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Approaches and Methodologies for the Synthesis of Aromatic Natural Products

Christina A. Goudreau
Colby College

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Approaches and Methodologies for the Synthesis of Aromatic Natural Products

Christina A. Goudreau

COLBY COLLEGE
Waterville, ME.
May, 1998
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Christina A. Goudreau

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

Approved:

[Signatures]

COLBY COLLEGE
Waterville, ME.

May, 1998
VITA

Christina A. Goudreau, daughter of Bernard Goudreau and Yvette Goudreau, was born in Manchester, New Hampshire on January 12, 1976. She completed her high school education at Manchester High School West in the spring of 1994 and then entered Colby College in the fall of 1994.

Once at Colby, she was involved in many different activities. During her sophomore year, Christina (or Tina as she is called) began focusing her attention on organic chemistry. Tina began research with Professor Bradford Mundy in the spring of her sophomore year and continued research through two Jan-Plans, and two summers at Colby. Tina was elected to Phi Beta Kappa in the spring of 1998 and graduated with a Bachelor of Arts with honors in Chemistry. She will be attending the University of Rochester in the fall of 1998 with the hope of attaining her Ph.D in chemistry.
Acknowledgements

It would be impossible to forget the professor to whom I owe so much. My love for chemistry, without a doubt, stems from Professor Brad Mundy. He has been an unending means of wisdom and support for the four years I have known him. As both a great friend and mentor, he will forever be an inspiration to me. Thank you Professor Mundy.

I must also offer my sincerest thanks to my father who has sacrificed so much in order to give me what I have today. Through his strength and perserverence, he has become my role model for life and I love him dearly. I would also like to dedicate all of my work in loving memory of my mother. I'm sure that she knows how thankful I am for all of her love and support through the years.
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Introduction

For many years, scientists have been intrigued by the numerous compounds isolated from nature and by their biological activity. Studies in natural products synthesis have increased exponentially since the dawning of Friedrich Wöhler’s synthesis of urea in 1828. In a letter to Jons Jacob Berzelius, Wöhler wrote, “I can make urea without the necessity of kidney, or even an animal, whether man or dog.” Now, almost two hundred years later, chemists are still continually engaged in bringing this study of reproducing naturally occurring organic compounds to a much higher level. Today, the study of natural products synthesis plays a major role in pharmaceutical advancement and production, agricultural betterment, and even environmental correction.

Chemists have been captivated by the ability of most natural products to exhibit biological activity which in effect has made them very attractive to pharmaceutical companies. Many over-the-counter drugs such as aspirin were first extracted from natural products and are now an integral part of most of our lives. More importantly, certain drugs such as taxol, which is used to treat breast cancer, initially came from the bark of a yew tree. Extracting these substances from their natural source and using them medicinally at the demand of the consumers would result in the destruction of the natural habitat. Oftentimes, the plants needed are rare or take many years to repair and grow back. Finding alternative means of generating natural compounds without having to use our natural resources is a challenge that organic chemists face daily.

The three natural products that my research targets, (±)cuparene, (±) herbertene, and 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone each demonstrate diverse biological activities.
I. Cuparene / Herbertene
Background

Terpenes, found in plants, mosses, liverworts and algae, are a family of natural products with important value. Terpenes are comprised of isoprene units (1) and demonstrate the remarkable ability of nature to innovatively use only one carbon skeleton.

Cuparene and herbertene are part of the sesquiterpene subgroup containing three isoprene units. Cuparene (2), isolated from the liverwort Bazzania pompeana, was characterized by Matsuo, et. al. Herbertene (3) was isolated from the liverwort Herberta adunca. An example of the liverwort family is shown in Figure 1.01.

Although several syntheses of these natural products have been reported, our research focused on finding a simpler and more efficient synthetic route. Barry Trost remarks, "A key goal must be synthetic efficiency in transforming readily available starting materials to the final target".

Reetz, et. al published the use of dimethylzinc with titanium (IV) chloride to form the dimethyltitaniumdichloride reagent. As shown in Scheme 1.01, this reagent allows the methylation of a tertiary alcohol or the dimethylation of a ketone. Originally, it was used to replace a halogen with methyl in a tertiary halide system. The general protocol provides an entry to other molecules with congested methyl groups occupying quaternary centers.
Figure 1.01 Example of the liverwort family
Scheme 1.01 Use of the Reetz reagent on tertiary alcohols and ketones

For alcohols it has been shown by Reetz and coworkers that only tertiary alcohols will react. In fact, work done by G. Posner suggests a carbocation-type mechanism (Scheme 1.02).

Scheme 1.02 Posner's Observation

Early work done by Wilkening at Montana State University\(^6\) illustrated the use of the Reetz reagent by dimethylating a ketone group as part of the synthesis of epi-modhephene (Scheme 1.03). Posner's carbocation theory along with the work done by Wilkening, prompted a further study of pinacol rearrangement chemistry which is illustrated in Scheme 1.04.
Scheme 1.03. Wilkening's methylation of a ketone

Scheme 1.04. Greenberg's pinacol rearrangement study.

A pinacol rearrangement study by Greenberg addressed the question whether the Reetz reagent would initiate a pinacol rearrangement, since the latter is a carbocation mediated reaction. Would capture of the hydroxyl group take place faster than molecular rearrangement? Experimentally, it was discovered that two products were obtained (Scheme 1.05). Methylation of an alcohol occurred before rearrangement in one product and after rearrangement in the other.

