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Studies Towards the Synthesis of (-)-Centrolobine via the Carbonyl Ene Reaction of Exocyclic Enol Ethers

A Capstone Project Submitted in Partial Fulfillment of the
Requirements of the Renée Crown University Honors Program at
Syracuse University

Brianna Shores

Candidate for Bachelor of Science
and Renée Crown University Honors
Spring 2017

Honors Capstone Project in Chemistry

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Dr. Nancy I. Totah

Capstone Project Reader: _____
Dr. James Kallmerten

Honors Director: _____
Chris Johnson, Interim Director

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Abstract

The goal of this study is the synthesis of centrolobine **7**, a naturally-occuring compound that exhibits anti-parasitic and anti-inflammatory activity.

The strategy is to utilize the carbonyl ene reaction to form the 2,6-disubstituted framework of centrolobine **7** from exocyclic enol ether **110** and aldehyde **111**. Exocyclic enol ether **110** would be synthesized via literature procedures starting from commercially available glutaric anhydride **11** and anisole **114**.

The work completed to date optimizing the following reactions: Friedel-Crafts acylation of glutaric anhydride **11** and anisole **114**, the reduction of alcohol **116**, and cyclization of alcohol **116** to lactone **112**. To form exocyclic enol ether **110** from lactone **112**. Difficulties with isomerization to the corresponding endocyclic enol ether **126** prevented an optimized converstion of lactone **112** to exocyclic enol ether **110**. The ene reaction of exocyclic enol ether **110** and aldehyde **111** showed some promise. Significant progress was made towards the synthesis of centrolobine **7** via the carbonyl ene reaction, and can be completed in future studies.

Executive Summary

One of the main focuses of organic chemistry is synthesis. Synthesis involves developing a series of reactions from commercially available starting materials to build a more complex molecule. The goal of a synthesis is to build a compound that may not be easily obtained. These compounds can be natural products; polymers; and biomolecules including peptides, carbohydrates, and nucleic acids. An ideal organic synthetis has few steps, a high overall yield, and produces minimal waste.

Natural products are of particular interest in organic synthesis. They are naturally occurring compounds that can be obtained from any living organism. Organic chemists synthesize these compounds because they often have a unique arrangement of atoms that require new chemistry to build. Additionally, novel structures presented by natural compounds represent new leads toward drug development.

To develop new pharmaceutical products, organic chemists need to be able to synthesize target compounds quickly and efficiently so that they can be tested for potential biological activity. Analogs of natural products, molecules with the same general structure but different substituents, often display a similar or enhanced bioactivity. An efficient synthesis of a natural product can be adapted to the preparation of analogs with useful pharmocology.

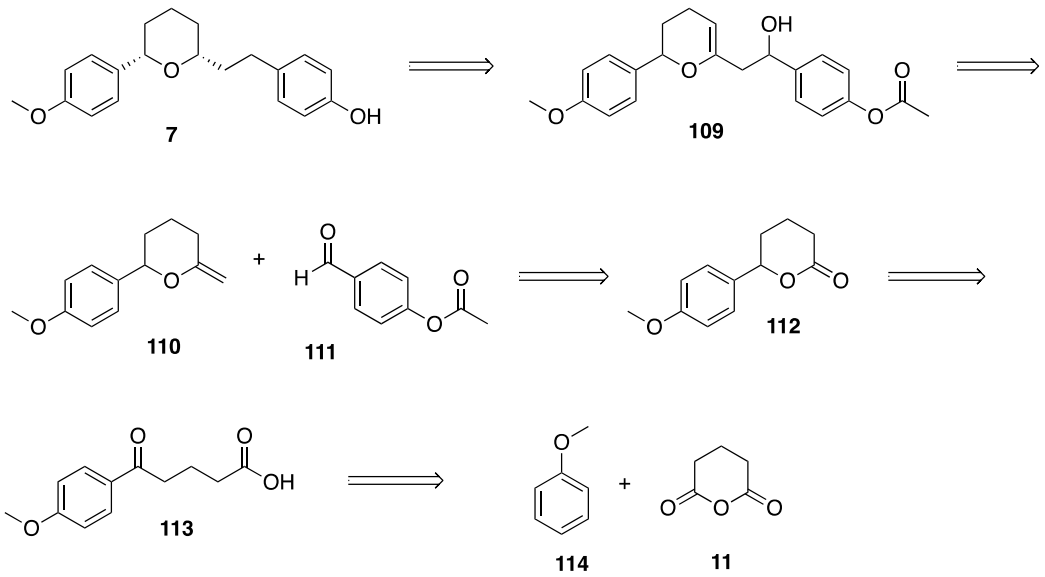
The target of this study is centrolobine. Centrolobine **7** displays antiparasitic and antinflammatory properties. Centrolobine **7** has a simple overall structure consisting of a central tetrahydropyran subunit with substituents on the C2 and C6 positions. It is a useful target to demonstrate new techniques to build a tetrahydropyran structure in a molecule. Other

biologically active molecules possess this tetrahydrofuranyl system, and strategies for construction of centrolobine **7** may be applicable to the synthesis of other bioactive compounds.

The goal of this research was to demonstrate the use of the ene reaction of exocyclic enroll ethers to synthesize centrolobine. The ene reaction is the key step in this synthesis, which would form the 2,6-disubstituted framework of centrolobine from an exocyclic enol ether and a carbonyl compound. The substituents on the exocyclic enol ether and the carbonyl compound can easily be changed, allowing access to new analogs of centrolobine.

To develop the synthesis of centrolobine using the ene reaction of exocyclic enol ethers, a retrosynthetic analysis of centrolobine was conducted (*Scheme i*). Retrosynthetic analyses are commonly employed in organic chemistry to determine how a complex molecule can be produced by working backwards from the desired product. It was anticipated that alcohol **109** can be transformed into centrolobine **7** by simultaneous reduction of the double bond and hydroxyl group, followed by cleavage of the protecting group on the phenol component. Alcohol **109** would result from the ene reaction of exocyclic enol ether **110** and aldehyde **111**. Exocyclic enol ether **110** can be made from lactone **112** via the Petasis reagent, whilc lactone **112** would be synthesized by the cyclization of carboxylic acid **113**. The Friedel-Crafts acylation of glutaric anhydride **11** and anisole **114** will produce carboxylic acid **113**.

Scheme i:



Modifications of the starting materials and components of the ene reaction will extend this synthesis to the preparation of centrolobine analogs. Optimization of each reaction will result in high yields for each product. The successful synthesis of centrolobine **7** will demonstrate the feasibility of the ene reaction of exocyclic enol ethers as an efficient route to molecules containing tetrahydropyran structures.

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Acknowledgements

I would like to thank Dr. Nancy Totah for her guidance throughout this project and for allowing me to conduct research for her. Additionally, thank you to Mike Robinson, Amanda Lieu, Ivanna Pohorilets, and Wenhong Lin for their help in the lab. Lastly, thank you to Dr. James Kallmerten and Dr. Ivan Korendovych for being my readers.

Chapter 1

Introduction

I. Importance of Tetrahydropyrans

One major branch of organic chemistry is the development of new reactions and strategies of new compounds. Of particular interest are naturally occurring compounds, targets that are complex and often found in small quantities from a natural source such as tree bark, bacteria, or a marine species.[1] Synthesizing a natural product often results in the discovery or application of new reactions because these molecules have unique arrangements. Furthermore, natural products are the most successful source of new drug leads. Researchers who are interested in developing new drugs do not have the time nor the resources to invest to synthesizing these compounds from scratch. Rather, they turn to academic groups to research efficient syntheses for natural compounds of interest.[2]

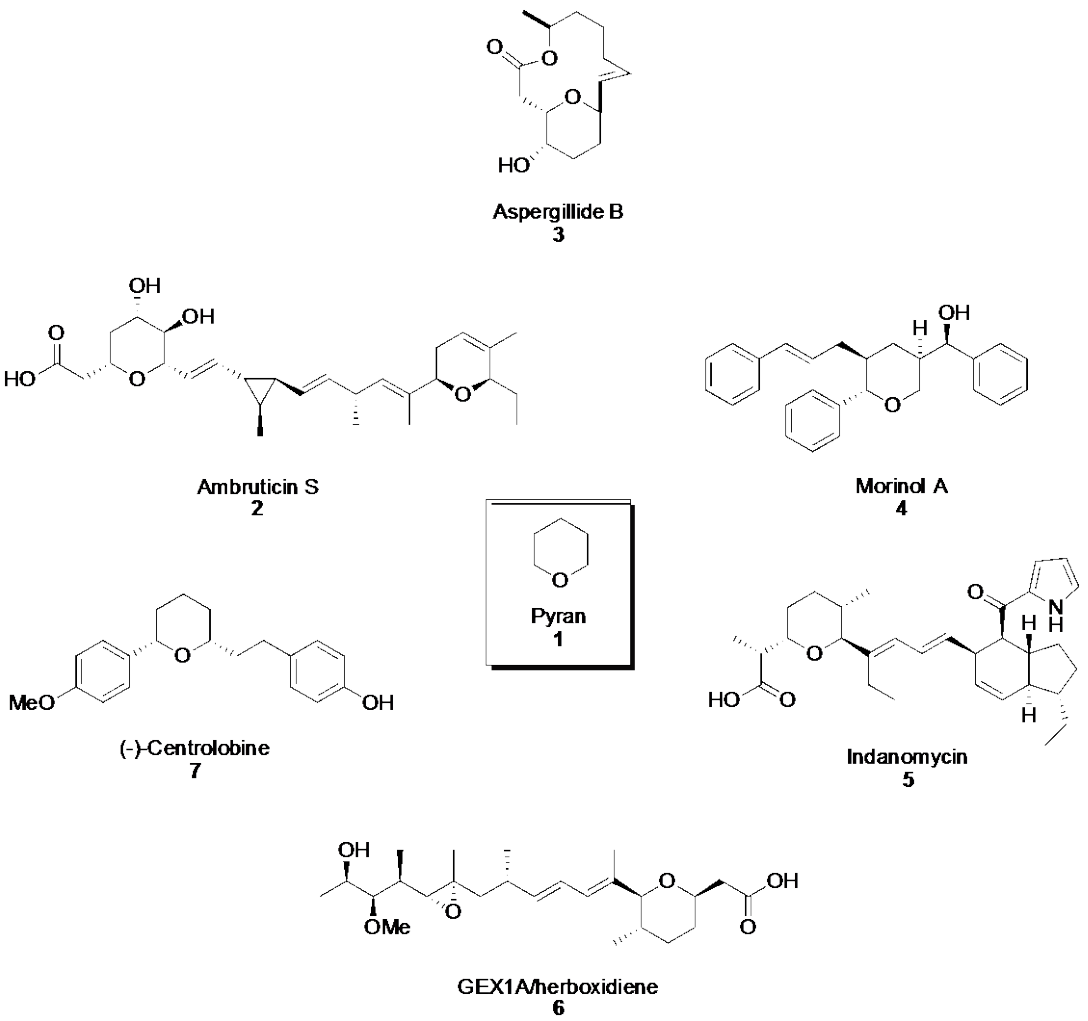
To develop new drugs, organic chemists need to synthesize natural compounds quickly so they can be tested for biological activity. Additionally, most drugs are developed from analogs of natural products. Developing a flexible synthesis, which allows for adjustment of reagents to produce these analogs, further leads to new drug discovery.[3]

A common substructure of natural products is the oxygen heterocycle tetrahydropyran **1**. Molecules containing this subunit can display antifungal, anticancer, and antibacterial

[1] Nicolaou, K. C. *P. Roy. Soc. Lond. A. Mat.* **2014**, *470*, 20130690.
[2] Harvey, A. *Rev. Salud Anim.* **2009**, *31*, 8.
[3] Karpf, M.; Kunisuke Izawa, K. I.; Konoike, T. In *Pharmaceutical Process Chemistry*; Shioiri, T., Ed.; Wiley, 2010.

properties.[4]. Examples of biologically active natural products with the tetrahydropyran structure **1** are shown below in *Figure 1*.

Figure 1:



Ambruticin S **2** is a naturally occurring antifungal isolated from the myxobacterium *Polyangium cellulosum*.[5] The structure and absolute stereochemistry of Ambruticin S **2** was

[4] Cossy, J.; Guérinot, A. *Advances in Heterocyclic Chemistry*, 2016, *119*, 107–142. DOI: 10.1016/bs.aihch.2016.03.002

[5] (a) Connor, D. T.; Greenough, R. C.; von Strandtmann, M. *J. Org. Chem.* **1977**, *42*, 3664. (b) Ringel, S. M.; Greenough, R. C.; Roemer, S.; Connor, D.; Gutt, A. L.; Blair, B.; Kanter, G.; von Strandmann, M. *J. Antibiot.* **1977**, 371.

determined using single crystal X-ray of degradation products.[6] Ambruticin S **2** and its analogs possess antifungal activity against *Aspergillus flavus, Blastomyces dermatitidis, Coccidioides immitis,* and *Hansenula anomala* that derives from interference with the osmoregulatory system of the fungi.[7] It is suggested that the ambruticins induce one of the structures involved in glycol signaling by targeting the histidine kinase hik1.[8]

Aspergillide B **3** is a secondary metabolite isolated from the marine fungus *Aspergillus ostianus* strain 01F313.[9] The structure of compound **3** was determined using IR spectroscopy and 1D and 2D ^{1}H and ^{13}C NMR.[9] This compound displays cytotoxic activity towards the mouse lymphatic leukemia cell with an LD_{50} value of 71.0 μg mL^{-1}.[9] Its most recent synthesis was reported by Loh who synthesized aspergillide **B** and its analog aspergillide **A**, where all the carbon atoms in both compounds originated from plant matter.[10]

Morinol A **4** is a compound isolated by Kusumi from the traditional Chinese medicinal plant *Morina chinensis* in 1999. The structure of compound **4** was determined via 2D NMR (^{1}H-^{1}H COSY, HSQC, HMBC, and NOESY) and HRFABMS spectroscopy.[11] In the same study, the bioactivity of Morinol A **4** on cytokine production was investigated. Morinol A **4** displayed a 62% inhibition of the cytokine IL-2. Another study by Yamauchi reported that Morinol A **4**

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[6] (a) Barnes, N. J.; Davidson, A. H.; Hughes, L. R.; Procter, G.; Rajcoomar, V. *Tetrahedron Lett.* **1981**, *22*, 1751. (b) Just, G.; Poitvin, P. *Can. J. Chem.* **1980**, *58*, 2173.

[7] Hanessian, S.; Focken, T.; Mi, X.; Oza, R.; Chen, B.; Ritson, D.; Beaudegnies, R. *J. Org. Chem. Soc.* **2010**, *75*, 5601. DOI: 10.1021/jo100956v

[8] (a) Wesolowski, J.; Hassan, R. Y. A.; Reinhardt, K.; Hodde, S.; Bilitewski, U. J. *Appl. Microbiol.* **2010**, *108*, 462. (b) Dongo, A.; Bataille-Simoneau, N.; Campion, C.; Guillemette, T.; Hamon, B.; Iacomi-Vasilescu, B.; Katz, L.; Simoneau, P. *Appl. Environ. Microbiol.* **2009**, *75*, 127. (c) Vetcher, L.; Menzella, H. G.; Kudo, T.; Motoyama, T.; Katz, L. *Antimicrob. Agents Chemother.* **2007**, *51*, 3734. (d) Knauth, P.; Reichenbach, H. J. *Antibiot.* **2000**, *53*, 1182.

[9] K. Kito, R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi and T. Kusumi. *Org. Lett.* **2008**, *10*, 225. DOI: 10.1021/ol702598q

[10] Koh, P.-F.; Loh, T.-P. *Green Chem.* **2015**, *17*, 3746. DOI: 10.1039/C5GC00900F

[11] Su, B.-N.; Takaishi, Y.; Kusumi, T. *Tetrahedron* **1999**, *55*, 14571. DOI: 10.1016/s0040-4020(99)00933-3

displayed an IC_{50} value of 23.8 μM against HeLa cells and an IC_{50} value of 34.7 μM against HL-60 cells.[12]

Indanomycin **5** is an antibiotic isolated from the bacterium *Streptomyces antibioticus*. The compound was first isolated in 1978 by ethyl acetate extraction of the fermentation broth by Westley.[13] Indanomycin **5** acts as a K^+ carrier in the mitochondrial membrane but is also capable of transporting di- and trivalent metal cations within the bacterium.[14] Indanomycin **5** is active *in vitro* against Gram-positive bacteria with a wide range activity against several strains including *Pseudomonas aeruginosa* ATCC 8709 and *Sarcina lutea* ATCC 9341.[15] The structure of compound **5** and absolute configuration were determined by single crystal X-ray analysis.[13a]

The antitumor compound GEX1A was isolated from the bacterium *Streptomyces chromofusces* in 1992.[16] The structure of compound **6** was established using IR, ^{1}H NMR, ^{13}C NMR, UV, and HRFAB-MS spectroscopy. Originally known as herboxidiene, this compound displays selective herbicidal activity against different weed strains. Later studies showed that GEX1A displayed antitumor activity against several human tumor cell lines including epidermoid carcinoma A431 cells, lung carcinoma A549 cells, and colon carcinoma DLD-1 cells with IC_{50} values of 0.0037 μM, 0.021 μM, and 0.051 μM respectively.[17] A later study showed

[12] Yamauchi, S.; Kawahara, S.; Wukirsari, T.; Nishiwaki, H.; Nishi, K.; Sugahara, T.; Akiyama, K.; Kishida, T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4923. DOI: 10.1016/j.bmcl.2013.06.067
[13] (a) Westley, J. W.; Evans, R. H., Jr.; Liu, C.-M.; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6784. (b) Westley, J. W.; Liu, C.-M. U.S. Patent 4100171, 1978.
[14] (a) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. (b) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501.
[15] Liu, C.-M.; Hermann, T. E.; Liu, M.; Bull, D. N.; Palleroni, N. J.; Prosser, B. L. T.; Westley, O. W.; Miller, P. A. *J. Antibiot.* **1979**, *32*, 95. DOI: 10.7164/antibiotics.32.95
[16] Miller-Wideman, M.; Makkar, N.; Tran, M.; Isaac, B.; Biest, N.; Stonard, R. *J. Antibiot.* **1992**, *45*, 914. DOI: 10.7164/antibiotics.45.914
[17] Sakai, Y.; Yoshida, T.; Ochiai, K.; Uosaki, Y.; Saitoh, Y.; Tanaka, F.; Akiyama, T.; Akinaga, S.; Mizukami, T. *J. Antiobiot.* **2002**, *55*, 855. DOI: 10.7164/antibiotics.55.855

that GEX1A could potentially serve as a splicing inhibitor because it binds to a protein responsible for pre-mRNA splicing.[18]

Centrolobine **7** was isolated from the heartwood of *Centrolobium robustum* tree in the Amazon in 1964 and from the stem of *Brosinum potabile*.[19] The structure of centrolobine **7** was determined by COSEY and NOESY 2D NMR experiments. At this time, the relative configuration of the compound was established by De Albuquerque based on an empirical model by Brewster however its absolute configuration was unknown.[20] This compound displays antiparasitic activity against *Leishmania amazonensis promastigotes*, a parasite that causes the disease leishmaniasis, a major health problem in Brazil.[21] Centrolobine **7** also displays some anti-inflammatory activity.[19c]

These are only a few of the many natural products containing tetrahydropyrans that display some degree of bioactivity.

