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Bakuchiol is a monoterpinoid compound found mainly in the seeds of *Psoralea coryfolia* Linn, which is indigenous to Southeast Asia. Since its discovery and isolation in 1967, it has been reported to contain a multitude of health benefits. It exhibits antitumor, antidiabetic, antimicrobial and recently discovered anti-aging properties. There are multiple ways in which bakuchiol has been synthesized. Research herein used the lactonization of an achiral hydroxydiester as the key step in a series of small molecule manipulations which formed compounds for the future synthesis of bakuchiol. The goal described in this thesis was to create a new synthetic pathway for bakuchiol. The steps included two lactonizations, two ring openings, two protections and subsequent deprotections of alcohol groups, a Horner-Wadsworth-Emmons, and a Grignard reaction. These steps built upon the all carbon quaternary center, which can be installed using the desymmetrization method developed by the Petersen lab, and were used to manipulate the molecule to form the desired bakuchiol precursors. Herein is presented the efforts and methodology developed towards the total synthesis of bakuchiol via small molecule manipulation upon a quaternary center. This pathway may also be of use for the development of various analogs of bakuchiol which may have various medicinal properties.

EFFORTS TOWARDS THE FORMAL SYNTHESIS OF BAKUCHIOL VIA SMALL MOLECULE MANIPULATION

by

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Date of Final Oral Examination

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ABBREVIATIONS

Ac	Acetyl
Aq	Aqueous
BHT	Butylated hydroxy toluene
BINOL	1,1'-binaphthol
Bn	Benzyl
DCM	Dichloromethane
DIBALH	Di-*iso*-butylalumnium hydride
DMAP	4-Dimethylaminopyridine
DMF	N, N-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDG	Electron-donating group
ee	Enantiomeric excess
Eq	Equivalents
EWG	Electron-withdrawing group
EtOAc	Ethyl acetate
LG	Good leaving group
HCl	Hydrochloric acid
HWE	Horner Wadsworth Emmons
im	Imidazole
MABR	Methylaluminum bis(4-bromo-2,6-di(*tert*-butyl)phenoxide
MOMCl	Chloromethyl methyl ether
MsCl	Mesyl chloride
MW	Molecular wieght
NMR	Nuclear magnetic resonance

Nu	Nucleophile
Pf	Protection Factor
Ph	Phenyl
pKa	Acid dissociation constant
PPG	Primary protecting group
pTSA	*para*-Toluenesulfonic acid
RT	Room temperature
SHMDS	Sodium hexamethyl disilazane
TBAF	Tetra-*n*-butylammonium flouride
TBSCl	t-Butyldimethylchlorosilane
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TsCl	Toluenesulfonyl chloride

CHAPTER I

INTRODUCTION TO BAKUCHIOL AND DESYMETRIZATION

1.1 Description

Bakuchiol (**1**), also know as 4-(3-ethenyl-3,7-dimethyl-1,6-octadienyl) phenol, is a phenolic monoterpinoid compound with one chiral center and is the major component of the seeds of *Psoralea coryfolia* L.[1] The plant is a common herbaceous weed found along road sides and in fields in China, India, Burma and Pakistan. It is an annual herb with grooved and gland dotted stems and branches.[2] The leaves are simple green with a broad and elliptically rounded shaped. They are speckled with small black dots and covered with fine white hairs on both sides. The flowers can be a blue purple color or yellow. The fruits of the plant are small, compressed, and pitted in appearance. They are used in traditional folk medicine as a laxative, and for the treatment of leprosy, psoriasis and inflammatory diseases of the skin.[3,4] The seeds are where bakuchiol is found. They are black and brown with a flat oblong shape.[5] The molecule was named after the Sanskrit name (Bakuchi) of the plant. Bakuchiol is a clear colorless liquid. It is soluble in hexane and insoluble in 10 % aqueous NaOH.[6] Figure 1 shows the molecular structure of (+)-bakuchiol.