Scheme 1.05. Reetz methylation of a pinacol.
Formation of the rearranged and methylated product resulted from dimethylation of the ketone (Scheme 1.06).

Scheme 1.06. Methylation of rearrangement product.

The conversion of an alcohol to a methyl group is a potentially significant step in a number of synthesis designs. As a result of our continuing interest in terpene chemistry, herbertene and cuparene were chosen as target molecules to demonstrate the advantages of the Reetz reagent. The formation of both herbertene and cuparene could be obtained by Reetz chemistry on the tertiary alcohol, $6.5$ The use of the Reetz reagent would result in a more concise methodology in comparison with previous syntheses ($\text{Appendix A}$)$.8$
Retrosynthetic Analysis

Reetz has shown that a tertiary hydroxyl group can be replaced by a methyl group using dichlorodimethyltitanium. As part of our original program designed to develop protocols for the rapid development of complex molecules, we envisioned a simultaneous replacement of the two adjacent hydroxyl groups of a 1,2-diol with two methyl groups (Scheme 1.07). The 1,2-diol, in turn, could be obtained from the opening of an epoxide which resulted from the epoxidation of an alkene. Simple dehydration of the tertiary alcohol formed by the first Grignard step could easily produce the alkene. Cuparene as well as herbertene could be synthesized using this original plan by merely replacing 3-bromotoluene with 4-bromotoluene as the starting material for the Grignard step.

Scheme 1.07. Retrosynthetic analysis of herbertene.

Our retrosynthetic plan for both herbertene and cuparene involved the methylation of a single tertiary alcohol instead of the double methylation of the 1,2-diol system (Scheme 1.08). Here we envisioned an epoxide opening to a tertiary alcohol and a tertiary methyl group. The epoxide was produced from the alkene in the same manner as the original retrosynthetic plan (Scheme 1.07). The alkene was produced upon dehydration of the tertiary alcohol which in turn was formed by the first Grignard step.
Scheme 1.08. Retrosynthetic analysis of herbertene.
**Results/Discussion**

I. Synthesis of Herbertene and Cuparene

The success of both the $(\pm)$ herbertene and $(\pm)$ cuparene syntheses is mainly due to Reetz chemistry. The ability to convert a tertiary alcohol to a methyl group proved extremely useful in the creation of vicinal quaternary centers which are constituents of both compounds.

The scheme for herbertene is shown in Scheme 1.09. Magnesium turnings were added to 4-bromotoluene in order to make the Grignard and then further reacted with 2-methylcyclopropanone to form the tertiary alcohol (3a). The resulting stereochemistry was not investigated since it would be lost in the following step. Purification by distillation yielded 50% dehydration conversion of the alcohol to the alkene. Since our next step was to dehydrate the alcohol, we deserted further attempts at purification and treated our product (3a) with tosic acid in toluene. This resulted in a 33% yield of the thermodynamic alkene. Thermodynamic vs. kinetic dehydration studies were done on this system when it was realized that acid-catalyzed dehydration alone using p-toluenesulfonic acid (tosic acid) resulted in the less substituted alkene as the major product. Initially dichloromethane was used as the solvent with the tosic acid and then heated under reflux.

The major product, still the less substituted alkene, was allowed to reflux for three days in order to counter the kinetic effect and cause the major product to be the more substituted alkene. When the solvent was changed to toluene, the more substituted alkene was the major product after a mere three hours of refluxing. This was attributed to the higher boiling point of toluene. Obtaining the more substituted alkene required that we overcome its larger activation energy by means of heating the system. By using a solvent with a higher boiling point the system could reflux at a higher temperature.
Scheme 1.09 Synthetic route to herbertene.

From Table 1.01 we see that a ratio of 55:45 kinetic to thermodynamic product is present before heat is applied. The final 9:91 ratio of kinetic to thermodynamic products is achieved after about three hours of reflux in toluene.

Table 1.01 Kinetic vs. Thermodynamic dehydration products of herbertene.

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It is also important to note that computational studies done on both the less substituted alkene (Figure 1.02) and the more substituted alkene (Figure 1.03) at the HF/ab initio 6-31G* basis level to calculate single point energies agree with our experiments. The anticipated configuration of the methyl group in the less substituted...
alkene product was axial. Notice that the methyl group is not at a 90° angle to the five-membered ring. It is also important to note the poor overlap of π electrons. Even in the more substituted alkene product, the π electrons do not overlap as might be expected for the more stable structure. The coplanarity of the π systems was not seen until higher levels of calculations were performed. It was found that there was an energy difference of 1.44 kcal/mol for the two alkenes. A 10:90 ratio is predicted on the basis of this energy difference. This supports our experimental results. The desired thermodynamic alkene was taken to the next step without further purification. Using MCPBA in dichloromethane at 0°C, an epoxide was formed and then purified by flash column chromatography to give 5a (51%). The epoxide product was reacted with close to five equivalents of trimethylaluminum in hexane at 0°C and then purified by radial thin layer chromatography to give a 38% yield of 6a.