II. Previous Syntheses of Centrolobine

[18] Hasegawa, M.; Miura, T.; Kuzuya, K.; Inoue, A.; Ki, S. W.; Horinouchi, S.; Yoshida, T.; Kunoh, T.; Koseki, K.; Mino, K.; Sasaki, R.; Yoshida, M.; Mizukami, T. *ACS Chem. Biol.* **2011**, *6*, 229. DOI: 10.1021/cb100248e
[19] (a) I.L. De Albuquerque, C. Galeffi, C.G. Casinovi, G.B. Marini-Bettòlo Gazz. *Chim. Ital.* **1964** 287. (b) C. Galeffi, C.G. Casinovi, G.B. Marini-Bettòlo Gazz. *Chim. Ital.* **1965**, 95. (c) Aragao Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869. (d) Alcantara, A. F. de C.; Souza, M. R.; Pilo´-Veloso, D. Fitoterapia **2000**, *71*, 613.
[20] Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5483.
[21] Nagarjuna, B.; Thirupathi, B.; Rao, C. V.; Mohapatra, D. K. *Tetrahedron Lett.* **2015**, *56*, 4916. DOI: 10.1016/j.tetlet.2015.06.084

The interesting biological activity of centrolobine **7** has stimulated much interest in the synthesis of this compound.[22, 23] As noted above, the tetrahydropyran structure is common throughout natural products, and the successful synthesis of centrolobine **7** may be extended to other compounds. Lastly, the simplicity of centrolobine **7** makes it a useful target to demonstrate new methods for tetrahydropyran synthesis.

a) First Enantioselective Synthesis of Centrolobine

The first enantioselective total synthesis of (-)-centrolobine **7**, reported by Colobert in 2002, resulted in the determination of its absolute configuration.[24] The key steps in the synthesis are the intramolecular cyclization of an enantiopure β-hydroxysulfoxide **9** and the stereoeselective reduction of β-ketosulfoxide **10**. Colobert's retrosynthetic analysis of centrolobine **7** is shown below in *Scheme 1*.

---

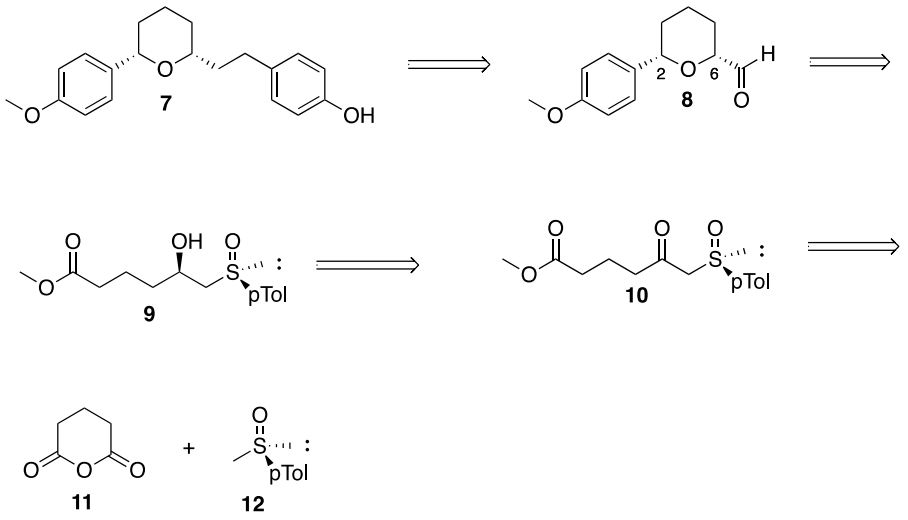
[22] (a) Vyvyan, J.; Longworth, H.; Nguyen, S. *Synlett* **2016**, *27*, 2221; (b) Hyoungsu, K.; Lee, D. *Synlett* **2015**, *26*, 2583; (c) Latif, M.; Yun, J. I.; Seshadri, K.; Kim, H. R.; Park, C. H.; Park, H.; Kim, H.; Lee, J. *J. Org. Chem.* **2015**, *80*, 3315; (d) Yang, Z.; Kim, H.-D. *Tetrahedron: Asymmetry* **2014**, *25*, 305; (e) Zeng, J.; Tan, Y. J.; Ma, J. *Chem. Eur. J.* **2014**, *20*, 405; (f) Sudarshanand, K.; Aidhen, I. S. *Eur. J. Org. Chem.* **2013**, 2298; (g) Kumaraswamy, G.; Rambabu, D. *Tetrahedron: Asymmetry* **2013**, *24*, 196; (h) Xie, J.-H.; Guo, L.-C.; Yang, X.-H.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 4758; (i) Ahmed, N.; Konduru, N. K. Beilstein *J. Org. Chem.* **2012**, *8*, 177; (j) Fujioka, H.; Yahata, K.; Kubo, O.; Sawama, Y.; Hamada, T.; Maegawa, T. Angew. *Chem., Int. Ed.* **2011**, *50*, 12232; (k) Schmidt, B.; Hölter, F.; Kelling, A. *J. Org. Chem.* **2011**, *76*, 3357; (l) Clarke, P. A.; Sellars, P. B.; Mistry, N. *Tetrahedron Lett.* **2011**, *52*, 3654; (m) Iqbal, M.; Mistry, N.; Clarke, P. A. *Tetrahedron* **2011**, *67*, 4960; (n) Jeong, Y.; Kim, D.-Y.; Choi, Y.; Ryu, J.-S. *Org. Biomol. Chem.* **2011**, *9*, 374; (o) Reddy, C. R.; Madhavi, P. P.; Chandrasekhar, S. *Synthesis* **2011**, *1*, 123; (p) Schmidt, B.; Berger, R.; Hölter, F. *Org. Biomol. Chem*. **2010**, *8*, 1406; (q) Reddy, C. R.; Madhavi, P. P.; Chandrasekhar, S. *Tetrahedron: Asymmetry* **2010**, *21*, 103; (r) Chazadaj, W.; Kowalczyk, R.; Jurczak, J. *J. Org. Chem.* **2010**, *75*, 1740; (s) Haruhiko, F.; Kenkichi, N.; Makoto, S. *Heterocycles* **2010**, *82*, 641; (t) Mohapatra, D. K.; Pal, R.; Rahaman, H.; Gurjar, M. K. *Heterocycles* **2010**, *1*, 219; (u) Schmidt, B.; Hölter, F. *Chem. Eur. J*. **2009**, *15*, 11948; (v) Takeuchi, T.; Matsuhashi, M.; Nakata, T. *Tetrahedron Lett.* **2008**, *49*, 6462; (w) Dziedzic, M.; Furman, B. *Tetrahedron Lett*. **2008**, *49*, 678; (x) Prasad, K. *Tetrahedron* **2007**, *63*, 1089; (y) Böhrsch, V.; Blechert, S. *Chem. Commun*. **2006**, 1968; (z) Lee, A. C.-H. *Tetrahedron Lett*. **2006**, *47*, 1641.

[23] (a) Clarke, P. A.; Santos, S. *Tetrahedron Lett.* **2005**, *46*, 6651. (b) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021; (c) Clarke, P. A.; Martin, W. H. C. *Tetrahedron* **2005**, *61*, 5433; (d) Lee, E.; Kim, H. J.; Jang, W. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1609; (e) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883; (f) Colobert, F.; Carreño, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, *68*, 7779; (g) Mazery, R. D.; Solladie, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723; (h) Marumoto, S. Org. Lett. 2002, 4, 3919.

[24] Colobert, F. C. A.; Mazery, R. D.; Solladié, G.; Carreño, M. C.. *Org. Lett.* **2002**, *4*, 172. DOI: 10.1021/ol025778z

Preparation of (-)-centrolobine was anticipated from the aldehyde **8** with introduction of the final side chain by Wittig reaction and reduction. In turn, preparation of aldehyde **8** could be achieved by cyclization of the β-hydroxysulfoxide **9** prepared by stereoselective reduction of the chiral β-ketosulfoxide **10**. This step introduced the absolute chirality to the scheme. β-Ketosulfoxide **10** was expected from the condensation reaction between glutaric anhydride **11** and sulfoxide **12**.

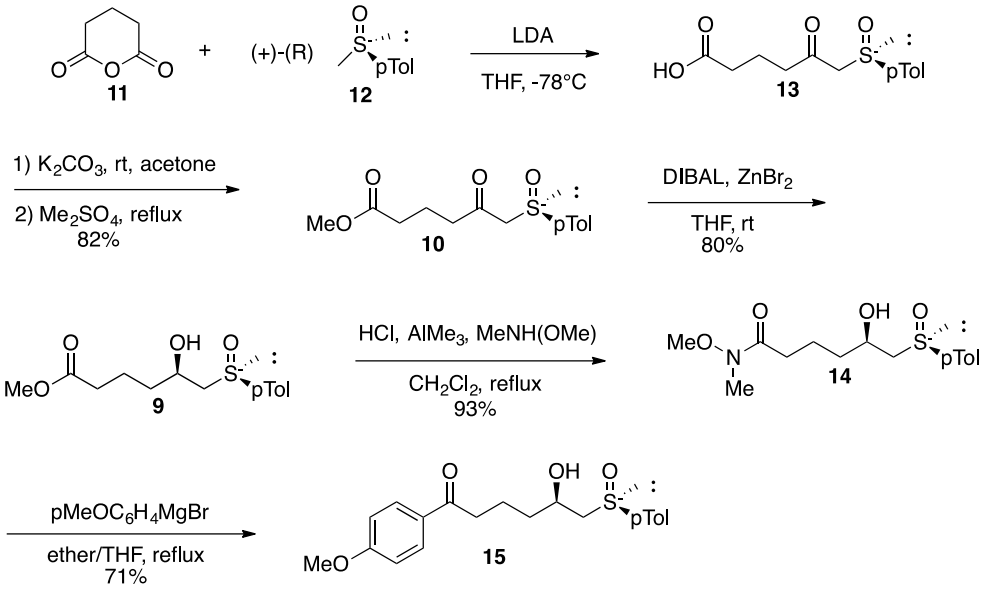
Scheme 1:



The first step in Colobert's synthesis is formation of carboxylic acid **13** by the condensation of glutaric anhydride **11** and the carbanion of (+)-(*R*)-methyl-*p*-tolyl sulfoxide **12** (*Scheme 2*). Esterification of carboxylic **13** to form β-ketosulfoxide **10** was completed by deprotonation and treatment with dimethylsulfate to give β-ketosulfoxide **10** in 82% yield from glutaric anhydride **11**. The yield of this literature sequence was improved by running the condensation reaction at -78°C. β-Ketosulfoxide **10** was reduced stereoselectively to give the β-hydroxysulfoxide **9** in 80% yield and 98% diasteriomeric excess (de) using diisobutylaluminum hydride (DIBAL) and zinc bromide. The stereochemistry of compound **9** was confirmed by

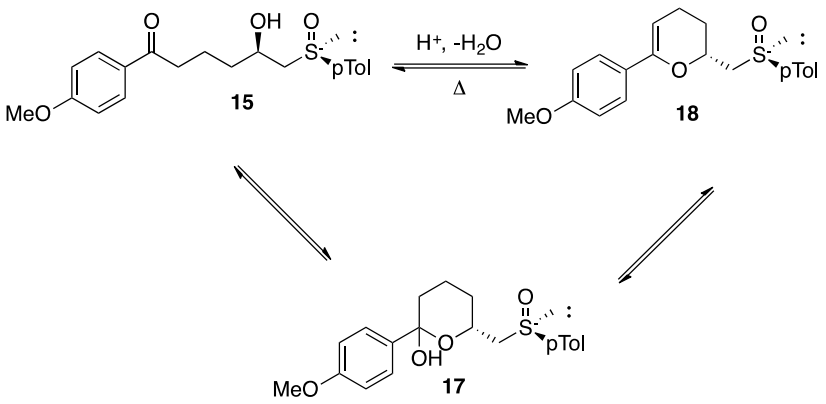
comparison of the ^{1}H NMR spectrum to an authentic sample. The β-hydroxysulfoxide **9** was transformed into hydroxyketone **15** by treatment of the intermediate Weinreb amide **14** with a Grignard reagent, affording ketone **15** in 66% yield over two steps.

Scheme 2:



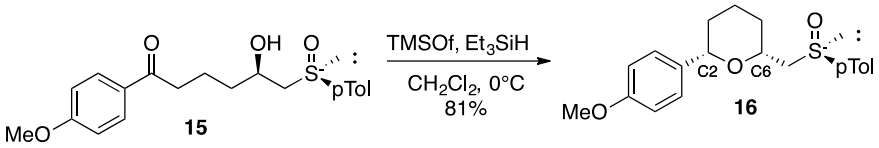
Formation of the tetrahydropyran **16** was investigated next. The inital approach to tetrahydropyran **16** involved cyclization of hydroxyketone **15** under acidic conditions in an effort to isolate a hemiketal **17** that could subsequently be reduced to give the desired compound **16** (*Scheme 3*). Under these conditions, a mixture of dihydropyran **18** and starting sulfoxide **15** was recovered. None of the anticipated hemiketal **17** was observed under these acidic conditions.

Scheme 3:



In an alternate approach, Colobert attempted to prepare the tetrahydropyran **16** using a reductive condensation reaction inspired by the work of Olah and Nicolaou.[25,26] Using an excess of triethylsilane and trimethylsilyl trifluoromethanesulfonate (TMSOTf) the desired sulfoxide derivative **16** was obtained from hydroxyketone **15** in 81% yield and with complete syn stereoselectivity at the C2 and C6 positions (*Scheme 4*). The stereochemistry was confirmed by NOESY experiments.

Scheme 4:

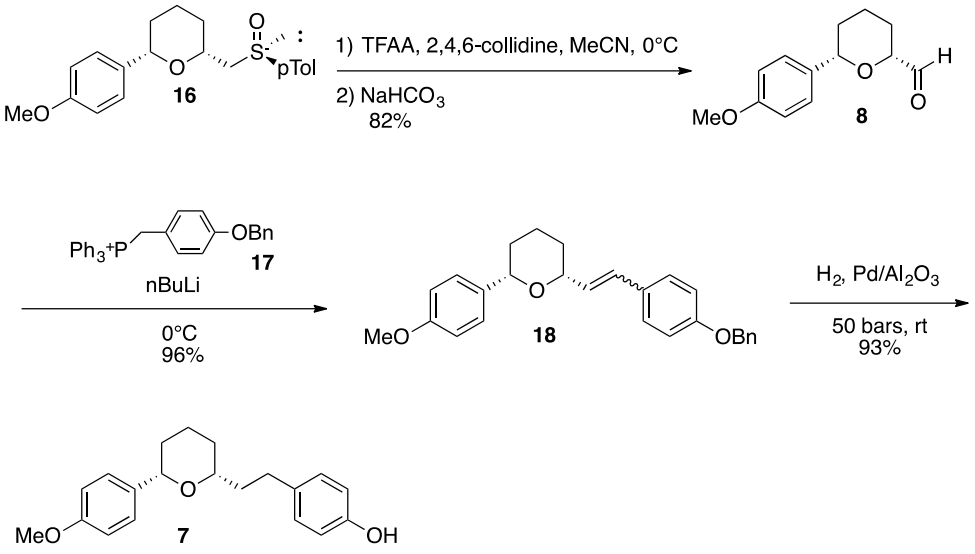


With conditions for the preparation of sulfoxide **16** were optimized, the synthesis of (-)-centrolobine was completed by the conversion of sulfoxide **16** aldehyde **8** in 82% yield using Pummerer conditions (*Scheme 5*). Subsequent formation of the olefin **18** was achieved by Wittig reaction of aldehyde **8** with benzyltriphenylphosphonium salt **17** (95%). Finally, catalytic

[25] Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314. DOI: 10.1021/jo00228a031
[26] Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc*, **1989**, *111*, 4136. DOI: 10.1021/ja00193a076

hydrogenation reduced the double bond and removed the benzyl ether protecting group of olefin **18** to give (-)-centrolobine **7** in 93% yield. The enantioselective synthesis of (-)-centrolobine **7** was achieved in nine steps and 26% overall yield from glutaric anhydride **11**.

Scheme 5:



^{1}H and ^{13}C NMR spectra, IR spectra, melting point, and optical resolution of the synthesized product were all identical to those of naturally occuring centrolobine **7**, confirming that the synthesized compound was the same as the target natural product. As a result of this work, the absolute stereochemistry of (-)-centrolobine **7** was revised by Colobert from [2(*R*), 6(*S*)] to [2(*S*), 6(*R*)] based upon the configuration of β-hydroxysulfoxide **9**.

b) Hetero-Diels-Alder Reaction to Synthesize Centrolobine

In 2007, Hashimoto applied the hetero-Diels-Alder (HDA) reaction to synthesize (-)-centrolobine **7** and one of its analogs.[27] The hetero-Diels-Alder reaction is a commonly strategy for construction of tetrahydropyran targets.[28] Hashimoto was the first to synthesize diarylheptanoid tetrahydropyran srructures employing the hetero-Diels-Alder reaction.

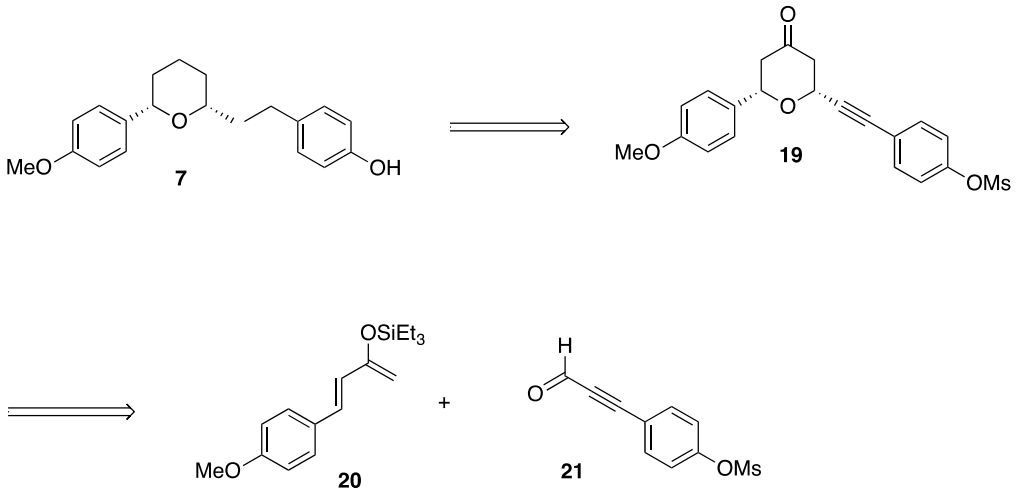
Hashimoto envisioned the preparation of centrolobine **7** was envisioned from chiral ketone **19**, the product of the hetero-Diels-Alder key reaction, by catalytic hydrogenation of the triple bond and removal of the carbonyl group (*Scheme 6*). Hashimoto had previously reported that dirhodium(II) tetrakis-[(*R*)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh_2-(*R*-BPTPI)$_4$, is an efficient Lewis acid catalyst for enantioselective hetero-Diels-Alder reactions.[29] Using this catalyst in the cyclization, the key intermediate ketone **19** would be prepared from protected diene **20** and phenylpropargyl aldehyde **21**.

