12H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 219.2, 141.9, 112.1, 46.8, 45.1, 27.1.

GCMS (*m/z*): 166.1.

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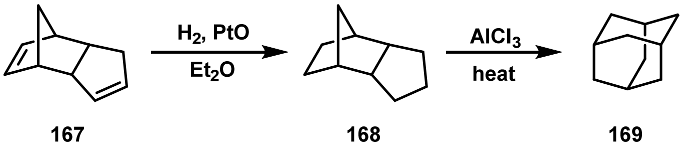
CHAPTER 3

Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonan-9-ones

INTRODUCTION

The unique, caged structure of adamantane has interested chemists for nearly a century. Even before its isolation in 1933 from petroleum,[1] chemists sought to synthesize this smallest unit cage structure of the diamond crystal lattice. The first attempted laboratory synthesis was in 1924 when Hans Meerwin reacted formaldehyde with diethyl malonate under basic conditions.[2] However, instead of adamantane, Meerwein obtained 1,3,5,7-tetracarbomethoxy-bicyclo[3.3.1]nona-2,6-dione instead; this compound was later named Meerwein's ester.

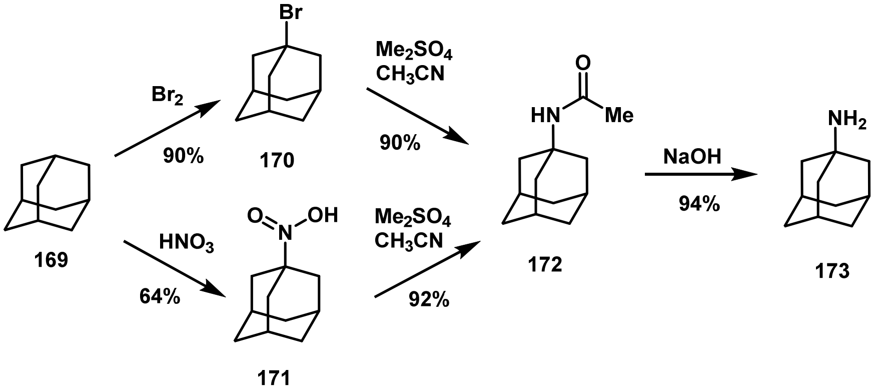
The first synthesis of adamantane was accomplished by Vladimir Prelog in 1941 in five steps from Meerwein's ester, with an overall yield of less than 1%.[3] Then, in 1957, Paul von Rague Schleyer accidentally synthesized adamantane **169** by first hydrogenating dicyclopentadiene **167** with platinum (II) oxide, then heating the product **168** with aluminum (III) chloride to 150 ˚C.[4] This method has been improved upon (from 30% to 60% yield) and is the current method of synthesizing adamantane today (Scheme 3-1).



Scheme 3-1. von Rague Schleyer's adamantane synthesis.

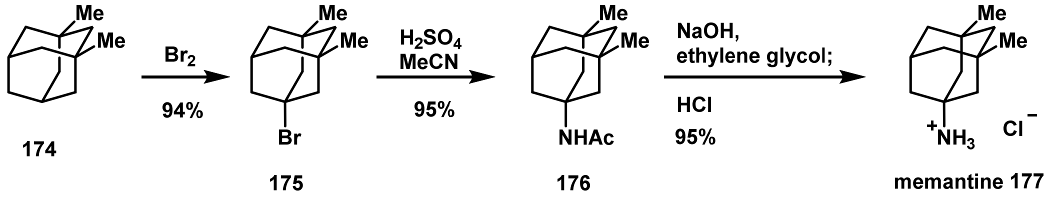
Adamantane possesses unique structural and physical properties with practical applications in drugs, polymeric materials, and lubricants. Studies have shown that adamantane is the most stable of the $C_{10}H_{16}$ isomers with an unusually high melting point of 270 ˚C. In addition, as the simplest diamondoid, adamantane consists of four connected cyclohexane rings all in a "chair" conformation. Almost contradictory, the structure is both extremely rigid but yet almost strain-free.

The first instance of the adamantane structure in medicinal chemistry involved 1-aminoadamantane **173**, commonly referred to as amantadine (Scheme 3-2). Developed by Du Pont, the selective antiviral agent was approved in 1966 for use against influenza.[5] Today, amantadine is no longer prescribed as an antiviral agent. Instead, it may be prescribed for the treatment of mild to moderate Parkinson's disease.[6]



Scheme 3-2. Commercial synthesis of amantadine **173**.

A number of other adamantane-containing small molecules have been approved for the treatment of various diseases, including adapalene, dopamantin, rimantadine, and tromantadine, to name a few. Today, the most common derivative is 3,5-dimethyl-1-aminoadamantane, or memantine, which has been approved for the treatment of Alzheimer's disease.[7,8] The current commercial synthesis involves bromination of 1,3-dimethyladamantane, then treatment with



Scheme 3-3. Commercial production of memantine **177**.

sulfuric acid in acetonitrile as solvent to form the acetamide **176**. Hydrolysis and treatment with HCl forms the hydrochloric salt of memantine (Scheme 3-3).

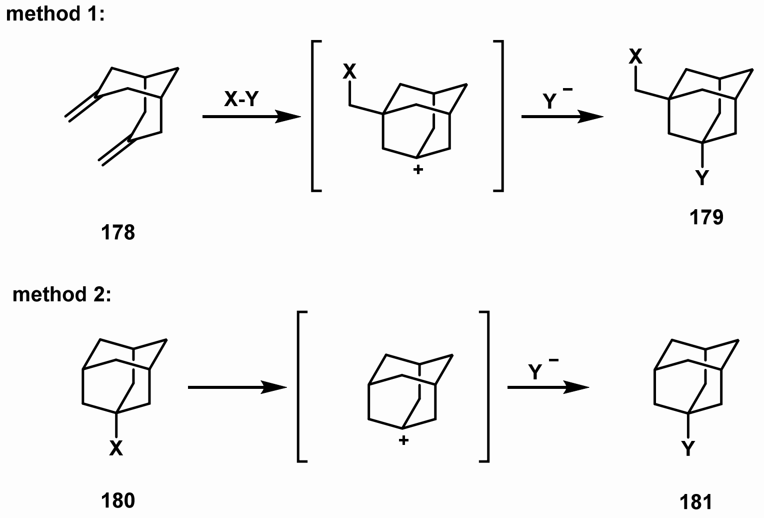
Although there are a number of adamantane drugs on the market, the biological mechanism of action of the adamantane derivatives is still unclear.[9] One hypothesis is that the size and shape of the adamantane core disrupts the transmembrane flow of protons within a helical viral matrix protein tetramer.[10] Another idea suggests that the adamantane unit binds between the membrane and the protein.

The medicinal properties of the adamantane core have been investigated[11] and found to possess four functions:

1. To change the Absorption, Distribution, Metabolism, or Excretion (ADME) properties of a small molecule.
2. To bind to an enzyme and inhibit viral replication.
3. To act as antagonists and prevent binding of a natural mediator.
4. To act as a rigid scaffold in the spatial positioning of functional groups.

Thus, adamantane is an important structural moiety in medicinal chemistry. In the literature, two methods are employed to form functionalized adamantanes (Scheme 3-4).

The first method is a one-step procedure that starts with the bicycle, 3,7-dimethylene-bicyclo[3.3.1]nonane, **178**, and carries out an electrophilic cyclization. It has been shown that reaction with a few reagents such as sulfuric acid, mercury acetate in water, and bromine produce the corresponding substituted adamantanes.[12]



Scheme 3-4. Two methods of formation of substituted adamantanes.

The second method is a two-step procedure that involves starting with a parent adamantane, treating with bromine or chlorine to prepare the mono-, di-, or polyhalogenated adamantane, e.g. **180**, and then effecting subsequent functionalization to afford the desired products, e. g., **181**. Often times, harsh conditions such as high temperature, long reaction times, and high pressure mercury lamps are used.[13]

Examples of Friedel-Crafts alkylation of aromatics with the adamantane core are limited. Inamoto, *et al.,* has shown that phenol and *o*-, *m*-, and *p*-cresol were able to undergo adamantylation with 1-bromoadamantane under sulfuric acid conditions.[14] Olah and coworkers have reported a boron tris(triflate)-catalyzed adamantylation of benzene and toluene with haloadamantanes.[15] Although the yields of the reaction are moderate (50-70%), a large amount of adamantane is recovered. In addition, only two aromatics, benzene and toluene, were studied.[16]

Both methods go through the same adamantyl carbocation intermediate. The adamantyl cation has a unique structure as the caged system of the molecule renders the carbocation non-planar. Compared to even its tertiary counterpart, the adamantyl carbocation is unusually stable. The crystal structure of 3,5,7-trimethyl-1-adamantyl cation Sb_2F_{11} **182** was obtained by Laube in 1986 (Figure 3-1).[17] The cationic center C1 is clearly flattened with bonds from C1 having an average length of 1.44 Å. Small C-C-C bond angles around the carbocation of 99° show that the atoms around C1 are more sp^2 hybridized than one would expect. This reflects that fact that the 1-adamantyl cation is stabilized by carbon-carbon hyperconjugation.[18]

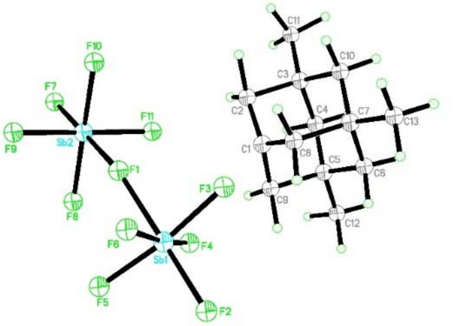
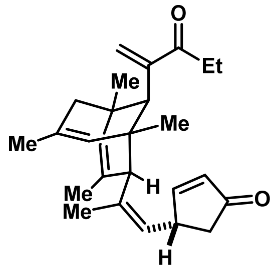


Figure 3-1. Laube's crystal structure of 3,5,7-trimethyl-1-adamantyl cation Sb_2F_{11} **182** and adamantane numbering scheme.

