Synthesis of 5-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-ol

Thesis submitted to
the Graduate College of
Marshall University

In partial fulfillment of
the requirements for the degree of
Master of Science
in Chemistry

by
Harlan Reid

Michael P. Castellani, Ph.D., Committee Chairperson
Robert J. Morgan, Ph.D.
John L. Hubbard, Ph.D.

Marshall University
December 2009

This thesis was accepted on as meeting the research requirements for the Master's Degree.

_____

Dr. Michael P. Castellani
Thesis Committee Chair

_____

Dr. Robert J. Morgan
Thesis Committee Chair

_____

Dr. John L. Hubbard
Thesis Committee

Acknowledgements

This author would like to first thank his wife, for enduring his time spent away from home. The author would also like to thank Dr. Michael Castellani, for his unique approach to advising. The author has developed self-reliance due to this, though Dr. Castellani is always available to help, if needed. The author also thanks Dr. Morgan and Dr. Hubbard for enlightening conversations involving the research performed herein. Finally, the author would like to thank all of the faculty in the Marshall University Department of Chemistry as well as chemists and lab technicians at Marathon Petroleum Company, for their generous aid in a variety of topics over the last year.

Table of Contents

Figures and Tables

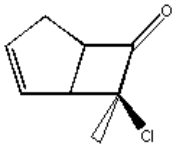
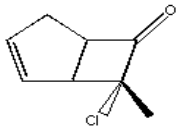
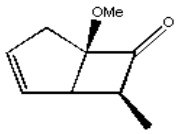
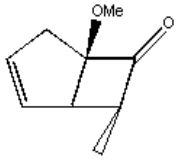
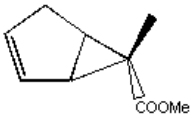
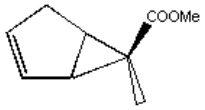
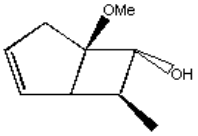
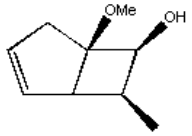
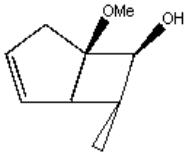
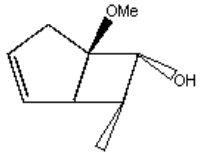
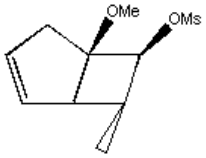
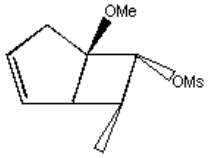
Abstract

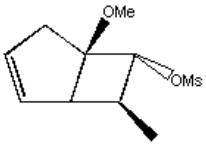
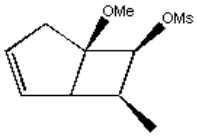
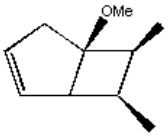
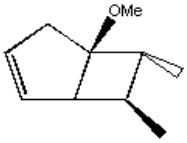
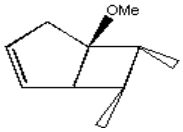
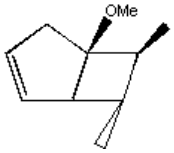
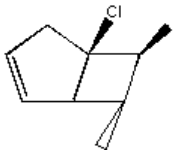
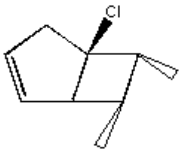
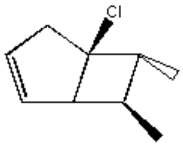
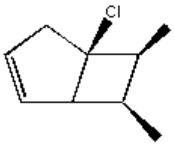
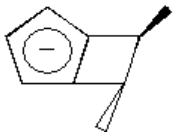
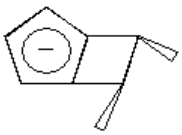
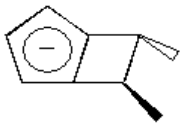
Synthesis of 5-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-ol

By Harlan Reid

In order to generate a chiral metallocene ligand similar to Kaminsky-Sinn catalysts, a multistep synthesis for the production of 6,7-dimethylbicyclo[3.2.0]hepta-1,3-dienyl anion was proposed. Experiments directed at the initial phase of the proposal are included, ending with the characterization of new alcohols in compounds 9 through 12. Two steps from the synthesis were successfully combined, leading to improved recovery of the alcohols.

Compounds

Compound	Structure	Compound	Structure
1	 148.24 g/mol	2	 66.1 g/mol
3	 156.61 g/mol	4	 156.61 g/mol
5	 152.19 g/mol	6	 152.19 g/mol
7	 152.19 g/mol	8	 152.19 g/mol
9	 154.21 g/mol	10	 154.21 g/mol
11	 154.21 g/mol	12	 154.21 g/mol
13	 232.30 g/mol	14	 232.30 g/mol

15	 232.30 g/mol	16	 232.30 g/mol
17	 152.23 g/mol	18	 152.23 g/mol
19	 152.23 g/mol	20	 152.23 g/mol
21	 156.65 g/mol	22	 156.65 g/mol
23	 156.65 g/mol	24	 156.65 g/mol
25	 119.18 g/mol	26	 119.18 g/mol
27	 119.18 g/mol		

CHAPTER I

Introduction

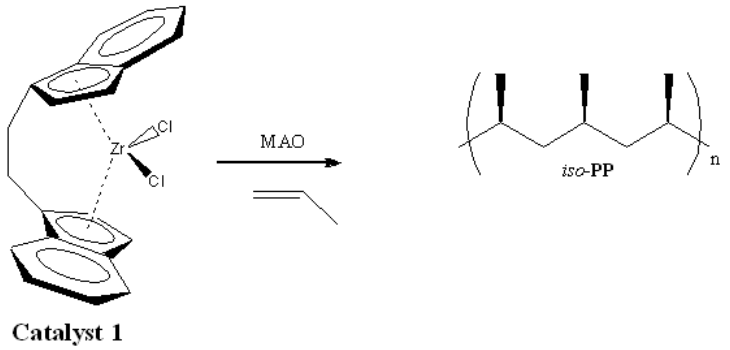
In various aspects of organic molecule creation, it may be necessary to generate a product of a specific orientation. For example, a complex drug can have many chiral centers, though only one conformation may interact with the body in a favorable way. Other configurations may not work at all or worse, may actually be harmful. If a variety of conformational isomers is produced, then they must be separated. Because diastereomers or enantiomers are so similar, separation is sometimes very difficult.

Another approach to having an isolated compound is to create only the product desired. When organic chemists wish to create a single form of a chiral compound, be it enantiomer or diastereomer, there are two basic, possible routes employed. The first begins with a single stereoisomer and involves reactions that will neither destroy the existing chirality nor give rise to additional stereocenters. When this process is not possible or is impractical, the alternative is asymmetric induction. In this method, when a new stereogenic center is created, reaction conditions favor a single configuration.

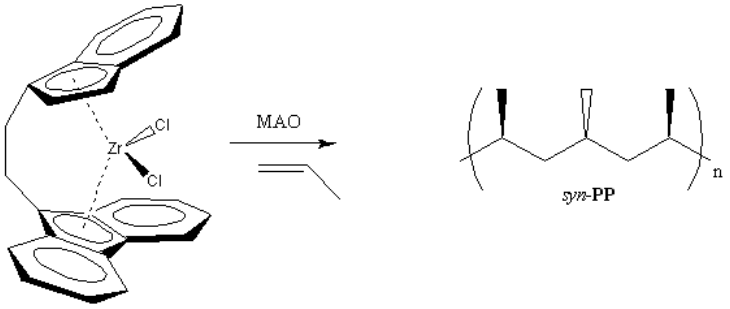
The need for stereoselective methods makes the development of catalysts that favor chiral products of a certain orientation critically important. In organometallic chemistry, substituted cyclopentadienyl (Cp) ligands are of interest because of their effect on reactivity of transition metal centers of metallocenes. Currently, chiral cyclopentadienes are employed as useful

catalysts in carboalumination [1] and in polymerization. [2] In these cases, product orientation is directed, and one chiral form is favored.

Excellent examples of metallocene catalysts used for directed polymerization are Kaminsky-Sinn type complexes, which are based on group 4 transition metals (Figure 1). [2] Initially, the transition metal binds to two halide ions. In the presence of excess methylalumoxane $(CH_3\text{-Al-O})_n$ (MAO), the halogens are replaced by methyl substituents. Binding between zirconium and methyl is very weak and one of these methyl bonds, too, may break. After the loss of a methyl ligand, the transition metal (zirconium) is stabilized by an agostic interaction with the remaining methyl group. [3] This leaves the metal complex poised for subsequent reactions with alkenes. The directed polymerization occurs because only a specific orientation of the olefin can enter the reactive site of the system and interact with the central metal complex.