Scheme 6:

[27] Washio, T.; Yamaguchi, R.; Abe, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron* **2007**, *63* 12037. DOI: 10.1016/j.tet.2007.09.003

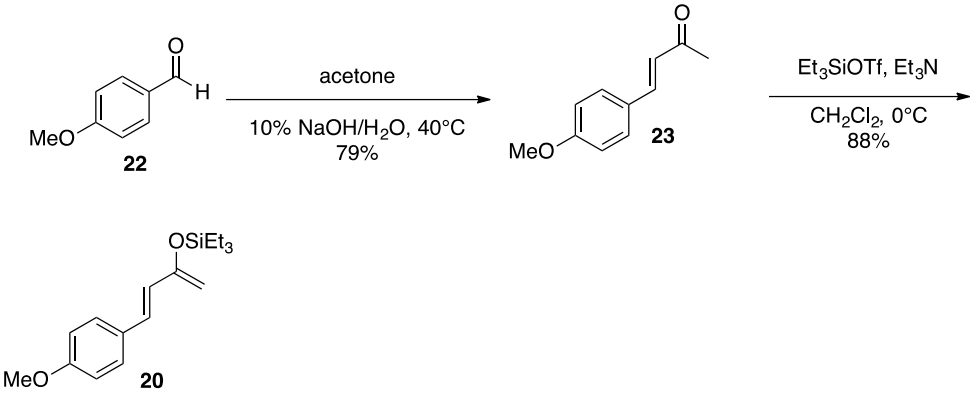
[28] (a) Danishefsky, S. J. *Aldrichimica Acta* **1986**, 19, 59; (b) Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, 2, 273; (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: New York, NY, 1987; Vol. 47; (d) Weinreb, S. M. *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 401; (e) Boger, D. L. *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 451; (f) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, 39, 3558; (g) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.

[29] Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. Angew. *Chem., Int. Ed*. **2004**, *43*, 2665. DOI: 10.1002/anie.200453821



To prepare diene **20**, 4-methoxybenzaldehyde **22** was treated with acetone and aqueous sodium hydroxide to form α,β-unsaturated ketone **23** (*Scheme* 7) in 79% yield.[30] The ketone was protected using Et_3SiOTf and triethylamine to produce the desired diene **20**.

Scheme 7:

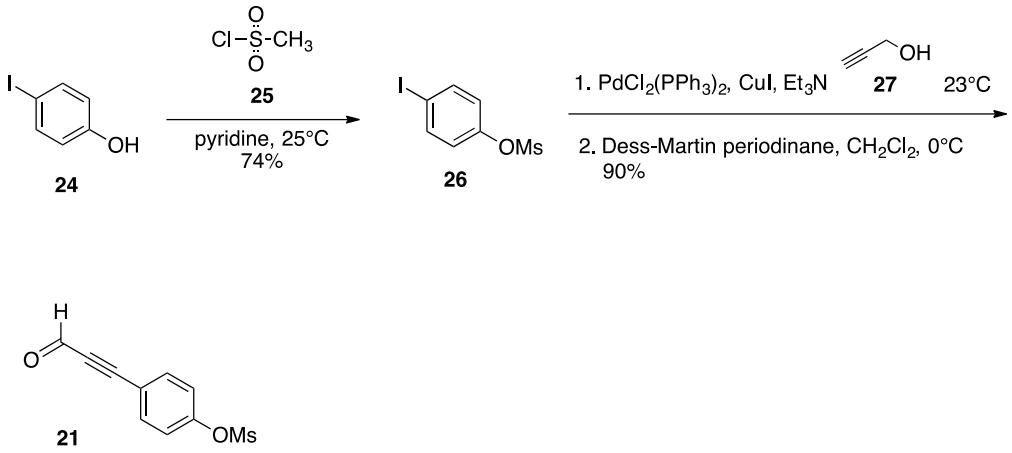


Phenylpropargyl aldehyde **21** was prepared by protection of the hydroxyl group on commercially available 4-iodophenol **24** with methanesulfonyl chloride **25** to form

[30] Knölker, H.-J.; Ahrens, B.; Gonser, P.; Heininger, M.; Jones, P. G. *Tetrahedron* **2000**, *56*, 2259. DOI: 10.1016/s0040-4020(99)01109-6.

methansulfonate **26**.[31] Phenylpropargyl aldehyde **21** was prepared in two steps by the Sonogashira coupling of methanesulfonate **26** with propargyl alcohol **27** and subsequent Dess-Martin oxidation.[32]

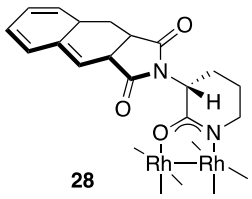
Scheme 8:



To prepare centrolobine **7**, the the Diels Alder cyclization of with diene **20** and phenylpropargyl aldehyde **21** was carried out in the presence of Rh_2-(*R*-BPTPI)$_4$ **28** (*Figure 2*). Subsequent treatment with tetra-*n*-butylammonium fluoride (TBAF) removed the silyl group to form ketone **19** in 87% yield and 93% enantiomeric excess (*Scheme 9*). The absolute stereochemistry of ketone **19** was established as (2*R*,6*S*) by the transformation into (-)-centrolobine **7**.

Figure 2:

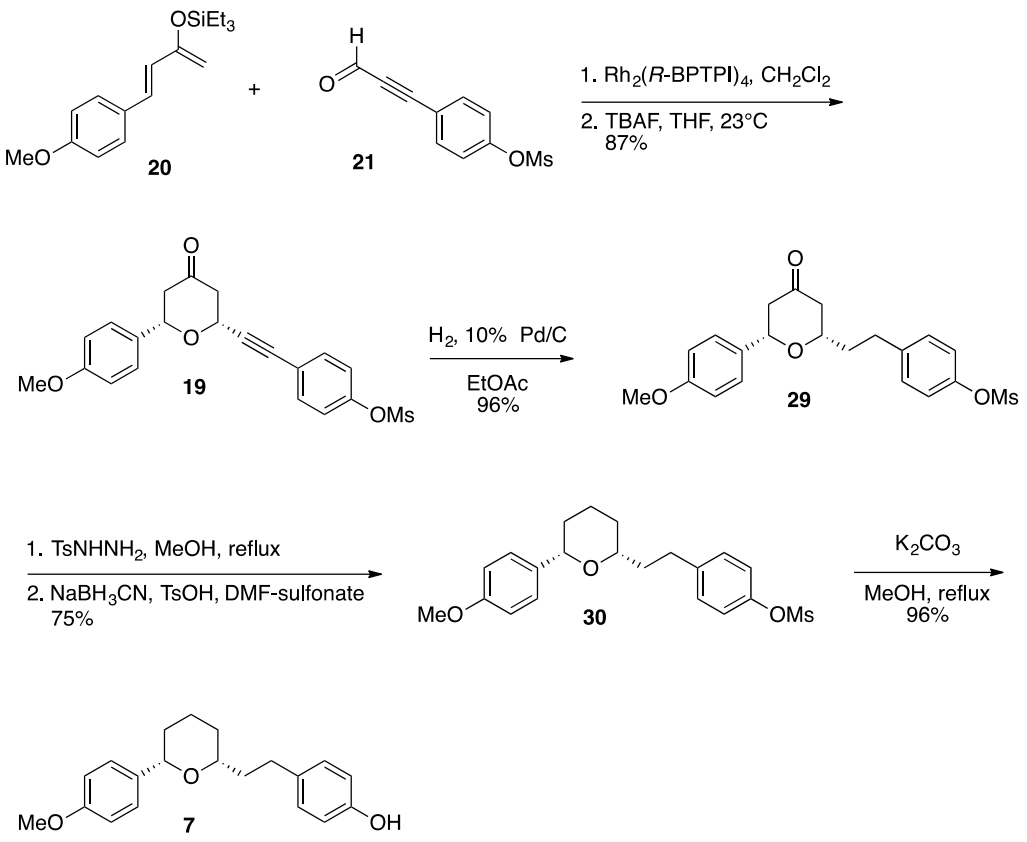
[31] Lee, T.-S.; Kim, J.; Bae, J.-Y. *Polymer* **2004**, *45*, 5065. DOI: 10.1016/j.polymer.2004.05.051
[32] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *50*, 4467. DOI: 10.1016/S0040-4039(00)91094-3



28

Catalytic hydrogenation of ketone **19** in 95% yield to reduced the triple bond to form ketone **29**. The carbonyl group on ketone **29** was removed and formation the tosylhydrazone with *p*-toluenesulfonyl hydrazine ($TsNHNH_2$). Reduction with sodium cyanoborohydride ($NaBH_3CN$) in the presence of *p*-toluenesulfonic acid formed tetrahydropyran **30** in 75% yield. The methanesulfonyl group of tetrahydropyran **30** was removed using potassium carbonate in methanol to form centrolobine **7**.

Scheme 9:



Hashimoto's synthesis provided (-)-centrolobine **7** in 41% overall yield over 7 steps starting with methanesulfonate **26**. The asymmetric hetero-Diels-Alder reaction can also be applied to synthesize other diarylheptanoid natural products.

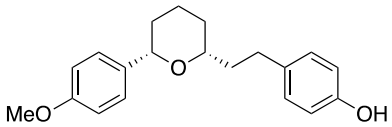
c) Chemoenzymatic Synthesis of the Four Stereoisomers of Centrolobine

In 2015, Mohapatra designed a chemoenzymatic approach that can be used to produce all four stereoisomers of centrolobine **7** (*Figure 3*).[33] All of the stereoisomers can be synthesized from the same starting material, 4-methoxybenzaldehyde **22**. The key steps of this strategy

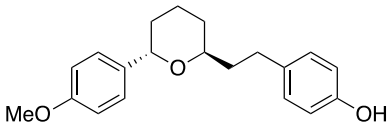
[33] Nagarjuna, B.; Thirupathi, B.; Rao, C. V.; Mohapatra, D. K. *Tetrahedron Lett.* **2015**, *56*, 4916. DOI: 10.1016/j.tetlet.2015.06.084

include enzymatic resolution, a cross-methasis reaction, and a tandem isomerization following a protocol developed in the Mohapatra lab.[34].

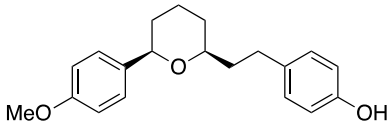
Figure 3:



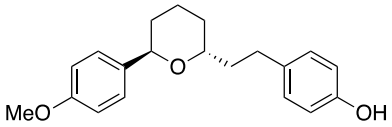
(2*R*,6*S*)-(-)-Centrolobine
7



(2*S*,6*S*)-*epi*-Centrolobine
31



(2*S*,6*R*)-(+)-Centrolobine
32

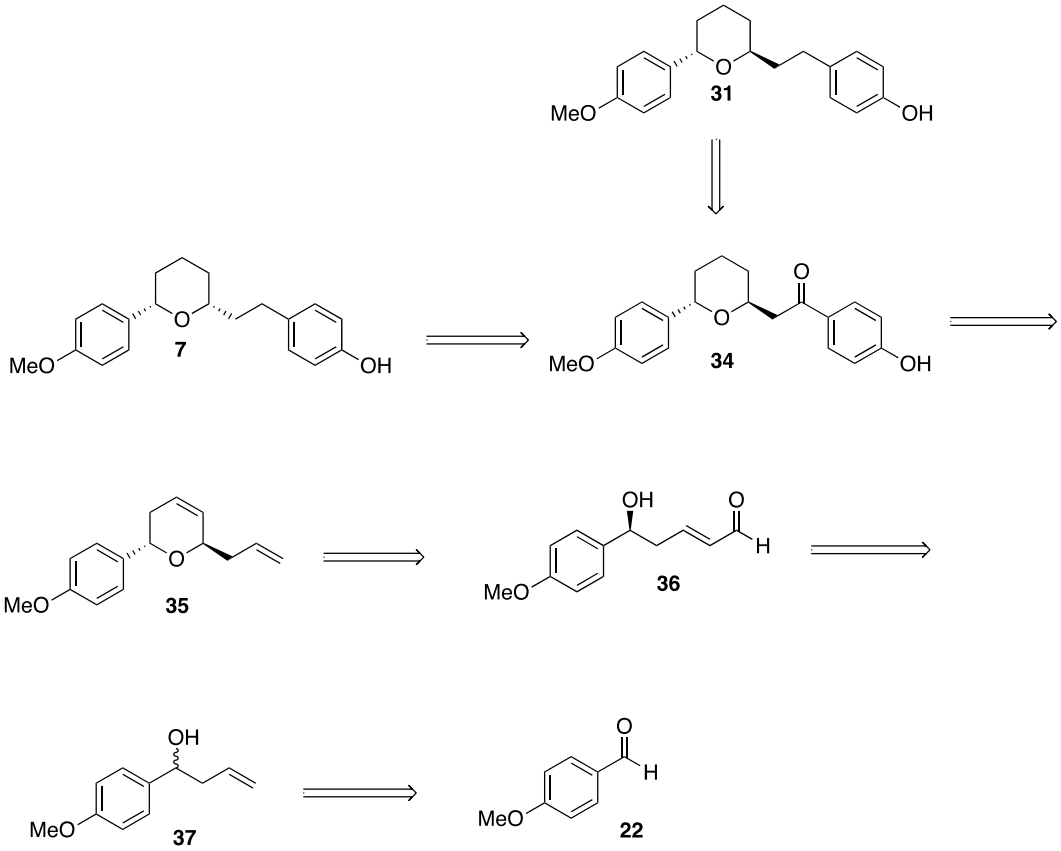


(2*R*,6*R*)-*epi*-Centrolobine
33

Both (-)-centrolobine **7** and (2*S*,6*S*)-epi-centrolobine **31** could be prepared by catalytic hydrogenation of ketone **34** (*Scheme 10*). Ketone **34** was anticipated from tetrahydropyran **35** using Jin's hydroxylation-oxidation protocol and a Grignard reaction. Tandem isomerization followed by C-C and C-O bond formation would produce tetrahydropyran **35** from aldehyde **36**. A cross-metathesis reaction would yield aldehyde **36**, which was expected from the enzymatic resolution of alcohol **37**. Alcohol **37** would be produced from a Grignard reaction of commercially available methoxybenzaldehyde **22.**

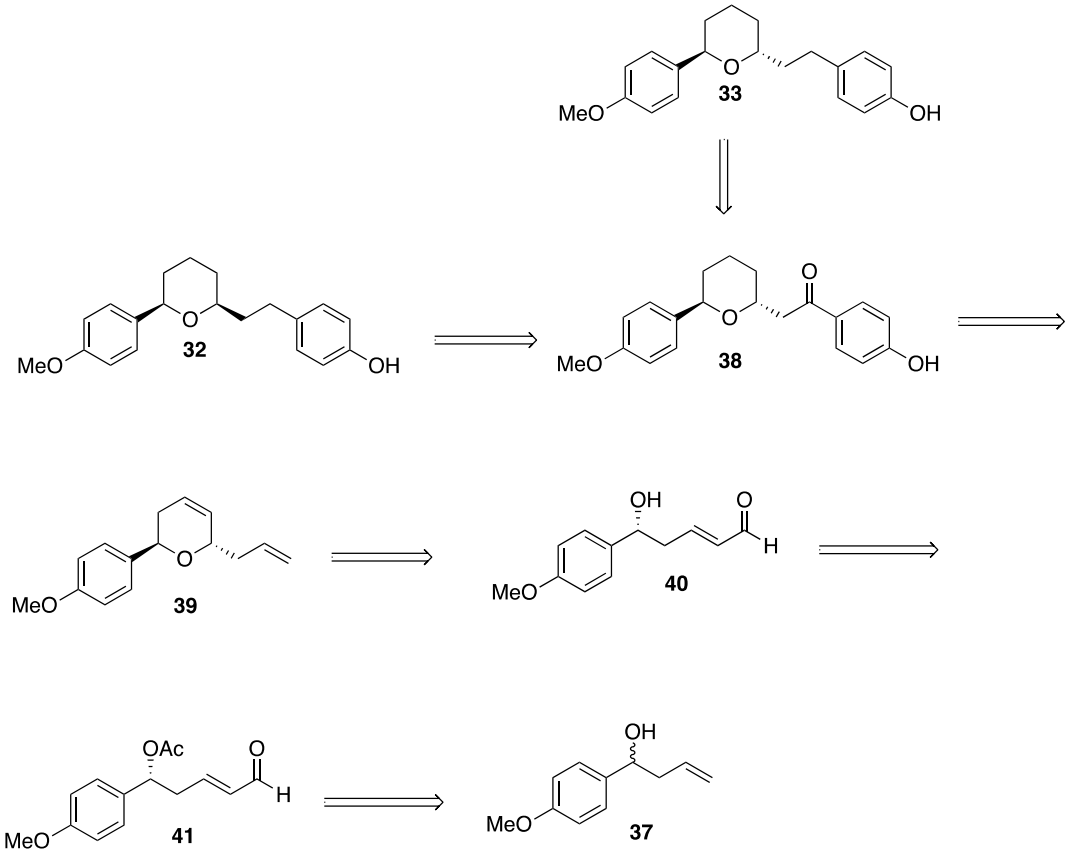
[34] Mohapatra, D. K.; Bhimireddy, E.; Krishnarao, P. S.; Das, P. P.; Yadav, J. S. *Org. Lett.* **2011**, *13*, 744. DOI: 10.1021/ol1029854

Scheme 10:



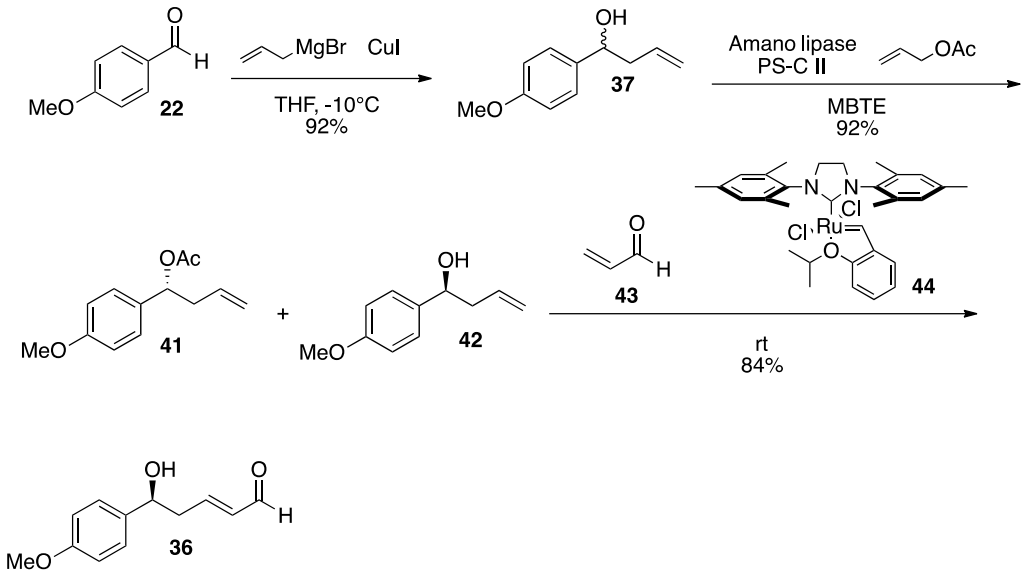
The remaining two stereoisomers of (-)-centrolobine **7**, (+)-centrolobine **32** and (2*R*,6*R*)-*epi*-centrolobine **33**, would result from a similar synthetic plan. The diastereomers would be formed by catalytic hydrogenation of the common intermediate ketone **38** (*Scheme 11*). The ketone intermediate **38** would be formed from the tetrahydropyran **39** using Jin's hydroxylation-oxidation protocol and a Grignard reaction. Tandem isomerization followed by C-C and C-O bond formation was expected to give tetrahydropyran **39** from aldehyde **40**. A cross-metathesis reaction would form aldehyde **40**. The side product of enzymatic resolution of alcohol **37**, acetate **41**, was used to form aldehyde **40**.