To our knowledge, no systematic study of the Friedel-Crafts alkylation and trapping of nucleophiles with adamantanes has been carried out. Thus, we were interested to see if one could efficiently construct substituted adamantanones, potential precursors to the corresponding adamantanes. In addition to lengthy syntheses and harsh conditions, limited reactions scope prompted us to investigate a more efficient way of rapidly constructing substituted adamantanes. If we were able to construct a large variety of substituted adamantanones in a highly efficient and simple manner, the resulting biological testing might point us in the right direction to investigate the mechanism of action of this structurally unique class of compounds.

RESULTS AND DISCUSSION

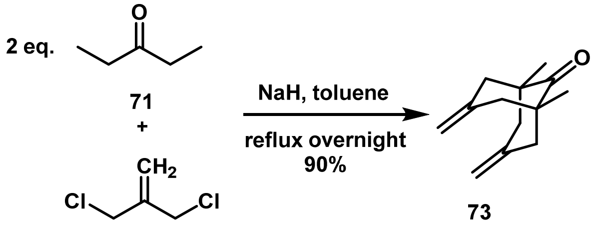
Initially, for our work towards the synthesis of rugulosone, **1** (Figure 3-2), we sought to construct the C_2 symmetric bicyclo[3.3.1]nonane core.[19] Thus, we prepared 1,5-dimethyl-3,7-dimethylene-bicyclo[3.3.1]nonan-9-one **73** by the very efficient quadruple alkylation of 3-pentanone **71** with 1,1-bis(chloromethyl)ethylene **72**, a reaction that proceeded in 90% yield (Scheme 3-5).[20]



Rugulosone, 1

Figure 3-2. Rugulosone **1.**

In our efforts to isomerize the exo-methylene groups of the bicyclononane **73** to the internal, trisubstituted alkenes, we tried a number of conventional transition metal catalysts. Wilkinson's Rh-based catalyst, as well as Crabtree's Ir-based catalyst, returned only starting material with no formation of isomerized product.[21] Similarly, reaction with palladium (II) acetate gave no reaction. Treatment with palladium (II) chloride under an atmosphere of hydrogen gave



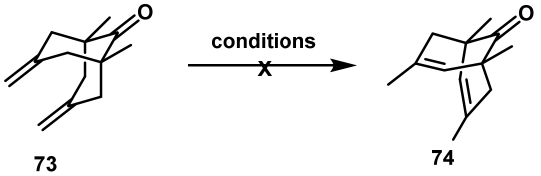
72

73

Scheme 3-5. Formation of bicyclononane **73**.

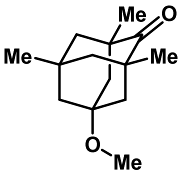
the completely saturated product. Under either basic, 4-(dimethylamino)pyridine, or slightly acidic, silver perchlorate, or microwave conditions with or without silica gel, again no reaction was observed.

Table 3-1. Attempts at isomerization of bicyclodiene **73**.



Entry	Conditions	Results
1	Wilkinson's catalyst ($RhCl(PPh_3)_3$)	No reaction
2	H_2, Crabtree's catalyst $[Ir(cod)(PCy_3)(py)]PF_6$	No reaction
3	$Pd(OAc)_2$, benzene reflux	No reaction
4	DMAP	No reaction
5	H_2, $PdCl_2$	Completely saturated product
6	$AgClO_4$	No reaction
7	MW, various temperatures, times, w/ or w/o silica gel	No reaction
8	$RhCl_3 \cdot H_2O$ (10 mol%), MeOH	40% side product

Finally, it was found that treatment with $RhCl_3 \cdot H_2O$ in a 1:1 ratio of $CHCl_3$:MeOH gave 40% of an unexpected product. This was determined to be the adamantanone methyl ether **183**.



183

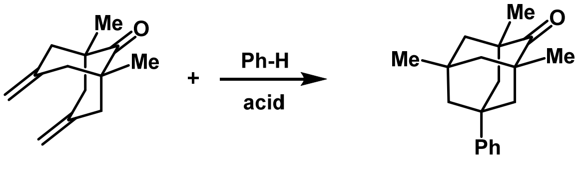
Figure 3-3. 5-Methoxy-1,3,7-trimethyladamantan-2-one **183.**

We believe that this resulted from formation of the adamantyl cation followed by trapping by the methanolic solvent. However, we hypothesize that slight traces of HCl in the $RhCl_3$ catalyst, instead of the Rh metal, triggered the formation of the cation, since Wilkinson's catalyst did not produce even trace amounts of product.[22]

Thus, we set out to develop a methodology to provide rapid access to the functionalized adamantanone core. Starting from the 3,7-dimethylenebicyclo[3.3.1]nonan-9-one core, we envisioned forming the adamantyl cation with acid, followed by trapping with various nucelophiles to obtain 5-substituted adamantan-2-ones.

We first screened various acidic conditions for the formation of the desired adamantanone product, 1,3,7-trimethyl-5-phenyladamantan-2-one **184** from **73** (Table 2-2). Without the presence of an added nucleophile, the cation can be quenched by the benzene solvent. Thus, treatment of the diene **73** with trimethylsilyl triflate in benzene afforded the 5-phenyl-substituted adamantanone **184** in 65% yield. Other Lewis acids, such as boron trifluoride etherate and aluminum (III) chloride, gave rise to **184** in moderate yields. Protic acids such as sulfuric acid and trifluoroacetic acid also gave the desired adamantanone core in yields of 21% and 59%, respectfully. Trifluoromethanesulfonic acid, triflic acid, was the best acid of those tested, resulting in a 90% isolated yield of **184**. Some Lewis acid catalysts, such as cupric triflate, did not provide any product but only returned starting material, as did the reaction without an additive.

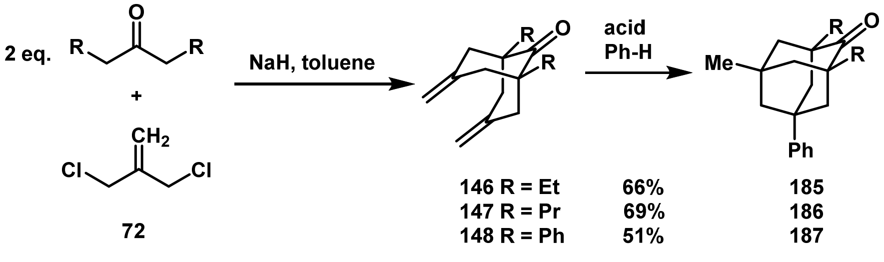
Table 3-2. Conversion of diene **73** to phenyladamantane **184.**



73 **184**

Entry	Acid	Yield (%)
1	TMSOTf	65
2	$BF_3 \cdot OEt_2$	78
3	$AlCl_3$	47
4	H_2SO_4	21
5	TFA	59
6	TfOH	90
7	$Cu(OTf)_2$	0
8	None	0

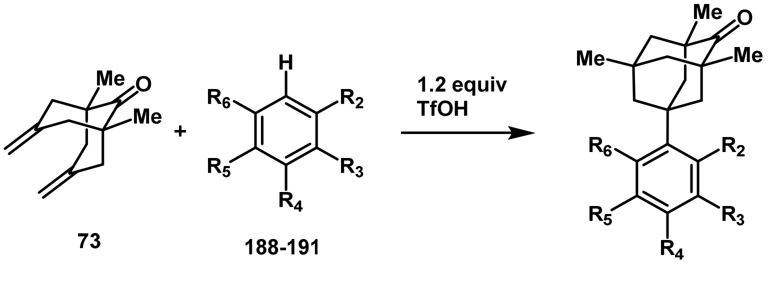
To expand our substrate scope, we prepared the additional compounds **146**, **147**, and **148** by the reaction of the corresponding commercially available ketones 4-heptanone, 5-nonanone, and 1,3-diphenylpropan-2-one with 3-chloro-2-(chloromethyl)prop-1-ene **72**, under conditions similar to those used before, to form the bicyclic analogues **146-148** (Scheme 3-6). Treatment of these dienes with triflic acid in benzene as the nucleophilic solvent gave the corresponding adamantanones **185**, **186**, and **187** in moderate yields.



Scheme 3-6. Cyclization of analogues **146-148** to give adamantanones **185-187**.

Next, we investigated the nucleophilic substrate scope of our reaction with 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonane **73** using the mild conditions of triflic acid at room temperature (Table 3-3). Various aromatic rings with electron-donating groups **188-191** reacted as good nucleophiles to produce the substituted adamantanones **192-196** in moderate yields. Toluene **188** gave a 76% combined yield of a 3:1 mixture of the 4-methyl and 2-methyl products, **192** and **193**. *p*-Xylene **189** gave the expected product **194** in 47% isolated yield; similarly, *m*-dimethoxybenzene **190** afforded the expected product **195** in 47% yield. The more hindered 1,3,5-trimethoxybenzene **191** gave the expected product **196** in only 21% yield, perhaps due to the steric hindrance of the only available aromatic position. Some other aromatic nucleophiles, such as anthracene, failed to yield any product. Not surprisingly, chlorobenzene did not trap, presumably due to its electron deficient nature.

Table 3-3. Reaction of **73** with aromatic rings **188-191** to give **192-196**.