Herbertene was obtained upon the addition of ten equivalents of the dimethyltitaniumdichloride Reetz reagent with 6a in dichloromethane at 0°C.
Figure 1.02 Kinetic alkene

Figure 1.03 Thermodynamic alkene
II. The Original Synthesis of Herbertene and Cuparene:

Similar to the synthesis used for making both cuparene and herbertene was our original plan involving a simultaneous diol methylation (Scheme 1.10). The first three steps of the synthesis mimic those of Scheme 1.09. The fourth step, however, involves the opening of the epoxide to form vicinal diols via perchloric acid catalyzed hydrolysis. However, using the Reetz reagent to dimethylate these vicinal diols resulted in a ketone. This occurred when the Reetz reagent removed the alcohol adjacent to the aromatic ring and forming a carbocation whereupon the adjacent methyl group rearranged to the positively charged carbon. This rearrangement creates a carbocation (where the methyl group used to be) which is stabilized by the electrons from the hydrogen of the alcohol forming a ketone (Scheme 1.11). It is important to note that although it was not as efficient as the plan previously discussed, methylation of the diol system did work.

Scheme 1.10 Synthetic route to cuparene.

Scheme 1.11 Mechanism for the formation of the ketone byproduct.
Experimental

General procedures

$^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were determined for CDCl$_3$ solutions containing ca. 1% TMS as an internal standard with a JEOL GSX-400/54 high resolution NMR spectrometer. GC/MS analyses were performed on a Hewlett-Packard 5890 gas chromatograph coupled to a 5970 series mass selective detector using Supelco 2-4026 15m x 0.25 mm capillary column packed with SPB-1 (0.25 μm). Preparative GC separations were performed on a Gow-Mac Series 350 gas chromatograph using a 8' x 0.25” 20% Carbowax 20M on Chrom-P 80/100 mesh column on Chrom-P 80/100 mesh column (injector port, oven, detector, and outlet port set to 200°C; He flow rate = 6 mL/min.). Radial thin layer chromatography was performed using a Harrison Research Chromatotron fitted with a 1 mm SiO$_2$ rotor. Toluene and Et$_2$O (anhydrous) were used as purchased from Fisher, while THF and dichloromethane were distilled from Na/benzophenone and CaH, respectively. Thin layer chromatography (TLC) on commercial silica gel plates (Baker-Flex IB-F) using UV absorption were used to monitor the progress of reactions. All of our reactions were done under argon unless otherwise stated.

Synthesis of Herbertene

Synthesis of 1-(3-methylphenyl)-2-methylcyclpentanol (3a)

To a solution of freshly ground magnesium metal turnings (1.6 g, 0.067 mol) in 40 mL of dry ether, 3-bromotoluene (1a) (11.4 g, 0.067 mol) was added and allowed to stir for 1.0 h. To this solution, 2-methylcyclpentanone (2a) (5.5 g, 0.056 mol) was injected dropwise at a rate of one drop per second and the solution was stirred for 24 h. It was quenched with wet ether, vacuum filtered and extracted with dichloromethane. The organic layer was dried with Na$_2$SO$_4$ (anhydrous), and solvent removed to give the crude alcohol (3a) (82% pure by GC).

Synthesis of E-(3-methylphenyl)-2-methylcyclpentene (4a)

Without purification, the alcohol (3a) was dissolved in toluene (20 mL) containing approximately 1.5 g of p-toluenesulfonic acid. This solution was heated under reflux for 3 h. The progress of the reaction was monitored by GC/MS. Upon completion, as much toluene as possible was removed by rotary evaporation. Using a saturated sodium bicarbonate solution and dichloromethane, the alkene (4a) was separated from residual acid. The organic layer was dried with anhydrous Na$_2$SO$_4$ and the product (4a) was collected as a clear colorless liquid by Kugelrhor distillation (100°C, 2.3 mmHg), (4.7 g,
67% pure by GC, 33% overall yield). The $^{13}$C NMR and $^1$H NMR of a purified sample of the alkene isolated by preparative GC provided the following data: $^{13}$C NMR $\delta$ 135.78, 135.56, 134.55, 134.52, 128.70, 127.47, 40.07, 37.26, 21.81, 21.15, 15.50; $^1$H NMR $\delta$ 7.19 (d, 2H), 7.14 (d, 2H), 2.72 (m, 2H), 2.49 (m, 2H), 2.34 (s, 3H), 1.89 (m, 2H), 1.84 (s, 3H). HRMS: experimental 172.1255, calculated 172.1252.

Synthesis of 3-methylphenyl-2-methylcyclopentane oxide (5a)
To a solution of the alkene (4a), (4.2 g, 0.024 mol) in dichloromethane (40 mL), MCPBA (57-86%) (7.6 g, 0.025 mol) was added and stirred for 24 h at 0°C. The reaction was allowed to warm to room temperature overnight. The resultant milky white mixture was washed three times with a saturated NaHCO$_3$ solution, and then washed with water and dried with anhydrous Na$_2$SO$_4$. Removal of the solvent gave the epoxide (5a) as a crude clear yellow liquid. Purification by flash column chromatography gave the final product (3.1 g, 89% pure by GC). HRMS: experimental 188.1206, calculated 188.1201.