Scheme 11:



In the forward synthesis, preparation of the racemic alcohol **37** was achieved by addition of allylmagnesium bromide to 4-methoxybenzaldehyde **22.** Treatment of the resulting racemic alcohol **37** with the enzyme Amano lipase PS-C II in the presence of vinyl acetate resulted in formation of homoallylic alcohol **42** (47%, ca. 99% ee) and the enantiomerically enriched acetate **41**. These compounds were separated by column chromatography. Homoallylic alcohol **42** was then subjected to a cross-methasis reaction with acrolein in the presence of the Hoveyda-Grubbs catalyst to form the δ-hydroxy α,β-unsaturated aldehyde **36**.

Scheme 12:



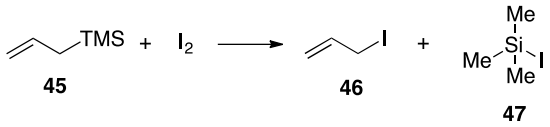
The olefin cross-metathesis reaction is one of the key steps in this synthesis. While cross-metathesis reactions had the potential to be useful in organic synthesis, it was difficult to predict the product's stereochemistry and selectivity. Grubbs explored the cross-metathesis reaction to make it more applicable to organic chemists[35]. First, Grubbs ranked different types of olefins basked on their ability to homodimerize into four types. Homodimerization occurs when an olefin undergoes the cross-metathesis reaction with itself. The more likely an olefin is to homodimerize, then the less likely it will be to undergo the cross-metathesis reaction with a different olefin. He then explored the reaction of each catagory with itself or with another cataogry with all the different catalysts available. Through his work, Grubbs successfully showed how one could predict the product of a cross-metathesis reaction based on the types of olefins used in the reaction and the catalyst. Mohapatra's choice of catalyst for this key step is based on

[35] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc* **2003**, *125*, 11360. DOI: 10.1021/ja0214882

Cossey's work on the synthesis of octalactins, in which a successful cross metathesis reaction using Hoveyda-Grubbs catalyst **30** and acrolein **29** as one of the compounds.[36]

The second key step of Mohapatra's synthetic plan is the cyclization of δ-hydroxy α,β-unsaturated aldehyde **36** to tetrahydrpyran **35**. Mohapatra developed a protocol to cyclize δ-hydroxy α,β-unsaturated aldehydes to *trans*-2,6-disubstituted-3,4-dihydropyrans using molecular iodine as a Lewis acid and allyltrimethylsilane as a nucleophile.[37] Molecular iodine reacts with allyltrimethylsilane **45** to form allyl iodide **46** and trimethylsilyl iodide **47** (*Scheme 13*). Without the presence of iodine, the reaction will not proceed.

Scheme 13:

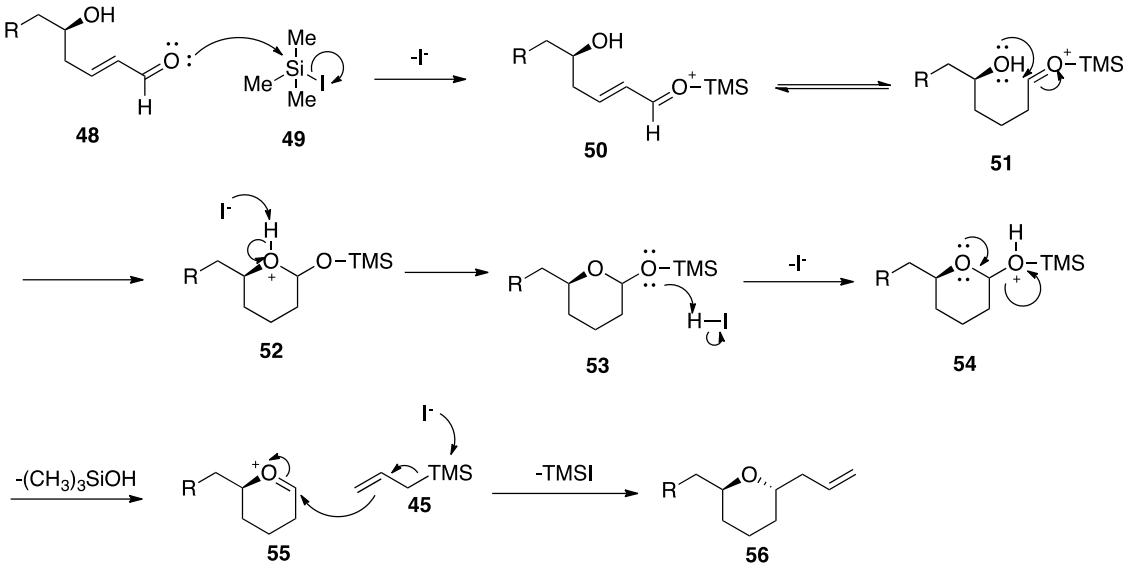


Activation of the carbonyl in aldehyde **48** with trimethylsilyl iodide **47** provided compound **50**, which then undergoes a conformation change to compound **51** (*Scheme 14*). The hydroxyl group added to the activated carbonyl to cyclize to tetrahydropyran **51**. The hydroxyl group was deprotonated from iodine anion. Protonation of the –OTMS substituent from hydrogen iodide provided compound **54**. The lone pair on the oxygen pushed down to remove trimethylsilanol to form olefin **55**. Additional of iodine anion to the trimethylsilyl group on allyltrimethylsilane **45** allowed for the addition of the alkene to the double bond on oxonium **55** to form tetrahydropyran **56**. The steric interactions from the substituent on C2 in oxonium intermediate **55** direct the incoming allyltrimethylsilane on the opposite side of the ring, forming the trans product. Their protocol produced the desired product in high yields and only as the

[36] Dinh, M.-T.; Bouzbouz, S.; Péglion, J.-L.; Cossy, J. *Tetrahedron* **2008**, *64*, 5703. DOI: 10.1016/j.tet.2008.04.026
[37] Mohapatra, D. E. K.; Das, P. P.; Pattanayak, M. R.; Yadav, J. S. *Chem. Eur. J.* **2010**, *16*, 2648. DOI: 10.1002/chem.201090036

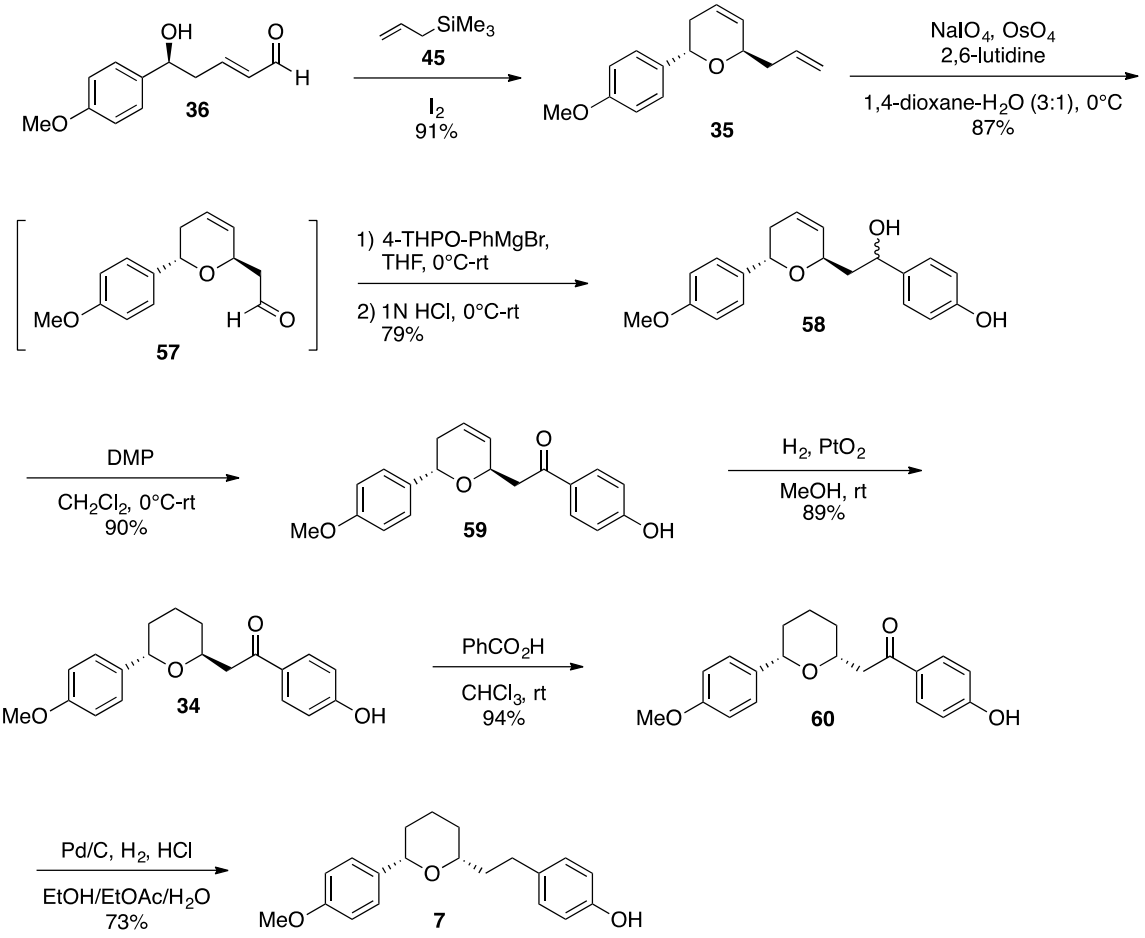
trans isomer. Their mechanism was confirmed by treatment of δ-hydroxy α,β-unsaturated aldehyde with a catalytic amount of trimethylsilyl iodide **47**, and the corresponding *trans*-2,6-disubstituted-3,4-dihydropyran was formed in ten minutes.

Scheme 14:



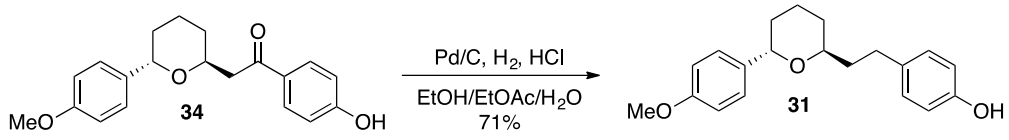
Treatment of the trans-δ-hydroxy α,β-unsaturated aldehyde **36** with allyltrimethylsilane **45** and catalytic iodine gave dihydropyran **35** as a single steroisomer (*Scheme 15*To complete the synthesis, dihydropyran **35** was converted to aldehyde **57** by oxidative cleavage of the terminal alkene. Subsequent Grignard reaction produced alcohol **58** as a 1:1 mixture of diastereomers. This mixture was oxidized with Dess-Martin periodinane to give ketone **59**. Catalytic hydrogenation then provided the tetrahydropyran **34** that can be used to prepare either *trans* or *cis* (-)-centrolobine isomers. The *trans*-pyran **34** was epimerized to the *cis* isomer **60** with benzoic acid, cis pyran **60** was hydrogenated again to form (-)-centrolobine **7**.

Scheme 15:



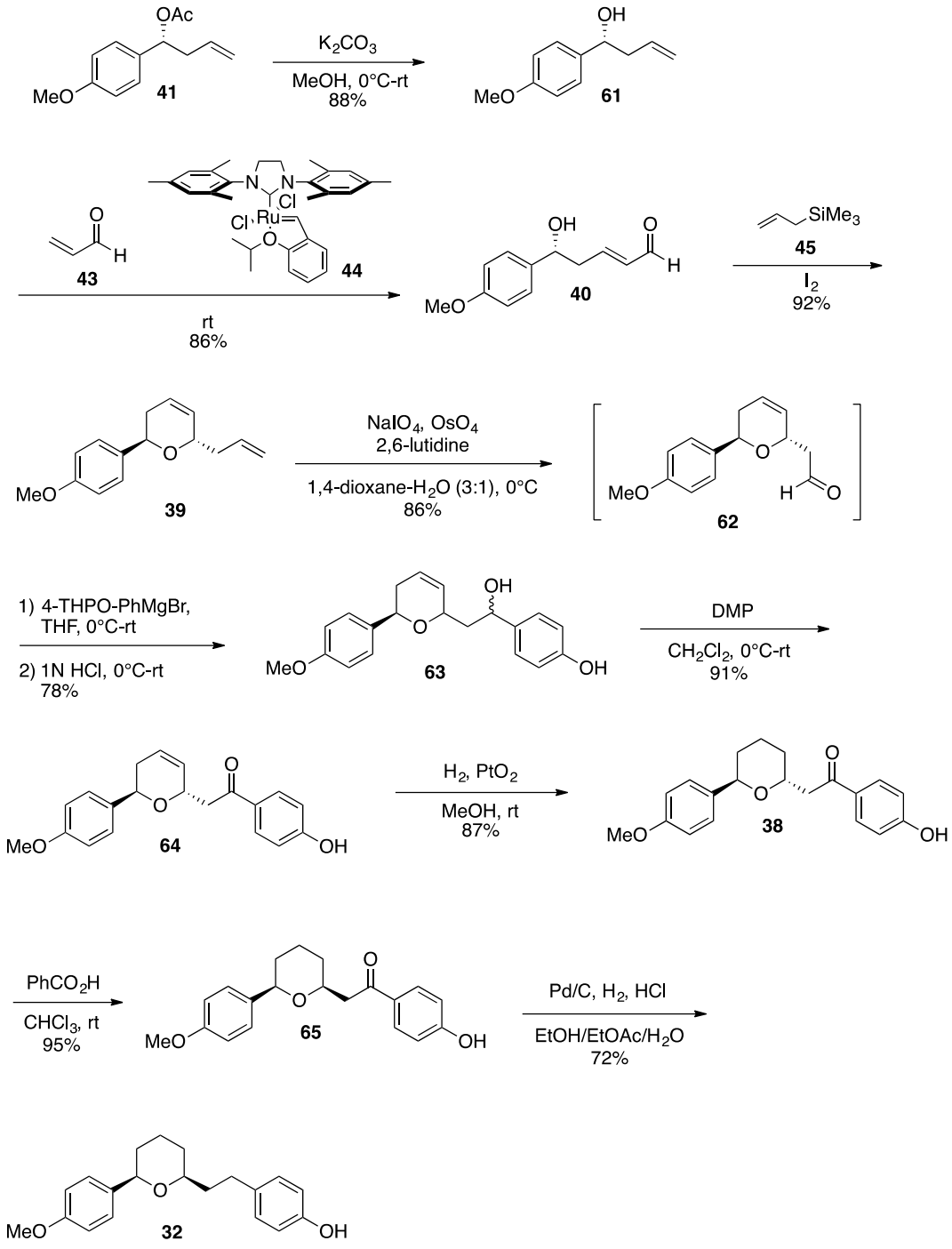
To form the *trans* (-)-centrolobine **31** isomer, ketone **34** was catalytically hydrogenated to form the desired product in 71% yield (*Scheme 16*):

Scheme 16:



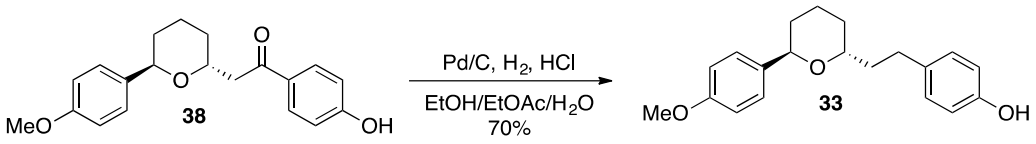
The synthesis of the (+)-isomers of centrolobine began by treating acetate **41** with potassium carbonate to form the homoallylic alcohol **61** (*Scheme 17*). The same scheme was followed as described above to form (+)-centrolobine **32**.

Scheme 17:



The *trans* isomer of (+)-centrolobine **33** was formed by catalytic hydrogenation of tetrahydropyran **38** (*Scheme 18*).

Scheme 18:



Mohapatra's scheme for the synthesis of centrolobine is very flexible, and each stereoisomer can be prepared in 26-28% yield from 4-methoxybenzaldehyde **22**. This work highlights the scope of the tandem isomerization reaction followed by C-O and C-C bond formations for the synthesis of pyran complexes. The sequence design is quite versatile and can be adopted to other natural products with structures similar to centrolobine.

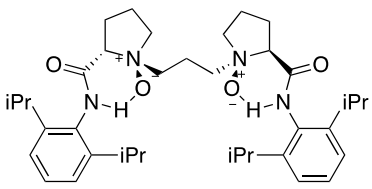
d) Application of Catalytic Asymmetric Halocyclization to Synthesize Centrolobine

The most recent synthesis of centrolobine **7** was reported by Zhou.[38] The key step in this sequence catalytic asymmetric halocyclization to form the tetrahydropyran framework based on Zhou's previous studies of the intra- and intermolecular haloetherification of enones.

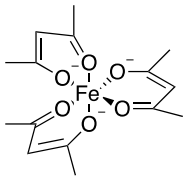
Zhou's general method for asymmetric intramolecular bromoetherification to form six-membered rings was based on the discovery that L-PiPr$_2$ **66** and Fe(acac)$_3$ **67** (*Figure 4*) form a complex that acted as a catalyst for the cyclization. For intermolecular haloetherification, L-RaPr$_2$ **68** and Sc(OTf)$_3$ **69** proved to be better suited for the cyclization.

[38] Zhou, P.; Cai, Y.; Zhong, X.; Luo, W.; Kang, T.; Li, J.; Liu, X.; Lin, L.; Feng, X. *ACS Catal.*, **2016**, *6*, 7778. DOI: 10.1021/acscatal.6b02048

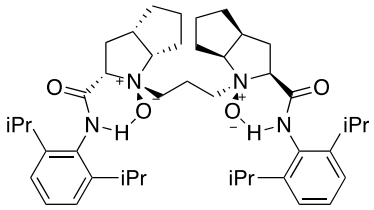
Figure 4:



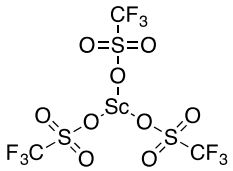
L-PiPr$_2$
66



Fe(acac)$_3$
67



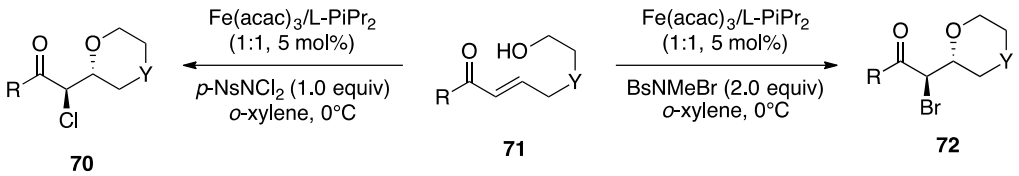
L-RaPr$_2$
68



Sc(OTf)$_3$
69

Once finding the best catalyst, Zhou moved onto the halogen source. *N*-bromo-*N*-methyl-benzenesulfonamide (BsNMeBr) was found to be the ideal bromine source. Using the optimized conditions, the desired product for bromocyclization was produced in high yields and high enantioselectivity (*Scheme 19*). Additionally, the same conditions can be applied to chloro- and iodocyclizations where *N*,*N*-dichloro-*p*-nitrobenzenesulfonamide (*p*-NsNCl$_2$) was the chlorine source and *N*-iodosuccinimide (NIS) was the iodine source. He examined the scope of the chlorocyclization using different enones.