73 **188-191** **192-196**

Entry	Nu	R^2	R^3	R^4	R^5	R^6	Yield (%)
1	**188**	H	H	Me	H	H	**192**, 57
		Me	H	H	H	H	**193**, 19
2	**189**	Me	H	H	Me	H	**194**, 47
3	**190**	OMe	H	OMe	H	H	**195**, 47
4	**191**	OMe	H	OMe	H	OMe	**196**, 21

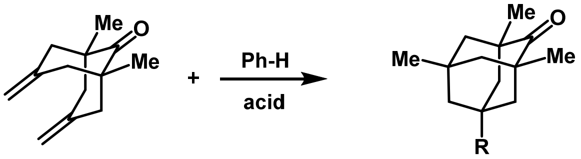
Again, there have been scattered reports of the trapping of adamantyl cations with benzenoid nucleophiles but no systematic study has been reported.[23]

To our knowledge, no heterocycles have ever been used to trap an adamantyl cation under acidic conditions. Therefore, we attempted to use several 5- and 6- membered heterocycles as nucleophiles for the non-planar carbocation generated *in situ*. Furan and *N*-methylindole gave poor results, generating a number of unidentified products. Morpholine and pyrrole only returned starting material under these conditions, presumably since protonation of the nitrogen atoms renders the substrate non-nucleophilic.

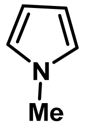
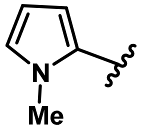
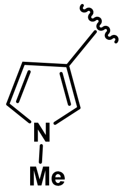
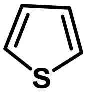
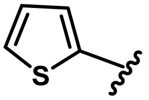
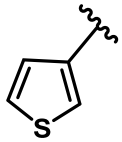
The reaction of **73** in the presence of triflic acid with *N*-methylpyrrole gave a mixture of the 2- and 3-substituted pyrrole products, **198** and **199**, in yields of 33% and 17% respectively. The assignment of the structures was based on the pattern of the absorptions in the proton NMR spectrum which matched literature data.[24] In this case, the ratio of the trapping at C2 vs C3 (1.9:1) is somewhat surprising, given that the reported ratio of trapping of a *tert*-butyl cation with *N*-methylpyrrole is 1:1.4 (C2:C3).[25] Similarly, reaction of **73** with thiophene in the presence of triflic acid afforded the 2- and 3-substituted products, **200** and **201**, in a 1.2:1 ratio in yields of 26% and 21%. The assignment was made by comparing the coupling constants for the three aromatic protons and by analogy to literature data.[26]

In addition to trapping the adamantyl cation with aromatic nucleophiles, we also investigated trapping with oxygen nucleophiles. There have been reports of similar nucleophilic trapping in the literature, but no systematic study has been carried out. Good yields of the expected trapping product were obtained using methanol and acetic acid as nucleophilic solvents, giving **202** and **203** in yields of 52% and 88%, respectively. In an attempt to obtain the tertiary alcohol

Table 3-4. Reactions of **73** with heterocyclic nucleophiles to give **197**.

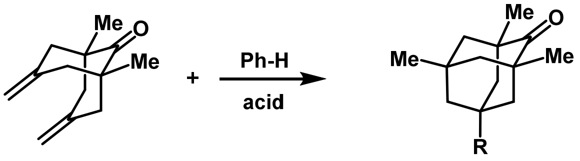


73 **197**

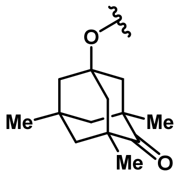
Entry	Nuc	R	Product, Yield (%)
1			**198**, 33
			**199**, 17
2			**200**, 26
			**201**, 21

204, we tried simple addition of water to triflic acid but that resulted in inactivation of the acid and no reaction was observed. We also attempted to hydrolyze the acetate **203** to afford the tertiary alcohol, but many harsh conditions such as strong acid, strong base, and heat, simply returned starting material. Finally, concentrated sulfuric acid was used as the solvent to obtain the desired alcohol product **204** in 74% yield. The initial product was probably the corresponding sulfate, but upon aqueous workup, it fell apart to the alcohol. Propargyl alcohol also trapped on oxygen to give the progargyl ether **205** in 35% yield. However, similar primary alcohols such as furfuryl alcohol and cinnamyl alcohol failed to give the corresponding ethers. Perhaps these substrates were unstable to the strongly acidic conditions.

Table 3-5. Reactions of **73** with oxygen and non-aryl carbon nucleophiles to give **197.**



73 **197**

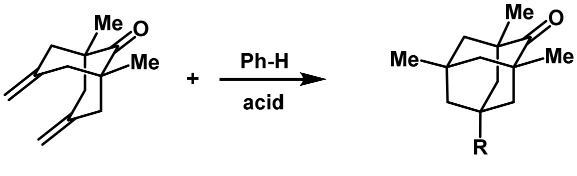
Entry	Nuc	R	Yield (%)
1	HOMe	OMe	**202**, 52
2	HOAc	OAc	**203**, 88
3	H_2O	OH	**204**, 74
4	$HOCH_2CCH$	$OCH_2C\equiv CH$	**205**, 35
5	HOPh	OPh	**206**, 36
6	HOTf	OSO_2CF_3	**207**, trace
			**208**, trace

Somewhat surprisingly, phenol gave only trapping on the oxygen atom to give **206** in 36% yield. No trapping on carbon, either C4 or C2, was observed. Pyridin-4-ol failed to trap at either O or N. In the absence of any external trapping agent, one obtains trace amounts of the triflate **207** and the symmetrical bis(ether) **208**.

A few thiols were attempted as nucleophiles, such as 2-propanethiol and ethanethiol. However, it is believed that under acid conditions, the thiol forms a thioketal from the ketone faster than trapping the adamantyl cation.

Next, we attempted to trap with hydride as our nucleophile. Thus, we tried to use BH_3·THF and Et_3SiH to afford hydride trapping, but no product formation was observed by GCMS.

Table 3-6. Trapping of **73** with non-aryl C and N nucleophiles.



73

197

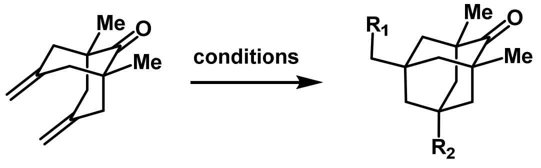
Entry	Nuc	R	Product, Yield (%)
1	TMS−C≡CH	C≡CH	**209**, 44
2	CH_3CN	NHCOMe	**210**, 88

We then moved on to non-aromatic carbon nucleophiles. Treatment with tetramethylsilane did not afford the tetramethylated adamantanone.[27] Vinyl silane and allyl silane failed to produce trapping at the tertiary carbocation.[28] Also, the preformed trimethylsilyl enol ether of acetophenone did not trap and simply returned acetophenone. Simple cyclohexene also failed to trap to give the cyclohexyl moiety. A possible reason for the failure of these reactions is that the trapping agents, especially the alkenes, may react preferentially with the strong acid. Finally, we were able to obtain C-C bond formation of a non-aromatic substrate, namely trimethylsilyl acetylene, to give the acetylene product **209** in 44% yield (Table 3-6).[29]

One can also carry out a Ritter reaction, namely treatment of **73** with triflic acid in acetonitrile as solvent, to generate the acetamide **210** in 88% yield.[30] This trapping would be useful for preparing analogues of memantine.

We also examined the addition of electrophiles other than proton to one of the exocyclic methylenes of **73** with the idea of triggering the cyclization to produce the adamantyl cation, which could then be trapped with simple nucleophiles. Reports of such dual addition of electrophiles and nucleophiles to similar dienes have appeared in the literature,[31] but here again no systematic study has been carried out. Thus treatment of the diene **73** with *N*-bromosuccinimide (NBS) in aqueous DMSO or in methanol gave the bromomethyl alcohol and methyl ether, **212** and **213**, in 66% and 89% yields, respectively (Table 3-9). Addition of either bromine or iodine to **73** in dichloromethane gave the dihalo products, **214** and **215**, in yields of 88% and 77%, respectively.

Table 3-7. Reactions of **73** with both electrophiles and nucleophiles to give **211**.



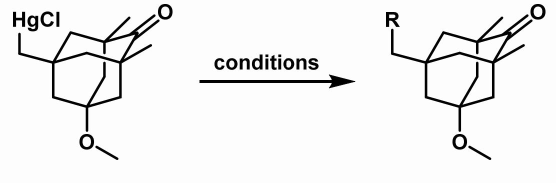
73 **211**

Entry	Conditions	R1	R2	Product, Yield (%)
1	NBS, aq. DMSO	Br	OH	**212**, 66
2	NBS, MeOH	Br	OMe	**213**, 89
3	Br_2, CH_2Cl_2	Br	Br	**214**, 88
4	I_2, CH_2Cl_2	I	I	**215**, 77
5	$Hg(OAc)_2$, MeOH; aq. NaCl	HgCl	OMe	**216**, 26

Non-halogenated electrophiles could also be used. Thus addition of mercuric acetate to **73** in methanol provided the acetoxymercurio ether, which, for ease of isolation, was converted into the chloromercurio ether by addition of NaCl to give **216** in 26% yield.

Many attempts were tried to utilize the mercury chloride salt as a functional handle to trap electrophiles, such as methyl methacrylate, acrylonitrile, and acrolein (Table 3-8).[32] Conditions attempted included radical conditions, trialkylsilanes, or KI in the dark. Though some product formation was observed by GCMS, all attempt to isolate the products proved futile.

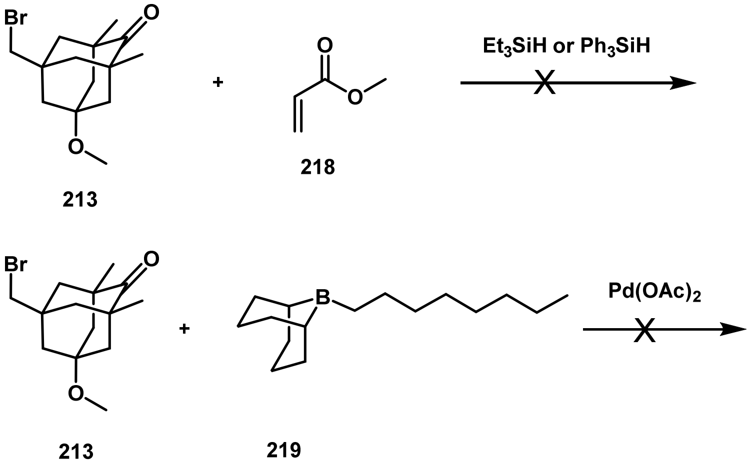
Table 3-8. Attempts to trap acrylate electrophiles onto mercuric salt **216**.