Synthesis of 2-(3-methylphenyl)-1,2-dimethylcyclopentanol (6a)
To the epoxide (5a) (1.6 g, 0.0083 mol) in hexane (150 mL), trimethylaluminum (8.4 mL, 0.017 mol. of a 2M solution in hexane) was injected and the solution was stirred for 48 h at 0°C. Methanol was then injected to quench the reaction, followed by water, and the solution was vacuum filtered to remove the resulting precipitate. As much solvent as possible was removed by rotary evaporation. The resulting solution was then extracted with dichloromethane. The organic layer was then dried with Na$_2$SO$_4$ (anhydrous) and evaporated to yield the alcohol (6a) (0.52 g, 91% pure by GC). After purification of (6a) by preparative GC: $^{13}$C NMR $\delta$ 144.27, 135.17, 128.54, 126.52, 82.37, 50.65, 39.06, 35.31, 25.61, 23.89, 20.90, 18.15; $^1$H NMR $\delta$ 7.32 (d, 2H), 7.10 (d, 2H), 2.37-2.23 (m, 2H), 2.32 (s, 3H), 1.92-1.68 (m, 2H), 1.35 (s, 3H), 1.32-1.23 (m, 2H), 0.93 (s, 3H). HRMS: experimental 204.1514, calculated 204.1514

(±) Herbertene (7a), from 6a.
To a solution of dimethylzinc (13 mL, 0.026 mol) and dichloromethane (10 mL), titanium tetrachloride (2.9 mL, 0.026 mol), and then (6a) (0.52 g, 0.0026 mol) was added dropwise. The reaction mixture stirred at 0°C for 24 h. Distilled water was added until it no longer reacted and the organic layer was extracted with dichloromethane, dried with
Na₂SO₄ (anhydrous), and the solvent removed by rotary evaporation to give 0.63 g of crude product. A pure sample obtained by preparative GC was analyzed for structure: ¹H NMR δ 7.25 (d, 2H), 7.09 (d, 2H), 2.50 (s, 1H), 2.32 (s, 3H), 1.85-1.48 (m, 6H), 1.26 (s, 3H), 1.06(s, 3H), 0.56 (s, 3H); ¹³C NMR δ 144.5, 134.71, 128.18, 126.92, 50.23, 44.20, 39.69, 36.81, 26.43, 24.37, 24.25, 20.83, 19.72. HRMS: experimental 202.1729, calculated 202.1722.

**Synthesis of Cuparene (Original Plan)**

2-Methyl-1-(4-methylphenyl)-cyclopentene (3b). To a solution of freshly ground magnesium metal turnings (1.53 g, 0.0630 mol) in 25 mL of dry ether, 4-bromotoluene (1b) (10.7 g, 0.0626 mol) was added and allowed to stir under reflux for 1.0 h until most of the Mg was consumed. To this solution, 2-methylcyclopentanone (2b) (6.08 g, 0.062 mol) in Et₂O (10 mL) was injected dropwise at a rate of one drop per second and the solution was heated under reflux for 3 h. It was quenched with 1M HCl and the organic layer was washed with water and then dried with Na₂SO₄ (anhydrous). The Et₂O was removed by rotary evaporation to give a clear yellow liquid. (3b) Without purification, the crude alcohol (3b) was dissolved in toluene (40 mL) containing approximately 1.5 g of p-toluenesulfonic acid. This solution was heated under reflux for 3 h whereupon the solution turned from slightly yellow to deep purple in color. The progress of the reaction was monitored by GC/MS. Upon completion, as much toluene as possible was removed by rotary evaporation. Using a saturated sodium bicarbonate solution and dichloromethane, the alkene (4b) was separated from residual acid. The organic layer was dried with anhydrous MgSO₄ and the product (4b) was collected as a clear colorless liquid by Kugelrhor distillation (120°C, 3.2 mmHg), (2.56 g, 29% overall yield) The product was found by GC/MS, to consist of 4b (91%) and 3b (9%).

2-Methyl-1-(4-methylphenyl)-cyclopentene oxide (5b). To a solution of the alkene (4b), (2.56 g, 0.0148 mol) in dichloromethane (120 mL), MCPBA (57-86%) (4.29 g, 0.0249 mol) was added and stirred for 24 h at 0°C. The reaction was allowed to warm to room temperature overnight. The resultant milky white mixture was washed three times with a saturated NaHCO₃ solution, and then washed with water and dried with anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation gave the epoxide (5b) as a crude clear yellow liquid. Purification by flash column chromatography (SiO₂) gave the final product (1.41 g, 51% yield). ¹H NMR (400 MHz) : 7.22-7.08 (m, 4H) 2.36 (s, 3H) 2.28-2.01 (m, 3H) 1.80-1.48 (m, 3H) 1.17 (s, 3H); ¹³C NMR (100 MHz) : 138.3,
2-Methyl-1-(4-methylphenyl)-cyclopentan-1,2-diol (6b). To a 1:1 THF/H$_2$O solution (35 mL) containing 5b (0.210 g, 0.00112 mol) 4 drops of 65-85% HClO$_4$ were added. The reaction was allowed to stir at room temperature for one week. The solvent was removed by rotary evaporation and the crude product was washed with hexane to yield a white powder (110 mg) in 48% yield: $^{13}$C NMR (100 MHz) : 140.0, 136.4, 127.6, 127.5, 126.5, 83.2, 81.9, 38.0, 35.8, 24.4, 21.0, 18.9.

Dichlorodimethyltitanium. The methylating reagent was prepared by adding 1 equivalent of Me$_2$Zn (purchased as a 2M solution in toluene) to 1 equivalent of TiCl$_4$ in CH$_2$Cl$_2$ at 0 °C under argon. The reagents are allowed to react with stirring for 10 min. before addition of substrate.

