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Exploratory chemistry in route to aromatic natural products

Nicholas P. Bizier
Colby College

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Exploratory Chemistry in Route to Aromatic Natural Products

Nicholas P. Bizier

COLBY COLLEGE
Waterville, ME.
May, 2001
Exploratory Chemistry: Approaches to Aromatic Natural Products

Nicholas P. Bizier

A thesis submitted to the Chemistry Department in partial fulfillment of the requirements for graduation with Honors in Chemistry

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May, 2001
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I am indebted to the faculty of Colby College. Through their dedication to students and scientific excellence, I have been shown what it takes to be an outstanding chemist. I would like to extend further thanks to Drs. Whitney King, and Bradford Mundy. Dr. King was kind enough to allow me my first research experience applying investigative techniques. Dr. Mundy provided supreme guidance and support during my senior research project. He will always be a standard of excellence for me.

I would also like to thank my parents, Evelyn and Michael Bizier. My mother has been a constant source of support and strength for me. My father instilled a work ethic for which I will always be grateful. Without their support and well wishes I could not have undertaken this work.
Vita

Nicholas P. Bizier was born in Waterville, ME to parents Michael and Evelyn Bizier on August 10, 1979. His sister, Kathryn, followed six years later and Jennifer three years after that. Nick lived his first eighteen years in Winslow, ME where he attended school. Nick graduated from Winslow High School in June 1997.

Entering Colby College in Waterville, ME in the fall of 1997. Nick began working with Professor Whitney King in the summer of 1998. The summer of 1999 was also spent in the same laboratory. Nick spent the second half of his junior year studying abroad in Cork, Ireland. Upon his return to Colby for his senior year Nick began his Honors Research project in the area of natural product synthesis under the direction of Professor Bradford Mundy.

Nick will be pursuing his Ph.D. at Montana State University in synthetic organic chemistry.
Abstract

The focus of this research was the synthesis of two natural products, 1-methyl-4-\((1,2,2\text{-trimethylcyclopentyl})\)benzene (formally cuparene), and 3-(1,2-dimethylcyclopentyl)-5-methylbenzene-1,2-diol (formally herbertene diol). Cuparene possesses anti-fungal and anti-arthritis properties. This molecule has been the target of a number of syntheses. Herbertene diol, a natural product itself, represents one retrosynthetic step back from mastigophorane; a compound isolated from the liverwort *Mastigophora diaclolades*. Mastigophorane has been shown to have neural network forming capabilities and has warranted complete synthetic efforts.

Through the same chemistry involve in the formation of cuparene, we sought a route to herbertene diol in two steps.

![Cuparene](image1)

![Herbertene Diol](image2)

We report a successful route to the synthesis of cuparene in its racemic form. We also report the successful synthesis of an analog of herbertene diol, as well as the proof that our concept can be used to add sterically congested systems to aromatic rings through the use of Friedel-Crafts alkylation methods.
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Introduction

"In the early nineteenth century scientists believed that the chemicals found in plants and animals were fundamentally different from those found in minerals. The separate branches of organic chemistry and inorganic chemistry thus developed but gradually chemists realized that the division was artificial and organic chemistry broadened to the study of carbon compounds in general."

The use of natural products has been an important part of the development of the human race. Throughout history, dyes from plants, medicine from herbs, and soaps from the fat of animals all served to make human life better. In 1828 Friedech Wöhler reported the first synthesis of the natural product, urea, from inorganic compounds, and without the addition of the "vital life" force thought to be an essential component to all organic compounds. Chemistry had entered a new era.

The area of natural product synthesis has progressed far from the days of urea. Within the bounds of current knowledge lies the ability to make compounds as complex as taxol. Taxol, a compound isolated from the Pacific Yew Tree (Taxus breifolia), has proven itself to be one of the most powerful weapons mankind has in its arsenal in the fight against the dreaded scourge of cancer. A synthetic route to this compound was quickly sought, for it took a century-old tree to provide enough taxol to treat one patient.

Fig 1. Chemical Structure of Taxol
While synthesis gives us the ability to make these compounds, an additional factor must be added to the synthetic design plan. If one desires the compound to be useful, its preparation must be feasible. For example, the compound Bryostatin, isolated from marine fauna, has proven to be the most powerful, and broad ranging anti-cancer drug ever discovered. This compound, like Taxol, can only be isolated in small quantities from large amounts of marine life. Synthetic efforts have produced Bryostatin in 70 steps, a number too large to be used by industry. However, through rational synthetic design, Wender has shown that a synthetic derivative can be made in only six steps, with a final product exhibiting even greater potency than the naturally occurring Bryostatin.