216 **217**

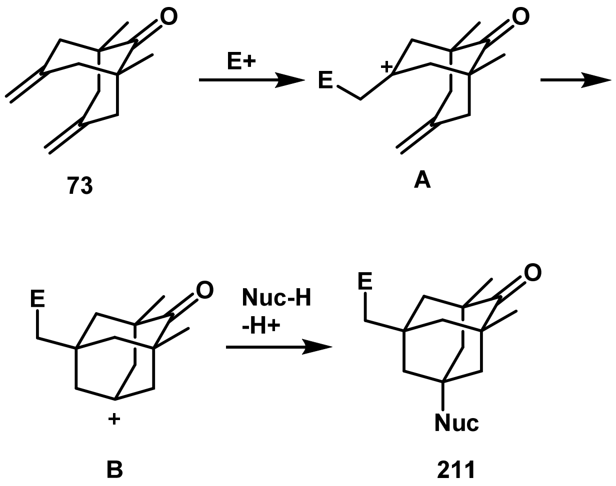
Entry	Electrophile	Conditions	Result
1	Methyl methacrylate	$NaBH_4$ in diglyme, DCM	1:1 ratio of desired product with Me-Ad-OMe
2	Acrylonitrile	$NaBH_4$ in diglyme, DCM	Mess
3	Acrolein	$NaBH_4$ in diglyme, DCM	Me-Ad-OMe
4	Acrylonitrile	KI, DMSO	Product formation; could not isolate
5	Methacrylate	KI, DMSO	Could not isolate
6	Acrylonitrile	KI, NH_4Br, DMSO	Mess
7	Methyl methacrylate	Et_3SiH, DMSO (w/ and w/o KI)	Small amount of product with Et_3SiH and Et_3SiOH
8	Methyl acrylate	Et_3SiH, DMSO (w/ and w/o KI)	Could not isolate
9	Methyl methacrylate	Ph_3SiH, DMSO (w/ and w/o KI)	Product formation; could not isolate
10	Methyl acrylate	Ph_3SiH, DMSO (w/ and w/o KI)	Could not isolate

We also attempted to react the resulting primary halide via cross-coupling conditions. However, treatment of the bromomethyl adamantyl methyl ether **213** and methyl methacrylate with triethylsilane or triphenylsilane failed to give rise to any product. Similarly, reaction with an organoborane and a palladium catalyst did not yield the expectant Suzuki cross-coupled product (Scheme 3-7).



Scheme 3-7. Attempts to cross-couple haloadamantanone **213**.

We believe the mechanism of this process (Scheme 3-8) involves the addition of an electrophile, E+ (H+, X+) to one of the two identical alkenes of **73** from the exo face to generate the tertiary carbocation **A**. Cyclization of the other alkene on this carbocation would then generate the adamantyl cation **B**, despite the instability inherent in a non-planar cation. Attack of the

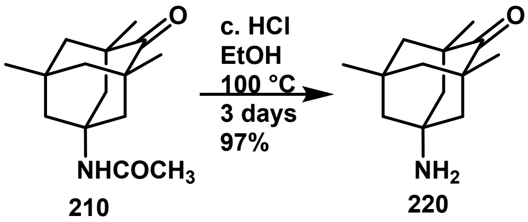


Scheme 3-8. Mechanism of formation of the adamantane core.

nucleophile on **B**, with loss of a proton, would afford the observed products **211**. Though the formation of adamantyl cations is well known,[33] they are often formed from adamantyl halides and not from bicyclo[3.3.1]diene systems.

Memantine, 3,5-dimethyladamantan-1-amine, was approved by the FDA in 2003 for the treatment of Alzheimer's disease under the trade name Namenda, marketed by Forest Labs, Inc. With over \$1.7 billion in sales revenue, it was ranked the 29th top selling drug in the United States in 2012.

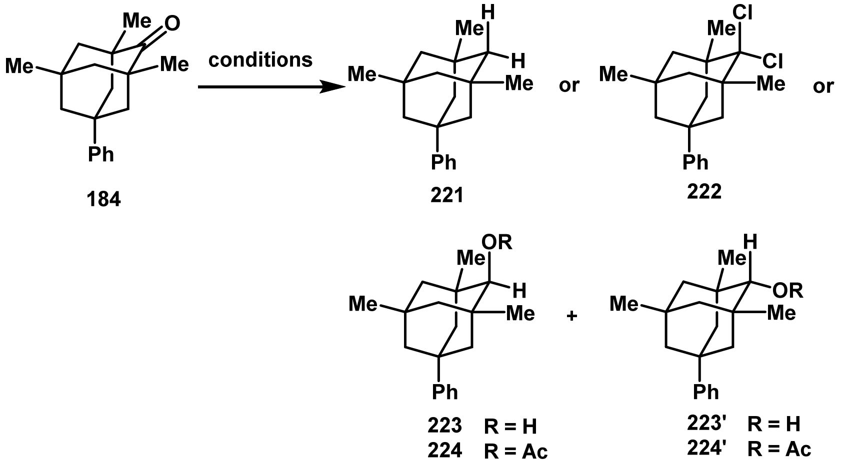
We decided to utilize our developed methodology to make an analogue of memantine. Thus, the acetamide **210**, obtained from **73** by the Ritter reaction, was subjected to a variety of hydrolysis conditions in order to produce the amine **220**. Quite harsh conditions were applied, such as a 1:1 v/v ratio of concentrated HCl:water, refluxing with potassium hydroxide in toluene, and catalytic palladium on charcoal, all of which gave no reaction. Finally, concentrated HCl in ethanol in a sealed tube at 100 °C for 3 days produced the primary amine **220** in 97% yield.



Scheme 3-9. Hydrolysis of **210** to give the memantine analog **220**.

We attempted to reduce the ketone of **220** to the methylene derivative under a variety conditions, as shown in Table 3-9. Entries 1-3 attempted to fully reduce the ketone to the methylene in a one-step procedure. As far as we can tell, there are references for a Wolff-Kishner reaction of very hindered ketones, but never a substituted adamantanone.[34] Thus, treatment of ketone **184**

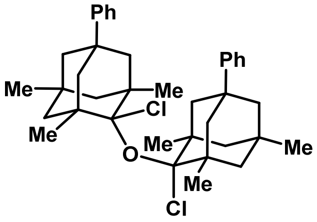
Table 3-9. Attempts to reduce ketone **184**.



Entry	Conditions	Result
1	NaOH, NH_2NH_2	No reaction
2	PtO_2, H_2	No reaction
3	Zn/Hg/Cl	30% conversion to unknown
4	PCl_3	No reaction
5	PCl_3:PCl_5	No reaction
6	WCl_6	Full conversion to tentative structure **225**
7	$LiAlH_4$	Multiple products
8	$NaBH_4$	Reduction to alcohols **223** and **223’**
9	Ac_2O on **223**, **223’**	Formation of acetate **224** and **224’** (R = Ac)
10	Na on **224**, **224’**	No reaction

with NaOH and hydrazine at high temperature gave no conversion to product. Reduction with platinum oxide under a hydrogen atmosphere also failed.[35] An attempted Clemmensen reduction with zinc amalgam and hydrochloric acid gave a 30% conversion to an unknown product, that might have been the fully reduced product, as its NMR had broad doublets that are characteristic of adamantanes.[36] However, this unknown product was never isolated in a pure state.

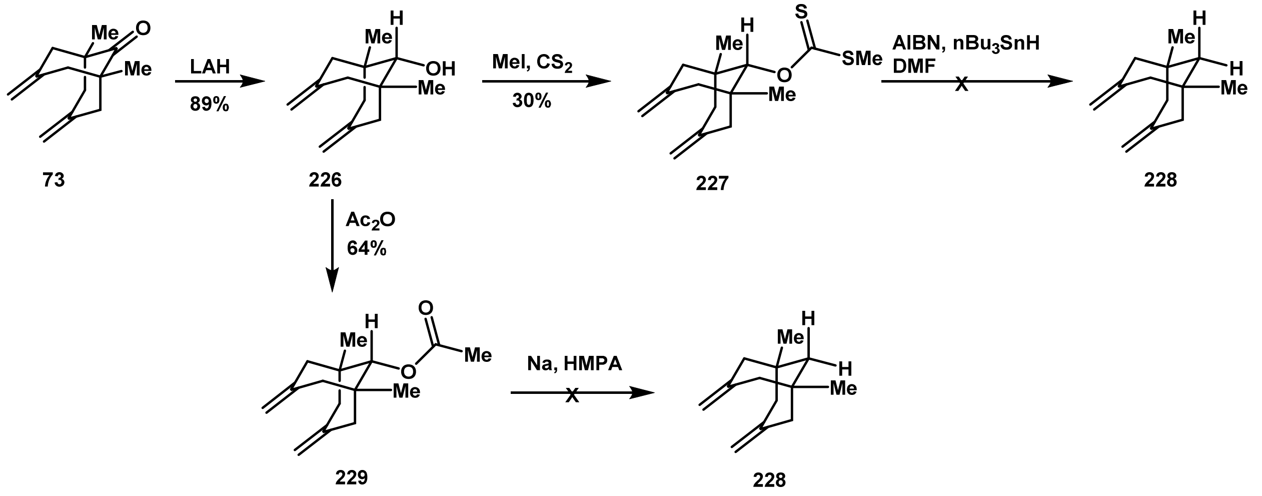
Entries 4-6 attempted to convert the ketone to the dichloride. However, treatment with phosphorus trichloride alone or in combination with phosphorus pentachloride gave no reaction.[37] Reaction with tungsten hexachloride[38] gave full conversion to an unknown product that appears to have two stereocenters, as observed from the unique coupling pattern in its proton NMR. We have tentatively assigned the structure **225** to this compound.