(±)-Cuaparene (7b) from 6b. To a solution of 10 equivalents of the dichlorodimethyltitanium, the diol product (6b) (0.524 g, 0.00256 mol) in CH$_2$Cl$_2$ (2 mL) was added dropwise. The reaction mixture stirred at 0°C for 24 h. Distilled water was added until it no longer reacted and the organic layer was extracted with dichloromethane, dried with MgSO$_4$ (anhydrous), and the solvent removed by rotary evaporation to give 0.312 g of crude product. A pure sample obtained by preparative GC was analyzed (60% yield) for the structure. $^1$H NMR (400 MHz) : 7.20-7.00 (m, 4H) 2.51 (m, 1H) 2.34 (s, 3H) 1.81-1.52 (m, 5H) 1.26 (s, 3H) 1.07 (s, 3H) 0.56 (s, 3H) ; $^{13}$C NMR (100 MHz) : 136.7, 127.8, 127.3, 126.0, 124.1, 50.4, 44.2, 39.7, 36.7, 26.5, 24.4, 24.3, 21.8, 19.7; HRMS (EI) m/z calculated = 202.1721, experimental = 202.1717.
## Supporting Spectra

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Acquired: 21 Nov 96 11:43 am using AcqMethod_OCHEM
Instrument: 5970B
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Vial Number: 1

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1e+07
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6000000
4000000
2000000
0

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200000
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m/z--->
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14.45

157
172
Acquired: 6 Dec 96 1:46 pm using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: herbertene epoxide after column purification
Vial Number: 1

Abundance

Scan 555 (14.453 min): TGPHERX3.D

m/z --> 20 40 60 80 100 120 140 160 180

18 43 51 65 77 105 119 131 145 157 173 188

TIC: TGPHERX3.D

5.00 10.00 15.00 20.00 25.00 30.00

Time-->
File: C:\HPCHEM\1\DATA\TGMEH2.D
Operator: Tina
Acquired: 9 Jan 97 10:30 am using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: me2Zn TiCl4 mixed and herbertene ol added.
Misc Info: o-chem sd=4 min
Vial Number: 1

Abundance

TIC: TGMEH2.D

Scan 664 (16.493 min): TGMEH2.D

precursor

herbertone-alcohol

m/z -->

0 20 40 60 80 100 120 140 160 180 200
Information from Data File:
File: C:\HPCHEM\1\DATA\TGHERB.D
Operator: Tina
Acquired: 14 Jan 97 12:04 pm using AcqMethod _OCHEM
Sample Name: herbertene product
Misc Info: o-chem
Vial Number: 1
CurrentMeth: C:\HPCHEM\1\METHODS\_OCHEM.M

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<th>Ratio %</th>
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<td>49982764</td>
<td>100.000</td>
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File: C:\HPCHEM\1\DATA\TGHERB.D
Operator: Tina
Acquired: 14 Jan 97 12:04 pm using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: herbertene product
Misc Info: o-chem
Vial Number: 1

Abundance

Scan 612 (15.514 min): TGHERB.D

m/z --> 18 28 41 55 65 77 91 105 145 159 174 187 202

0 20 40 60 80 100 120 140 160 180 200
Scan 669 (14.597 min): TGCK21.D

Abundance

File: C:\HPCHEM\1\DATA\TGCK21.D
Operator: tina
Acquired: 18 Jul 96 10:45 am using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: 2nd shot at Cup./ vial 1of kugeled
Misc Info: ochem
Vial Number: 1

Abundance
File: C:\HPCHEM\1\DATA\TGCH2CU.D
Operator: tina
Acquired: 26 Jul 96 3:14 pm using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: ch2cl2 layer of cup. prod
Misc Info: ochem
Vial Number: 1

Abundance
1.2e+07
1e+07
8000000
6000000
4000000
2000000
0
Time-->
0 4.00 6.00 8.00 10.00 12.00 14.00 16.00 18.00 20.00

Scan 475 (10.948 min): TGCH2CU.D

m/z-->
0 20 40 60 80 100 120 140 160
18 27 39 59 75 85 91 113 125 139 155 172

alkene - Cuparene
File: C:\HPCHEM\1\DATA\TGB2COH.D
Operator: tina
Acquired: 23 Jan 97 2:55 pm using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: 2nd band of cuparene alcohol sep.
Misc Info: o-chem s.d.=4 min
Vial Number: 1

Abundance TIC: TGB2COH.D

Time--> 6.00 8.00 10.00 12.00 14.00 16.00 18.00 20.00

Abundance Scan 682 (16.831 min): TGB2COH.D

m/z--> 20 40 60 80 100 120 140 160 180 200

alcohol precursor - cuparene
II. 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone
Background

The natural product, 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone, is found as part of the extract from iron deficient cultures of the brown rot fungus of the class Basidiomycetes. The brown rot fungus Figure 2.01, *Gloeophyllum trabeum*, was studied by Dr. Frank Fekete of the Colby College Department of Biology in conjunction with colleagues from the department of Forest Biology the University of Maine, Orono.9

Their research involved isolating and characterizing compounds from the brown rot fungus. It was discovered that the extract contained iron chelating components responsible for lignocellulose degradation via a nonenzymatic catalysis with hydrogen peroxide.10 The suggested structure (4) for the brown rot fungus extract is not reported in the literature and is based on spectral data from a minute isolated sample.