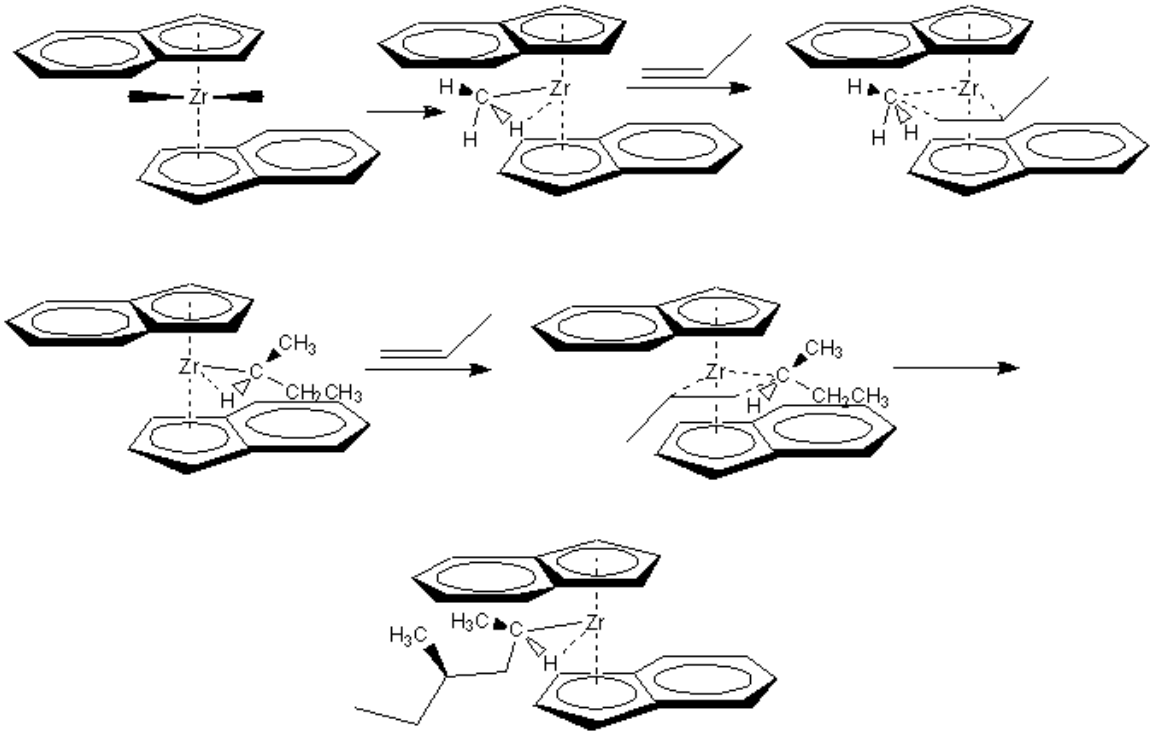
Catalyst 1



Catalyst 2

Figure 1: Kaminsky-Sinn type Catalysts. The dichlorozirconocenes react with propylene in the presence of excess MAO to give the polymer products.

Propylene enters between the indene rings of **Catalyst 1** (Figure 1) in an orientation directed by steric effects (Scheme 1). [4] Prior to addition to the alkane chain forming on zirconium, the methyl portion of the incoming propylene orients away from the unsubstituted portion of the indene rings. An agostic interaction is re-established, now in an orientation that is opposite the initial interaction. The next propylene to react must have an approach reverse that of the previous propylene; additionally, the orientation of the methyl portion of the olefin, too, is opposite that of the original. With both the reactive site and the approaching reactant reversed from the first conditions, the system is effectively rotated. Propylene is always added to the system in the same manner which results in an isotactic product.



Scheme 1: Isotactic Zirconocene Polymerization Mechanism. The olefin must approach from the side opposite the residing methyl group, with a specific orientation.

With **Catalyst 2** (Figure 1), only the bicyclic ligand influences the orientation of the approaching alkene. In this system, the methyl groups of propylene are always oriented toward the Cp ligand. The approach of propylene still occurs from successively alternating sides and yields syndiotactic poly-propylene. [2]

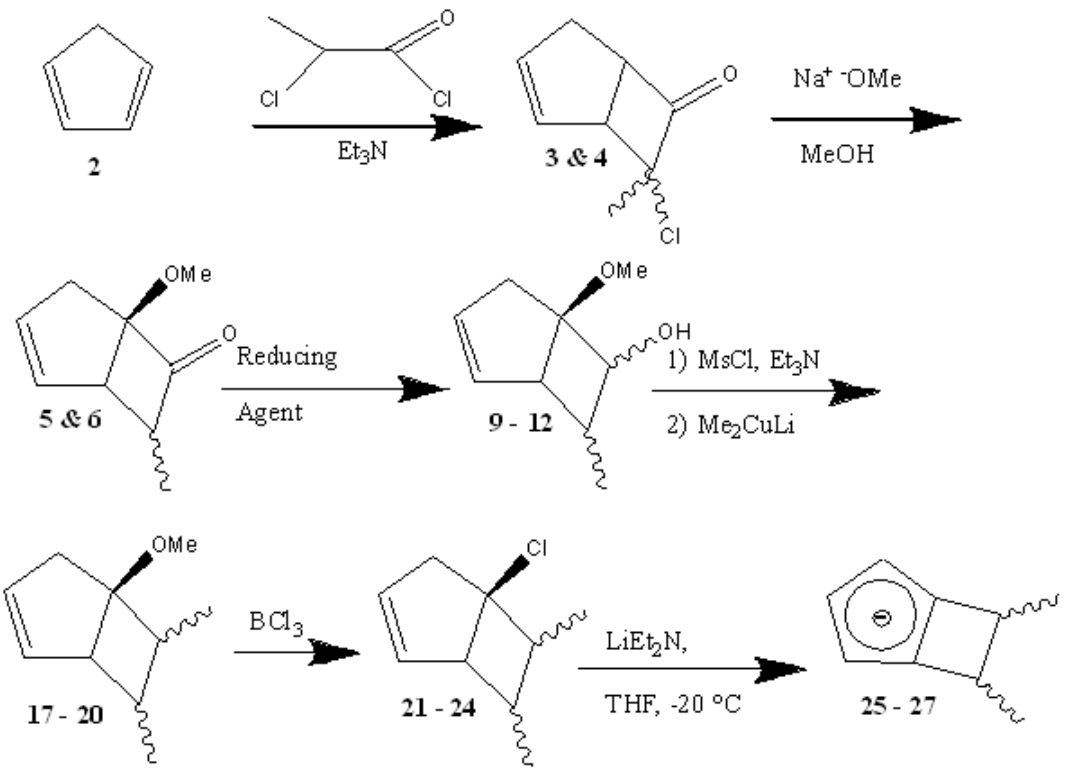
A potential alternative to the planer chiral rings of Kaminsky-type catalysts is small-ring annulated cyclopentadienyl complexes. These are desirable because they are rigid and the proximity of ligands to the reactive metal complex may further promote the adoption of a preferred conformation in the course of a reaction, giving even higher stereoselectivity than Kaminsky-type catalysts. At this

time, however, cyclobutane annulated cyclopentadienyl systems are virtually unknown, with only the unsubstituted bicyclo[3.2.0]heptadienyl anion reported. [5]

Substituted Bicyclo[3.2.0]heptadienyl Synthesis

The goal of this research is the synthesis of the dimethylbicycloheptadienyl anions (Compounds 25-27) displayed in Scheme 2. This complex was chosen because it appeared to be the simplest substituted bicycle[3.2.0]heptadienyl anion. Because the methyl groups are small relative to other alkyl groups, their interference with reactivity during synthesis should be the most limited. However, this may allow for a mixture of conformations. The limited selectivity demands the development of techniques for isolating the various stereoisomers that may be produced. Once isolated, stereospecific metallocenes can be created and the reactivities compared.