225

Figure 3-4. Compound **225**.

In a longer approach, we attempted reduction to the alcohol first (entry 8). Although lithium aluminum hydride gave a mixture of products, reduction with sodium borohydride gave approximately a 1:1 mixture of diastereomeric alcohols **223** and **223'**. Reaction of this mixture with 1,1'-thiocarbonyldiimidazole (TCDI), MeI and CS_2 in THF, and phenyl chlorodithioformate gave no reaction, presumably because of the steric hindrance around this neopentyl secondary alcohol. Although treatment with acetic anhydride easily gave the corresponding mixture of acetates **224** and **224'**, treatment with sodium metal did not furnish the fully reduced bicycle.



Scheme 3-10. Attempts to reduce ketone **73**.

Attempts were then made on the bicyclic dienone **73** (Scheme 3-10). If reduction was to occur, then one could then trap the corresponding hydrocarbon with any nucleophile and produce a whole range of adamantane analogues in two simple steps. However, after reducing the ketone **73** to the alcohol **226** and reaction with carbon disulfide and methyl diodide to form dithioate **227**, we were unable to reduce **227** to the hydrocarbon **228** under the normal radical conditions.

Although we were unable to effect the reduction of either the bicyclic ketone **73** or the adamantanone **184**, we believe that under the right conditions, the reaction could be made to occur.

CONCLUSION

In conclusion, we have shown that the readily available 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-2-one **73** can be easily converted into a wide variety of adamantanone derivatives by treatment with various electrophiles, especially proton, in the presence of a trapping agent. Aromatic and heteroaromatic nucleophiles have proven to be successful, and oxygen and nitrogen nucleophiles can provide access to a wide variety of functionality at the newly formed tertiary position. Many of these results have been published recently.[39]

EXPERIMENTAL

General

All reactions were carried out under an argon atmosphere unless otherwise specified. Methylene chloride was distilled from calcium hydride under an argon atmosphere. Trifluoromethanesulfonic acid was purchased from Acros Organics in 99% purity. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). Thin-layer chromatography (TLC) was carried out using pre-coated silica gel sheets (Merck 60 F254). Visual detection was performed using phosphomolybdic acid or iodine. Flash chromatography was performed using SilicaFlash™ P60 (60 A, 40-63 µm) silica gel from SiliCycle Inc. with compressed air. High resolution mass spectrometry was taken on a Thermo Fisher Scientific Exactive Plus mass spectrometer equipped with an IonSense ID-CUBE DART ion source.

General Procedure for Acid Promoted Cyclization in Benzene

To a solution of diene **73** (0.200 g, 1.05 mmol) in benzene (5 mL) was added trifluoromethanesulfonic acid (0.111 mL, 1.26 mmol) at 0 ˚C. The reaction was let warm to 21 ˚C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with hexanes (3 X 20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the phenyladamantanone **184** (0.253 g, 0.94 mmol, 90%) as a light yellow oil.

General Procedure for the Triflic Acid Promoted Cyclization and Trapping of Nucleophiles

To a solution of diene **73** (0.200 g, 1.05 mmol) in dichloromethane (5 mL) was added *m*-dimethoxybenzene **190** (0.030 mL, 5.25 mmol) then trifluoromethanesulfonic acid (0.111 mL, 1.26 mmol) at 0 ˚C. The reaction was let warm to 21 ˚C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with dichloromethane (3 X 20 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give a crude light yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the 2,4-dimethoxyphenyladamantanone **195** (0.162 g, 0.49 mmol, 47%) as a light yellow oil.

General Procedure for the Addition of Various Electrophiles and Subsequent Trapping of Nucleophiles

To a solution of the diene **73** (0.100 g, 0.525 mmol) in 1:1 methanol:dichloromethane (6 mL) was added NBS (0.121 g, 0.068 mmol) at 0 ˚C. The reaction was warmed to 21 ˚C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with dichloromethane (3 X 15 mL) and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give crude bromomethyl methoxyadamantanone **213** (0.140 g, 89%) as a light yellow oil.

1,3,5-Trimethyl-7-phenyladamantan-2-one, 184.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

7.38 – 7.31 (m, 4H)

7.23 (bt, *J* = 7.0 Hz, 1H)

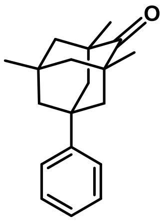
1.98 (bd, *J* = 12.0 Hz, 2H)

1.88-1.85 (m, 4H)

1.64 (bd, *J* = 12.5 Hz, 2H)

1.57-1.54 (m, 2H)

1.01 (s, 9H).


184

^{13}C NMR (125 MHz, CDCl$_3$) δ 218.5, 147.7, 128.3, 126.2, 124.9, 52.5, 51.5, 48.1, 45.9, 38.4, 32.1, 28.8, 22.6.

HRMS (ESI, *m/z*): 269.1895, calculated for $C_{19}H_{25}O$ $(M+H)^+$ 269.1905.

1,3-Diethyl-5-methyl-7-phenyladamantan-2-one, 185.

^{1}H NMR (500 MHz, CDCl$_3$) δ

7.39 (bd, *J* = 8.4 Hz, 2H)

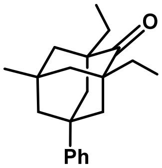
7.34 (bt, *J* = 7.6 Hz, 2H)

7.22 (bt, *J* = 6.8 Hz, 1H)

1.94 (bd, *J* = 12 Hz, 2H)

1.87 (s, 2H)

1.84 (bd, *J* = 12.4 Hz, 2H)



185

1.56 (m, 4H)

1.48 (q, *J* = 7.2 Hz, 2H)

1.47 (q, *J* = 7.2 Hz, 2H)

1.04 (s, 3H)

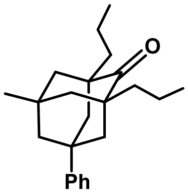
0.85 (t, *J* = 7.6 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 218.0, 147.9, 128.2, 126.1, 124.8, 49.3, 48.6, 48.55, 48.50, 37.9, 31.6, 29.1, 28.3, 7.8.

HRMS (ESI, *m/z*): 297.2209, calculated for $C_{21}H_{29}O$ (M+H)$^+$ 297.2218.

5-Methyl-7-phenyl-1,3-dipropyladamantan-2-one, 186.

^{1}H NMR (500 MHz, CDCl$_3$) δ



186

7.38 (bd, *J* = 8.0 Hz, 2H)

7.34 (bt, *J* = 7.5 Hz, 2H)

7.23 (bt, *J* = 7.0 Hz, 1H)

1.95 (bd, *J* = 12.5 Hz, 2H)

1.86 (s, 2H)

1.85 (d, *J* = 12.0 Hz, 2H)

1.60 (d, *J* = 12.5 Hz, 2H)

1.55 (d, *J* = 12.5 Hz, 2H)

1.38 (m, 4H)

1.28 (m, 4H)

1.02 (s, 3H)

0.92 (t, *J* = 7.0 Hz, 6H).

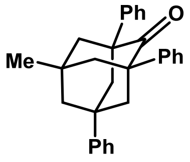
^{13}C NMR (125 MHz, CDCl$_3$) δ 218.1, 148.0, 128.4, 126.2, 124.9, 50.0, 49.1, 48.8, 48.6, 38.4, 38.0, 31.8, 29.3, 16.7, 15.0.

HRMS (ESI, *m/z*): 325.2522, calculated for $C_{23}H_{33}O$ $(M+H)^+$ 325.2531.

5-Methyl-1,3,7-triphenyladamantan-2-one, 187.

^{1}H NMR (500 MHz, CDCl$_3$) δ

7.51 (d, J = 7.0 Hz, 2H)



187

7.42-7.20 (m, 13H)

2.81 (d, *J* = 12.0 Hz, 2H)

2.45 (d, *J* = 12.5 Hz, 2H)

2.38 (d, *J* = 12.5 Hz, 2H)

2.09 (d, *J* = 12.5 Hz, 2H)

2.05 (s, 2H)

1.24 (s, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 212.7, 147.4, 142.8, 128.9, 128.8, 128.6, 128.1, 127.1, 126.6, 54.0, 50.7, 49.8, 48.2, 38.6, 32.4, 29.7.

HRMS (ESI, *m/z*): 393.2204, calculated for $C_{29}H_{29}O$ $(M+H)^+$ 393.2218.

1,3,5-Trimethyl-7-(4-methylphenyl)adamantan-2-one, 192, 193.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

7.25 (d, *J* = 8.0 Hz, 2H)

7.16 (d, *J* = 8.0 Hz, 2H)

2.33 (s, 3H)

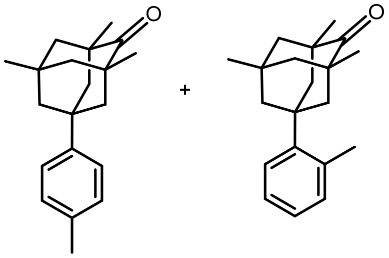
1.96 (m, 2H)

1.85 (m, 4H)

1.65 (bd, *J* = 12.5 Hz, 2H)

1.54 (m, 2H)

1.00 (s, 9H).



192 + **193**

^{13}C NMR (125 MHz, CDCl$_3$) δ 218.6, 144.7, 135.7, 129.1, 124.8, 52.5, 51.5, 48.1, 45.9, 38.5, 32.1, 28.8, 22.8, 20.9.

HRMS (ESI, *m/z*): 283.2051, calculated for $C_{20}H_{27}O$ $(M+H)^+$ 283.2062.