Fig 2. Chemical structure of Bryostatin.
"One of the most promising areas for the future development of organic chemistry is synthesis. The lessons learned from the synthetic challenges presented by various natural products can serve as a basis for this ever-developing area."

The search for viable synthetic routes to natural products is of great importance to humankind. As our knowledge of biologically active compounds increases, we must also increase our ability to produce these compounds in fast and economically feasible ways. In the following pages we describe our research in this area.
Background

The phylum Bryophyta includes the liverworts, the first terrestrial plants to inhabit the earth. Because the biology of these plants remains essentially unchanged, these plants have become a source for many interesting and biologically important molecules. Of interest to our research efforts are the two molecules cuparene, isolated from the liverwort *Bazznia pompeana*, and herbertene diol isolated from the liverwort *Herbertus aduncus*.

Cuparene has been the target of several synthetic designs, including successful efforts put forth by this research group. The previous scheme developed by the efforts of Tina Goudreau had reported the quickest and most efficient synthesis to date, at seven steps, outlined in Scheme 1.

![Scheme 1. Previous Synthesis of Cuparene](image-url)
In the prior effort, much of the previous work centered on decoration of a cyclopentyl system once the addition to the aromatic ring had been completed. In our work, we envisioned building the cyclopentyl system first and then using a carbocation intermediate and Friedel-Crafts alkylation chemistry. This involves a planer intermediate, causing the loss of sterochemistry. However, both enanitomers of cuparene show biological activity; thus, it was not a concern in our synthetic procedure.

The second molecule of interest to our group was herbertene diol. This molecule has the same cyclopentyl group as that present in cuparene. This approach would avoid protection of phenol the functionality necessary as in approaches such as Scheme 1. Electrophilic substitution at the 6 position (Figure 3) was also a concern of this synthesis.

Previous literature reports by Pobsil and Taimer, et.al. suggested that attack at the desired position was favored, as represented in Scheme 2.
Herbertene diol provided interest to our research group due to its intermediacy in the formation of the neural active compound mastigophorane (Figure 4). This compound was isolated from the liverwort *Mastigophora diacololades*, found in Southeast Malasia. Mastigophorane has been shown to exhibit nerve growth and network formation acceleration activities. Due to difficulties in isolation, a synthetic route to this compound for extended biological testing was sought. A radical coupling of the precursor herbertene diol, extracted from a natural source, has been used to produce Mastigophorane in its atropic isomeric form (Scheme 3).
By use of the Friedel-Crafts alkylation method, we set about to develop a total synthesis for cuparene, and herbertene diol. With these targets in mind we also hoped to develop new insight into how carbocations can be used in synthesis of natural products containing aromatic rings.
Retrosynthetic Analysis

Our research goals centered using an aromatic system, already in its preconstructed state. Cuparene could be generated from the aromatic electrophillic substitution of toluene by a cyclopentyl carbocation. The carbocation would be generated from the dehydration intermediate formed from the tertiary alcohol. The alcohol could in turn be made from methylation from the commercially available 2,2-dimethylcyclopentanone (Scheme 4).

\[
\begin{align*}
&\text{Me} \quad \quad \quad \text{Me} \\
&\quad \quad \quad \text{Me} \\
&\quad \quad \quad \text{Me}
\end{align*}
\]

Scheme 4. Retrosynthetic analysis of Cuparene

The retrosynthetic plan for the synthesis of herbertene diol involved the same plans as those for cuparene, with substitution of 4-methylcatechol, providing the necessary aromatic ring for substitution.

An alternate route for the formation of the carbocation intermediate was also envisioned, for reason discussed in later sections. Our alternate route still contained the final step of electrophilic substitution; however, the cyclopentyl carbocation was to be generated from a cyclobutyl tertiary carbocation. Similar to the plan outlined above, the dehydration intermediate would be provided from a tertiary alcohol. Generation of this alcohol could be achieved through a double
methylation of the cyclobutyl ester. The ester itself could be generated by methylation of the anion produced with removal of the acidic proton, located at the alpha position of the ester. Esterfication of the commercially available cyclobutanecarboxylic acid with EtOH would lead to the generation of the starting material (Scheme 5).