The proposed synthesis (Scheme 2) was developed to create the first of these substituted bicyclic molecules. The literature suggests that each step should give moderately high yields. [5,6,7,8,9,10] The steps for reduction and alkyl-de-hydroxylation are utilized because traditional methods of converting a carbonyl into an alkyl group in analogous systems has destroyed the [3.2.0]bicyclic structure. [9]

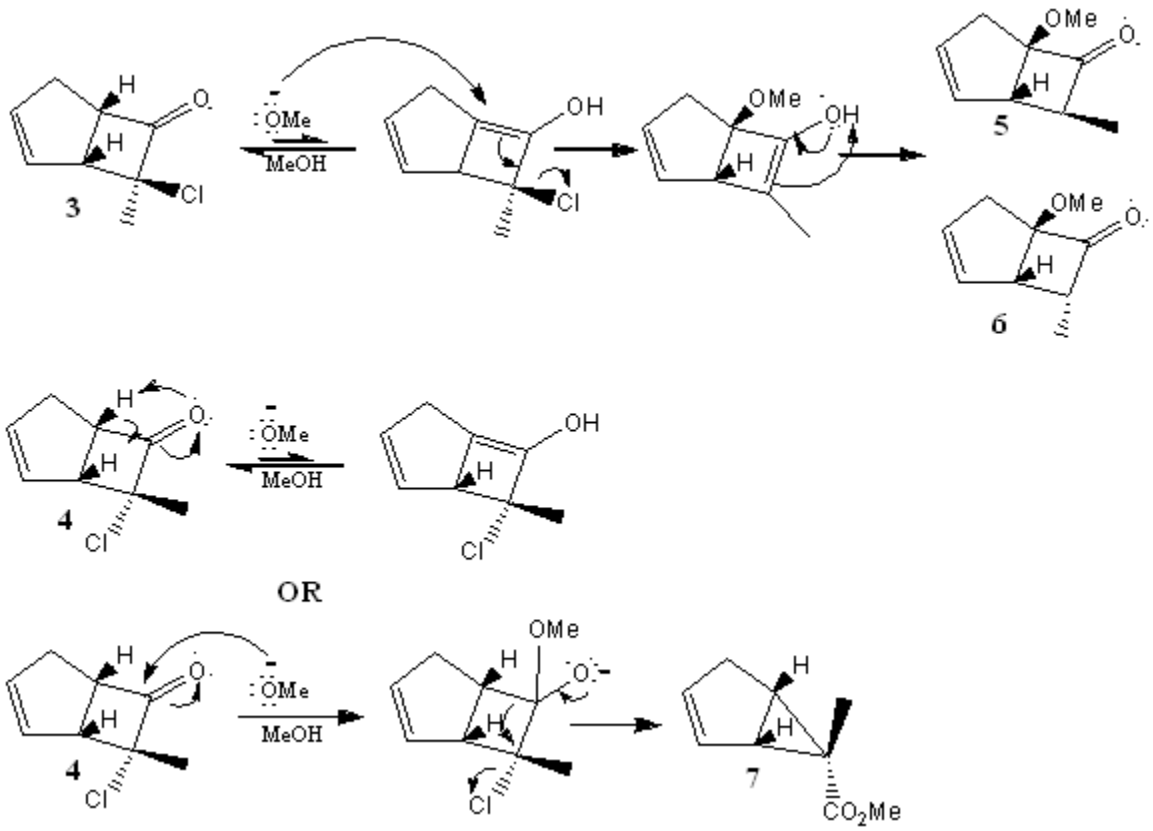


Scheme 2: Proposed synthesis of 6,7-dimethylbicyclo[3.2.0]hepta-1,3-dienyl anions

There are extensive literature precedents for the formation of bicyclo-ketones. [12,7,6] Reaction of acid chlorides with a base, such as triethylamine, are known to generate a ketene. Ketenes may react with alkenes in [2+2] cycloadditions, generating bicyclobutanones. [12] Here, cyclopentadiene is combined with the ketene prepared from 2-chloroproprionyl chloride to form 7-methyl-7-chloro-bicyclo[3.2.0]hept-2-en-6-one as a mixture of 4 stereoisomers. [7] The *endo*-methyl product (**3**) is favored and exists in a 4:1 ratio to its conformer (**4**). A larger alkyl substituent should promote higher stereoselectivity. The diastereomers formed are separable via fractional distillation.

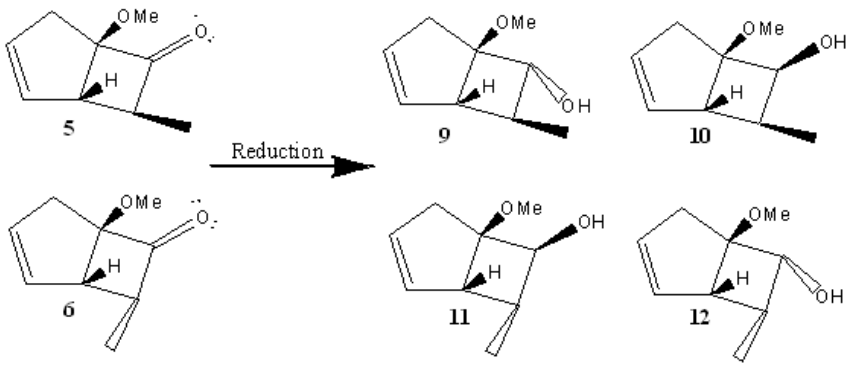
Methoxylation and dehalogenation of the *endo*-methyl product (**3**) with sodium methoxide in methanol give a mixture of **5** and **6**. It has been proposed

that the reaction occurs via an enol intermediate (Scheme 3).[8] The major product is the the *exo*-product (**5**), favored 2:1. Under these conditions, compound 4 undergoes an undesirable rearrangement.



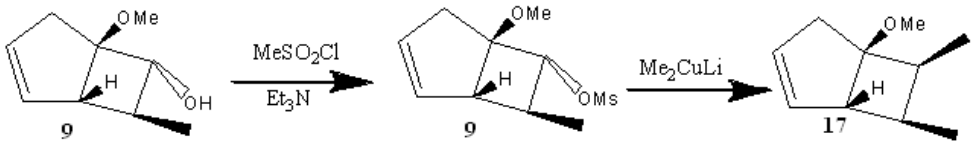
Scheme 3: Mechanism for Methoxylation at the Bridgehead

Following methoxylation, the ketone products (**5** and **6**) are reduced to alcohols (Scheme 4). Because a diastereomeric mixture is used as the starting material, four different alcohols should be obtained (**9** - **12**). Based on yields, sodium borohydride [9] is the reducing agent of choice, although lithium aluminum hydride [13] has performed well. The resulting alcohols may be separated via fractional distillation.



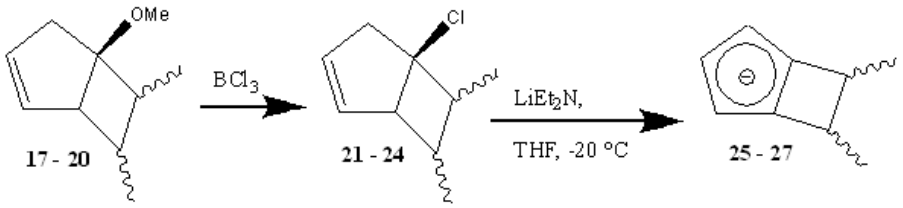
Scheme 4: Predicted Reduction to Alcohols

Direct methyl substitution is unlikely to succeed because alcohols typically are poor leaving groups. In the presence of methanesulfonyl chloride under basic conditions, a mesylate ester is formed (Scheme 5). Reaction of mesylates with lithium dimethyl cuprate will give rise to oxidative addition/reductive elimination (**17** - **20**). [10]



Scheme 5: Methyl Substitution. Only one diastereomeric reaction is shown, for clarity.

To generate the final anion, an elimination reaction of the mesylates (**17** - **20**) must be performed. First, demethoxylation/halogenation through the use of boron trichloride gives **21** through **24** (Scheme 6). The newly placed bridgehead halogen should be removed readily by a halo-elimination through reaction with lithium diethylamide to give dimethylbicyclo anions (**25** – **27**). [11]



Scheme 6: The final steps of the proposed synthesis.

CHAPTER II

Equipment

General Data: ^{1}H NMR spectra were obtained at 499.22 MHz using a Varian Unity+ 500 MHz NMR spectrometer. Spectra were collected in $CDCl_3$ (Aldrich) with no further purification. GC-MS spectra were recorded using both a Varian Saturn 2000 GC-MS with electron impact or chemical ionization equipped with a quadrapole ion trap mass analyzer (5% methyl siloxane column with an inlet temperature of 300 °C, an initial oven temperature of 50 °C holding for two minutes, and a temperature ramp of 20 °C/min for 12 minutes with a final temperature of 250 °C) as well as an HP 6890 GC System equipped with HP 5973 Mass Spectrometer utilizing electron impact with a quadrapole mass analyzer (5% methyl siloxane column with an inlet temperature of 325 °C, an initial oven temperature of 40 °C holding for 20 minutes, then a temperature ramp of 3 °C/min for 90 minutes and holding an additional five minutes at the final oven tempearature of 325 °C).

Synthesis

Cyclopentadiene (2): Cyclopentadiene was prepared by thermally cracking dicyclopentadiene following the method of Moffett. [14] The colorless purified cyclopentadiene was stored in an amber bottle at -45 °C.

7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-one (3 and 4): To a 300 mL round bottom flask immersed in an ice-water bath containing chilled hexanes (200 mL) was added to cyclopentadiene (30.0 g, 454 mmol) followed by triethylamine (36.1

g, 357 mmol). Under rapid stirring, 2-chloropropionyl chloride (45.5 g, 358 mmol) was added dropwise via an equal-pressure addition funnel over the course of an hour. The solution was then allowed to warm to ambient temperature over the course of a day, whereupon it was vacuum filtered to separate the $[Et_3NH]Cl$ solid from the solution. The dark orange liquor was then placed on a rotary evaporator to remove solvent at 35 °C, yielding a dark brown oil (48.0 g, 306 mmol).