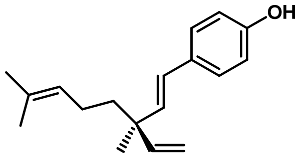

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Figure 1. (+)- Bakuchiol

Since the first discovery of bakuchiol in 1966, it has been found to occur naturally in other plants, such as the leaves of *P. grandulosa* in 1996,[7] *Ottholobium pubescens* in 1999,[8] *P. drupaceae* in 2010,[9] *Ulmus davidiana* in 2010,[10] and *Piper longum* in 2010.[11]

1.2 Medicinal Properties

Bakuchiol has been used in traditional Indian and Chinese medicine to treat a variety of diseases. In 1992, Rangari et. al. discovered that bakuchiol has cytotoxic activity and this has been a main point of study since.[12] In a study done by Haraguchi et. al. in 2000, bakuchiol proved to be effective in protecting mitochondrial functions by preventing lipid peroxidation in mitochondria and inhibiting oxygen consumption. It also protected the mitochondrial respiratory enzyme activities against peroxidation injury.[13]

In 2002, another study was conducted by Haraguchi and coworkers, and it was concluded that *P. coryfolia* contains phenolic compounds that exhibited effectiveness in protecting biological membranes against various oxidative stresses.[14] In 2003, a study was conducted by Jiangning et. al. to determine the antioxidant effects of bakuchiol in lard. The double bond directly next to the phenol extends the conjugation of the molecule and this system helps to stabilize the free radical oxygen after the loss of the hydrogen.

The antioxidant activity of the molecule was found to have a protection factor (Pf) of 3.1 at 0.02 % and 3.8 at 0.04 % in lard at 100 °C. It was suggested that the plant may be a good source of antioxidants if it were to be used as an additive in food.[15]

Another study conducted by Adhikkari et. al. in 2003 confirmed that bakuchiol is a potent antioxidant that inhibits the oxygen consumption of microsomes induced by lipid peroxidation and protects human red blood cells from rupturing (haemolysis).[16]

In 2005, a study was done by Jiangning et. al. to determine the anthelmintic activity of *P. corylifolia* seeds on flatworms and roundworms. It was found that radiolabeling bakuchiol greatly increased the uptake of bakuchiol by cells.[17] Table 1 shows the cell uptake of Iodine labeled bakuchiol in lymphoma cells at various concentrations while Table 2 shows the cell uptake of Iodine labeled bakuchiol in barcl-95 cells at various concentrations.

Table 1. Uptake Studies of ^{125}I-bakuchiol in Lymphoma Cells (37 °C, 30 min)

Concentration of I-bakuchiol (μM)	1.25	2.5	6.25	12.5
% cell uptake	26.5 ± 1	39.5 ±1	40.5 ± 1	41 ± 2
% Blank	2.4 ± .5	1.6 ± .4	1.1 ± .06	1.2 ± .04
Mean ± SD, n=3				

Table 2. Uptake Studies of ^{125}I-bakuchiol in Barcl-95 Cells (37 °C, 30 min)

Concentration of I-bakuchiol (µM)	1.25	2.5	6.25	12.5
% cell uptake	17.6 ± .5	31.6 ± .4	26.4 ± .5	20.2 ± .6
% Blank	0.9 ± .1	0.7 ± .4	1.4 ± .1	1.1 ± .3
Mean ± SD, n=3				

Bakuchiol also exhibits antitumor properties *in vitro*. One study done by Park and coworkers in 2007 found that bakuchiol exhibits antitumor effects in rat livers by inducing apoptosis mitochondria in rat liver myofibroblasts.[18] Another study done on human lung cells (alveolar adenocarcinoma cells) in 2010 by Chen and coworkers showed that bakuchiol induced apoptosis in the mitochondrial signaling pathway.[19]

Bakuchiol exhibits antibacterial activity[20] notably against Staphylococcus *aureus* at only 2-4 µg/mL.[21] In 2001, bakuchiol was tested as an antimicrobial agent against various oral microorganisms. It inhibited growth in no less than eleven various strains of *Streptococcus* tested in sucrose. It was determined that bakuchiol had potential for use in food additives and mouthwash in order to prevent and treat dental cavities. The development of bakuchiol as an antibacterial agent against oral pathogens had great potential.[22]