Scheme 5. Alternate retrosynthetic plan for cuparene using cyclobutonate as a starting material.
Results and Discussion

The key step in our synthetic plan was the electrophilic addition of the carbocation to the aromatic ring. However due to higher costs associated with cyclopentanones versus the more readily available cyclohexanones, synthetic work began with the cyclohexyl rings. This work provided preliminary background to help us understand the procedures and the conditions necessary for the reaction sequence.

The first test involved the synthesis of the tertiary alcohol, 1,2-dimethylcyclohexanol (2), followed by addition of toluene, catalyzed by various Lewis acid catalysts (Scheme 6). Substitution is shown at the para position, due previous literature reports by Sidorova et al. Lack of ortho- substitution is due to steric interactions between the methyl groups of toluene and 2.

An addition of MeLi to 2-methylcyclohexanone (1), yielded racemic 2. This alcohol was then was reacted with toluene, in the presence of the Lewis acids H$_2$SO$_4$, TiCl$_4$, and BF$_3$ in catalytic amounts. Data analysis was provided by GC/MS. Results of this work showed the molecular ion peak of 202 m/z to be present in the reactions catalyzed by H$_2$SO$_4$ and TiCl$_4$ (Appendix 1,2). No indication of reaction was present in the case of BF$_3$, leading us to discontinue its use (Appendix 3). At this juncture it was decided that H$_2$SO$_4$ would be the primary regent of choice due to its ease of use, and its precedence in literature reports.
With the success of the reactions of cyclohexyl model reactions, we moved on to a reaction involving cyclopentanone systems. Our initial model reaction, involved a MeLi addition to 2-methylcyclopentanone (4). After work-up it was found that the product was not 1,2-dimethylcyclopentone (7) as expected (Scheme 7). GC/MS analysis showed the major competent to be a compound having a molecular ion of 178 m/z (Appendix 4).

The formation of this compound can be explained by the highly acidic proton in the α-position of cyclopentanone systems. This proton is readily removed by base, leading to the aldol condensation product (7), through the mechanism proposed in Scheme 8.
A search of current literature revealed that the methylation of cyclopentanones through the use of lithium or Grignard reagents frequently show the problem that we were experiencing in our system. Lowering of the temperature as well as adding the cyclopentanone to MeLi, proved to be the easiest solution. By adding the cyclopentanone slowly, and in relatively dilute form, we felt that we would be promoting reaction with MeLi, rather than the highly basic alkoxide which is formed once a small fraction of the addition product had been produced (scheme 9).
To combat the problem noted above, a solution of MeLi in Et₂O was brought down to -78 °C, through the use of a dry ice/isopropyl alcohol bath. The 2,2-dimethylcyclopentanone (7) was slowly added, drop-wise, over an extended period of time, while the solution was kept at low temperature. GC-MS analysis, showed the alcohol, denoted by a small molecular ion peak at 128 m/z, and a large peak at 110 m/z correlating to the expected loss of water (Appendix 5).
With this careful addition, only the desired 1,2,2-trimethylcyclopenta-1-ol (8), and unreacted 7, were detected as the major constituents (Scheme 10). No attempts at purification through distillation were performed, for fear of thermal degradation of the product, by elimination of water.

![Scheme 10. Successful methylation of 7, to yield desired alcohol 8](image)

Model reactions of the Freidel-Crafts alkylation step were first attempted using, the commercially available 1-methylocyclopentan. Addition of this compound to toluene, promoted by H₂SO₄, was determined to by successful through GC/MS analysis, yielding compound 8 (Scheme 11). The m/z used to confirm success were those of the molecular ion M⁺ = 174, and M-15 which denotes the loss of a methyl group (Appendix 6).
A similar reaction for the model of herbertene diol was carried out, using 4-methyl catechol, as the aromatic component (Scheme 12). Due to the acidic nature of the phenolic protons, a base wash, followed by silca gel column chromatography, allowed for the isolation of addition product 9. This product was identified by GC/MS, in which the M$^+$, and the M-15 fragments, similar to cuparene model were identified (Appendix 7). Analysis by $^{13}$C NMR (Appendix 8) was also performed, and the spectrum compared to a computer prediction so that the site of addition could be determined (Appendix 17).
Due to the success of the model reactions, it was decided to attempt the synthesis of both cuparene and herbertene diol, on a microscale level, using relatively impure (9). The successful synthesis of racemic cuparene was achieved by reaction of 9, which was dissolved in toluene with the addition of H$_2$SO$_4$ as a catalyst (Scheme 13). GC/MS analysis of the products revealed a M$^+$ with the correct m/z and expected m-15 peak (Appendix 10).