Iron is an essential element for many organisms. It is often a cofactor and complexing center for enzymes. In addition, iron has various oxidation states and has the ability to form a hexacoordinate system. Iron is most common in nature as the ferric (+3) oxidation state which cannot be dissolved or directly absorbed by organisms in nature. Furthermore, free Fe\(^{3+}\) has the ability to catalyze hydroxyl radical formation. These undesired radicals are some of the strongest known oxidizing agents and as a result, have the potential to cause mutations in living cells. 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone was found to bind to iron (III) which allows it to penetrate wood cell walls. Two possible schemes are hypothesized for the manner in which the iron binds. In one scheme the iron (III) binds to the two hydroxyl groups (Figure 2.02) while in the other it binds to one of the hydroxyl groups and the carbonyl oxygen to the iron (III) atom (Figure 2.03).11
Figure 2.01. Example of the shelf-like brown rot fungus.
Early attempts of synthesizing this natural product involved the addition of butyl lithium and a methyl propargyl ether chain to 2,3-dihydroxybenzoic acid and then further reduction of the chain with hydrogen and palladium to obtain the desired product (Scheme 2.01). The failure of this synthesis could be attributed to an electronic difference. The methyl propargyl ether nucleophile has a negative charge on an sp hybridized carbon while the partially positive charge of the butyl lithium carbon is sp$^3$ hybridized. This difference can account for the low reactivity of the two species with one another and further react with the carboxylic acid.

Scheme 2.01 Earlier attempts to synthesize 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone.
A second attempt entailed the addition of a completed synthesized side chain onto the 2,3-dihydroxybenzoic acid. The synthesis of the side chain was successful (Scheme 2.02); however, the model reaction that was performed (Scheme 2.03) has not yet been analyzed.

![Scheme 2.02](image)

Another approach involved the synthesis of the chain via iodination of a tosylated side chain ether (Scheme 2.04).

![Scheme 2.04](image)

This chain, combined with 2,3-dihydroxybenzoic acid in the presence of t-butyllithium, could form the suspected ketone product (Scheme 2.05). Unfortunately, this process was unsuccessful again, due to complications involving the diphenolic moiety of the benzene ring.

![Scheme 2.05](image)
It is important to note that none of the reactions discussed utilized the protection of the two hydroxyl groups. Consequently, whether the completed side chain was reacted with the 2,3-dihydroxybenzoic acid or whether a chain was added and then further reacted to form the final product, the hydroxyl groups proved to be highly reactive.
Retrosynthesis Analysis

In our original plan to synthesize 1-(2',3'-dihydroxyphenyl)-4-methoxy-1-butanone, we expected that the 1,2-diol system would have to be protected to ensure that the hydroxy groups would remain undisturbed (Scheme 2.06). Methoxy groups were chosen as the means for protection in Scheme 2.06. The carbonyl group could come from oxidation of the secondary alcohol. It was then thought that the methoxy group at the end of the chain could be formed from the primary alcohol which could be obtained from the hydroboration of an alkene. The secondary alcohol could be formed by way of the Grignard reaction of 1-propenylmagnesium bromide.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
\end{align*}
\]

Scheme 2.06 Retrosynthetic analysis of 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone.

Another retrosynthesis was derived (Scheme 2.07) for the preparation of 1-(2',3'-dihydroxyphenyl)-4-methoxy-1-butanone. In this scheme we again obtained the diol at the end of the reaction sequence by simply deprotecting the hydroxy groups. The methoxy propane chain off of the carbonyl was made by deprotonation of a hydrogen \( \alpha \) to the carbonyl group and reacting the resulting anion with bromoethyl methyl ether. By deprotecting the hydroxy groups retrosynthetically, we recognize that the intermediate, 2,3-dihydroxy acetophenone, could be obtained from catechol.
Scheme 2.07 Retrosynthetic analysis of 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butane.
Results / Discussion

Previous work of synthesizing the brown rot extract involved completing the side chain and adding it to 2,3-dihydroxybenzoic acid via lithium chemistry. Since these approaches did not involve protection of the hydroxy groups, our group designed methods incorporating the protection of these groups. Our first thoughts entailed the use of catechol, which is a relatively inexpensive starting material, and then brominating it in order to do Grignard chemistry or use it as a leaving group. We first protected the hydroxy groups using potassium fluoride and distilled DMF and dibromomethane. This was a high yielding reaction. The next step involved bromination of the compound on the aromatic ring. This was unsuccessful since a dibrominated species was continually obtained even though only one equivalent of bromine was being used (Scheme 8).

![Scheme 2.08 Bromination of the protected catechol](image)

Placement of the chain off of the aromatic ring was the challenging aspect of this project. We had to do it in such a way as to leave the hydroxyl groups undisturbed yet obtain the very functionalized character of the chain. Scheme 2.09 reveals a synthesis that is a mere one step away from completion. Starting with the abundantly available catechol, we reacted it with zinc chloride and used glacial acetic acid as both the solvent and reagent. This solution was heated under reflux for about four hours or until the solution turned a blood red color. The result was the addition of a ketone onto the aromatic ring. This compound is unavailable for purchase in catalogs. The hydroxy groups were protected in the next step using the same method as described above. The purification of this product is the limiting step in the synthesis. TLC plates were prepared for this protected product and there did not seem to be a good solvent system with which to run a column for separation. Distillation by means of a kugelrhor was successful in removing most of the unreacted catechol, however, there still remained some catechol along with 2c.

Although we are still trying to improve our purification methods for 3c, test reactions have been performed on similar compounds for the subsequent steps. Using acetophenone as our model compound, we abstracted an α proton utilizing LDA in THF at
-77°C and then added bromomethyl ethyl ether to be attacked by the anion at the α position, forcing the bromine to leave. This experiment (Scheme 2.10) was a success. Our last step involved removing the protecting group from the diol with acid. This reaction was accidentally observed when catechol was initially protected and then reacted in the glacial acetic acid and ZnCl₂ to add the ketone. The result was an unprotected product (2c).