The $[Et_3NH]Cl$ precipitate, from the filtration step, was dissolved in distilled water, then placed in a 500 mL separatory funnel with hexane (150 mL). The organic layer was washed with distilled water (3 x 50 mL). The clear yellow organic layer was dried with magnesium sulfate and placed on a rotary evaporator to yield a brown oil (3.36 g, 21.5 mmol).

The crude products were combined and the oil was then vacuum distilled with careful observation of vapor-temperature changes in a round-bottom flask using a Vigreaux column (6 in), water-cooled condenser, and a “cow-type” receiver equipped with four 25 mL round bottom flasks. The fractions typically contained a mixture of **3** and **4**, with 90-95% pure *endo*- product (**3**) and comprised 30-55% yield. *^{1}H NMR (499 MHz, cdcl3) δ 5.99 (dq, J = 5.8, 2.0 Hz, 1H), 5.78 – 5.74 (m, J = 7.9, 2.3 Hz, 1H), 4.29 (ddd, J = 9.1, 7.8, 1.3 Hz, 1H), 3.81 – 3.66 (m, 1H), 2.74 – 2.66 (m, 1H), 2.48 (ddq, J = 17.5, 9.3, 2.1 Hz, 1H), 1.50 (s, J = 24.8 Hz, 3H).*

Further vacuum distillation of the material remaining in the distillation flask gave a mixture of **3** and **4,** with 75-95% pure *exo*-product at 15-25% yield. *^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dq, J = 7.8, 2.0 Hz, 1H), 5.79 – 5.73 (m, J = 7.9, 2.2 Hz, 1H), 3.92 (t, J = 8.2 Hz, 1H), 3.64 – 3.55 (m, J = 4.2, 2.1 Hz, 1H), 2.78 – 2.67 (m, 1H), 2.50 (ddq, J = 17.2, 9.1, 2.0 Hz, 1H), 1.79 (s, 3H).*

5-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-one (5 and 6): A 500-mL, three-neck round bottom flask equipped with an equal pressure addition funnel and an air-cooled condenser with a nitrogen inlet was immersed in an ice-bath. Methanol (300 mL) was added to the flask, followed by small pieces of sodium metal (3.5 g, 167 mmol) under stirring. Upon complete reaction of the sodium, a solution of *endo*-7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-one (12 g, 0.077 mol) in methanol (30 mL) was dripped into the vessel under rapid stirring over the course of 24 hours. Water (50 mL) was slowly added to the flask through the addition funnel.

The solution was then transferred to a 1 L separatory funnel and extracted with n-hexane (3 x 150 mL). The cloudy white organic layer was dried with magnesium sulfate, leaving a near colorless clear liquid. The drying agent was removed by vacuum filtration followed by solvent removal by rotary evaporation. The crude diastereomers (70-80% yield) were obtained as a light yellow oil.

5-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-ol (9-12):

Method A: To a 50 mL three-neck round bottom flask equipped with an equal-pressure addition funnel and water-filled condenser with nitrogen inlet was added lithium aluminum hydride (0.2 g, 5.27 mmol). 5-Methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-one (**5** and **6**) (1.1 g, 7.2 mmol) was dripped into the vessel under rapid stirring over the course of 6 min. Additional ether (4 mL) was then rinsed through the addition funnel. The solution was heated to reflux for 30 minutes, allowed to cool and stirred for 24 hours. A yellow film covered a gray slurry; nearly all the ether had evaporated. Enough 1M H_2SO_4 was added to the material such that all remaining $LiAlH_4$ was neutralized. After the addition of ether (20 mL), the product was isolated via separatory funnel with rinses of ice water (3 x 15 mL). The ether layer was dried with $MgSO_4$. After vacuum filtration and rotary evaporation (35 °C), a golden oil was recovered (0.5 g, 70% yield).

Method B: To a 50 mL three-neck round bottom flask equipped with an equal-pressure addition funnel and water-filled condenser with nitrogen inlet was added ethanol (13 mL). To this was added powdered sodium borohydride (0.25 g, 6.6 mmol). 5-Methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-one (**5** and **6**) (0.50 g, 3.3 mmol) was then added under rapid stirring,. The solution was allowed to warm to ambient temperature and was stirred for 21 hours. A cloudy yellow solution was obtained.

The solvent was removed using rotary evaporation, leaving a white residue, which was then dissolved in diethyl ether and acidified with 1M H_2SO_4. The colorless solution was extracted with diethyl ether (2 x 25 mL). The aqueous

layer was cooled in an ice-water bath, made basic (pH 9) by adding solid NaOH, and extracted with diethyl ether (2 x 25 mL). The organic layers were combined and dried with magnesium sulfate, followed by vacuum filtration and solvent removal by rotary evaporator (35 °C). A light-yellow oil was obtained (0.41 g, 82% yield).

Method C: A 500-mL, three-neck round bottom flask equipped with an equal pressure addition funnel and an air-cooled condenser with a nitrogen inlet was immersed in an ice-bath. Methanol (300 mL) was added, followed by small pieces of sodium (3.7 g, 140 mmol). A solution of *endo*-7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-one (**3**) (15.3 g, 97.7 mmol) in methanol (30 mL) was dripped into the vessel under rapid stirring and allowed to react over the course of 24 hours.

The ice-water bath was replenished and, under rapid stirring, 6.0 g of powdered sodium borohydride was added. The solution was then allowed to warm to ambient temperature and stirred over 22 hours, upon which a cloudy yellow solution was observed. The flask was then attached to a rotary evaporator to remove the alcohol solvent, leaving a white residue which was dissolved in diethyl ether. The ether solution was then acidified with 1M HCl. The colorless solution was then extracted in a separatory funnel with diethyl ether (2 x 25 mL). The aqueous layer was cooled in an ice-water bath and made basic (pH 9) with solid NaOH, then extracted with diethyl ether (2 x 25 mL). The organic layers were combined and dried with magnesium sulfate, followed by

vacuum filtration and solvent removal by rotary evaporation (35 °C). A light-yellow oil was obtained (11.9 g, 79.0 % yield).

The conformer with the lowest boiling point was isolated through distillation. *^{1}H NMR (499 MHz, $CDCl_3$) δ 5.87 – 5.79 (m, J = 7.7, 5.0, 2.6 Hz, 1H), 5.77 – 5.66 (m, 1H), 4.17 – 3.99 (m, 1H), 3.29 (d, J = 32.0 Hz, 3H), 2.74 – 2.66 (m, J = 17.6, 3.2, 2.1 Hz, 1H), 2.66 – 2.61 (m, J = 3.5, 3.0, 1.9 Hz, 1H), 2.32 – 2.25 (m, J = 17.6, 4.9, 2.4 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.08 (d, J = 12.4 Hz, 3H).*

CHAPTER III

Results and Discussion

The first steps in the proposed synthesis have strong literature precedent and, although the reactions are sufficiently detailed in their publications to allow for reproducibility, some difficulties were encountered. By modifying these preparations; recovery and purity of the bicyclic ketones (**3** and **4**) were improved over those reported. Methoxylation of the ketone yields compounds **5** and **6**. Reduction of these compounds has culminated in the generation of the new alcohols: **9** through **12**. Due to similar reaction conditions, it was determined that both methoxylation and reduction can be carried out in a single flask. With respect to the starting ketones (**3** and **4**), overall yield of the alcohols (**9** – **12**) was improved by approximately 10% when performing both steps together.

7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-one (3 and 4): The reaction between cyclopentadiene and chloromethyl ketene, generated by reaction between triethylamine and chloropropionyl chloride, initially presented some minor difficulties. Cyclopentadiene and the acid chloride were placed in a round bottom flask, without the presence of solvent. A purple, white and brown swirl of warm viscous material was generated immediately. Hexane was added, followed by slow addition of triethylamine. The final crude material generated was full of unidentified side-products with no appreciable yield of desired material achieved.