5-(2,5-Dimethylphenyl)-1,3,7-trimethyladamantan-2-one, 194.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

7.13 (s, 1H)

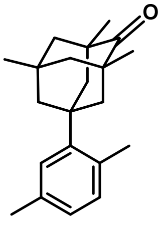
7.03 (d, *J* = 8.0 Hz, 1H)

6.95 (d, *J* = 7.5 Hz, 1H)

2.55 (s, 3H)

2.32 (s, 3H)

2.07 (m, 4H)



194

1.99 (s, 2H)

1.64 (d, *J* = 12.0 Hz, 2H)

1.56 (d, *J* = 12.0 Hz, 2H)

1.03 (s, 6H)

1.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6, 144.1, 135.4, 133.4, 132.7, 127.0, 126.9, 52.4, 49.8, 46.2, 45.9, 39.9, 32.2, 29.0, 23.2, 22.8, 21.2.

HRMS (ESI, *m/z*): 297.2197, calculated for $C_{21}H_{29}O$ $(M+H)^+$ 297.2218.

1,3,5-Trimethyl-7-(2,4-dimethoxyphenyl)adamantan-2-one, 195.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

6.46 (s, 1H)

6.44 (m, 2H)

3.80 (s, 3H)

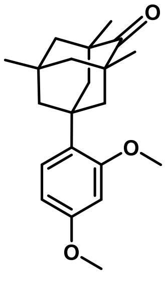
3.79 (s, 3H)

2.15 (d, *J* = 11.5 Hz, 2H)

1.97 (d, *J* = 9.0 Hz, 2H)

1.55 (m, 6H)

0.98 (s, 9H).



195

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 159.4, 159.2, 127.5, 126.9, 103.6, 99.7, 55.2, 54.9, 52.7, 49.2, 45.9, 45.8, 38.4, 32.0, 29.0, 22.8.

HRMS (ESI, *m/z*): 329.2100, calculated for $C_{21}H_{29}O_3$ $(M+H)^+$ 329.2117.

1,3,5-Trimethyl-7-(2,4,6-trimethoxyphenyl)adamantan-2-one, 196.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

6.13 (s, 2H)

3.78 (s, 3H)

3.74 (s, 6H)

2.36 (bd, *J* = 12.5 Hz, 2H)

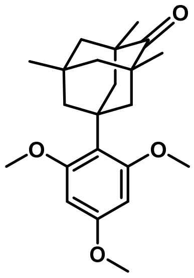
2.25 (bd, *J* = 12 Hz, 2H)

2.16 (s, 2H)

1.53 (s, 4H)

0.95 (s, 6H)

0.92 (s, 3H).



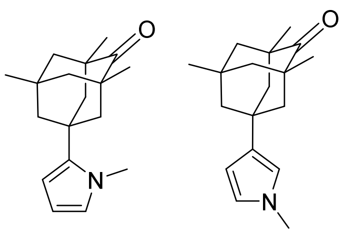
196

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.9, 160.5, 158.9, 115.4, 93.1, 55.8, 55.1, 52.5, 50.4, 46.1, 45.8, 41.1, 31.9, 29.3, 23.0.

HRMS (ESI, *m/z*): 359.2210, calculated for $C_{22}H_{31}O_4$ $(M+H)^+$ 359.2222.

1,3,5-Trimethyl-7-(1-methyl-1*H*-pyrrol-2-yl)adamantan-2-one, 198.

1,3,5-Trimethyl-7-(1-methyl-1*H*-pyrrol-3-yl)adamantan-2-one, 199.


198 + 199

^{1}H NMR (500 MHz, CDCl$_3$) δ:

6.53 (t, *J* = 2.5 Hz, 1H)

6.48 (t, *J* = 2.5 Hz, 1.9H)

6.40 (t, *J* = 2.0 Hz, 1H)

6.04 (t, *J* = 2.0 Hz, 1H)

6.01 (t, *J* = 2.5 Hz, 1.9H)

5.94 (t, *J* = 2 Hz, 1.9H)

3.76 (s, 5.7H)

3.60 (s, 3H)

2.05 (d, *J* = 12.0 Hz, 4H)

1.95 – 1.87 (m, 10H)

1.77 (m, 4H)

1.62 (d, *J* = 12.5 Hz, 4H)

1.60 – 1.50 (m, 8H)

0.99 (s, 18H)

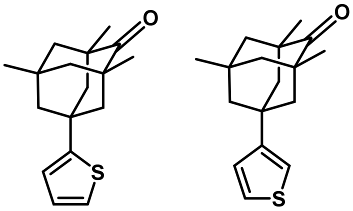
0.96 (s, 9H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 219.1, 218.2, 138.0, 132.6, 124.4, 121.6, 116.8, 106.1, 105.9, 105.1, 52.7, 52.4, 49.8, 49.1, 46.5, 45.9, 45.6, 37.2, 36.4, 36.1, 34.6, 32.0, 31.8, 28.8, 28.7, 22.65, 22.60.

HRMS (ESI, *m/z*): 272.2005, calculated for $C_{18}H_{26}NO$ $(M+H)^+$ 272.2014.

1,3,5-Trimethyl-7-(thiophen-2-yl)adamantan-2-one, 200.

1,3,5-Trimethyl-7-(thiophen-3-yl)adamantan-2-one, 201.



200 + 201

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.28 (dd, *J* = 5.0, 3.0 Hz, 1H)

7.16 (dd, *J* = 5.0, 1.0 Hz, 1H)

7.07 (dd, *J* = 5.0, 1.5 Hz, 1H)

6.98 (dd, *J* = 3.0, 1.5 Hz, 1H)

6.94 (m, 1H)

6.84 (dd, *J* = 3.5, 1.5 Hz, 1H)

2.02 (d, *J* = 12.0 Hz, 2H)

1.97 (d, *J* = 12.0 Hz, 2H)

1.90 (m, 4H)

1.83 (m, 4H)

1.62 (d, *J* = 12 Hz, 4H)

1.56 (m, 4H)

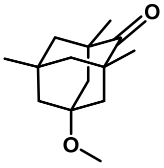
1.00 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 217.8, 153.8, 149.8, 126.5, 125.6, 125.3, 122.6, 121.2, 118.2, 52.7, 52.5, 52.4, 51.6, 49.7, 48.4, 46.0, 45.9, 38.1, 37.3, 32.3, 32.0, 28.7, 28.5, 22.5, 22.4.

HRMS (ESI, *m/z*): 275.1460, calculated for $C_{17}H_{23}OS$ $(M+H)^+$ 275.1470.

5-Methoxy-1,3,7-trimethyladamantan-2-one, 202.

^{1}H NMR (500 MHz, CDCl$_3$) δ:



202

3.25 (s, 3H)

1.77 (bd, *J* = 15.0 Hz, 2H)

1.68-1.65 (m, 4H)

1.53 (bd, *J* = 15.0 Hz, 2H)

1.47-1.43 (m, 2H)

0.98 (s, 3H)

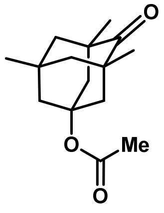
0.97 (s, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 217.3, 72.5, 52.5, 48.8, 47.7, 46.1, 45.4, 33.5, 28.2, 22.2.

HRMS (ESI, *m/z*): 223.1689, calculated for $C_{14}H_{23}O_2$ $(M+H)^+$ 223.1698.

3,5,7-Trimethyl-4-oxoadamantan-1-yl acetate, 203.

^{1}H NMR (500 MHz, CDCl$_3$) δ:



203

2.13 – 2.02 (m, 6H)

1.97 (s, 3H)

1.52 (s, 4H)

0.96 (bs, 9H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 216 4, 170.1, 79.2, 52.1, 47.7, 46.3, 45.2, 33.8, 28.0, 22.0, 21.9.

HRMS (ESI, *m/z*): 251.1638, calculated for $C_{18}H_{26}NO$ $(M+H)^+$ 251.1647.

5-Hydroxy-1,3,7-trimethyladamantan-2-one, 204.

To a solution of the diene **2** (0.050 g, 0.26 mmol) in DMSO (1 mL) was added conc. H_2SO_4 (1 mL) and water (0.1 mL) at 0 ˚C. The reaction was let warm to 21 ˚C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL), extracted with dichloromethane (3 X 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10mL), dried with $MgSO_4$, filtered and concentrated in vacuo to give the hydroxyadamantanone **204** (0.041 g, 0.20 mmol, 74%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

1.77 (m, 2H)

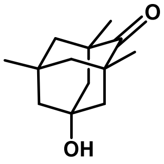
1.65 (m, 4H)

1.49 (m, 4H)

1.23 (s, 1H)

0.97 (s, 3H)

0.95 (s, 6H).



204

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 69.0, 52.3, 51.8, 49.8, 46.4, 33.9, 28.1, 22.1.

HRMS (ESI, *m/z*): 209.1538, calculated for $C_{13}H_{21}O_2$ $(M+H)^+$ 209.1542.

1,3,5-Trimethyl-7-(prop-2-yn-1-yloxy)adamantan-2-one, 205.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

4.14 (d, *J* = 2.5 Hz, 2H)

2.39 (t, *J* = 2 Hz, 1H)

1.83 (bd, *J* = 11.0 Hz, 2H)

1.73 (s, 2H)

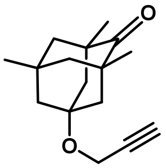
1.75-1.72 (m, 2H)

1.52 (bd, *J* = 12.5 Hz, 2H)

1.46 (bd, *J* = 10.0 Hz, 2H)

0.98 (s, 3H)

0.97 (s, 6H).



205

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0, 81.2, 74.4, 73.6, 52.2, 49.8, 48.1, 46.3, 45.9, 33.7, 28.2, 22.2.