Scheme 19:



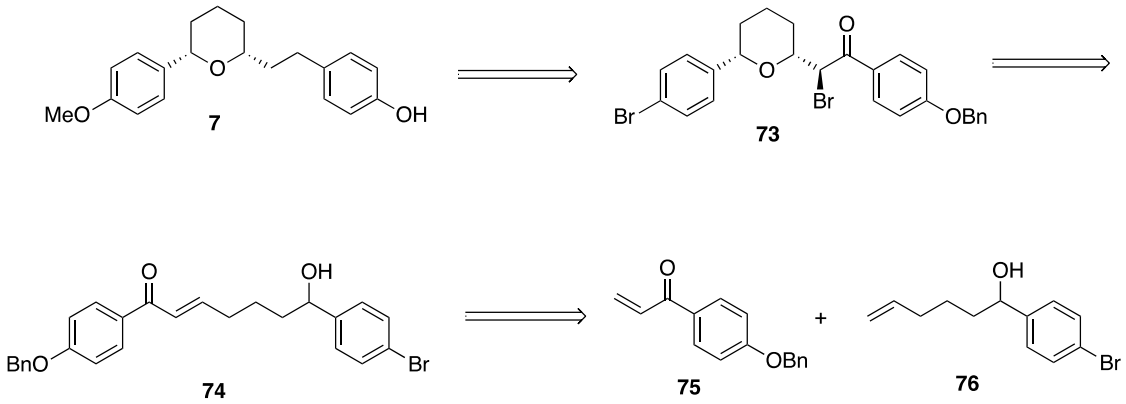
70 **71** **72**

Next, Zhou attempted to use the same conditions to form seven-membered chiral oxepanes. However, the conditions only produced 40% ee for the major isomer. The conditions were optimized again and he discovered that changing the metal from $Fe(acac)_3$ to $Ce(OTf)_3$ and adding *m*-chloroperbenzoic acid as a proton additive greatly improved the enantioselectivity. Again, the scope of the seven-membered chloro- and bromocyclization was investigated.

Once the protocol for intermolecular haloetherification was developed, Zhou began to explore intramolecular haloetherification. The haloetherification would be facilitated from the chalcone and an external alcohol would be the nucleophile. The reaction conditions were optimized and they found the complex L-$RaPr_2$ **68**/$Sc(OTf)_3$ **69** for the catalyst, methanol for the nucleophile, and running the reaction in toluene at 35°C produced the best results. Zhou reported the first asymmetric haloetherification of chalcones using his protocol.

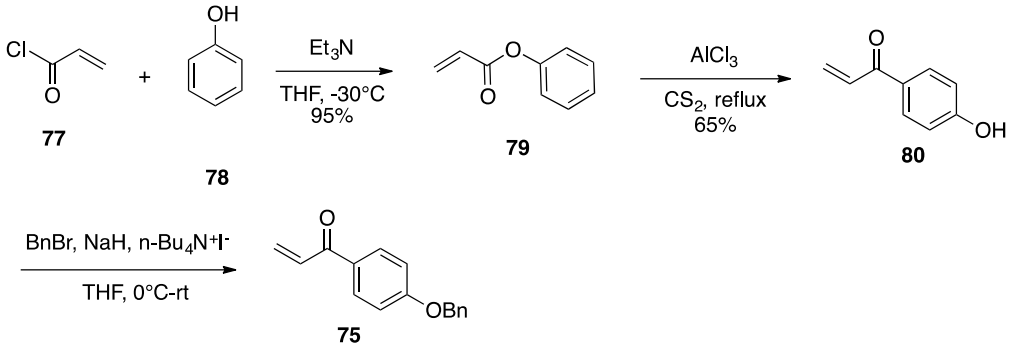
Zhou applied his methodology to the synthesis of (-)-centrolobine **7**. Following his protocol, centrolobine **7** was projected from the tetrahydropyran **73**. Tetrahydropyran **73** would be formed by bromocyclization of the corresponding enone **74** (*Scheme 20*). The enone **74** was produced by the cross-metathesis reaction of α,β-unsaturated ketone **75** and alcohol **76**.

Scheme 20:



Formation of α,β-unsaturated ketone **75** could proceed by treatment of *p*-hydroquinone **78** with acryloyl chloride **77** to form phenyl acrylate **79** based on literature procedures.[39] Reacting phenyl acrylate **79** with aluminum chloride at reflux formed alcohol **80**, which also could be completed by literature procedures.[40] Subsequent protection of the hydroxyl on alcohol **80** would produce the desired α,β-unsaturated ketone **75**.

Scheme 21:



Formation of alcohol **76** could proceed by reduction of acetate **81** with lithium aluminum hydride (*Scheme 22*) to form alcohol **82** following literature procedures.[41] Oxidation of alcohol **82** with 2-iodoxybenzoic acid **83** would produce aldehyde **84**, also based on literature procedures.[42] Subsequent Grignard reaction of aldehyde **84** formed the desired alcohol **76** following literature procedures.[43]

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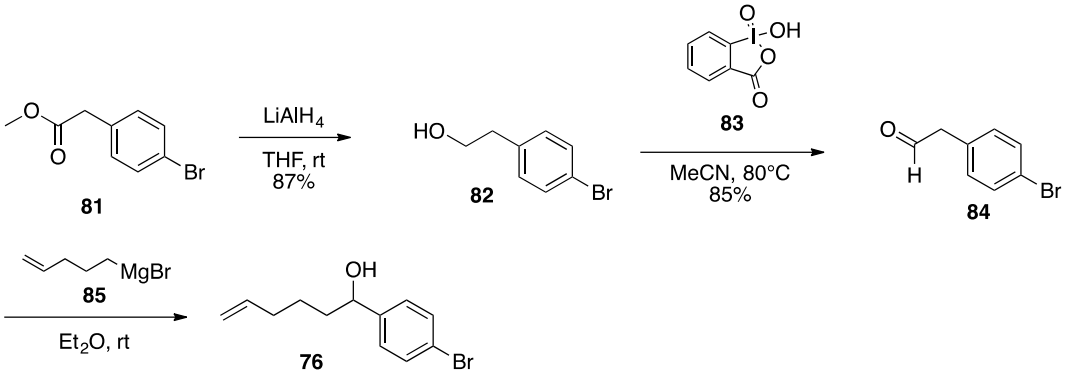
[39] Kim, J. H.; Park, E.-S.; Shim, J. H.; Kim, M.-N.; Moon, W.-S.; Chung, K.-H.; Yoon, J.-S. *J. Agric. Food Chem.* **2004**, *52*, 7480. DOI: 10.1021/jf0499018
[40] Ma, L.; Guo, Y.; Feng, R.; Xiang, P.; Li, C. *J. Chin. Chem. Soc.* **2014**, *61*, 583. DOI: 10.1002/jccs.201300372
[41] Piscitelli, F.; Ligresti, A.; Regina, G. L.; Coluccia, A.; Morera, L.; Allarà, M.; Novellino, E.; Marzo, V. D.; Silvestri, R. *J. Med. Chem.* **2012**, *55*, 5627. DOI: 10.1021/jm201485c
[42] Hesse, S. C. A.; Revelant, G.; Dunand, S.; Kirsch, G. *Synthesis* **2011**, 2935. DOI: 10.1055/s-0030-1261032
[43] Greig, I. R.; Coste, E.; Ralston, S. H.; Hof, R. J. V. T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5548. DOI: 10.1016/j.bmcl.2010.07.055

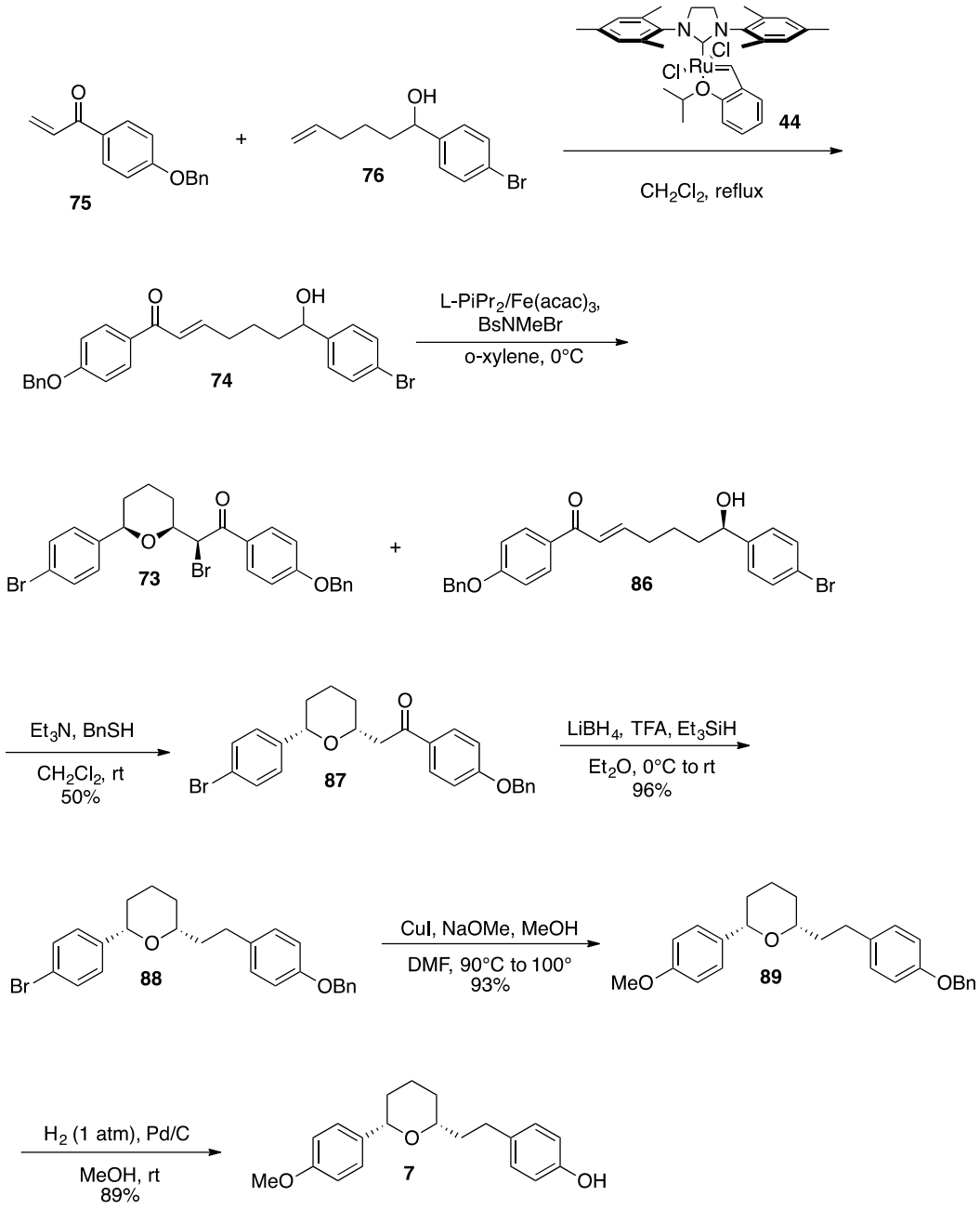
Scheme 22:



Cross-metathesis reaction of α,β-unsaturated ketone **75** and alcohol **76** (*Scheme* 23) formed enone **74.**[44] Enone **74** was treated with 10% $Fe(acac)_3$/L-$PiPr_2$ in the presence of the brominating reagent BsNMeBr to form ketone **73** and (+)-alcohol **86** in >93% and 99% ee, respectively. Ketone **73** was debrominated to form tetrahydropyran **87** in 99% enantiomeric excess after purification. Tetrahydropyran **87** was deoxygenated using $LiBH_4$ to give compound **88**. An Ullman cross coupling of compound **88** yielded compound **89**; deprotection of the benzyl ether provided (-)-centrolobine **7**.

[44] Lu, Y.; Zou, G.; Zhao, G. *ACS Catal.* **2013**, *3*, 1356. DOI: 10.1021/cs4002332

Scheme 23:



Zhou's inter- and intramolecular asymmetric haloetherification provides a useful method to form chiral tetrahydropyrans and oxepanes. The mild reaction conditions and broad substrate

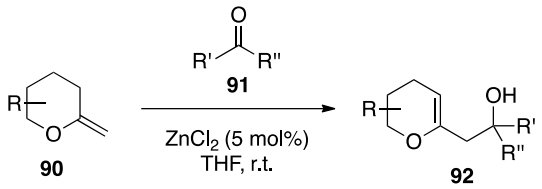
scope make the haloetherification applicable to produce unique tetrahydropyran systems. Additionally, the high yields and good to excellent enantiomeric excess also make the haloetherification reaction even more useful to produce compounds stereoselectively. The application of his reaction towards the synthesis of centrolobine **7** can also be applied to the synthesis of other natural products with a similar tetrahydropyran framework.

The examples included are only a few of the many syntheses of centrolobine **7**. The synthesis of centrolobine **7** can highlight the new and different methods of tetrahydropyran preparation.

III. Carbonyl Ene Reaction of Exocyclic Enol Ethers

The Totah group has demonstrated the use of 2-methylenetetrahydropyrans in the carbonyl ene reaction with aldehydes and electron deficient ketones (*Scheme 24*).[45]

Scheme 24:

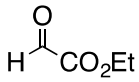
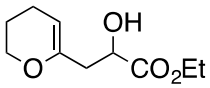
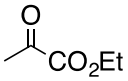
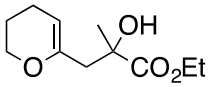
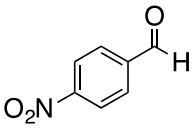
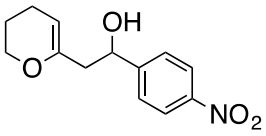
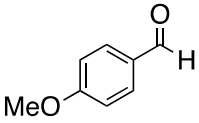
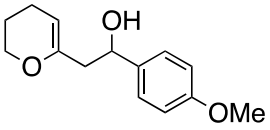
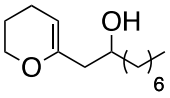
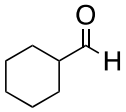
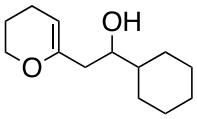
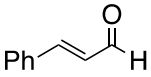
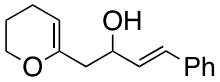
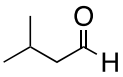
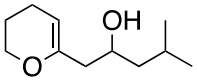


The benefits of the carbonyl ene reaction of exocyclic enol ethers include the mild reaction conditions, the use of catalytic Lewis acid, and high yields ranging from 69-99%. Additionally, broad substrate scope (*Table 1*) allows for the formation of a wide range of tetrahydropyran systems. The reaction works well with both electron rich, as shown by the 95%

[45] (a) Liang, G.; Bateman, L. J.; Totah, N. I. *Chem. Commun.* **2009**, 6457. DOI: 10.1039/b916190b (b) Liang, G.; Sharum, D. T.; Lam, T.; Totah, N. I. *Org. Lett.* **2013**, *15*, 5974. DOI: 10.1021/ol402843s

yield of the reaction with 4-methoxybenzaldehyde **22** and electron deficient aldehydes, as shown by the 90% yield of the reaction with *p*-nitrobenzaldehyde **95**.

Table 1:

Entry	Carbonyl Compound		Product		Yield
1		**93**		**101**	92%
2		**94**		**102**	90%
3		**95**		**103**	90%
4		**22**		**104**	95%
5		**97**		**105**	93%
6		**98**		**106**	85%
7		**99**		**107**	75%
8		**100**		**108**	81%

This methodology provides a direct route for the preparation of substituted tetrahydropyrans, and the results discussed above suggest that this method will be useful for the preparation of tetrahydropyran natural products. Application of this method toward the synthesis of centrolobine is discussed in the following chapter.

Chapter 2

Results and Discussion

I. Synthetic Plan

Previous work in the Totah lab has demonstrated the utility of the carbonyl ene reaction of exocyclic enol ethers for the formation of functionalized pyran deriviatives.[45] Application of this chemistry to the synthesis of centrolobine **7** is outlined below (*Scheme 25*). Formation of the natural product is expected in two steps from alcohol **109**: simultaneous reduction of both hydroxy and alkene groups in alcohol **109** then cleavage of the protecting group on the phenol. In turn, alcohol **109** can be prepared using the carbonyl ene reaction of an exocyclic enol ether. In the key step, the centrolobine framework is derived from two components – an exocyclic enol ether **110** and a suitably protected aldehyde **11.** The exocyclic enol ether can be synthesized from the corresponding lactone **112** via the Petasis reaction.[46] Lactone **112** can be prepared in three steps from commercially available anisole **114** and glutaric anhydride **22**. In this sequence, the desired syn stereochemistry at the C2 and C6 carbons of centrolobine **7** is expected upon reduction of the double bond in alcohol **109**. Attack of the hydride opposite the C6 aromatic side chain will control the sterochemistry at C2.

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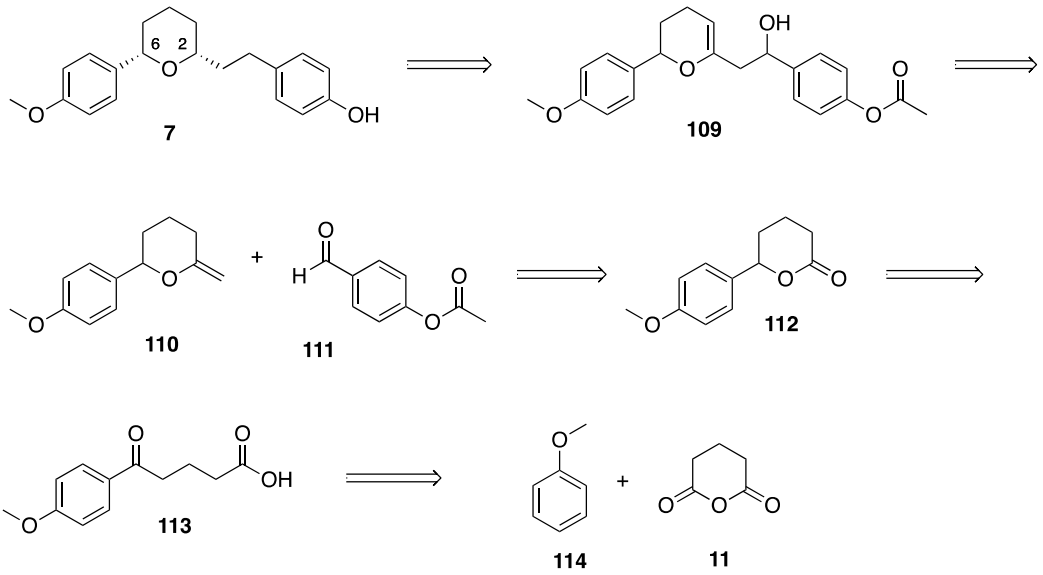
[46] (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, 112, 6392. DOI: 10.1021/ja00173a035 (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, 36, 2393. DOI: 10.1016/0040-4039(95)00320-C

Scheme 25:



II. Lactone Synthesis

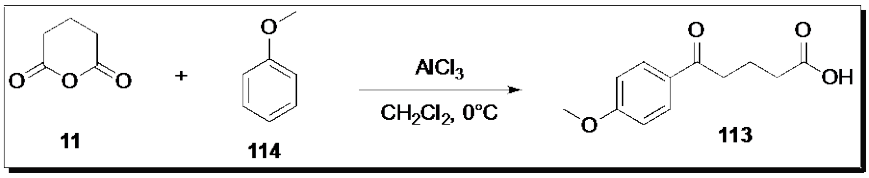
To begin the synthesis of centrolobine **7**, the components for the ene were prepared. First was the synthesis of lactone **112**, prepared in three steps from commercially available glutaric anhydride **22** and anisole **114**.

a. Preparation of the Ketoacid

The first step in the synthesis of lactone **112** was the Friedel-Crafts acylation of glutaric anhydride **22** with anisole **114** to form the carboxylic acid **113**. Following a procedure reported

by Dillard, these reactants were combined in the presence of aluminum chloride and stirred at 0°C.[47] The effect of stoichiometry and reaction time are shown in Table 2.