The spectrum also correlated with that of cuparene from a known library. The product was shown quite impure by GC analysis, and because this lab had produced other synthesis of cuparene, steps were not taken to isolate the compound, or improve on its preparation. Our attention was now directed to the synthesis of herbertene diol.

**Scheme 13. Successful synthesis of racemic Cuparene**

Synthesis of herbertene diol was attempted in a similar manner to that used in the successful model reaction (Scheme 14). However analysis of all the fractional components of the reaction mixture revealed no evidence of successful addition. Unreacted 11 and the dehydration product of 8, 1,5,5-trimethylcyclopentene were the major components of the reaction. There was
evidence of a compound with a $M^+$ of 218 m/z. This origin of this compound is unknown, and it may represent substitution of one the hydroxyl groups, a reaction which should not be feasible. Due to a lack of solubility of 4-methylcatechol in CH$_2$Cl$_2$ (a problem, which did not prevent success in the model reaction of this compound), other solvents were explored. However, the use of H$_2$SO$_4$ presents a problem with other solvents due to its oxidative properties. Toluene and Et$_2$O, were two readily available choices, and were tried without positive results. A range of temperatures was also tested, from refluxing CH$_2$Cl$_2$ down to -78 °C, each proved to be unsuccessful.

We were puzzled at this point. Our model reaction (Scheme 13) showed us that our idea was feasible; however, we could not seem to promote addition of compound 8. This was compounded by the fact that we had been successful in the synthesis of cuparene (Scheme 12). A competition reaction was done to see if addition favored toluene or the catechol 12. Equal-molar equivalents of toluene, 11, and 9 were mixed in the presence H$_2$SO$_4$. After analysis by GC/MS, it was found that addition was only found to occur with 11, to form 12 (Appendix 11). Thus, it was determined that activation of aromatic ring of 11 was not the underlying problem in this reaction.

Calculations at the AM1 level gave frustrating results, as well. The transition states for the addition reaction appear to be the same, regardless of the methyl-substitution level at the 2 position. At this juncture, the alternative may be to go to a radically new solvent system such as 5 M LiClO$_4$/Et$_2$O solution with
trifluoroacetic acid, as the acid catalyst. It is hoped that perhaps a more polar medium could promote addition, by stabilizing the transition state.$^{13}$

As an alternative route to the carbocation generated by 9, we also envisioned a reaction in which a ring opening rearrangement of a cyclobutyl system provided by dehydration of 2-cyclobutylpropanol (12), could give us the desired carbocation (Scheme 14).

![Scheme 14. Alternate route for generation of the cyclopentyl cation](image)

Synthetic procedure for the generation of compound 13 began by deprotonating diethyl malonate, followed by $S_N2$ displacement of one of the bromide functional groups of 1,3-dibromopropane. A second deprotonation followed by intramolecular $S_N2$ displacement of the remaining Br to yield cyclobutane-1,1-dicarboxylic acid diethyl ester 14 (Scheme 15). This reaction was carried with NaOCH$_2$CH$_3$ acting as the base.$^{12}$ Analysis of the organic fraction by GC/MS revealed a small amount of the desired product and a multitude of other products including intramolecular reaction to give 2,6-bis-
Scheme 15. Mechanism of formation of 14

ethoxycarbonyl-heptanedioic acid diethyl ester (14) (Appendix 12,13), as an undesired major product of this reaction. Hydrolysis of the complete reaction mixture, in presence of HCl, did produce a small amount of the desired product cyclobutylcarboxylic acid (Scheme 16). The commercial availability of this product led us to circumvent this step of the synthesis.
The commercially provided cyclobutylcarboxylic acid (16), was then esterified in excess EtOH, with H$_2$SO$_4$ present as a catalyst (Scheme 17).
Dehydration was influenced, by the dehydrative effects of H₂SO₄, as well as the addition of 4 Å molecular sieves. Purification was performed through fractional distillation at 67 °C and 25 mm Hg. Analysis via GC/MS showed that the main component of the reaction was a compound with the desired molecular ion of m/z=128 (Appendix 16). ¹H NMR analysis also showed peaks in the region of 4.13 ppm consistent with protons adjacent with an ester, which were not present in the initial acid starting precursor.

\[
\begin{align*}
\text{O} & \text{O} \\
\text{OH} & + \text{HOCH₂CH₃} \\
\text{16} & \xrightarrow{\text{H₂SO₄}} \text{O} \text{Me} \\
\text{17} & \\
\end{align*}
\]