Scheme 2.09 Synthetic route to 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone.

Scheme 2.10 Acetophenone reacted with bromoethyl methylether.

Original Synthesis of 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone (Scheme 2.12).

Our original ideas for the synthesis of 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone involved the slightly more expensive starting material, 2,3-dimethoxy benzaldehyde. This compound was reacted with allyl grignard in THF to form a secondary alcohol. Although this was a successful reaction, the same problems with purification occurred as in the synthesis previously discussed. Again, models were used to test subsequent steps of the synthesis. Scheme 2.11 shows the use of cyclohexene being
reacted with 9-BBN in THF to form the alcohol. This was a successful reaction and awaits its use on our purified product (2d). Our next step would involve methylation of the primary alcohol formed upon hydroboration. Using methyl iodide and silver oxide and methylcyanide, we would selectively methylate the primary alcohol. Oxidation of the secondary alcohol could easily be accomplished using any such oxidants as PCC or chromic oxide. The final step in this synthesis would involve the removal of the protecting group with the use of a strong acid, although this method has not been tested on the already prepared methoxy protecting groups. We predict that the benzyl groups might be removed more easily.

Scheme 2.11 Hydroboration of cyclohexene.

Scheme 2.12 Synthetic route to 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone.
Experimental

General procedures

$^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were determined for CDCl$_3$ solutions containing ca. 1% TMS· as an internal standard with a JEOL GSX-400/54 high resolution NMR spectrometer. GC/MS analyses were performed on a Hewlett-Packard 5890 gas chromatograph coupled to a 5970 series mass selective detector using Supelco 2-4026 15 m x 0.25 mm capillary column packed with SPBM-1 (0.25 μm). Preparative GC separations were performed on a Gow-Mac Series 350 gas chromatograph using a 8' x 0.25'' 20% Carbowax 20M on Chrom-P 80/100 mesh column on Chrom-P 80/100 mesh column (injector port, oven, detector, and outlet port set to 200°C; He flow rate = 6 mL/min.). Radial thin layer chromatography was performed using a Harrison Research Chromatotron fitted with a 1 mm SiO$_2$ rotor. Toluene and Et$_2$O (anhydrous) were used as purchased from Fisher, while THF and dichloromethane were distilled from Na/benzophenone and CaH, respectively. Thin layer chromatography (TLC) on commercial silica gel plates (Baker-Flex IB-F) using UV absorption were used to monitor the progress of reactions. All of our reactions were done under argon unless otherwise stated.

2c from catechol. In excess glacial acetic acid (50 ml), ZnCl$_2$ (22.2 g, 0.163 mol) was dissolved with the aid of heat. To this stirring solution, catechol (15.0 g, 0.136 mol) was added very slowly and allowed to heat under reflux until the solution turned a deep red color. The reaction was quenched with water and a continuous extraction was run for 24 h with dichloromethane. The organic layer was dried with Na$_2$SO$_4$ (anhydrous) and the solvent was removed by rotary evaporation. The results of the crude liquis were analyzed by GC/MS and TLC. Using a Hirsch suction funnel coated with silca gel, a thin top layer of sand and 50:50 EtOAc and hexanes, the crude product was dissolved in ether and separated from the catechol starting material. The solvent was removed by rotary evaporation and the pure 1,2-dihydroxyacetophenone was obtained (0.01 g).

Protection of the Diol. Into distilled DMF (25 ml), KF (0.30 g, 0.003 mol) was vigorously shaken into solution and heated slightly to aid in theis process. Once dissolved, the 1,2-dihydroxyacetophenone (0.10 g, 6.58x$10^{-4}$ mol) was added and the solution was allowed to cool. To this stirring solution, dibromomethane (0.08 ml, 6.58x$10^{-4}$ mol) was added and the reaction was then heated under reflux for 2 h. The reaction mixture was quenched with water and then extracted using Et$_2$O. The organic layer was then dried.
using Na₂SO₄ (anhydrous) and the solvent removed by rotary evaporation. The crude product was analyzed by GC/MS and TLC.

Addition of bromoethyl methylether to Acetophenone. To a stirring solution of distilled THF (50 ml) and LDA (19.1 ml, 0.038 mol) at -77°C using an acetone/CO₂ bath, acetophenone (3.0 ml, 0.038 mol) was added dropwise at a rate of one drop per second. The solution was allowed to stir for 1 h and then bromoethyl methyl ether (3.37 ml, 0.0383 mol) was added to the solution mixture. This reaction continued stirring for an additional 2 h with the temperature maintained at -77°C. The solution was cooled to room temperature and quenched with water and extracted with dichloromethane. The organic layer was dried with Na₂SO₄ (anhydrous) and the solvent removed by rotary evaporation. The crude product was analyzed by GC/MS and TLC plates.

(2d) from Grignard. Using a round bottom flask attached to a calcium chloride drying tube, 2,3-dimethoxy benzaldehyde (1d) (3.0 g, 0.018 mol) was added to a stirring solution of Et₂O (20 ml) and allyl magnesium bromide (3.10 ml, 0.018 mol). The solution was allowed to stir under reflux for 40 minutes. It was then cooled to room temperature with additional cooling in an ice water bath. The solution was quenched with wet ether and then extracted. The organic layer was dried with Na₂SO₄ (anhydrous) and the solvent removed by rotary evaporation. The resulting crude liquid was analysed by GC/MS.