Table 2:



Entry	Scale	Reaction Time	Acidification Time	Yield
1	5 g	3.5 h	20 mins	104%
2	5 g	3 h	12 h	79%
3	10 g	17 h	10 min	N/A
4	5 g	18 h	30 min	68%

For entry 1, the reaction was completed successfully and after acidification the crude product was isolated. Recrystallization with ethyl acetate was attempted in an effort to purify the compound. However, because the yield of the purified compound was higher than 100% and the melting point, 163-169°C, was higher than the literature reported values of ketoacid **113**, 140-141°C, the desired product was not obtained.[48] Subsequent purifications were completed using ethanol which was the solvent used to recrystallize ketoacid **113** in the procedure.

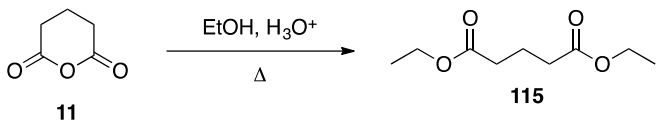
[47] Dillard, R. D.; Hahn, R. A.; Mccullough, D.; Carr, F. P.; Rinkema, L. E.; Roman, C. R.; Fleisch, J. H. *J. Med. Chem.* **1991**, *34*, 2768. DOI: 10.1021/jm00113a014

[48] Cheng, X.; Yang, B.; Hu, X.; Xu, Q.; Lu, Z. *Chem. Eur. J.* **2016**, *22*, 17566. DOI: 10.1002/chem.201604440

In order to obtain larger quantities of starting material, the reaction was run on a larger scale. In one case (entry 3), 10 g of glutaric anhydride was utilized and the reaction stirred for 17 hours, much longer than the previous attempts. After three hours, TLC of the reaction mixture indicated the presence of glutaric anhydride **22**, so the reaction was allowed to continue overnight. Unfortunately, repeated attempts to recrystallize the crude material were not successful; no crystals formed even when the ethanol solution was concentrated or when seed crystals of the pure carboxylic acid **113** were added to in an attempt to induce recrystallization, At this point a small sample of the solution was concentrated via rotary evaporator and a evaluated by ^{1}H NMR. This spectrum showed significant impurities, and carboxylic acid **40** was present only as minor product. This factor prevented it from recrystallizing.

Examination of the original ^{1}H NMR revealed that the crude reaction mixture contained the diethyl ester of glutaric acid **115**. It was suspected that the crude crystals of the carboxylic acid **113** were not rinsed sufficiently during the filtration and still contained both HCl and glutaric anhydride **22**. When hot ethanol was added to recrystallize the product, the residual HCl catalyzed the reaction of ethanol with glutaric anhydride **22** to form the diethyl ester of glutaric anhydride **115** as shown (*Scheme 26*). Attempts to separate the desired carboxylic acid **113** by extraction of this mixture with 5% NaOH were not successful. Efforts to isolate carboxylic acid **113** were ceased.

Scheme 26:



Due to the difficulties encountered in scale-up attempt, the scale of the reaction was reduced to 5 g, and the synthesis attempted for a fourth time (entry 4). The mixture was allowed

to stir in acid for 30 minutes to ensure complete protonation, and the crude crystals were filtered. Drying was continued overnight using the vacuum filtration apparatus. A crude ^{1}H NMR of the resulting product showed no sign of impurities. No recrystallization was necessary, and a 68% yield of pure carboxylic acid **113** was obtained.

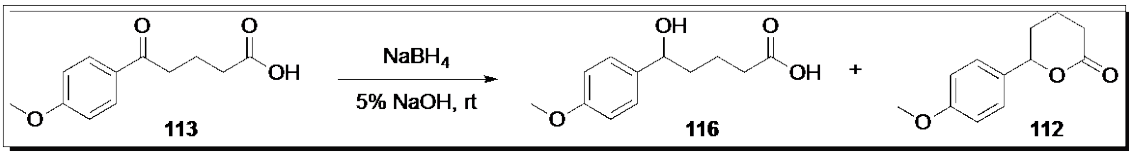
To ensure success of the Friedel-Crafts acylation of glutaric anhydride **22** and anisole **114**, all product must be protonated during the acidic workup. If the reaction is run on a larger scale then the crude product must be washed thoroughly to prevent the formation of by-products during recrystallization. Cold ethanol is crucial during this process to ensure the crude material does not dissolve. Lastly, recrystallization may not be necessary as shown by excellent results in the last experiment (entry 4). Others have reported the preparation and use of carboxylic acid **113** without purification.[49]

b. Ketone Reduction

With preparation of the carboxylic acid **113**, the next step was reduction of the ketone functional group to the alcohol **116** (*Table 3*). This reaction was based on a procedure reported by Chiappe for the synthesis of 6-phenylvalerolactone.[50]

[49] McCalmot, W.F. *Bioorg. Med. Chem.* **2005,** *13*, 3821. DOI: 10.1016/j.bmc.2005.03.004
[50] Boschi, A.; Chiappe, C.; De Rubertis, A.; Ruasse, M.F. *J Org. Chem.* **2000**, *65*, 8470. DOI: 10.1021/jo000799x

Table 3:



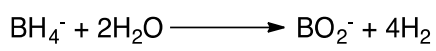
Entry	Scale	$NaBH_4$	Reaction Time	% Yield Alcohol	% Yield Lactone
1	0.5 g	1.8 eq	48 h	17%	1%
2	2 g	1 eq	24 h	21%	1%
3	1 g	4 eq	45 h	36%	4%
4	0.5 g	3 eq	48 h	92%	5%
5	2 g	3 eq	48 h	83%	8%
6	1.4 g	2 eq	40 h	62%	32%
7	5 g	2 eq	48 h	81%	12%

Following the procedure, the ketoacid **113** was dissolved in 5% NaOH then 1.2 equivalents of $NaBH_4$ was added (entry 1). Normally, sodium borohydride reductions are conducted in ethanol. However, the carboxylic acid **42** is not very soluble in this solvent. In order to adjust, the reaction is run in 5% NaOH in water. The sodium hydroxide deprotonates

carboxylic acid **113**, and the resulting sodium salt dissolves in the aqueous solution. The reaction stirred at room temperature for 24 hours and after checking the reaction by TLC, there was still a large amount of starting material present. An additional 0.6 equivalents of $NaBH_4$ was added and stirred at room temperature for an additional 24 hours. The mixture was acidified and extracted immediately after using CH_2Cl_2. The crude ^1H NMR showed the presence of both alcohol **116** and lactone **112**. These compounds could be separated by column chromatography, and recovered alcohol **116** in 17% yield and lactone **112** in 1% yield.

Initially, the reduction of carboxylic acid **113** was quite troubling; the yields reported were at best 22% and a large amount of starting material was present even after 48 hours of reaction time (entries 1,2). One contributor to the poor yields could be the hydrolysis of $NaBH_4$. Since the reaction must be run in 5% NaOH, some $NaBH_4$ hydrolyzes to form hydrogen gas and oxido(oxo) borane as shown in Scheme 27.[51]

Scheme 27:



To accommodate for the possible hydrolysis of sodium borohydride, the amount of reagent used was increased. In entry 1, additional $NaBH_4$ was added after 24 hours because TLC did not show completion. In entry 2, after 24 hours the reaction showed completion by TLC so additional $NaBH_4$ was not added. In entry 3, excess $NaBH_4$ was used at the start of the reaction and was added after 24 hours because TLC did not show completion.

[51] Schlesinger, H. I.; Brown, H. C.; Finholt, A. E.; Gilbreath, J. R.; Hoekstra, H. R.; Hyde, E. K. *J. Am. Chem. Soc.,* **1953**, *75*, 215. DOI: 10.1021/ja01097a057

Another step to ensure the reduction of all of carboxylic acid **40** was to use vigorous stirring. Even though carboxylic acid **113** will dissolve in 5% NaOH, it does so slowly. With gentle stirring, some of carboxylic acid **113** remained stuck on the side of the flask where it cannot be reduced. By using a larger flask for the reaction, more vigorous stirring can be accomplished so that all of the starting material can be dissolved.

When sodium borohydride was added to the aqueous reaction mixture, the hydrogen gas that formed caused the mixture to bubble slowly. Over time, these bubbles formed a foam above the reaction solvent that contained some carboxylic acid **113**. When trapped in this foam, the carboxylic acid could not be reduced, as it was not in solution.

This problem was addressed in two ways in the next reaction (entry 3). First, the use of a larger flask with more vigorous stirring helped to break up the foam and re-dissolve the carboxylic acid. Second, adding sodium borohydride to the reaction mixture in portions minimized the rate of hydrogen gas formation, and in turn reduced the amount of foam that was formed.

As noted above, incomplete protonation of the carboxylic acid salt during the reaction workup can also lead to poor yields. In the next reaction (entry 3), the following steps were taken to ensure that protonate the carboxylic acid salt **116** was complete. First, the pH of the reaction mixture was checked during workup to be sure enough aqueous Hall was added to acidify the solution. The mixture was then stirred for 30 minutes and the pH checked again. If needed, more acid was added with stirring to be sure that all of alcohol **116** could be recovered from the aqueous layer.

In addition, it was determined that alcohol **116** does not dissolve well in dichloromethane, and that when this solvent was used for extraction, the majority of the product

remained in the aqueous layer. Again in the next reaction (entry 3), the aqueous layer was saturated with sodium chloride to prior to extraction in an attempt to move more of the product into the organic layer. Even with all the measures taken as described above for entry 3, the yields still remained low at 40%.

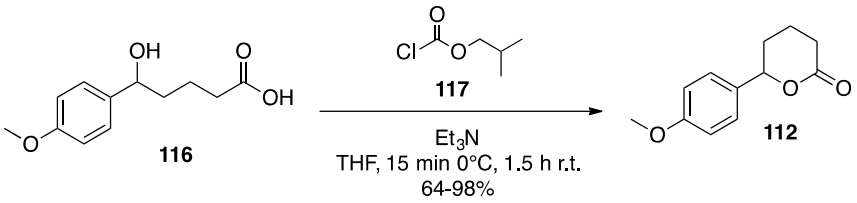
In a final effort to improve the yield of this reaction the choice of extraction solvent was investigated (entry 4). The reduction was set up as described above, but during work up the solvent used in the extraction was changed from dichloromethane to ethyl acetate. Since ethyl acetate is more polar than dichloromethane, it was anticipated that alcohol **116** would dissolve more readily in this solvent. This expectation was confirmed by TLC. After extracting the aqueous layer three times with ethyl acetate, TLC of a small fourth extract confirmed that all of the product **116** had been recovered and the yield improved to 97% yield. Following these adjustments, yields remained high for subsequent reactions (entries 5-7).

Overall, efforts to improve the yield of the reduction of ketoacid **113** were extremely successful. Adding an excess of $NaBH_4$ at the beginning of the reaction and additional after 24 hours if needed ensured that all of the starting material can be reduced. Vigorous stirring dissolved all of ketoacid **113** into the reaction mixture and helped break up the foam containing ketoacid **113** that formed upon addition of $NaBH_4$. Changing the extraction solvent from dichloromethane to ethyl actetate extracted all of alcohol **116** from the aqueous reaction mixture, which greatly contributed to the improved yields.

c. Cyclization of the Ketoalcohol

The cyclization of alcohol **116** to lactone **112** *(Scheme 28*) was conducted based on a procedure published in a patent by Sato in 1998.[52] In that report, 4-(4-methoxyphenyl)butyric acid was cyclized to γ-(4-methoxyphenyl)-γ-butyrolactone. The same reaction conditions were used to cyclize alcohol **116** to lactone **112**.

Scheme 27:



The reaction of alcohol **116** with isobutyl chloroformate **117** proceeded smoothly to form the desired lactone **112**. There were not any issues during this reaction and the conditions were followed exactly as written in the literature every time. Over time, yields for the reaction decreased from 98% to 64%. One possibility for the decreased yields could be the age of the reagent isobutyl chloroformate **117**. The use of new reagent would presumably bring yields back to the initial level. Because the lower yields were identified towards the end of the research, this option was not pursued. The reduction ketoacid **113** and the cyclization reaction were able to generate substantial quantities of lactone **112** for use in subsequent experiments.

II. Preparation of Carbonyl Ene Components

The next stage in the synthesis of centrolobine **7** was preparation of the components for the ene reaction. The exocyclic enol ether **110** was prepared from lactone **112** via the Petasis reaction. Several types of aldehydes were expected to be used; some were commercially

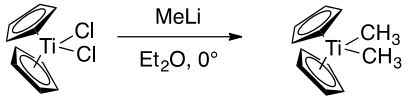
[52] Sato, Y.; Yamada, K.; Nomura, S.; Ishida, R,; Yamamura, M. *Eur. Pat. Appl*. **1998**, *EP 270093 A2***,** 30-31.

available and others were not. The aldehyde needed for centrolobine **7** synthesis was not commercially available and was prepared from 4-hydroxybenzaldehyde **124**. Successful preparation of these components sets the stage for the key step of this synthesis.

a. Synthesis of the Exocyclic Enol Ether

Preparation of the exocyclic enol ether **110** could be achieved by treatment of lactone **112** with dimethyltitanocene **119**, the Petasis reagent.[45] This reagent was named after its founder Nicos Petasis in 1990 and can be used for the methylenation of aldehydes, ketones, α,β unsaturated ketones, esters and lactones. For this sequence the Petasis reagent was prepared according to the method of Clauss and did not pose any difficulties.[53] The preparation of this reagent is shown below in *Scheme 28*.

Scheme 28:

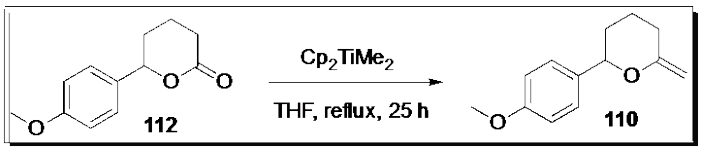


118 **119**

Lactone **112** was then treated with 2 equivalents of Petasis reagent **119** and the resulting mixture warmed to reflux overnight (Table 4, entry 1). Upon cooling, the reaction mixture was diluted with hexanes, then the mixture filtered and concentrated again to give the crude exocylic enol ether **110**. This process was used to remove some of the titanium by-products from the reaction mixture. Exocyclic enol ether **37** is very soluble in hexanes but by-products from the Petasis reagent are not.

[53] Clauss, K.; Bestian, H. *Annalen der Chemie*, **1962**, *654*, 8.

Table 4:

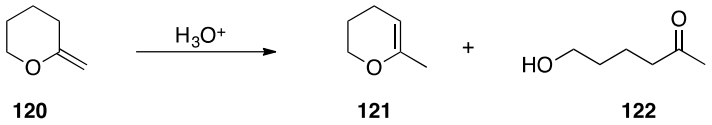


Entry	Scale	Reaction Time	Exo:Endo	% Yield
1	0.1 g	25 h	1:1	45%
2	0.1 g	25 h	13:8	21%
3	0.2 g	25 h	11:10	39%
4	0.2 g	25 h	5:2	31%
5	0.5 g	22 h	9:5	28%
6	0.1 g	25 h	9:2	24%
7	0.2 g	24 h	1:1	36%

In the presence of acid, exocyclic enol ethers **120** are prone to isomerization to give the more stable endocylic enol ether **121**. In the presence of water, hydrolysis may also occur

(*Scheme 29*). For these reasons, some precautions were taken during workup, purification, and characterization of the lactone product **110**.

Scheme 29:

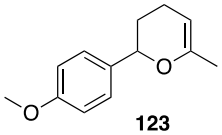


120 **121** **122**

Use of the workup procedure described above minimized the chance of hydrolysis since no water was used in the process. Additional steps were taken in an effort to prevent isomerization from occurring. First, because the silica gel used in column chromatography is slightly acidic, solvents used to pack and elute the product during column chromatography all contained 5% triethylamine. This process deactivates the silica and makes it more basic. Second, the $CDCl_3$ solvent in which the product was dissolved in order to take ^1H NMR spectra was filtered through a plug of basic alumina immediately before use. As a further precaution, the $CDCl_3$ was also removed from the sample *in vacuo* immediately after taking the ^1H NMR.

Unfortunately, the first time the reaction was conducted (entry 1) no triethylamine was included in the solvent used to pack the silica nor to elute the product during purification. As a result most of the product isolated was the endocyclic enol ether **123** (*Figure 5*). A 1:1 ratio of exo to endocyclic enol ethers were isolated in 45% yield. These compounds could not be separated. In addition, both the crude and the pure ^1H NMR spectra showed that a large amount of the reagent by-products remained in the mixture.

Figure 5:



123

In the second attempt to make exocyclic enol ether **110** (entry 2), the basic experiment remained the same, but several modifications were made to the workup procedure. Upon cooling, the reaction mixture was concentrated *in vacuo* to remove THF before the hexanes were added. The crude mixture was then stirred in hexanes for 20 minutes at room temperature, then filtered through a celite pad and concentrated again. This process greatly diminished the amount of titanocene material remaining in the crude product based on the ^{1}H NMR. Upon purification by column chromatography, which included the use of triethylamine, exocyclic enol ether **110** and endocyclic enol ether **123** were isolated in a 13:8 ratio and 21% yield.

The third attempt at the reaction (entry 3) was completed on a larger scale to prepare sufficient material for the ene reaction. The reaction set up was followed as described above and the crude ^{1}H NMR showed no indication of isomerization. However due to the length of time the compound spent in the column during the purification process, the pure ^{1}H NMR revealed a 11:10 ratio of exocyclic enol ether to end cyclic enol ether. In subsequent reactions (entries 4-5) a faster airflow was used during purification, which increased the ratio of exocyclic enol ether to endocyclic enol ether.

At the fourth attempt in the reaction (entry 4), rather than letting the crude mixture stir in hexanes for 20 minutes at room temperature, after dilution with hexanes the mixture was allowed to sit in hexanes overnight. This process also diminished the amount of titanocene material and improved the ratio of exocyclic enol ether to endocyclic enol ether, shown by a 5:2 ratio after purification. This process was not completed in the following reaction (entry 5) and the ratio of exocyclic enol ether to endocyclic enol ether decreased to 9:5.

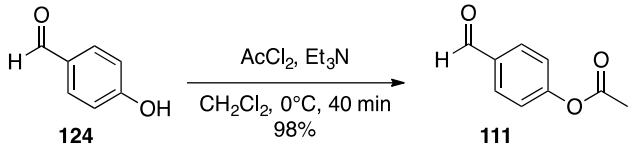
In order to make material suitable for the ene reaction, the column chromatography step was omitted in an effort to reduce isomerization. Removal of the titanocene impurities was

crucial in order for the ene reaction to proceed. The process of diluting with hexanes, sitting in the freezer overnight, and filtering through celite was completed three times. At each step, the amount of hexanes was reduced from 30 mL in the initial dilution to 5 mL in the second and 0.5 mL in the third. Each times hexanes was added to the crude residue, more of the titanocene byproducts precipitated out of the mixture. Using less hexanes for each dilution helped prevent the reagent from re-dissolving into solution. The crude ^{1}H NMR showed very little presence of the titanocene byproducts, though some of the endocyclic enol ether was observed. Nonetheless, enough of the desired product was present that the material could be used in the ene reaction.

b. Protection of the Aldehyde

The second component needed for the ene reaction is a protected *p*-hydroxyl aldehyde derivative. The hydroxyl group needed to be protected to prevent side reactions during the ene reaction. The acetate group was chosen because it would be stable to the conditions of the ene reaction. The desired aldehyde was synthesized from 4-hydroxybenzaldehyde (*Scheme 30*) following a literature procedure by Schmidt.[54]

Scheme 30:



[54] Schmidt, B.; Elizarov, N.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* **2013**, *11*, 3674. DOI: 10.1039/c3ob40420j

4-hydroxybenzaldehyde **124** was reacted with acyl chloride and triethylamine at 0°C for 40 minutes to produce the desired protected aldehyde **111**. The crude mixture was purified through a silica plug to isolate aldehyde **111** in a 98% yield.