Mol. Wt.: 128.17

Scheme 17. Successful esterification reaction

In order to create a compound which we could use as a model for our electrophilic substitution reaction, an excess of MeLi was added to 17, at 0 °C. After a wash with H₂O, the compound was solubilized, in a small amount of CH₂Cl₂, and combined with an excess of toluene (Scheme 18). After a reaction time of 2 hours, the reaction was quenched with H₂O, and the organic fraction analyzed through GC/MS. While a small peak was found with the correct molecular ion weight of 188 m/z, the fragmentation pattern did not support rearrangement to the five-membered ring (Appendix 15). The major fragment of 132 m/z represents the relatively facile loss of the cyclobutyl group, and does not
have any easily conceivable counterpart from a system that contains a cyclopentyl component (Scheme 19).

Scheme 18. Synthetic model reaction for cuparene.

Scheme 19. Fragmentation products for possible electrophilic adducts.
A synthesis of the intended precursor 13 was also attempted. This method involved deprotonation of ethyl ester, followed by addition of Mel, to alkylate the ester at the α-position to produce compound 13. The initial reaction of 17 with LDA and Mel produced a dark brown substance that proved impossible to purify. Speculation as to the apparent failure of this reaction lies in the LDA used to deprotonate the ester. LDA is a substance that has a propensity to degrade over time, and should be prepared fresh before its use. The prior lifetime of this reagent, which we used, for this procedure was unknown. If this procedure were to be undertaken again, it is strongly recommended that fresh LDA be used. A second synthesis of compound 12 was not attempted due to the lack of ring expansion product presented in Scheme 19.

Due to the additional steps and the lack of ring expansion evidence, we decided to discontinue research in this direction. Our attention began to focus exclusively on the addition of cyclopentyl carbocation to the aromatic systems, as described previously.
Conclusions

The purpose of this work was to explore ways to quickly achieve the synthesis of aromatic natural compounds. In this we were successful. We have shown that cuparene can be made in two simple steps. We have also shown that analogs of herbertene diol can be made just as easily. Variations of this method using more traditional Friedel-Crafts techniques, such as addition of the alkyl halide using AlCl₃ warrant investigation for the synthesis of herbertene diol. Our work with the cyclobutyl systems is also of interest, for compounds that call for this functionality in their synthesis.

The concern of chemical industry is to make compounds as quickly, and as efficiently as possible. Our work has shown that it is possible to use preconstructed ring systems to expedite the synthesis of aromatic natural compounds.
References

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13 Personal communication with Paul Greico
Experimental

General Procedures

GC/MS analyses were performed on a Hewlett-Packard 5890 gas chromatograph (temperature range 100 to 220 °C for 18 min) coupled to 5970 series mass selective detector using Supelco 2-4026 15m X .25 mm capillary column pack with SPB-1 (0.25 μm). \(^1\)H (400 MHz) and \(^{13}\)C NMR was performed using a Bruker Avance 400 NMR. All MeLi used was 1.6 M in EtO\(_2\). All reactions were run at room temperature unless otherwise noted.

Synthesis of 1,2-dimethylcyclohexanol (2): To a solution containing 100 mL of anhydrous Et\(_2\)O, 2-dimethylcyclohexanone (11.1 g, .0991 mol) was added. The reaction flask was evacuated of O\(_2\) and placed under argon. To this solution 58 mL (.092 mol) of MeLi was injected through a syringe. This solution was allowed to react for two days. To this reaction a mixture of 10 mL Et\(_2\)O and 1 mL H\(_2\)O was added, form a yellow liquid and a white precipitate. The Et\(_2\)O layer was washed with 20 mL of H\(_2\)O (x3), and dried over sodium sulfate. The Et\(_2\)O was removed under reduced pressure to form yellow oil. Distillation of this liquid a 240 °C gave 2 mL of 2.

Freidel Crafts Alkylations of Toluene with 2: To three separate 1-mL solutions of toluene 0.5 mL of 1,2-dimethylcyclohexanol was added. To these solutions one of the three different catalysts were added. To solution 1 was added 0.4 mL of TiCl\(_4\). To solution 2 was added 0.2 mL of BF\(_3\) etherate, and to solution 3 was added 0.1 mL of H\(_2\)SO\(_4\). The reactions were magnetically stirred for one hour. After this
time period reaction 1 was noted to be a yellow color while reactions 2 and 3 were noted to be slightly brown in color. To each solution 2 mL of H₂O was added. The organic layer was collected and dried over Na₂CO₃. GC-MS m/z (identification peaks): 202 (M⁺), 187 (M-Me).