HRMS (ESI, *m/z*): 247.1686, calculated for $C_{16}H_{23}O_2$ $(M+H)^+$ 247.1698.

1,3,5-Trimethyl-7-phenoxyadamantan-2-one, 206.

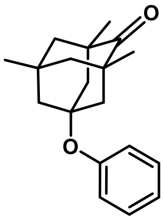
^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.28 (bt, *J* = 8.5 Hz, 2H)

7.13 (bt, *J* = 7.5 Hz, 1H)

6.98 (bd, *J* = 8.5 Hz, 2H)

1.91 (bd, *J* = 10.5 Hz, 2H)



206

1.81 (s, 2H)

1.79-1.78 (m, 2H)

1.52 (bd, *J* = 12.5 Hz, 2H)

1.47-1.44 (m, 2H)

0.98 (s, 3H)

0.97 (s, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 217.0, 153.8, 129.0, 124.7, 124.2, 77.5, 52.3, 49.3, 47.2, 46.4, 33.9, 28.2, 22.2.

HRMS (ESI, *m/z*): 285.1849, calculated for $C_{19}H_{25}O_2$ $(M+H)^+$ 285.1855.

3,5,7-Trimethyl-4-oxoadamantan-1-yl trifluoromethanesulfonate, 207.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

1.79 (m, 2H)

1.70 (bs, 2H)

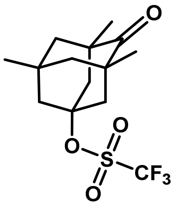
1.77 (bd, *J* = 13.0 Hz, 2H)

1.52 (bd, *J* = 15.0 Hz, 2H)

1.47 (m, 2H)

0.99 (s, 3H)

0.96 (s, 6H).



207

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 69.3, 52.2, 51.5, 49.6, 46.3, 33.9, 27.9, 21.8 (one low-field carbon not observed).

GCMS (EI+) found 340.1, calculated for $C_{14}H_{19}F_3O_4S$ 340.0.

7,7'-Oxybis(1,3,5-trimethyladamantan-2-one), 208.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

1.89 (d, *J* = 11.5 Hz, 4H)

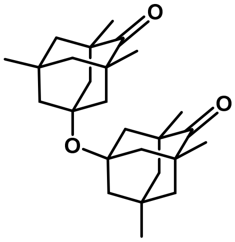
1.78 (m, 4H)

1.56 (s, 4H)

1.48 (m, 8H)

0.97 (s, 6H)

0.96 (s, 12H).



208

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 75.2, 52.3, 52.2, 50.1, 46.6, 33.9, 28.5, 22.4.

GCMS (EI+) found 398.4, calculated for $C_{26}H_{38}O_3$ 398.3.

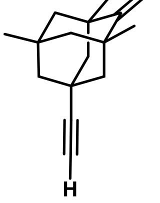
5-Ethynyl-1,3,7-trimethyladamantan-2-one, 209.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

2.13 (s, 1H)

1.91 (bd, *J* = 12.5 Hz, 2H)

1.83-1.80 (m, 4H)



209

1.52-1.47 (m, 4H)

0.95 (s, 6H)

0.94 (s, 3H).

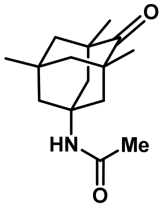
^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 89.4, 68.0, 52.2, 50.5, 47.5, 45.5, 31.5, 31.3, 28.5, 22.3.

HRMS (ESI, *m/z*): 217.1581, calculated for $C_{15}H_{22}O$ $(M+H)^+$ 217.1592.

N-(3,5,7-Trimethyl-4-oxoadamantan-1-yl)acetamide, 210.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

5.41 (bs, 1H)



210

1.97 (s, 4H)

1.94 (s, 2H)

1.90 (s, 3H)

1.51 (s, 4H)

0.94 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.2, 169.8, 52.9, 52.3, 48.5, 45.9, 45.8, 32.7, 28.2, 24.5, 22.2.

HRMS (ESI, *m/z*): 250.1799, calculated for $C_{15}H_{24}NO_2$ $(M+H)^+$ 250.1807.

5-(Bromomethyl)-7-hydroxy-1,3-dimethyladamantan-2-one, 212.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

3.27 (s, 2H)

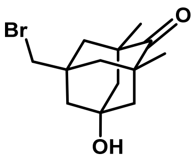
2.60 (s, 1H)

1.79 (m, 4H)

1.69 (m, 2H)

1.59 (s, 4H)

0.99 (s, 6H).



212

^{13}C NMR (125 MHz, CDCl$_3$) δ 216.1, 68.8, 51.7, 48.3, 46.1, 45.9, 43.5, 37.7, 22.0.

HRMS (ESI, *m/z*): 287.0628, calculated for $C_{13}H_{20}BrO_2$ (M+H)$^+$ 287.0647.

5-(Bromomethyl)-7-methoxy-1,3-dimethyladamantan-2-one, 213.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

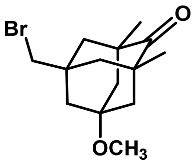
3.27 (s, 2H)

3.25 (s, 3H)

1.78 – 1.70 (m, 6H)

1.62 – 1.56 (m, 4H)

1.00 (s, 6H).



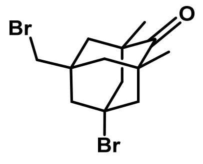
213

^{13}C NMR (125 MHz, CDCl$_3$) δ 216.2, 72.5, 49.1, 48.5, 47.7, 45.7, 43.7, 41.9, 37.3, 22.2.

HRMS (ESI, *m/z*): 301.0785, calculated for $C_{14}H_{22}BrO_2$ $(M+H)^+$ 301.0803.

5-Bromo-7-(bromomethyl)-1,3-dimethyladamantan-2-one, 214.

^{1}H NMR (500 MHz, $CDCl_3$) δ:



214

3.23 (s, 2H)

2.33 (m, 4H)

2.21 (m, 2H)

1.67 (s, 4H)

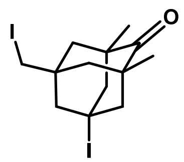
0.99 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 59.1, 55.5, 49.5, 48.0, 47.6, 42.9, 38.7, 21.8.

HRMS (ESI, *m/z*): 348.9797, calculated for $C_{13}H_{19}Br_2O$ $(M+H)^+$ 348.9803.

5-Iodo-7-(iodomethyl)-1,3-dimethyladamantan-2-one, 215.

^{1}H NMR (500 MHz, $CDCl_3$) δ:



215

3.06 (s, 2H)

2.52 (s, 2H)

2.51 (d, J = 11.0 Hz, 2H)

2.41 (d, J = 12.5 Hz, 2H)

1.75 (d, J = 12.0 Hz, 2H)

1.68 (d, J = 11.5 Hz, 2H)

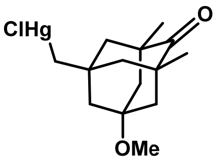
0.98 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 58.8, 53.7, 49.0, 48.6, 39.9, 37.5, 21.6, 19.1.

HRMS (ESI, *m/z*): 444.9519, calculated for $C_{13}H_{19}I_2O$ $(M+H)^+$ 444.9525.

((7-Methoxy-3,5-dimethyl-4-oxoadamantan-1-yl)methyl)mercury(II) chloride, 216.

^{1}H NMR (400 MHz, $CDCl_3$) δ:



216

3.16 (s, 3H)

2.05 (s, 2H)

1.67 (m, 4H)

1.55 (m, 4H)

1.44 (m, 2H)

0.89 (s, 6H).

5-Amino-1,3,7-trimethyladamantan-2-one, 220.

To a solution of the acetamide **210** (0.087 g, 0.35 mmol) and ethanol (2 mL) was added conc. HCl (0.5 mL) and water (0.1 mL) in a sealed tube. The vessel was heated to 100 ˚C for 3 d. The solution was then cooled to 0 ˚C and quenched with a saturated solution of $NaHCO_3$ (20 mL). The mixture was extracted with dichloromethane (3 X 20 mL), and washed with brine (20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give the crude 5-aminoadamantanone **220** (0.070 g, 0.34 mmol, 97%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

1.65 (d, J = 11.5 Hz, 2H)

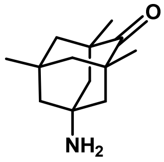
1.53 (m, 4H)

1.43 (d, *J* = 11.5 Hz, 2H)

1.24 (s, 2H)

0.96 (s, 3H)

0.94 (s, 6H).



220

^{13}C NMR (125 MHz, CDCl$_3$) δ 218.0, 53.3, 52.4, 50.8, 49.1, 46.0, 33.1, 28.2, 22.2.

HRMS (ESI, *m/z*): 208.1691, calculated for $C_{13}H_{22}NO$ (M+H)$^+$ 208.1701.

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-ol, 226.

To a solution of the bicycle **73** (0.50 g, 2.62 mmol) in 1:1 MeOH:THF (16 mL) was added $NaBH_4$ (0.20 g, 5.24 mmol) and the reaction stirred for 1 h. The solution was then quenched with a saturated solution of $NaHCO_3$ (20 mL), extracted with dichloromethane (3 X 30 mL) and washed with brine (30 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the alcohol **226** (0.45 g, 2.33 mmol, 89%) as a light yellow oil.

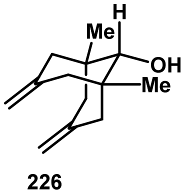
^{1}H NMR (500 MHz, CDCl$_3$) δ:

4.52 (q, *J* = 2.5 Hz, 4H)

3.25 (s, 1H)

2.36 (d, *J* = 15.0 Hz, 2H)

2.21 (d, *J* = 15.0 Hz, 2H)



226

2.10 (d, *J* = 15.0 Hz, 2H)

1.96 (d, *J* = 15.0 Hz, 2H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 145.0, 144.1, 110.3, 109.4, 47.8, 40.6, 36.3, 27.1.