To improve the yield and purity of the ketones (**3** and **4**), cyclopentadiene and triethylamine were placed into a flask containing hexane solvent. Upon

addition of 2-chloropropionyl chloride, the ketene was generated which then reacts with cyclopentadiene, giving rise to the [2+2] addition product. The scale of this reaction was continually increased to generate more material for subsequent steps. At the 10 gram scale, however, yield began to decrease. In large scale reactions, the triethylammonium chloride by-product trapped appreciable amounts (5 - 10%) of the product. Dissolving the solid in water and then isolating the once-trapped products in an organic layer helped to recover some of the lost material, giving a 92% yield of crude ketones. GCMS analysis shows a 4:1 favoring of the diastereomer with the lower boiling point (Figure 2). Based on NMR data, the upfield position of the methyl group indicates that this is the *endo*-methoxy product. [6,8]

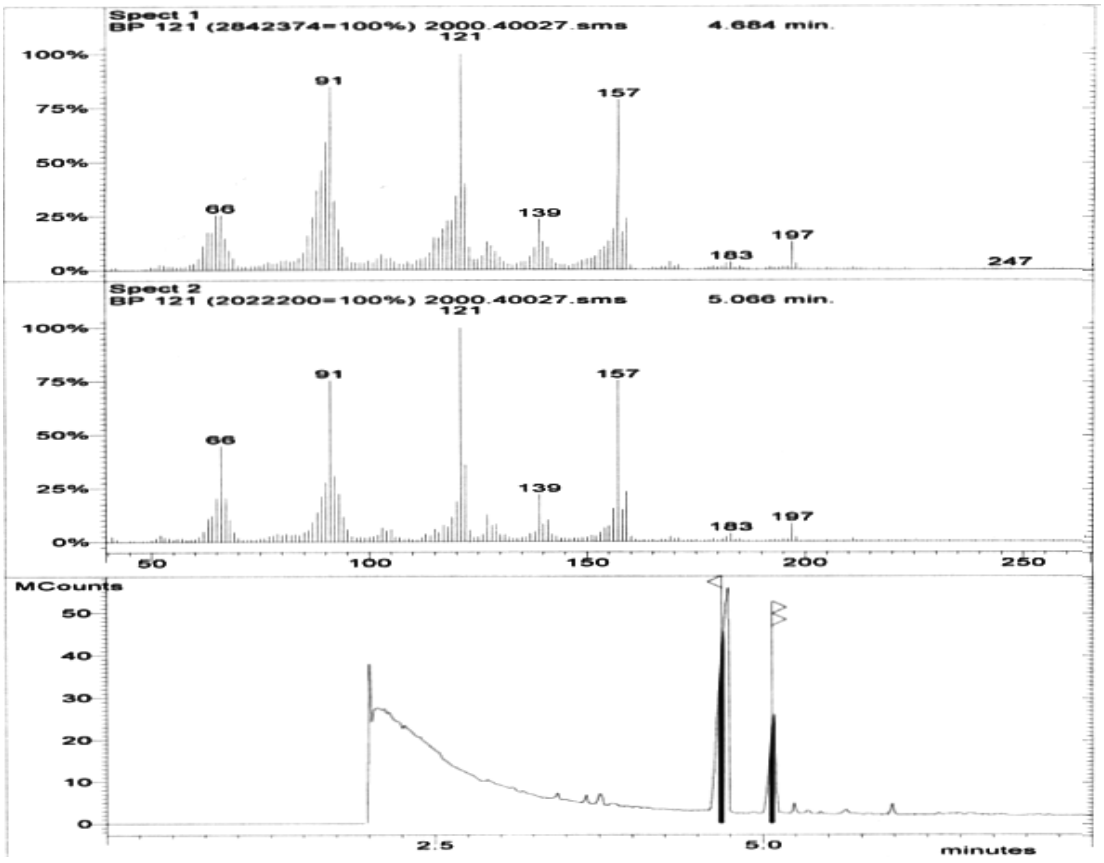


Figure 2: GC/MS spectra for the crude product from reaction A. The near-identical mass spectra are a strong indication that the two main products are closely related, as would be expected for these diastereomers.

A Schlenk line capable of reducing pressure of a system to *ca*. 2 torr was utilized. Because the compounds co-distill at ambient temperature at this pressure, a bleed was placed on the line to increase pressure of the system to an unknown value. Compound 3 can be nearly completely distilled, with crude compound 4 being the residual material in the distillation flask. The NMR (Figure 3) spectra of the separated compounds are in agreement with the literature. [6,7]

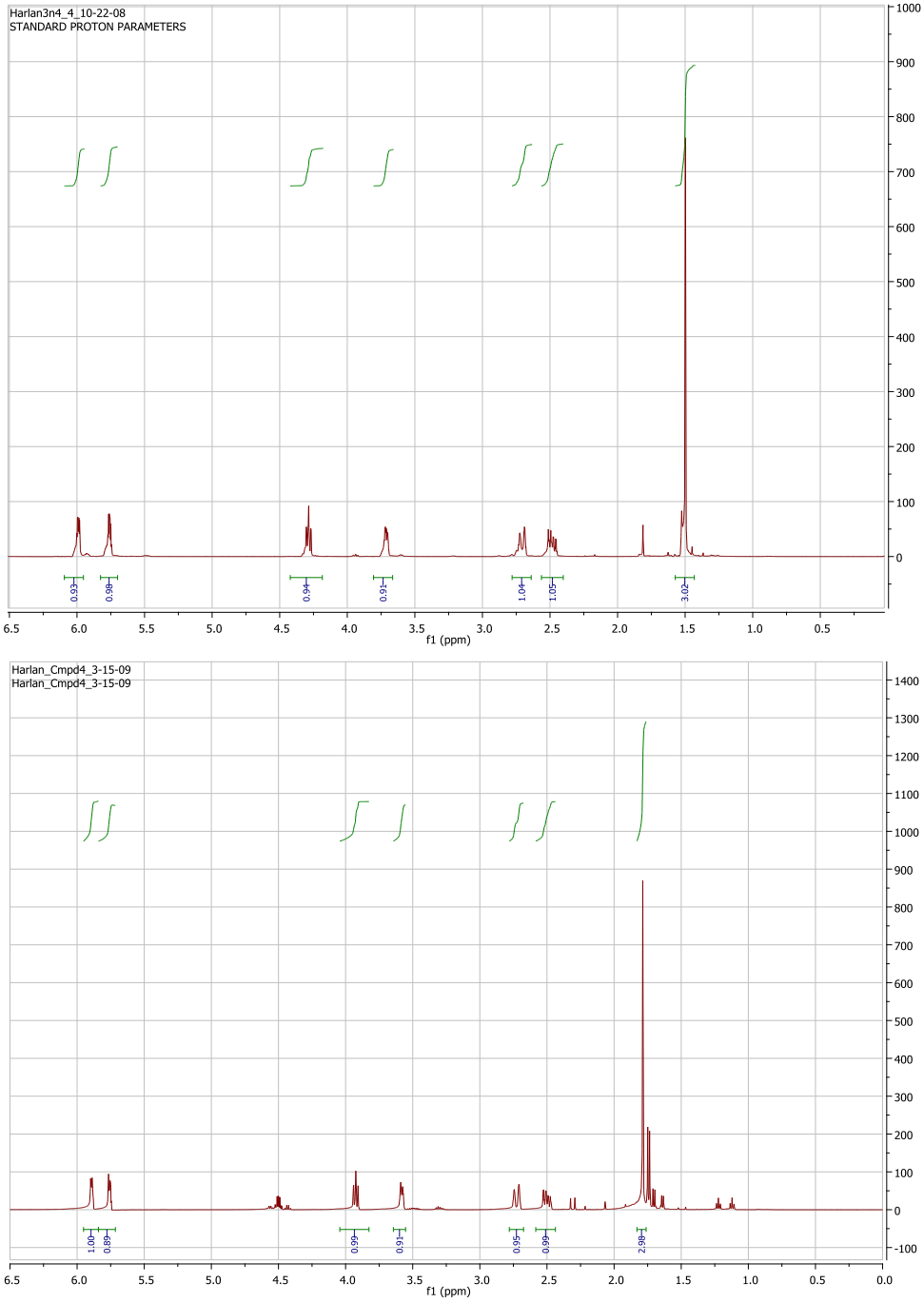


Figure 3: NMR spectra for compounds 3 (top) and 4 (bottom). Slight peak shifts are evident, especially at the methyl group.

*5-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-one (5 and 6):*Though this procedure involves addition of sodium metal to methanol, it is not violent at the concentrations used. The production of hydrogen gas, although not violent, is still potentially dangerous, so the solution was kept cold and under a nitrogen atmosphere

The ketones (**3** and **4**) appear to have low solubility in methanol and a suspension must be formed before adding to the addition funnel for slow addition. The methoxyketone products (**5** and **6**) have been observed as a white solid, or as a suspension. If the *exo*-ketone (**4**) is present, the reaction with methoxide ion will induce a ring contraction yielding a bicyclohexanoate (**7**) (Figure 4). [15,8]