Once *p*-acetoxybenzaldehyde **111** was prepared, all the components for the key step in the synthesis of centrolobine **7** were ready.

III. Attempted Ene Reactions

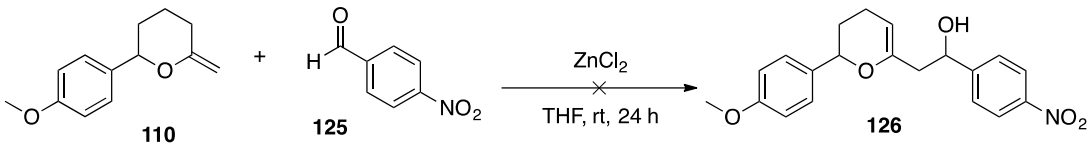
With the preparation of both the exocyclic enol ether **110** and a suitably protected aldehyde **111**, the next step was the carbonyl ene; the key step in this synthesis. Successful execution of this step would provide the final carbon framework of centrolobine from exocyclic enol ether **110**. Both commercially available p-nitrobenzaldehyde **125** and *p*-acetoxybenzaldehyde **111**, prepared as described above were evaluated in this reaction. While the product of the first reaction could not readily be converted to centrolobine **7**, it was of interest for the preparation of centrolobine analogs. Both reactions were conducted according to the procedure published by Totah.[45]

a. Ene Reaction with *p*-Nitrobenzaldehyde

The reaction of exocyclic enol ether **110** with *p*-nitrobenzaldehyde **125** was first explored (*Scheme 31*). Exocyclic enol ether **110** that had been purified by column chromatography was used. The reactants were combined in THF, followed by addition of catalytic $ZnCl_2$. During the workup, the reaction mixture was concentrated directly without aqueous workup. Though *p*-nitrobenzaldehyde **125** had previously been used successfully in ene reactions of this type, the

crude ^{1}H NMR showed no indication that the desired product had formed; only peaks corresponding to *p*-nitrobenzaldehyde **125** were observed.

Scheme 31:

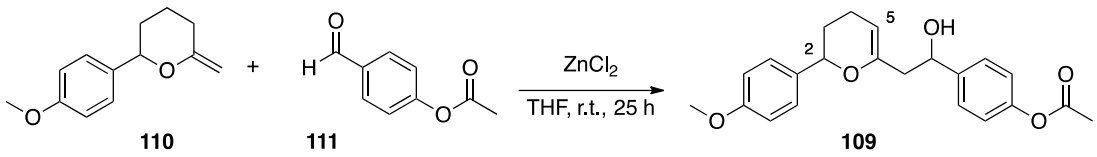


Several factors may have contributed to the failure of this reaction. First, since the exocyclic enol ether **110** was purified by chromatography, it was possible that the compound had isomerized to endocyclic enol ether **123** prior to the attempted ene reaction. Previous work in the Totah lab has shown that endocyclic enol ethers do not participate in this reaction. In addition, the reaction was carried out on a very small scale. In this situation the presence of even trace amounts of water could result in the formation of some HCl and facilitate isomerization or even hydrolysis of the exocyclic enol ether **110**.

b. Ene Reaction with *p*-Acetoxybenzaldehyde

In a second attempt the ene reaction was conducted using crude exocyclic enol ether **110** and *p*-acetoxybenzaldehyde **111** (*Scheme 32*). As before, these reactants were combined, treated with catalytic $ZnCl_2$ and allowed to stir at rom temperature overnight. Unlike in the previous reaction, one drop of triethylamine was added to the reaction mixture prior to concentration in order to neutralize any HCl that might form.

Scheme 32:



110 111 109

Though only a small quantity of material was isolated after column chromatography, the ^{1}H NMR was promising, showing peaks that could correspond to the hydrogens at C2 and C5 of alcohol **109**. Though at the point synthesis of this advanced intermediate cannot be confirmed unequivocally, the reaction looks promising and provides a basis for further optimization. Key to the success of this process will be the ability to generate quantities of the exocyclic enol ether **110** without isomerization.

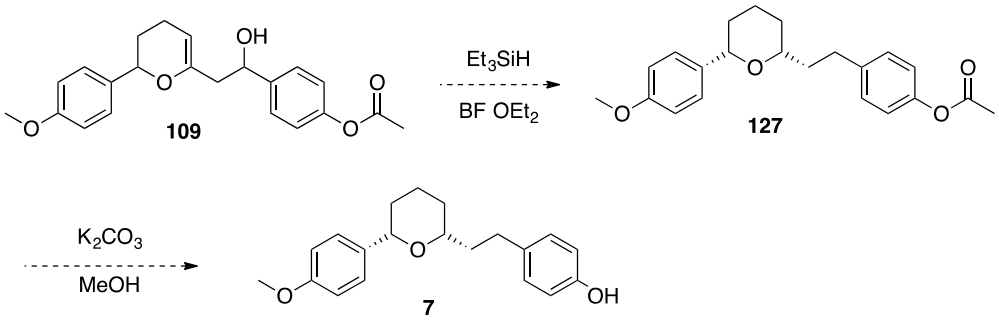
VI. Conclusion and Future Work

Overall, significant steps were taken towards the complete synthesis of centrolobine **7** via the ene reaction. The Freidel-Crafts acylation of glutaric anhydride **11** and anisole **114** showed to be an effective method to produce carboxylic acid **113**. The reaction conditions of the sodium borohydride reduction to form alcohol **116** were optimized to improve the overall yield from 18% to 97%. A good method was discovered to prepare lactone **112** with few complications. Though the results of the formation of exocyclic enol ether **110** obtained improved significantly over the course of these studies, more work is needed to fully optimize the reaction conditions and to prevent isomerization. Lastly, the ene reaction of exocyclic enol ether **110** with aldehyde **111** showed some promise, and paves the way for additional work.

Once the ene reaction is optimized, reduction of both the double bond and hydroxyl group in alcohol **109** is expected to give tetrahydropyran **127** (*Scheme 33*). The syn stereochemistry is expected because of the steric hinderence from substituent pointing back at

the C2 position, so reduction will proceed from the front of the molecule. Finally, removal of the acetate in under basic conditions will give centrolobine **7**.

Scheme 33:



This route is readily modified for the preparation of centrolobine analogs. Use of different aromatic compounds during the Friedel-Crafts acylation or different aldehydes in the ene reaction would lead to side chain analogs of centrolobine **7**. Because the 2,6 disubstituted tetrahydropyran framework appears in a number of molecular frameworks, this synthetic plan could potentially be applied to the synthesis of other natural products. Though more time is needed to complete the synthesis of centrolobine **7** by this route, the ene reaction of exocyclic enol ethers remain a viable key step for the synthesis of this and related compounds.

Chapter 3

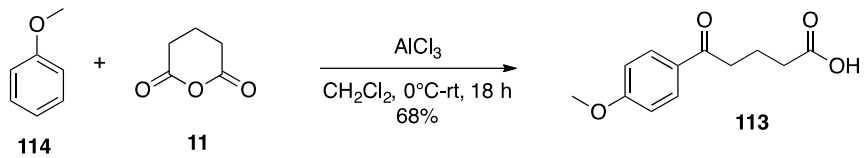
Experimental

General Methods:

All air sensitive reactions were performed in oven dried glassware under an argon atmosphere. Reaction solvents were dried over CaH_2 (dichloromethane) or sodium/benzophenone ketyl (tetrahydrofuran, diethyl ether) and were distilled just prior to use. Zinc (II) chloride was fused under vacuum immediately prior to use, then dissolved in anhydrous THF to prepare a solution of known concentration. All other reagents were reagent grade and

purified as necessary. Analytical thin layer chromatography was performed on EM silica gel F_{254} glass plates (0.25 mm). Melting points were recorded using an Electrothermal melting point apparatus and are uncorrected. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) from SiliCycle, Inc. ^{1}H NMR spectra were recorded on a Bruker Advance DPX-300 or ASCEND-400 spectrometers. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CDCl_3$ (δ 7.27 ppm) as the internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (75 MHz) or ASCEND-400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CDCl_3$ as the internal standard (δ 77.0 ppm). IR spectra were obtained with a Thermo Nicolet IR-100 spectrometer on NaCl plates. Elemental analyses were performed on a Costech ECS 4010 elemental analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50°C. High resolution mass spectra were obtained using the positive ion electrospray mode on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source at Old Dominion University, Norfolk, VA. Optical rotations were measured at the sodium D line (589 nm) on a Rudolph Research Analytical Autopol III polarimeter in reagent grade solvent.

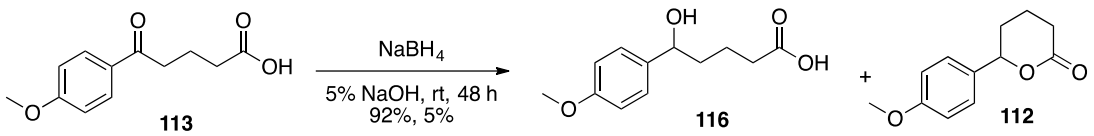
Experimental Procedures:



114 11 113

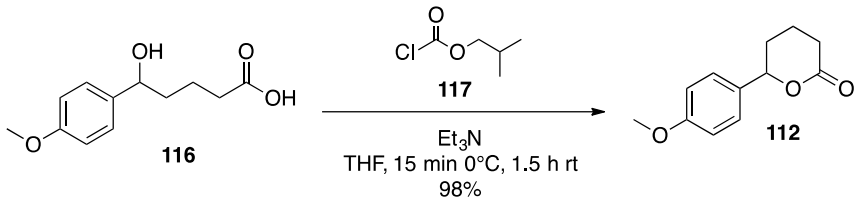
5-(4-methoxyphenyl)-5-oxopentanoic acid 113: A mixture of 5.00 g of glutaric anhydride **11** (0.0438 mol) and 7.11 g anisole **114** (0.0657 mol) was dissolved in 110 mL

dichloromethane. The resulting solution cooled in to 0°C in an ice-ethanol bath and then 16.6 g $AlCl_3$ (0.124 moll) was added in portions. The reaction stirred in the ice-ethanol bath and warmed for 3 hours to room temperature then stirred at room temperature for an additional 15 hours. The reaction mixture was poured into 200 mL of 20% HCl and stirred for 20 minutes. The crude crystals were collected via vacuum filtration and dried on the filtration apparatus overnight to give the ketoacid (6.60 g, 68%) as a white solid (m.p. 140-141°C). The product can be purified further by recrystallization from ethanol. Characterization for this compound was consistent with that found in the literature.[48] TLC: R_f=0.65 (hexanes:EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 Mz): δ 7.97 (2H, d, *J* = 8.8 Hz), 6.96 (2H, d, *J* = 8.8 Hz), 3.88 (3H, s), 3.06 (2H, t, *J* = 14.4 Hz), 2.53 (2H, t, *J* = 14.1 Hz), 2.12 (2H, quint, *J* = 28.4 Hz).

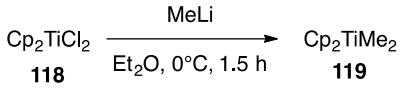


5-hydroxy-5- (4-methoxyphenyl)valeric acid 42: To a solution of 0.50 g carboxylic acid **40** (2.25 mol) in 11 mL 5% NaOH was added 0.17 g $NaBH_4$ (4.5 mmol) in portions with vigorous stirring. After 24 hours an additional 0.08 g $NaBH_4$ (2.25 mmol) was added in portions, and stirring continued for 24 hours more. The reaction mixture was acidified with 10% HCl and stirred for 20 minutes. The mixture was extracted with ethyl acetate (5 mL x 3). The organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified via column chromatography (SiO_2; hexanes:EtOAc, 1:1-1:2) to provide alcohol **116** (0.46 g, 92%) as a colorless oil and lactone **112** (0.02 g, 5%) as a white solid. Characterization for this compound was consistent with that found in the literature.[50] Characterization data for lactone **112** found below. TLC: R_f = 0.09 (hexanes:EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 Mz) δ 7.25 (2 H, d, *J* = 4

Hz), 6.84 (2H, d, *J* = 4 Hz), 5.29 (1H, t, *J* = 16 Hz), 3.78 (3H, s), 2.50 (2H, t, *J* = 16 Hz), 2.00 (4H, m).

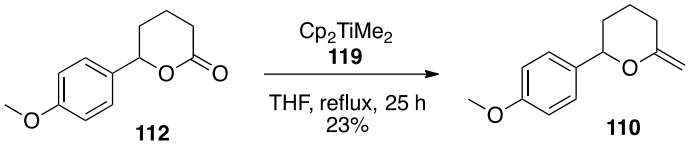


6-(4-methoxyphenyl)tetrahydro-2H-pyran-2-one 39: Alcohol **116** (0.20 g, 0.89 mmol) was combined with triethylamine (0.13 mL, 1.0 mmol) and placed in an ice salt bath and diluted with 4.8 mL THF. The mixture stirred for 10 minutes, then isobutyl chloroformate **43** (0.1 mL, 1.0 mmol) in 0.5 mL THF was added turning the mixture cloudy and stirred for an additional 10 minutes. The mixture was removed from the bath and stirred at room temperature for 90 minutes. The mixture was concentrated *in vacuo*, then 5 mL diethyl ether was added. The mixture was washed with distilled water (5 mL x 3x). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified via column chromatography (SiO_2; hexanes:EtOAc, 2:1-1:2) to provide lactone **112** (0.17 g, 98%) as a white solid (m.p. 61-63°C). TLC: R_f = 0.39 (hexanes:EtOAc, 1:1). Characterization for this compound was consistent with that found in the literature.[55] ^{1}H NMR ($CDCl_3$, 400 Mz) δ 7.30 (2H, d, *J* = 6.4 Hz), 6.92 (2H, d, *J* = 6 Hz), 5.31 (1H, dd, *J* = 4.8, 4.4 Hz), 3.82 (3H, s), 2.60 (2H, m), 2.01 (4H, m).

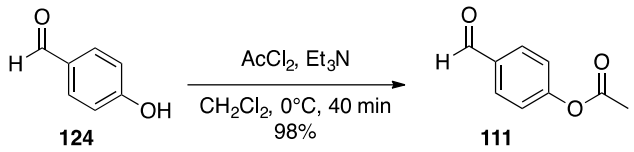


[55] Gupta, S. K.; Sahoo, S. K.; Choudhury, J. *Organometallics* **2016**, *35*, 2462. DOI: 10.1002/chem.201604440

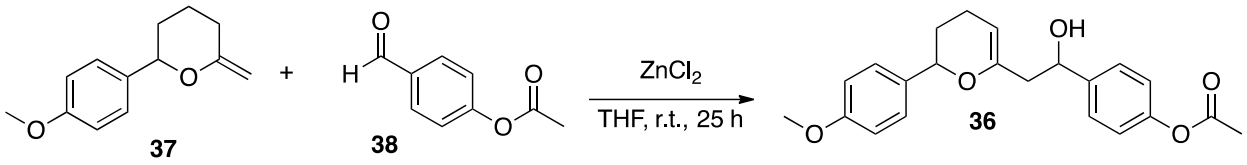
Dimethyltitanocene (Petasis reagent) 119: Titanocene dichloride **118** (1 g, 4.02 mmol) was dissolved in 18 mL diethyl ether and cooled to 0°C. Methyllithium (6 mL, 10.04 mmol, 1.6 M in Et_2O), was slowly added, turning the reaction bright orange. The reaction stirred for 90 minutes then the septum was removed and 20 mL distilled water was added. The organic layer was washed with distilled water (10 mL x 3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to almost dryness. The orange solids were dissolved in 8 mL THF to prepare a solution of 0.5 M.



Exocyclic enol ether 110: Lactone **112** (0.1 g, 0.51 mmol) was dissolved in Petasis reagent solution **119** (8 mL, 4 mmol, 0.5 M in THF). The apparatus and flask were tented with aluminum foil and heated to reflux. The mixture stirred at reflux for 25 hours then cooled to room temperature. The mixture was concentrated *in vacuo* then 30 mL hexanes was added. The mixture sat in the freezer overnight, filtered through celite, and concentrated *in vacuo*. The process was repeated two more times, adding 5 mL hexanes the second time then 0.5 mL hexanes the third time. The crude product was isolated as a yellow oil (0.024 g, 23%) and used without further purification. TLC: R_f = 0.56 (hexanes:EtOAc, 10:1). ^{1}H NMR ($CDCl_3$, 400 Mz) δ 7.32 (2H, d, *J* = 8.8 Hz), 6.94 (2H, d, *J* = 8.4 Hz), 4.58 (1H, dd, *J* = 2.4, 2.4 Hz), 3.81 (3H, s), 2.28 (2H, m), 1.88 (4H, m).