HRMS (ESI, *m/z*): 193.1587, calculated for $C_{13}H_{21}O$ $(M+H)^+$ 193.1592.

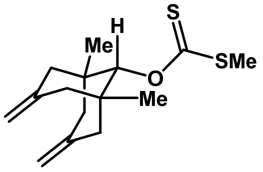
O-1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-yl) S-methyl carbonodithioate, 227.

To a solution of the alcohol **55** (0.16 g, 0.84 mmol) in 1:1 THF:CS$_2$ (20 mL) was added sodium hydride (0.10 g, 2.5 mmol) and the reaction stirred for 3 h. The solution was then quenched with a saturated solution of NaHCO$_3$ (20 mL), extracted with dichloromethane (3 X 30 mL) and washed with brine (30 mL). The combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the carbondithioate **227** (0.07 g, 0.25 mmol, 30%) as a light yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ:

5.85 (s, 1H)

4.59 (m, 4H)



227

2.57 (s, 3H)

2.39 (d, *J* = 15.0 Hz, 2H)

2.28 (s, 4H)

2.09 (d, *J* = 15.0 Hz, 2H)

0.91 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.8, 144.1, 142.7, 111.3, 110.3, 90.7, 47.6, 42.2, 36.9, 26.7.

HRMS (ESI, *m/z*): 283.1185, calculated for $C_{15}H_{23}OS_2$ $(M+H)^+$ 283.1190.

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24. The 2-substituted isomer has one absorption at low field, δ 6.7, and two absorptions at higher field, δ 6.1 and 6.0, while the pattern for the 3-substituted isomer was the opposite, namely two absorptions at low field, δ 6.8 and 6.9, and one absorption at higher field, δ 6.15. For similar examples, see: von der Saal, W.; Reinhardt, R.; Stawitz, J.; Quast, H. *Eur. J. Org. Chem.* **1998**, 1645.
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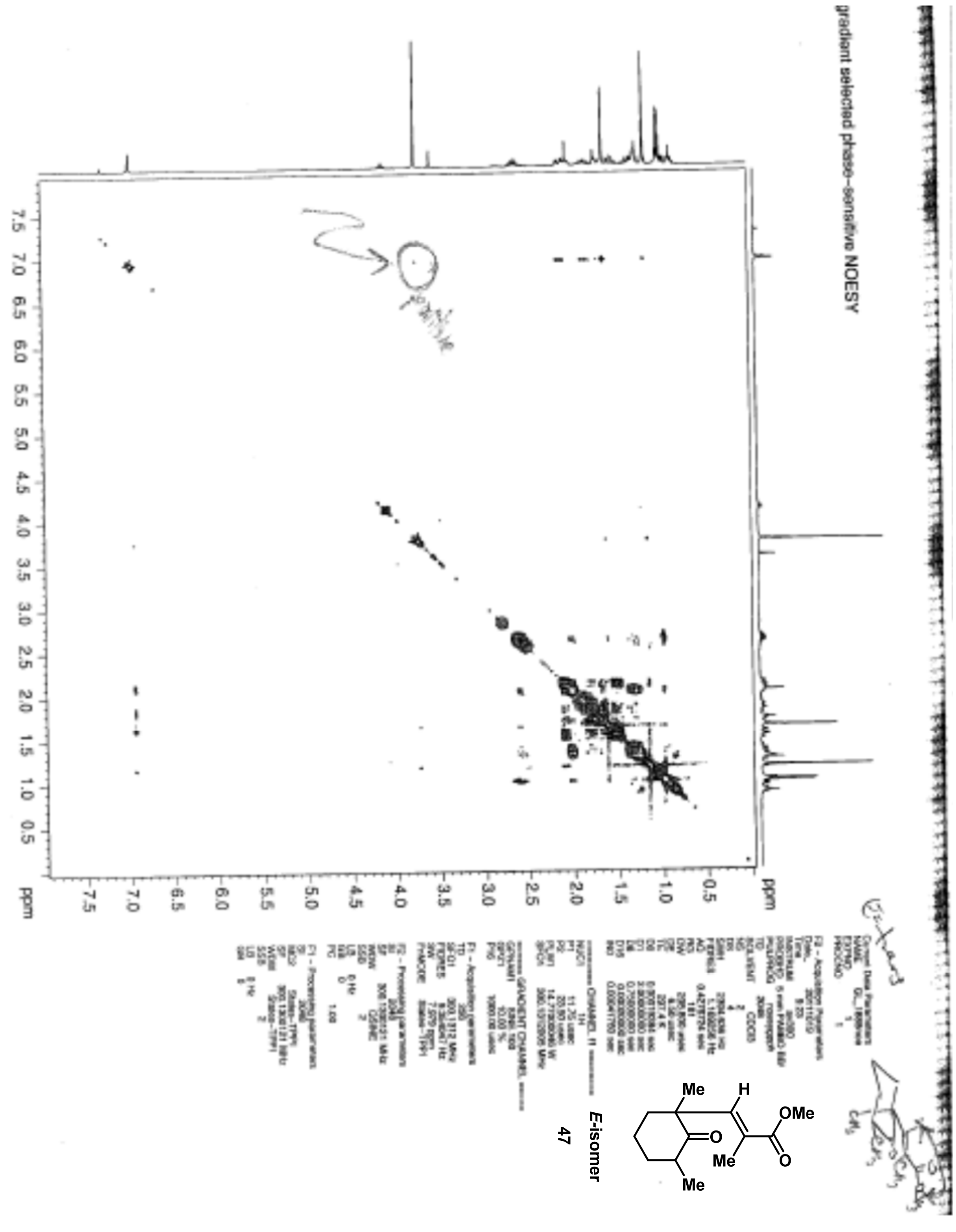
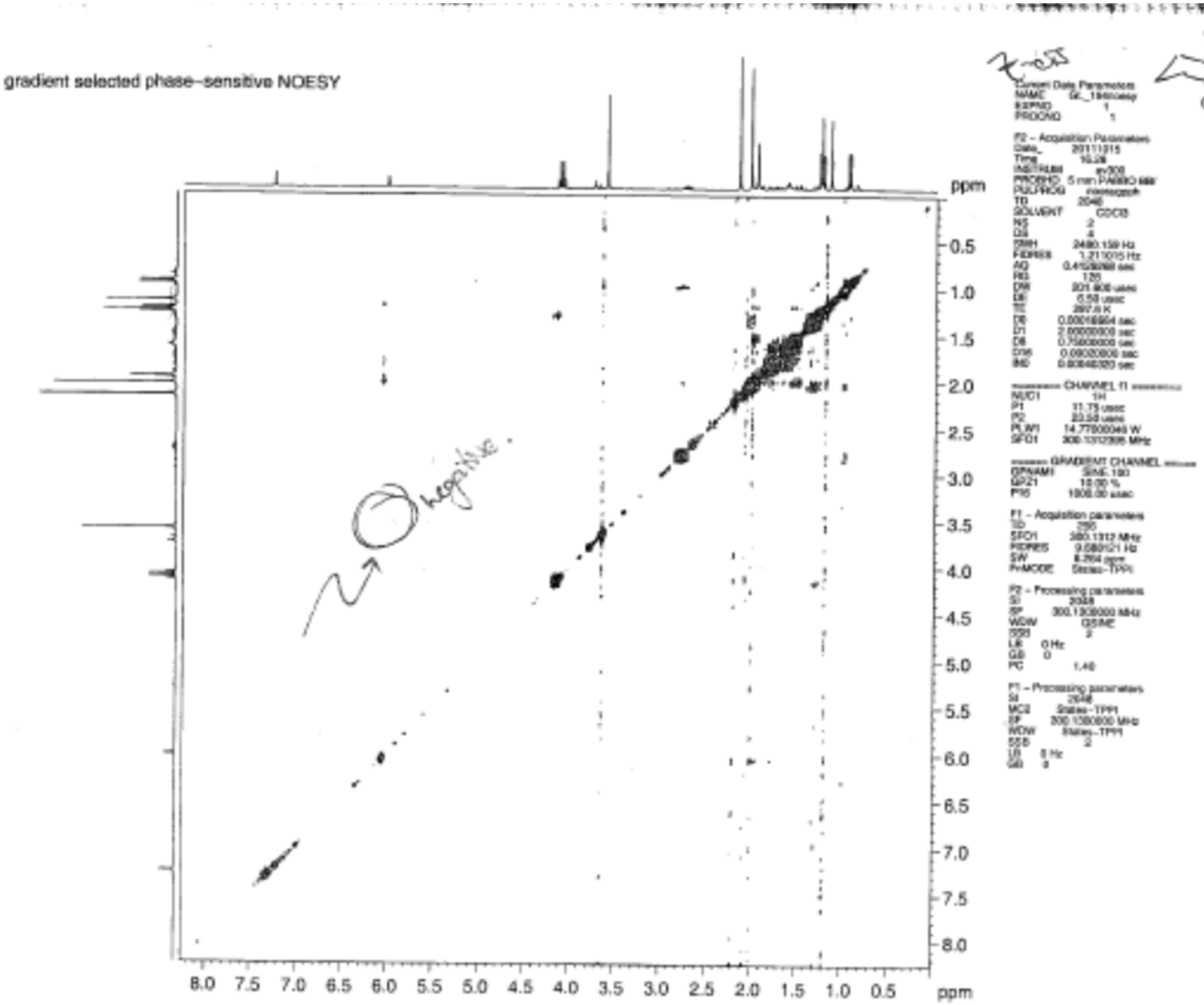
APPENDIX A



E-isomer
47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negative
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2.0
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6.5
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7.5
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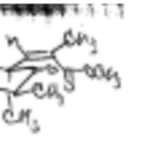
ppm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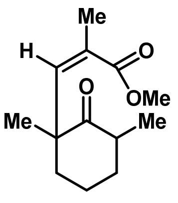
CH3



Z-isomer

51