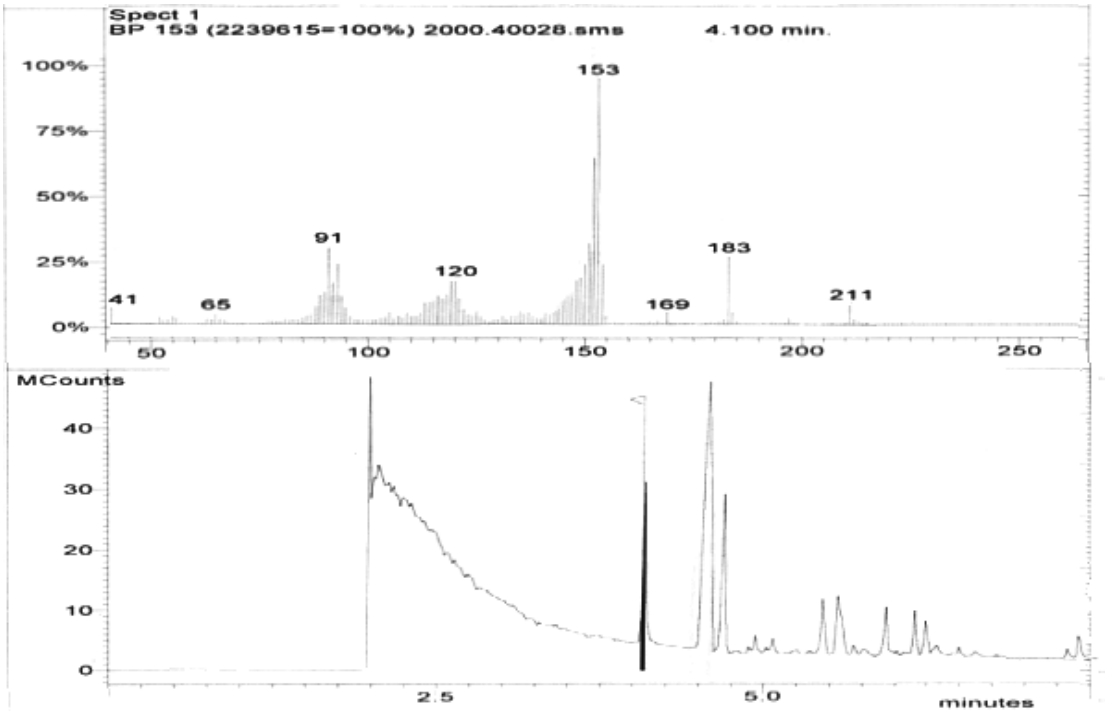


Figure 4: GCMS of the crude products from methoxylation showing compound 7's peak and fragmentation pattern . There was a significant concentration of compound 4 in the starting material, which gave this side-product.

The main products exist in a 2:1 ratio with the isomer in excess having the lower boiling point (Figure 5). According to the literature, the *exo*-methyl product is favored, which is opposite that of the previous step. [8] Attempts to separate the diastereomers with fractional distillation have been unsuccessful.

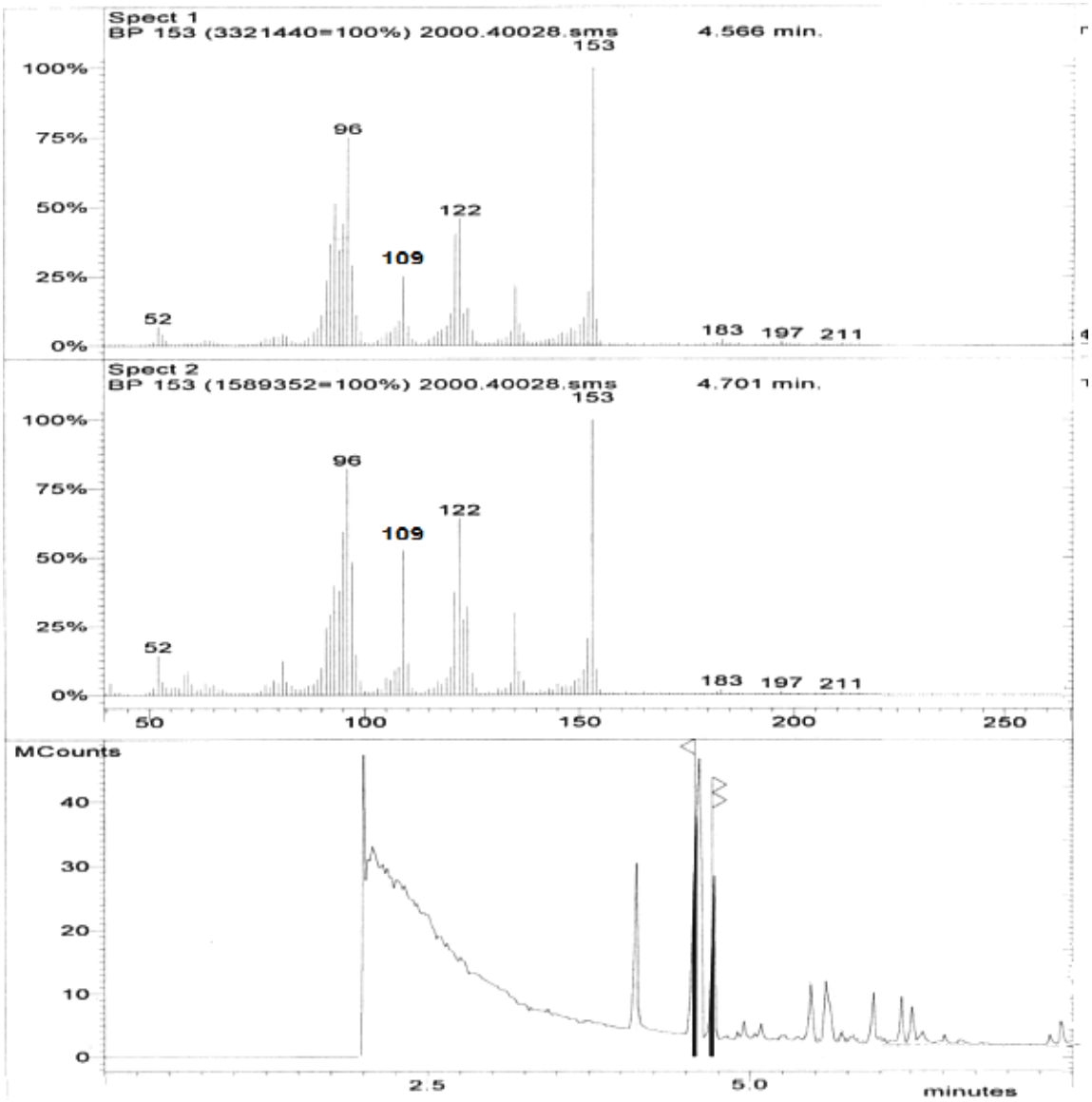


Figure 5: GCMS of the crude products from methoxylation, with compound 5 and 6 selected. The similarity of mass spectra strongly indicate structural similarity, which is in agreement with the nature of the diastereomers

Due to differences in boiling points, diastereomeric methoxyketones **5** and **6** can be isolated from the bicyclohexanoate side product **7** (Figure 6) and other contaminants. The pair are not easily differentiated from one another by ^{1}H NMR spectroscopy (Figure 7).

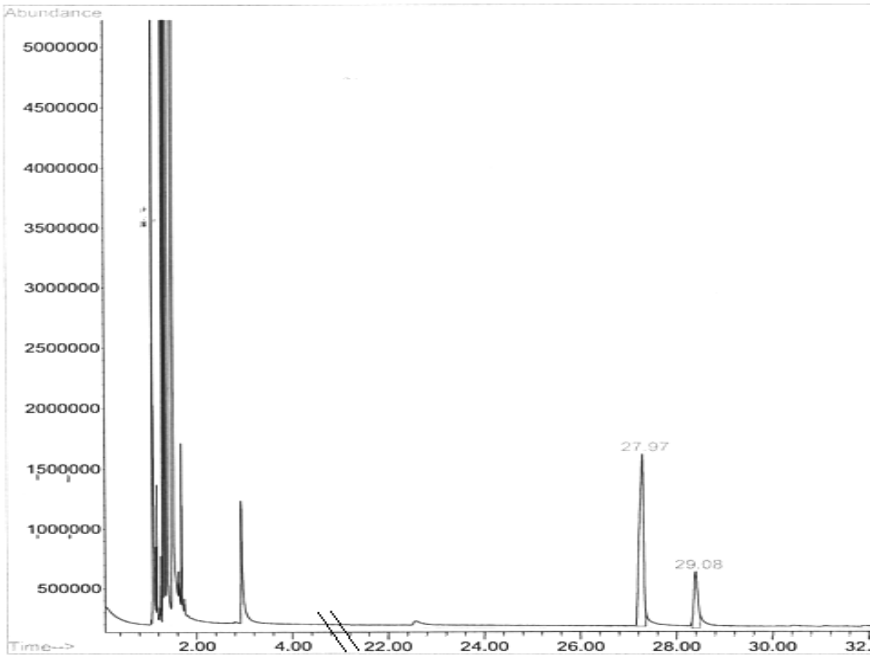


Figure 6: A Gas chromatogram of isolated compounds 5 and 6, in hexane. The small peak at 22.6 minutes is the remaining contamination of compound 7.