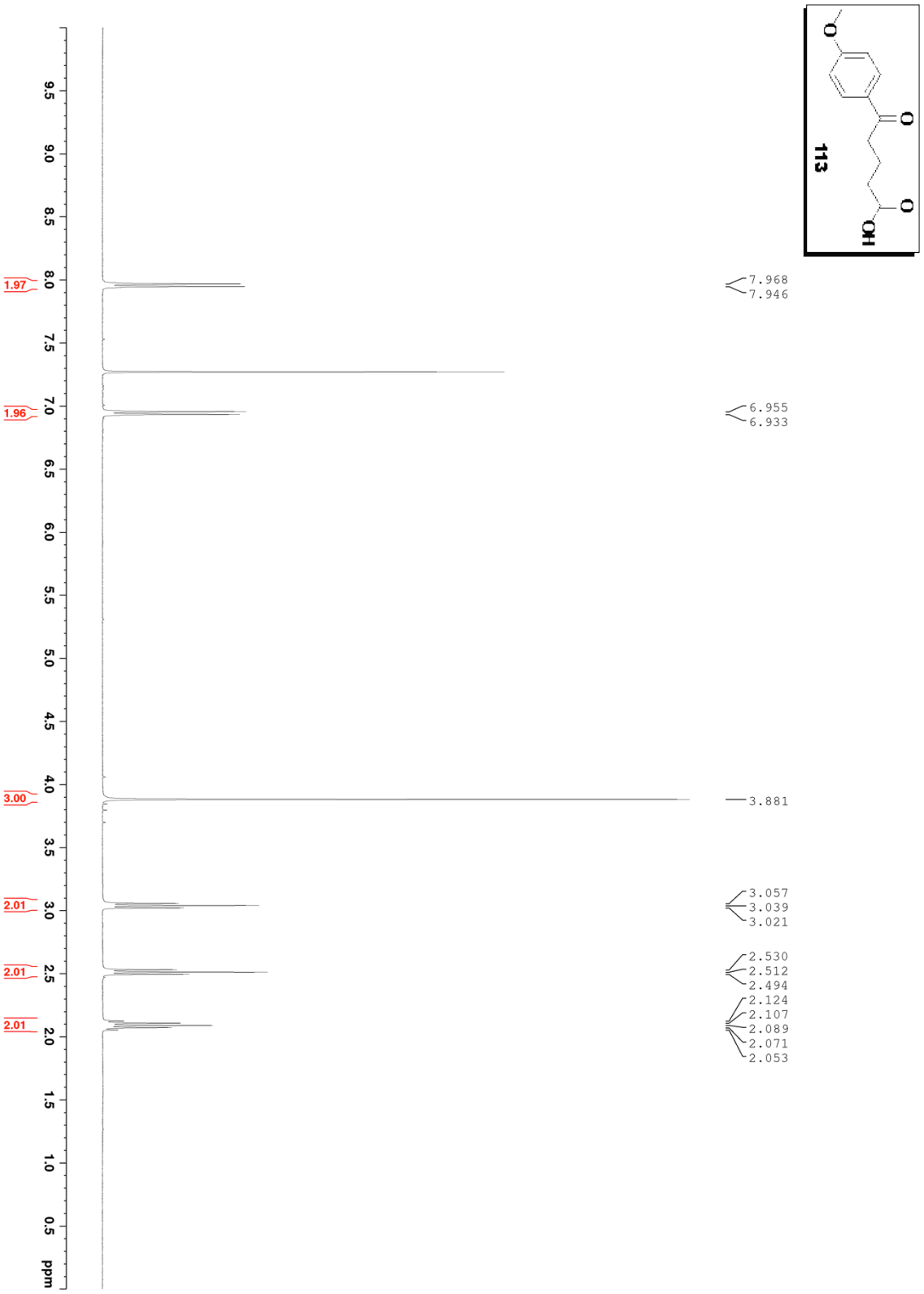
4-acetoxybenzaldehyde 111: Triethylamine (0.6 mL, 4.09 mmol) and 4-hydroxybenzaldehyde **124** (0.5 g, 4.09 mmol) were dissolved in 12.3 mL dichloromethane and cooled to 0°C. Acyl chloride (0.3 mL, 4.09 mmol) was added dropwise and stirred for 40 minutes. The mixture was washed with 20 mL of sodium bicarbonate and the aqueous layer was extracted with dichloromethane (10 mL x 3x). The organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified through a silica plug (hexanes:EtOAc, 4:1) to provide aldehyde **111** (0.55 g, 98%) as a tan liquid. Characterization for this compound was consistent with that found in the literature.[56] TLC: R_f = 0.59 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 Mz) δ 9.97 (1H, s), 7.90 (2H, d, *J* = 8.4 Hz), 7.26 (2H, d, *J* = 8.8 Hz), 2.32 (3H, s).



Alcohol 36: Exocyclic enol ether **110** (0.024 g, 0.117 mmol) and 4-acetoxybenzaldehyde **111** (0.013 g, 0.097 mmol) were combined in 0.2 mL THF. Freshly prepared $ZnCl_2$ solution (0.01 mL, 0.005 mmol, 0.5 M in THF) was added dropwise. The mixture stirred at room temperature for 25 hours then one drop of triethylamine was added. The mixture was concentrated *in vacuo*. The residue was purified via column chromatography (SiO_2; hexanes:EtOAc 5% Et_3N, 4:1) TLC: R_f = 0.31 (hexanes:EtOAc, 2:1).

[56] Gupta, S. K.; Sahoo, S. K.; Choudhury, J. *Organometallics* **2016**, *35*, 2462. DOI: 10.1021/acs.organomet.6b00337

Appendices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6.933
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3.021
2.530
2.512
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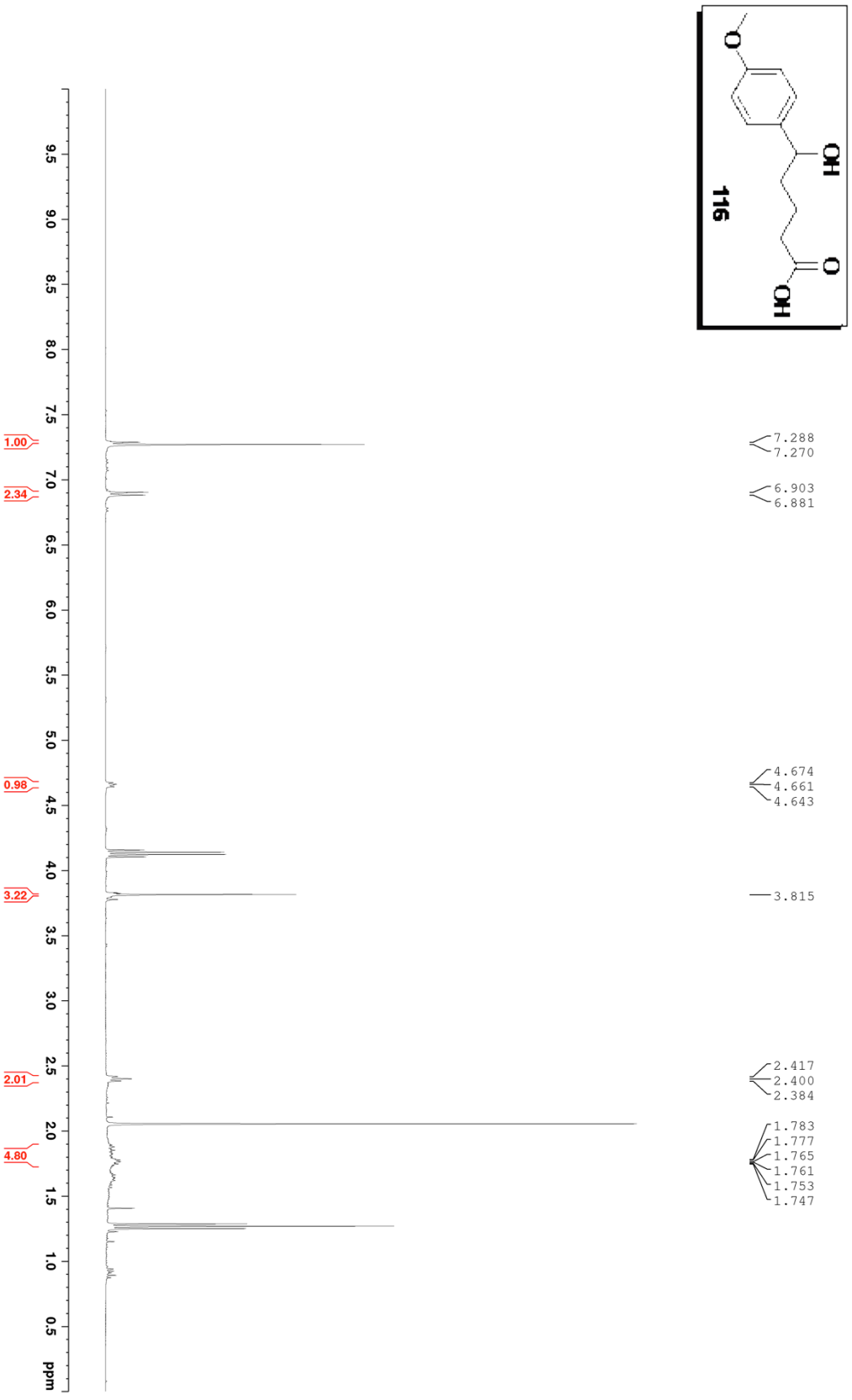
2.107
2.089
2.071
2.053
1.97
1.96
3.00
2.01
2.01
2.01
ppm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1.783
1.777
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1.753
1.747
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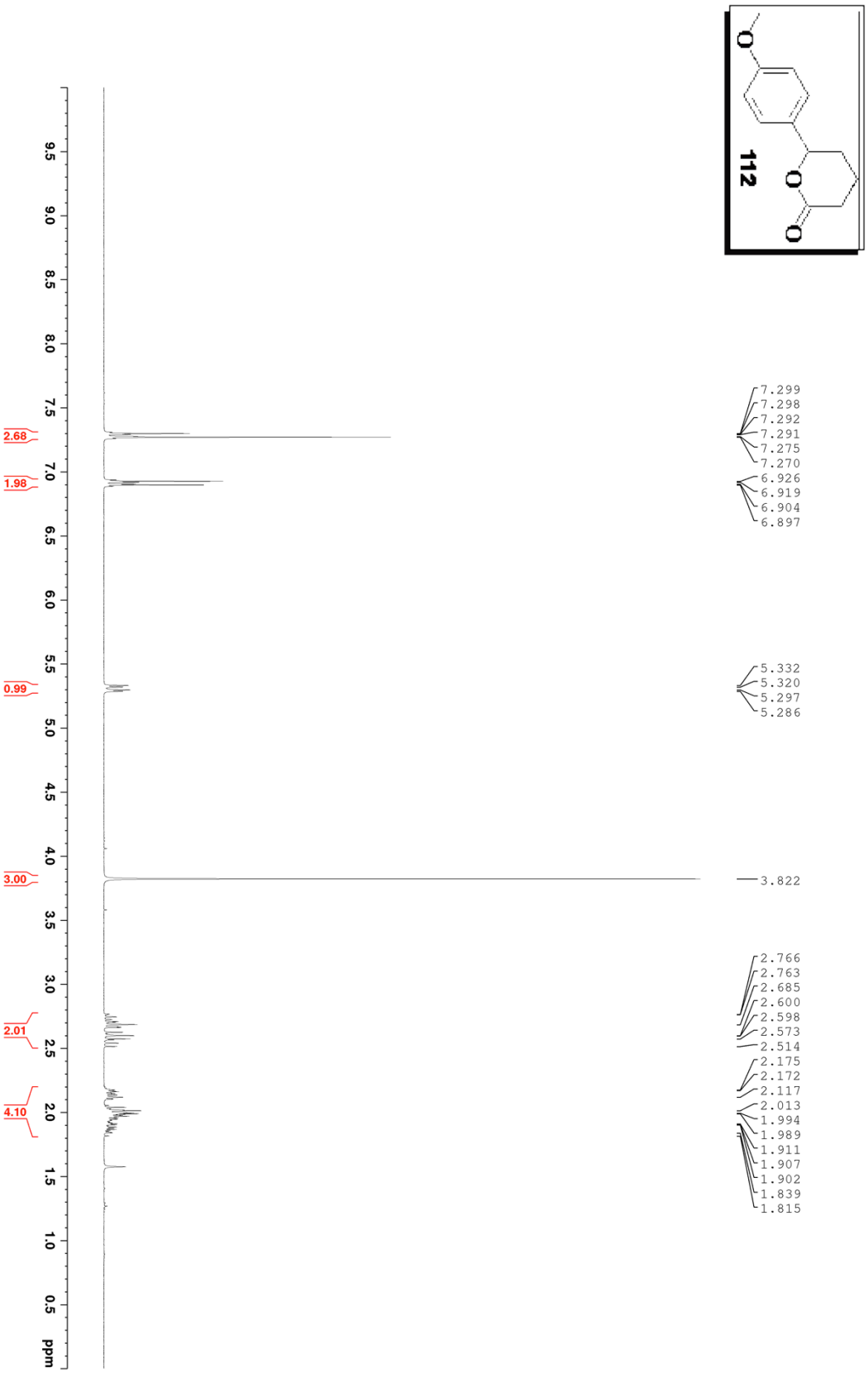
2.34
0.98
3.22
2.01
4.80
ppm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7.270
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6.904
6.897
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5.320
5.297
5.286
3.822
2.766
2.763
2.685
2.600
2.598
2.573
2.514
2.175
2.172
2.117
2.013
1.994
1.989
1.911
1.907
1.902
1.839
1.815
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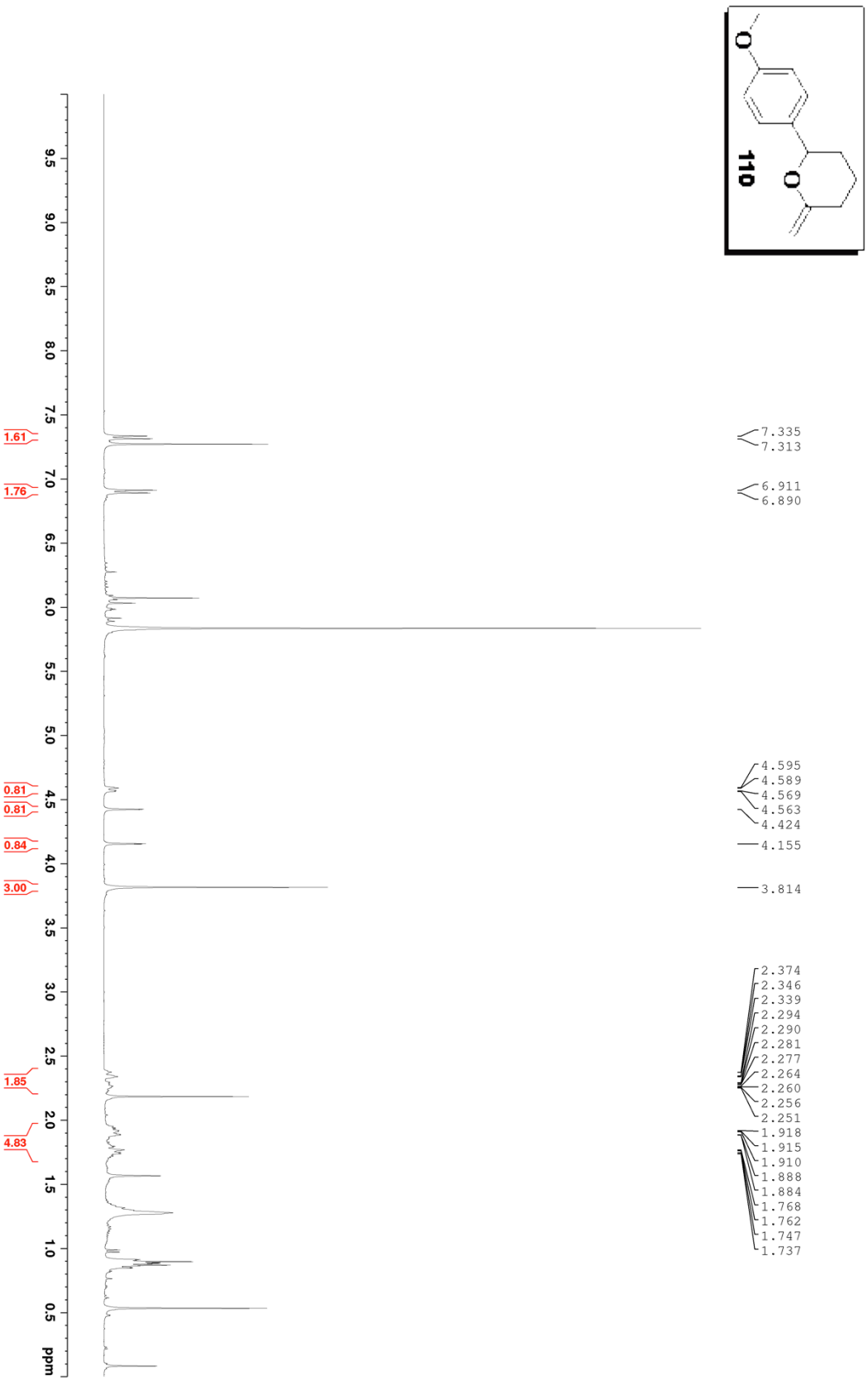
1.98
0.99
3.00
2.01
4.10
ppm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4.569
4.563
4.424
4.155
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2.374
2.346
2.339
2.294
2.290
2.281
2.277
2.264
2.260
2.256
2.251
1.918
1.915
1.910
1.888
1.884
1.768
1.762
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1.61
1.76
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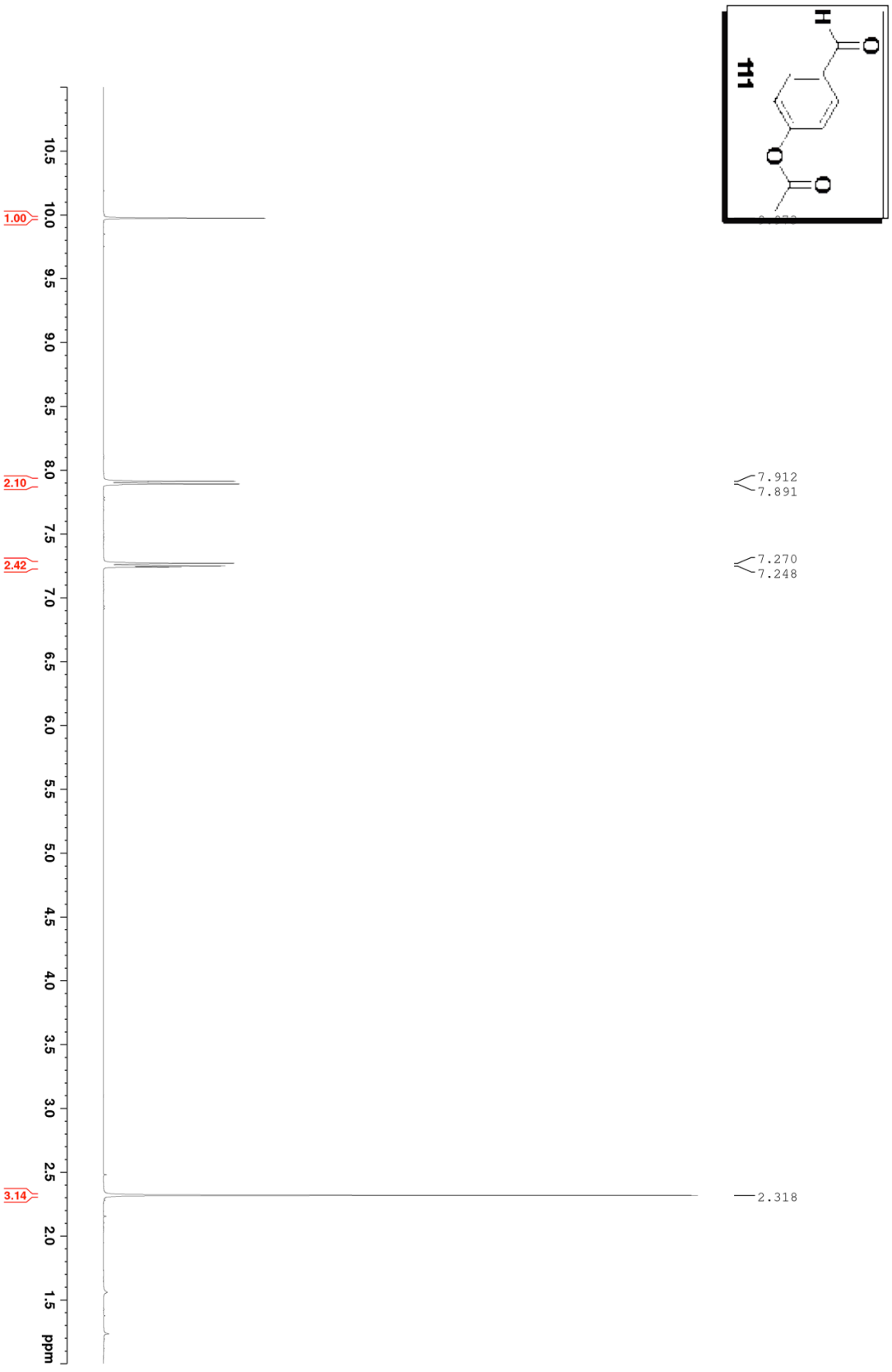
ppm


H
O
O
O
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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
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2.318