Bakuchiol has numerous other medical benefits. It exhibits weak anti-inflammatory activity at 10 µM, but is toxic to cells at more than 30 µM.[23] It performed as a beta-site APP cleaving enzyme-1 (BACE-1) inhibitor in vitro.[24] It also exhibits antimutagenic activity[25] and hepatoprotective activity in human liver cells with a dose of only 1.0 μg/ml.[26] It exhibited an antidiabetic affect in rats with type 2 diabetes without affecting lean rats. It reduced blood glucose and triglyceride levels.[27] It has also been shown to be effective against breast cancer.[28]

Recently, a study was undertaken by Chaudhuri et. al. to determine the anti-aging effects that bakuchiol has and the results were compared to retinol (Vitamin A), a well known anti-aging agent used in many cosmetics. A 0.5 % solution of bakuchiol was applied topically twice a day to seventeen test subjects (females ages 40-65 years old) for twelve weeks. While bakuchiol is not structurally similar to retinol, it was found that they affect certain key anti aging genes and proteins the same way. Bakuchiol also has the advantage of being more photochemically and hydrolytically stable than retinol. These findings suggest that bakuchiol could become a key ingredient in dermatological and cosmetic products.[29]

Analogs of bakuchiol have also proven useful. One study done by Cha et. al. concluded that that some of its analogs were effective against tumor cells. One analog of bakuchiol (**2**) in particular (Figure 2) had an ED_{50} of 13.1 μM which, when compared to the ED_{50} of **(+)**-bakuchiol of 36.2 μM, exhibits more of an inhibitory effect on the proliferation of human tumor cells.[30] While this is still considered inactive, other analogs of bakuchiol may be more potent.

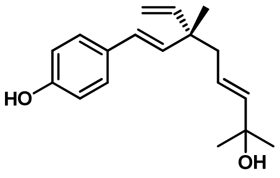

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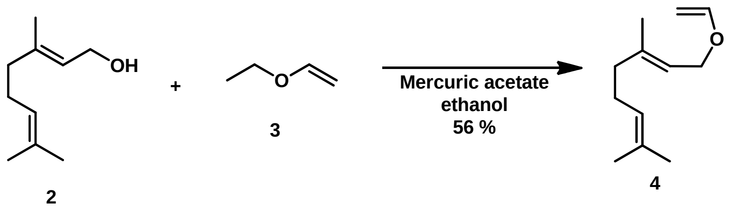
Figure 2. Analog of Bakuchiol

1.3 Previous Synthesis of Bakuchiol

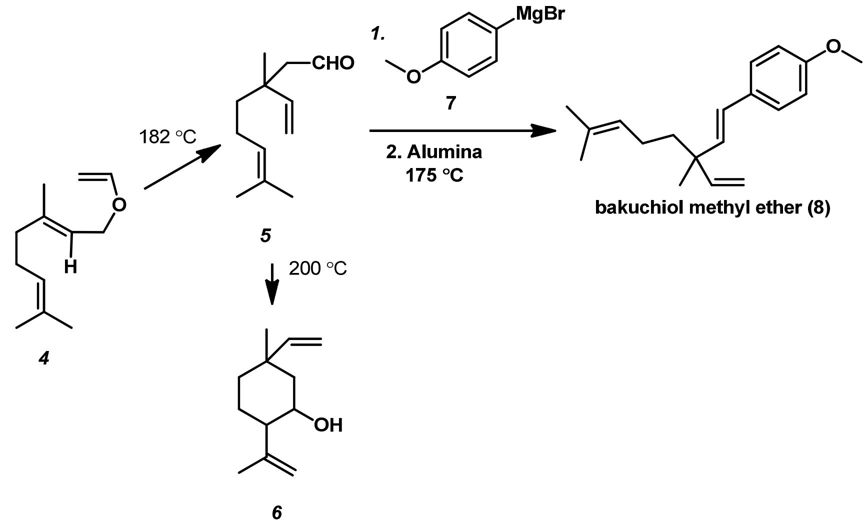
Since its discovery in 1966, Bakuchiol has been synthesized using a number of different strategies. The medicinal properties and broad range of biological activity have made bakuchiol an attractive target for synthesis. The structure is small but contains a phenol, a vinyl group, and one quaternary center along the alkyl chain. The quaternary center has been the most challenging and also the main focus for most of the different synthetic pathways that have been established. The synthesis of bakuchiol has been done racemically and there have been multiple methods of installing the quaternary center.