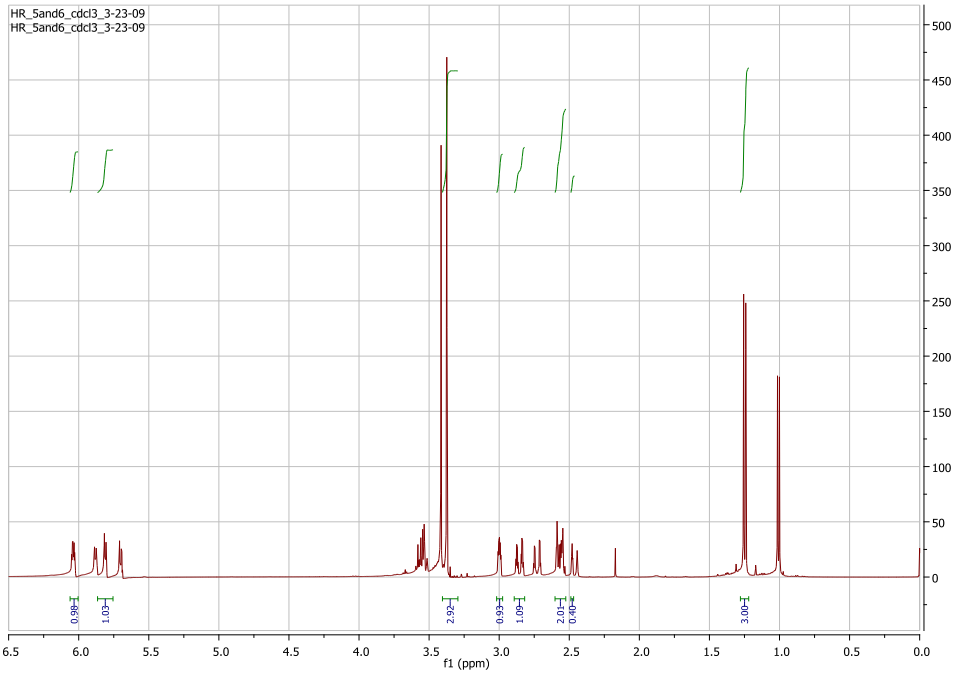


Figure 7: Proton NMR of a mixture of compounds 5 and 6. Their similar concentration makes peak assignment difficult.

5-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-ol (9-12): The use of lithium aluminum hydride (**Method A**) or sodium borohydride (**Method B**) generated four products (Figure 8). Total yields were higher with sodium borohydride, with the four major products in comparable ratios to that from **Method A** (Figure 9).

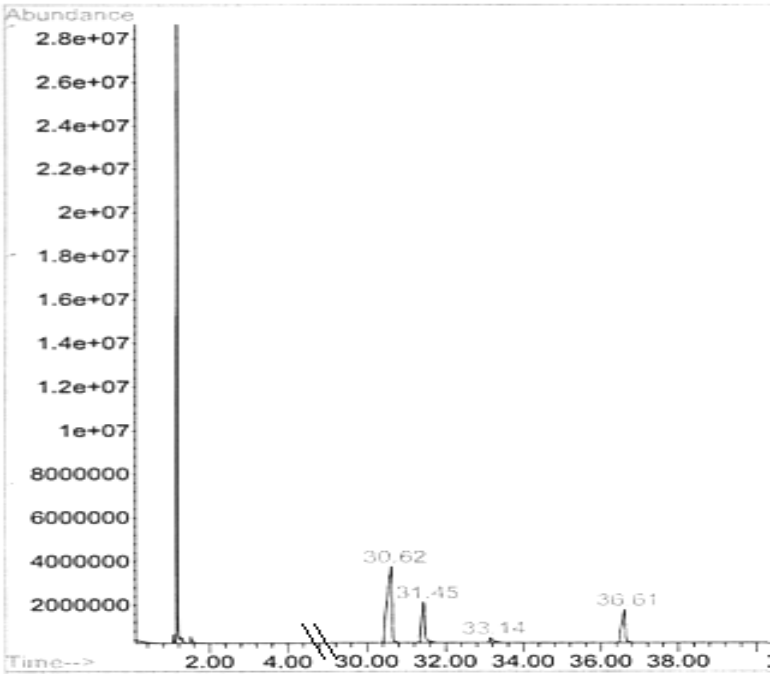


Figure 8: GC of compounds 9-12 from reduction of compounds 5 and 6 by $LiAlH_4$. According to peak area, product concentrations, in order of elution, are 56, 20, 4 and 20% by volume.

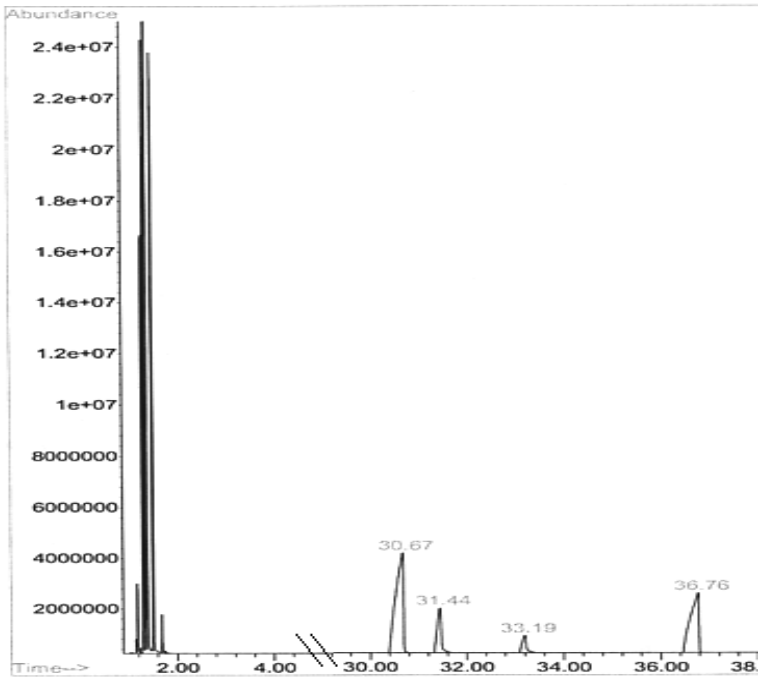


Figure 9: GC of compounds 9-12 from reduction of compounds 5 and 6 by $NaBH_4$. According to peak area, product concentrations, in order of elution, are 50, 12, 5 and 33% by volume.

The main products share identical fragmentation patterns. Noteworthy is the similarity of the fragmentation pattern of the alcohols (**9** – **12**) to the methoxyketone starting material (**5** and **6**) (Figure 10). This is not unexpected. With only the reduction of the ketone differentiating them, structural similarity is high.

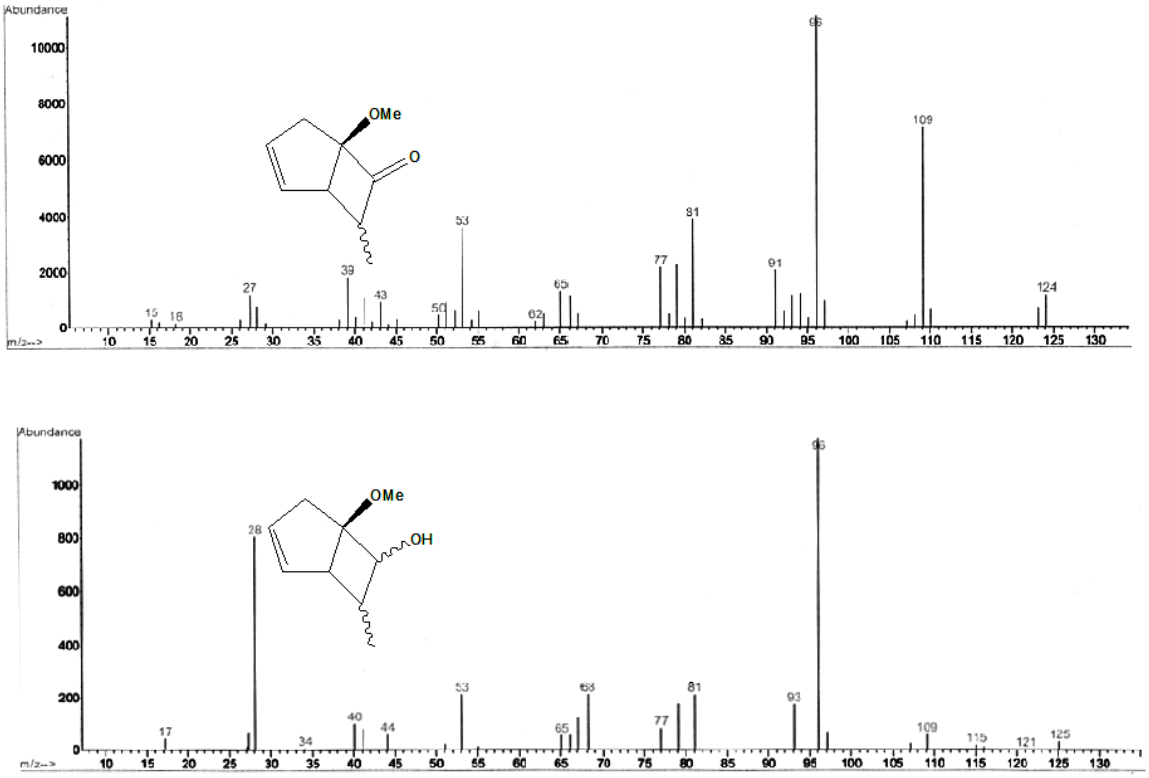


Figure 10: Mass Spectra comparison of compounds 5 and 6 to compounds 9-12. The fragmentation similarity suggests a strong structural similarity.