Alcohol by Hydroboration. To a solution of distilled THF (20 ml) and cyclobutene (2.0 ml, 0.020 mol), a 0.5 M solution of 9-BBN (40 ml, 0.02 mol) was added. The solution was allowed to stir overnight and then quenched with hydrogen peroxide and 3M NaOH until unreactive. This solution was also allowed to stir overnight. The solvent volume was then reduced by rotary evaporation and the solution was then extracted with dichloromethane. The organic layer was dried with Na₂SO₄ (anhydrous) and the remaining solvent removed by rotary evaporation. The resulting crude product was analysed by GC/MS.

Methylation of Butanol. To a stirring solution of Ag₂O (5.0 g, 0.0216 mol) and methyl iodide (1.3 g, 0.0216 mol) and CH₃CN (10 ml) distilled with CaH₂, butanol (0.395 ml, 0.0043 mol) was added slowly. The reaction was allowed to stir for 48 hours in the dark. The residue was analyzed by TLC using hexanes and ethylacetate in a 50:50 ratio.
Supporting Spectra II.

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<td>Total Ion Chromatograph and Mass Spectrum of cyclohexanol</td>
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<td>Mass spectrum of cyclohexanol with library comparison</td>
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Instrument: 5970B
Sample Name: Acylated catechol 2nd dichloro extraction
Misc Info: ochem.m
Vial Number: 1

Abundance TIC: TG2DIRED.D

Abundance Scan 428 (12.062 min): TG2DIRED.D
File: C:\HPCHEM\1\DATA\TGBRFINL.D
Operator: Tina
Acquired: 16 Jul 97 2:36 pm using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: acidic protons taken +BrCH2CH2OCH3
Misc Info: _occhem.m
Vial Number: 1

[Graph of Abundance vs Time]

TIC: TGBRFINL.D

[Graph of Abundance vs m/z]

Scan 579 (14.929 min): TGBRFINL.D

BRF - protected d:α
File: C:\HPCHEM\1\DATA\TGEXP1.D
Operator: Tina
Acquired: 13 Jan 98 11:13 am using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: acetophenone with NaH+bromoethylmethylene
Misc Info: o-chem
Vial Number: 1

Abundance TIC: TGEXP1.D

Scan 584 (15.528 min): TGEXP1.D - CORRUPT
File: C:\HPCHEM\1\DATA\TGEXP1.D
Operator: Tina
Acquired: 13 Jan 98 11:13 am using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: acetophenone with NaH+bromoethylmethylether
Misc Info: o-chem
Vial Number: 1

Abundance

TIC: TGEXP1.D

Scan 767 (18.983 min): TGEXP1.D - CORRUPT

m/z --> 45 77 105 133 178 434
File: C:\HPCHEM\1\DATA\TG9BBN.D
Operator: Tina
Acquired: 13 Jun 97 11:16 am using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: 9-BBN on cyclohexene for hydroboration
Misc Info: ochem.m
Vial Number: 1

Abundance

TIC: TG9BBN.D

Scan 103 (5.946 min): TG9BBN.D
Library Searched: C:\DATABASE\NBS75K.L
Quality: 95
ID: Cyclohexanol

Scan 103 (5.946 min): TG9BBN.D (*)

Abundance: 

#63375: Cyclohexanol (*)

m/z ---> 10 20 30 40 50 60 70 80 90 100
File: C:\HPCHEM\1\DATA\TSGRIGN.D
Operator: shana and tina
Acquired: 6 Feb 98 10:55 am using AcqMethod _OCHEM
Instrument: 5970B
Sample Name: grignard test on 2,3-dimethoxybenzaldehyde
Misc Info: ochem
Vial Number: 1

Abundance
3.5e+07
3e+07
2.5e+07
2e+07
1.5e+07
1e+07
5000000
4.82
5.09
7.537
13.27
5.09
7.537
13.27
17.13
19.05
21.05
17.13
19.05
21.05
17.46

Scan 713 (17.451 min): TSGRIGN.D
167
139
191
208

m/z --> 20 40 60 80 100 120 140 160 180 200
Appendix A

Selected previously Reported Syntheses of Herbertene and Cuparene

![Chemical reaction diagram](image)

**Cuparene**  
12 steps

1. NH$_2$
2. I

1. H$_2$S
2. HCl

1. Light
2. Benzene

1. B$_2$H$_6$
2. H$_2$O$_2$ / OH$^-$

1. NH$_2$'
2. Mel

Cuparene
13 steps

\[
\begin{align*}
\text{COOEt} & \quad \text{MgBr} \\
\text{Br} & \quad \text{Me}_2\text{CuLi} \\
\text{CHO} & \quad \text{Wolf-Kishner}
\end{align*}
\]

Cuparene

7 steps

1. $\text{Me}_2\text{CuLi}$
2. $\text{MeI, } t-\text{AmO}^-$

$\text{Wolf-Kishner}$

$\text{CrO}_3$

$\text{H}_2\text{O}_2$

1. $\text{CH}_2\text{N}_2$
2. LAH

$\text{PCC}$

$\text{Wolf-Kishner}$

Herbertene

9 steps
References and Notes


(c) M. T. Reetz, J. Westermann, R. Steinbach. J. Chem. Soc. Commun. 1981, 237-239. In this work, the use of the reagent to dimethylate a ketone was exemplified by the conversion of 2-methyl-2(p-tolyl)cyclopentanone to cuparene in 34%.