The first attempt at the synthesis of bakuchiol was done in 1967 by the Dev group and it resulted in bakuchiol methyl ester. It started by reacting geraniol (**2**) and ethyl vinyl ether (**3**) with mercuric acetate as shown in scheme 1 to yield compound **4** in 56 % yield.



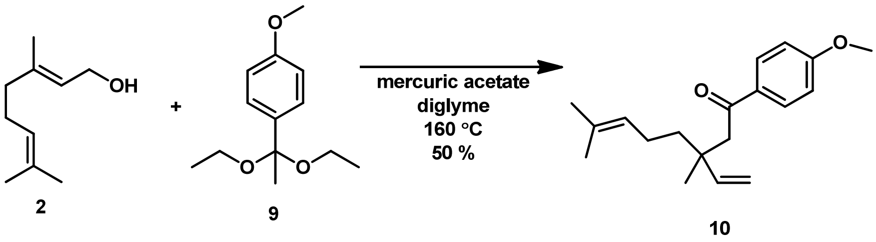
Scheme 1. Geraniol and Ethyl Vinyl Ether

As shown in scheme 2, when **4** was heated at 182 ºC, aldehyde **5** was produced in 90 % yield via a Claisen rearrangement. It is important to note that when **4** was heated at 200 ºC, or aldehyde **5** was heated to 200 °C, alcohol **6** was formed via Ene reaction. Aldehyde **5** was then reacted with phenyl magnesium bromide **7** and dehydrated with alumina at 175 ºC to form the bakuchiol methyl ether (**8**).[31]



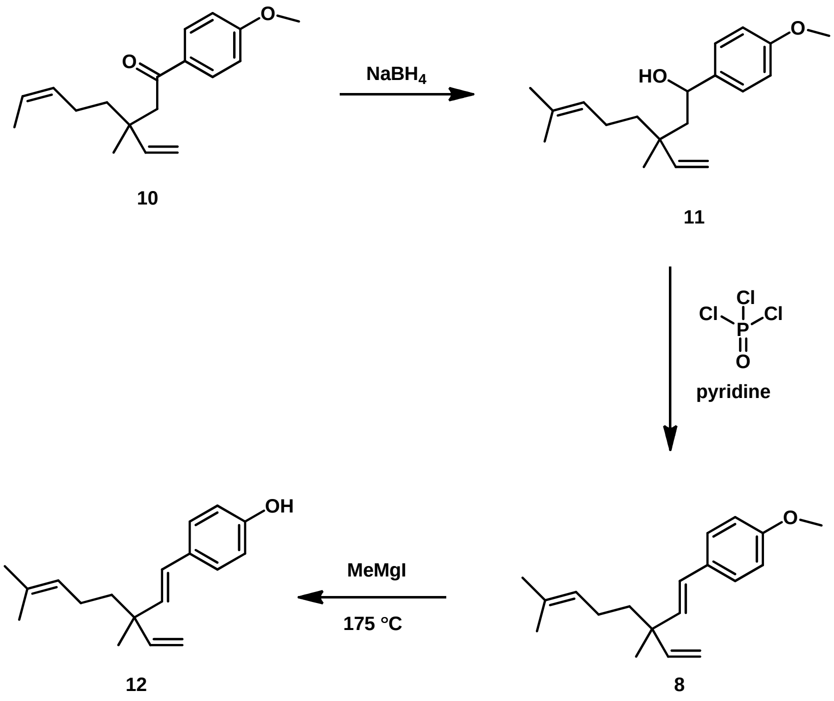
Scheme 2. Claisen Rearrangement to Form Aldehyde then Bakuchiol Methyl Ether

Only ten days later, the first total synthesis of racemic bakuchiol was received by another journal. This synthesis was done by the Miller group and also used geraniol (**2**). The geraniol was heated with *p*-methoxyacetophenone diethyl ketal (**9**) and mercuric acetate in diglyme at 160 ºC to form ketone **10** via Claisen rearrangement with a 50 % yield. This reaction is shown in scheme 3.