The proton NMR, too, is similar to that of the starting material (Figure 11). A doublet was expected to present between 3 and 4 ppm for the proton at C6 and, although the spectra contains contaminates, the appearance of new doublet peaks at the 4.09 and 4.40 ppm positions strongly suggests that a reduction

occurred, especially given that this peak correlates to the peak position of an analogous system. [9]

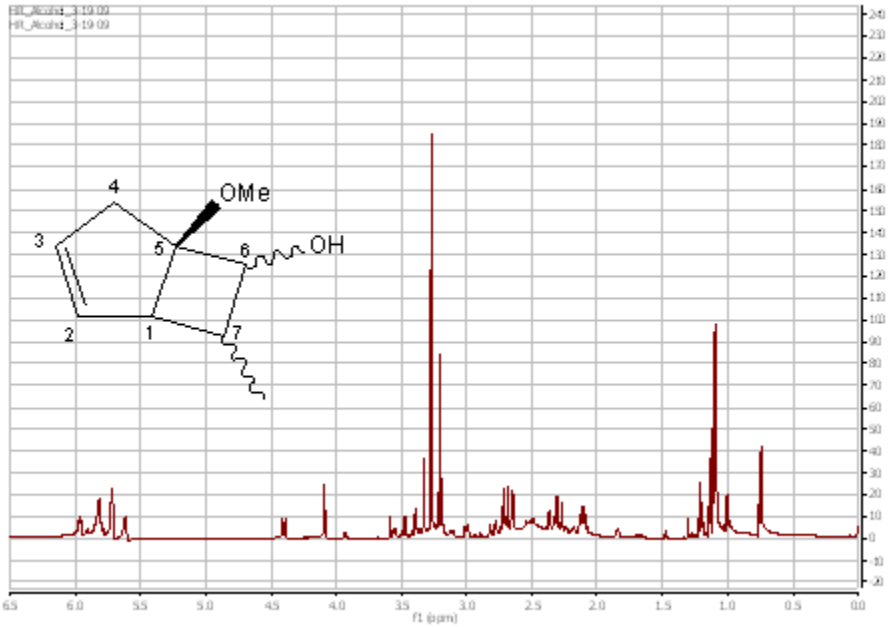


Figure 11: Proton NMR of compounds 9-12. The spectra, although somewhat plagued by contaminant peaks, shows the formation of a new peak near the expected position.

After the difficulty in separating the methoxyketones (**5** and **6**) became apparent, there was no necessity in purification at this step. Therefore, attempting to go directly from the ketones (**3** and **4**) to the formation of the alcohols (**9** - **12**) in a single pot became viable with **Method C**. The ratio of the alcohol products from **Method C** is similar to that from **Method B** (Figure 12). The peaks at 21.44 and 23.47 minutes are undesired side products which were easily removed during purification.

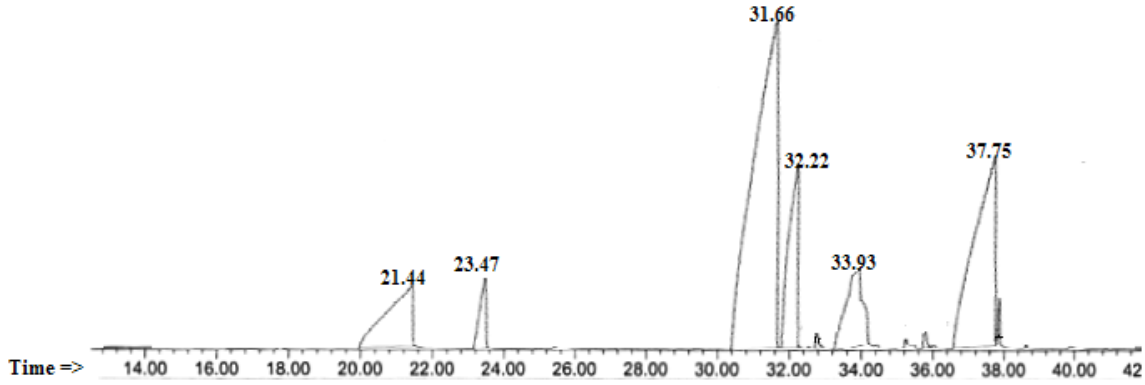


Figure 12: GC of the crude product containing compounds 9-12 from a one pot reaction.

Conclusion

The first steps in the proposed scheme for creation of a bicyclo[3.2.0]heptadienyl anion have been successful. Previously reported procedures have been improved upon, either in yield or in scale. [6,7,12] Reduction of the methoxyketone diastereomers (**5** and **6**) has generated four new bicylic alcohols (**9** – **12**). Combining the methoxylation and reduction steps as **Method C** was a novel procedure that enhanced the yield of these alcohols.

The stage is now set to mesylate or tosylate the alcohols. If successful, the use of an organocuprate in alkylation/dehydroxylation will generate the appropriate dimethyl substituted systems (17-20), and the two remaining reactions should proceed with relative ease. However, with very few stable, disubstituted bicyclo[3.2.0]heptenes created in appreciable yields, there is the possibility of further difficulties. Previous attempts have failed because the bicyclic compound has lost the bridge, creating cycloheptane derivatives. [16]

References

1. Shaugnessy, K. H.; Waymouth, R. M. *J. Am. Chem. Soc.* **1995,** *117,* 5873.

2. Kaminsky, W. Highly active metallocene catalysts for olefin polymerization. *J.C.S. Dalton Trans.* **1998,** *1418,* 1413.

3. Hayes, P. G. Mechanism for Olefin Polymerization. http://classes.uleth.ca/200701/chem4000a/Class Notes Web Pages/Olefin Polymerization/Olefin Polymerization.pdf (accessed Sept 18, 2009).

4. Metallocene Catalysis Polymerization. http://pslc.ws/macrog/mcene.htm (accessed March 20, 2009).

5. Oda, M.; Breslow, R. A Facile 1,5 Alkyl Shift Converting Bicyclo[3.2.0]Hepta-1,3-Diene into Spiro[2,4]Hepta-4,6-Diene. *Tet. Lett.* **1973,** *14* (27), 2573-2540.

6. Brady, W. T.; Holifield, B. M. Halogenated Ketenes. III. Methylchloroketene. *Tet. Lett.* **1966,** 5511-5515.

7. Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A. S. Stereochemische Aspekte der Addition von Ketenen an Cyclopentadien. *Helv. Chim. Acta* **1970,** *54* (2), 417-432.

8. Garin, D. L.; Cammack, K. L. Substitution vs. Rearrangement in 7-Chloro-7-methylbicyclo[3,2,0]hept-2-en-6-ones. The importance of C-7 Stereochemistry. *J.C.S. Chem. Comm.* **1972,** *36* (14), 333-334.

9. Behrendt, U.; Gabor, B.; Mynott, R.; Butenschön, H. Rearrangement of a Bicyclo[3.2.0]hept-2-ene toa Bicyclo[4.1.0]hept-4-ene. *Liebigs Ann.* **1996,** 1167-1173.

10. Johnson, C. R.; Dutra, G. A. Reactions of Lithium Diorganocuprates(I) with Tosylates. II. Stereochemical, Kinetic, and Mechanistic Aspects. *J. Am. Chem. Soc.* **1973,** *95* (23), 7733-7738.

11. Toda, M.; Okada, K.; Oda, M. Synthesis of 3,4;7,8;9,10-tribenzobicyclo[4.2.2]deca-1,3,7,9-tetraene: A new strained bridgehead olefin. *Tet. Lett.* **1988,** *29* (19), 2329-2332.

12. Blomquist, A. T.; Kwiatek, J. The Addition of Ketene to Cyclic Conjugated Dienes. *J. Am. Chem. Soc.* **1951,** *73,* 2098-2100.

13. Roberts, J. D.; Sauer, C. W. Small-Ring Compounds. III. Synthesis of Cyclobutanone, Cyclobutanol, Cyclobutene, and Cyclobutane. *J. Am. Chem. Soc.* **1941,** *71* (12), 3925-3929.

14. Moffett, R. B. Cyclopentadiene and 3-Chlorocyclopentene. *Org. Syn., Coll.* **1963,** *4,* 238.

15. Brady, W. T.; Hieble, J. P. Halogenated Ketenes. XX. Substitution vs. Rearrangement of Halogenated Ketene Olefin Cycloadducts. *J. Org. Chem.* **1971,** *36* (4), 2033-2034.

16. Butenschön, H. Synthesis of 5-Methoxy- and 5-(Dialkylamino)bicyclo[3.2.0]hept-2-en-6-one Derivatives by cine Substitution with Methoxide Anions and Dialkylamines. *Chem. Ber.* **1994,** *27* (1), 137-144.