**Attempted Synthesis of 1,2-dimethylcyclopenta-1-ol (5):** To a solution of 50 mL of anhydrous Et₂O, 2.7 g (0.027 mol) of 2-methylcyclopentanol was added. The reaction flask was placed under argon. To this solution 0.82 mL of MeLi, and allowed to react for 3 days. At the end of this period, a yellow solution was noted as well as solid white precipitate formed. To this solution, 25 mL of H₂O was added. The mixture was then washed with and additional 20 mL of H₂O, and the organic fraction collected. It was noted at this point that major component of the reaction consisted of aldol condensation product (6), and thus this reaction was excluded form further use. GC-MS m/z (identification peaks): 178. (M⁺)

**Synthesis of 1,2,2-trimethylcyclopenanol (8):** A solution containing 20 mL of anhydrous Et₂O was brought to -78 °C, purged under argon. To this solution was added 16 mL of MeLi (0.027 mol) and stirred magnetically. A solution containing 2,2-dimethylcyclopentanone (3.0 g, 0.027mol) (7) dissolved in 10 mL of anhydrous Et₂O was added drop-wise over a period of 1 hr. This solution was allowed to react for 3 hr. The reaction was then quenched with 5 mL of H₂O. The resulting mixture was combined with 20 mL of CH₂Cl₂, and then washed with 20 mL of H₂O (x3). The organic layer was collected and combined, and dried over Na₂SO₄. The solvent was then removed under reduced pressure, to yield 7.22 g of
the yellow liquid 8. 88.7% yield. GC-MS m/z (identification peaks): 128 (M^+), 110 (M - H_2O).

Synthesis of 1-Methyl-4-(1-methylcyclopentyl)benzene (10): To a solution of toluene (5 mL, 0.06 mol) was added 1-methylcyclopentanol (0.1 g, 0.001 mol) (9). Once the solid was visibly dissolved, 1 mL of H_2SO_4 was added and solution was allowed to react for 2 hours. The reaction was quenched with 5 mL of H_2O. The organic fraction was separated and collected. GC-MS m/z (identification peaks): 174 M^+, 159 (M-Me).

Synthesis of 5-Methyl-3-(1-methyl-cyclopentyl)benzene-1,2-diol (12): Into a solution containing 100 mL CH_2Cl_2 were dissolved 4-methylcatechol (4.0 g, 0.033 mol) (12) and 1-methylcyclopentanol (3.2 g, 0.032 mol). To this solution 2 mL of H_2SO_4 was added, and allowed to react for 3 hr. After this time period the reaction was quenched with H_2O (20 mL). The mixture was then extracted 4 times with 1 molar NaOH (30 mL) and the aqueous fraction was combined and acidified with HCl until neutral. The aqueous layer was then washed 3 times with CH_2Cl_2 (30 mL). The organic layer was combined and the solvent was removed under reduced pressure to yield a crude brown oil. Thin-layer chromatography revealed a component of the mixture that had a higher Rf value then the 4-methylcatechol (5:5 hexane/ethyl acetate). A portion of this oil (1 mL) was then dissolved in a minimal amount of hexane and added to a column containing silica gel (height 19 cm, diameter 3 cm), 60-200 mesh. Successive fractions (20 mL) were collected with hexane/ethyl acetate solutions ranging from 100% hexane- 0% ethyl acetate to 0% to 100% ethyl acetate, in 10 percent decreasing increments of hexane. The
fraction containing 5:5 hexane/ethyl acetate was then subject to an additional
column containing silica, 60-200 mesh with 7:3 hexane/ethyl acetate ratio. The
fraction (5 mL) was collected and the solvent allowed to evaporate, and .011
grams brown solid collected (12). GC-MS m/z (identification peaks): 206 (M\(^+\)),
191 (M-Me). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 143.3 (C-OH), 139.9 (C-OH), 136.8
(C, Ar), 129.1 (C, Ar), 199.0 (C-H), 113.5 (C-H), 145.6 (C), 38.7 (2CH\(_2\)), 26.4
(2C, CH\(_3\)), 23.5 (2CH\(_2\)), 20.9 (CH\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): 6.51 (s, 2H,
Ar), 5.18 (s, 2H, OH), 2.22 (s, 3H, Ar-CH\(_3\)), 1.92 (dd, 4H, CH\(_2\)), 1.61 (dt, 4H,
CH\(_2\)), 1.28 (s, 3H, CH\(_3\)).