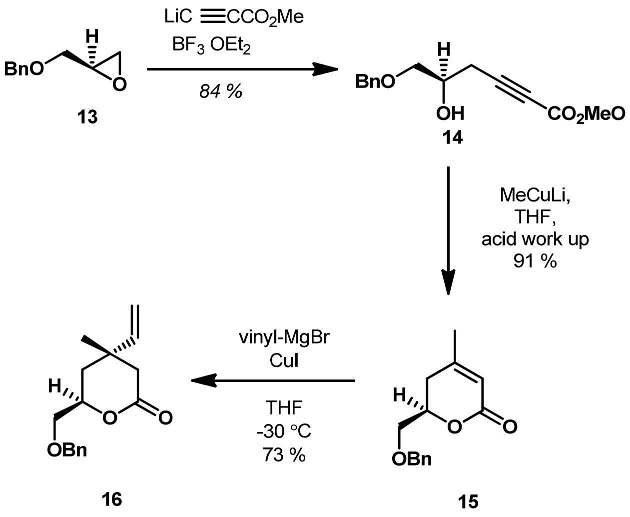
Scheme 3. Geraniol and *P*-methoxyacetophenone Diethyl Ketal to Form Ketone **10**

Ketone **10** was then reduced with sodium borohydride to form alcohol **11**. The alcohol **11** was dehydrated by refluxing phosphorous oxychlorine in pyridine to form the methyl ether **8** in 76 % yield. The ether **8** was then demethylated by heating with methylmagnesium iodide at 175 ºC to form racemic bakuchiol (**12**) as shown in scheme 4.[32]



Scheme 4. Reduction, Dehydration and Demethylation to Form Racemic Bakuchiol

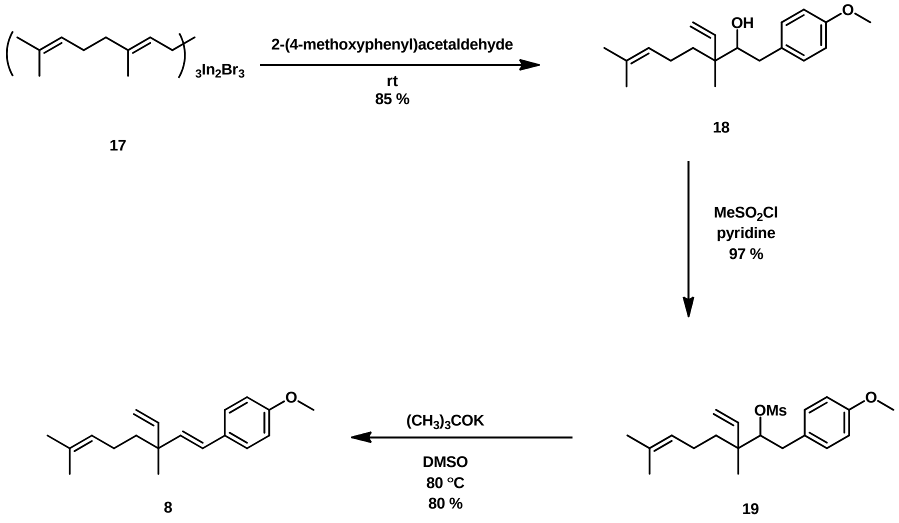
From 1967 to 1990, there were no new syntheses of bakuchiol. This was due to the difficulty of installing the quaternary center at the heart of the molecule. In 1990, the first enantioselective synthesis of **1** was performed by the Ogasawara group (Scheme 5). The synthesis started by treating the chiral starting material (*S*)-O-benzylglycol (**13**) with methyl lithiopropiolate in the presence of boron trifliuoride etherate to form **14** which was then cyclized to form δ-lactone **15**. The key step to form the chiral center of bakuchiol was for the δ-lactone **15** to react with vinylmagnesium bromide in the presence of copper (I) iodide which proceeded in a stereoselective fashion from the stereoelectronically favorable face of the molecule to give the δ-lactone **16** with a quaternary center. This is the quaternary center that makes up the heart of the bakuchiol molecule. The total synthesis of enantioenriched bakuchiol was completed by manipulating the molecule around the chiral center in a total of twelve steps with an overall yield of 16 %.[33] This method required the purchase of chiral starting material to facilitate the establishment of the chiral quaternary center of bakuchiol.