**Microscale synthesis of Cuparene:** To a solution containing 1 mL of toluene
was added 0.5 mL of the crude product 8, and 0.1 mL of H\(_2\)SO\(_4\). The solution was
allowed to react for 2 hr, at which time it was quenched with 5 mL of H\(_2\)O. The
organic fraction was collected and dried over Na\(_2\)CO\(_3\). GC-MS m/z (identification
peaks): 202 (M\(^+\)), 187 (M-Me).

**Competition reaction between toluene and 11:** To a solution containing 5 mL
CH\(_2\)Cl\(_2\) was added the following reagents: 10 (1.22 g, 0.0134 mol), 12 (1.66 g,
0.0134 mol), and toluene (1.43 mL, 0.0134 mol). This mixture was stirred until all
components were visibly dissolved, at which point 2 mL of H\(_2\)SO\(_4\) was added.
The solution was allowed to react for 2 hr, at which time the reaction was
quenched with H\(_2\)O. The organic layer was collected, and dried over Na\(_2\)CO\(_3\).
GC-MS m/z (identification peaks): 206 (M\(^+\)), 191 (M-Me).
Synthesis of cyclobutan-1,1-dicarboxylic acid diethyl ester: A solution containing 100 ml of EtOH (1.7 mol) and Na (4.6 g, 0.21 mol), heated to reflux, until the Na had visible disappeared. A portion of this solution (60 mL) was added to a flask containing diethyl malonate (19 g, 0.12 mol). This resulting mixture was brought to reflux, at which time 1,3 dibromopropane (20.5 g, 0.10 mol) and the remaining NaOEt solution (40 mL) was added drop-wise, over a time period of 1 hr. After addition was complete, mixture was heated at reflux for an additional 2.5 hr. Formation of white precipitate was noted. The solution was filtered, and the excess EtOH was removed under reduced pressure. The resulting oil was combined with 100 mL of CH₂Cl₂ and was washed (x3) with H₂O (50 ml). The solution was dried over Na₂SO₄, and the solvent removed to yield a yellow liquid. GC-MS m/z (identification peaks): 200 (M⁺) 155 (M-OCH₂CH₃).

Synthesis of ethylcyclobutanonate (17): A solution containing 6.0 mL (0.10 mol) of EtOH was combined with 3.1 g (.031 mol) of cyclobutylcarboxylic acid. The acid catalyst H₂SO₄ was added (2.0 ml) and the mixture heated under reflux for 3 hrs. Once this time period had elapsed, the solution was allowed to cool, and 25 mL of CH₂Cl₂ was added, and the solution was then dried under 4 Å molecular sieves (4 A). The solution was washed with 20 mL of H₂O (x3). The solvent was then removed under reduced pressure. Fractional distillation of the resulting product at 67° C at 35 mm of Hg, produced 2 mL of the clear liquid 16. GC-MS m/z (identification peaks): 128 (M⁺), 83 (M-OCH₂CH₃). ¹H NMR (400 MHz, CDCl₃, δ): 4.13 (t, 2H, -OCH₂-), 3.18 (t, 1H, HC), 1.98 (dt, 2H, -CH₂-), 1.27 (t, 3H, -CH₃).
Synthesis of 2-cyclobutylpropane-2-ol (18), and use in Friedel-Crafts Alkylation: The ester, product 17 (was dissolved in 5 mL of anhydrous THF, and brought to 0 °C. To this solution 3 mL of MeLi (excess) was added and allowed to react for 4 hours. After this time period a solution containing THF (20 mL), and H₂O (1 mL) was added to quench the reaction. The solvent was removed and 5 mL of CH₂Cl₂ to the resulting oil. The solution was added to toluene (10 mL, 0.12 mol). This solution was allowed to react for 2.5 hrs. At the end of this time period, the solution was noted to be a yellow color. GC-MS m/z (identification peaks): 188 (M⁺), 132 (M- HCCH₂CH₂CH₂).
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## Appendix 1

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![Molecular Structure]

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Appendix 2

Abundance

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Average of 7.358 to 7.423 min.: H2SO4.D

m/z --> 50 100 150 200 250 300 350 400 450 500 550
Appendix 3

Abundance

Time -> 4.00 5.00 6.00 7.00 8.00 9.00 10.00 11.00

Average of 7.539 to 7.655 min.: BF3.D

m/z -> 50 100 150 200 250 300 350 400 450 500 550
Appendix 4

Ion 96.00 (95.70 to 96.70): SRINGOL.D

Average of 7.153 to 9.251 min.: SRINGOL.D
Appendix 5

Abundance

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Scan 285 (3.156 min): MAR17CTR.D
Appendix 6

Scan 368 (6.982 min): FREIDEL2.D

Abundance

Time---> 4.00 5.00 6.00 7.00 8.00 9.00 10.00 11.00

Scan 368 (6.982 min): FREIDEL2.D

Abundance

m/z---> 50 100 150 200 250 300 350 400 450 500
Appendix 7

Scan 687 (10.427 min): 73FRAl.D

m/z = 206

m/z = 191

Abundance

Time -->

m/z -->

2000000
1500000
1000000
500000
0

4.00 6.00 8.00 10.00 12.00 14.00

Scan 687 (10.427 min): 73FRAl.D

m/z = 191

m/z = 191
Appendix 9

Current Data Parameters
NAME: Feed9-500-thum
EXPNO: 10
PROCNO: 1

F2 - Acquisition Parameters
Date: 2000/1209
Time: 17:40
SPECTRUM: spec1
PROCEDURE: 5 mm 081 600
POLARITY: +170
ID: 00536
SOLVENT: CCl4
NG: 1
DG: 0
SW: 6278.146 Hz
FIDRES: 0.126214 Hz
AD: 3.0564143 sec.
NS: 143.7
DW: 600 usec
DE: 0.00 usec
FE: 300 0 k
DI: 20000000 sec

--------- CHANNEL 1 ---------
MHC: 18
PL: 6.12 usec
PL: 1.00 usec
S10: 440 1324110 Hz

F2 - Processing parameters
ST: 32768
SF: 400 1300160 Hz
MCH: 64
SDB: 0
LB: 0.00 Hz
BG: 0
PC: 1.00

1D NMR plot parameters
Cv: 20.00 cm
Cy: 12.50 cm
F1P: 7.992 ppm
F1: 3/59.30 Hz
F2P: -0.278 ppm
F2: -111.21 Hz
PMCH: 0.41357 ppm/cm
MCH: 160.47095 Hz/cm
Appendix 10

Abundance

TIC: SUCCUP.D

Appendix 10

Scan 468 (8.069 min): SUCCUP.D
Appendix 11

Abundance
9000000
8000000
7000000

Time --> 5.00 10.00 15.00 20.00 25.00

Scan 697 (10.536 min): COMP.D

191

m/z --> 50 100 150 200 250 300 350 400 450 500 550
Appendix 12
Appendix 13

Scan 1037 (14.204 min): MAL5.D

Abundance

Time -->
4.00 6.00 8.00 10.00 12.00 14.00 16.00

TIC: MAL5.D

Abundance

m/z -->
50 100 150 200 250 300 350 400 450 500 550

55 173 201

95 213 315

109 269 318 361
Appendix 14

Abundance

TIC: CYCBUT.D

Average of 7.626 to 8.789 min.: CYCBUT.D
Appendix 15

Current Data Parameters

Date: 2001/01/16
IME: 10.0
PROG: 1

1D - Acquisition Parameters

Date: 2001/01/16
IME: 10.0
PROG: S an E70 E70
PROG: 70.30
ID: 0659.6
SEGMENT 1001
SEQ: 16
GS: 2
SM: 2.276 168 Hz
FO: 8.12831 Hz
DF: 3.95600 sec
SE: 180
QW: 60.400 usec
DF: 6.00 usec
DS: 100.0 sec
DR: 1.00000000 sec

********** CHANNEL 1 **********

P1: 6.12 usec
P2: 1.00 dB
P3: 400.132412 MHz

1D - Processing parameters

S1: 32.768
S2: 400.12399 MHz

M: 0.00
G: 0
C: 3.30 Hz
G: 0
PC: 1.00

1D - Plot parameters

EX: 20.00 cm
FY: 12.50 cm
FIP: 12.425 ppm
F1: 2.350 Hz
F2: 6.64 ppm
F2: 25.77 Hz
DB: 0
ABC: 5.23884 ppm/cm
HBC: 175.4201 MHz/cm
Appendix 16

TIC: FREIDEL.D

m/z = 132

m/z = 188

Scan 702 (7.652 min)
Appendix 17

ChemNMR C-13 Estimation

ChemNMR C-13 Estimation