Scheme 5. Ogasawara Method for Chiral Center Insertion

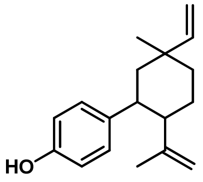
In 1991, another method of synthesizing racemic bakuchiol in 3 steps was developed by Araki and Bustugan, utilizing organometallic chemistry. Geranylindium sesquibromide (**17**) was reacted with 2-(4-methoxyphenyl)acetaldehyde as shown in scheme 6 to form alcohol **18** in 85 % yield. The alcohol **18** was then mesylated with mesyl chloride-pyridine to form mesylate compound **19**.

Potassium *tert*-butoxide was used to treat the crude mesylate (**19**) and gave the methyl ether **8** with an overall yield of 66 %.



Scheme 6. Araki and Bustugan Synthesis of Racemic Bakuchiol Methyl Ester

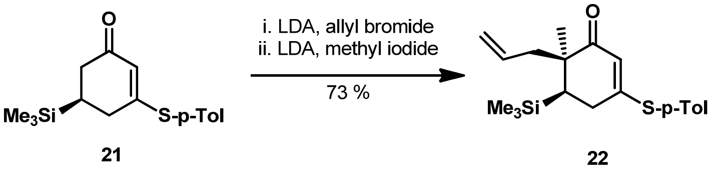
The mesylate **19** was sensitive to silica gel and would cyclize on a column. It was important to note from this synthesis the effects that the acidic conditions of silica gel column chromatography had on molecule **19**, and that bakuchiol is an acid labile molecule. Upon treatment with acid, bakuchiol cyclizes to the p-meth-8-ene derivative **20** (Figure 3).[34]



20

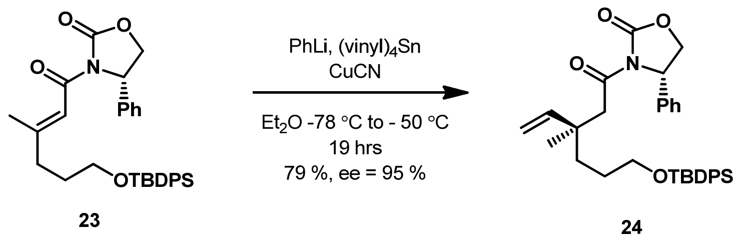
Figure 3. Cyclized Bakuchiol

In 1998, a new synthesis of (+)-bakuchiol (**1**) was developed by the Osaoka group. This method used a silyl group to direct stereoselective alkylation to construct the chiral quaternary carbon center early in the synthetic pathway. Lithium diisopropylamide (LDA) followed by allyl bromide and LDA followed by methyl iodide were reacted with cyclohexenone **21** to yield cyclohexenone **22**. Scheme 7 shows this chiral center being established in **22**. After the chiral center was established, **22** was manipulated over a total of 16 steps to yield (+)-bakuchiol (**1**) with an overall yield of 5 %.[35] This method required the purchase of a chiral starting material. The bulky silyl group acted as a chiral auxiliary to help set the desired stereochemistry in (+)-bakuchiol (**1**).



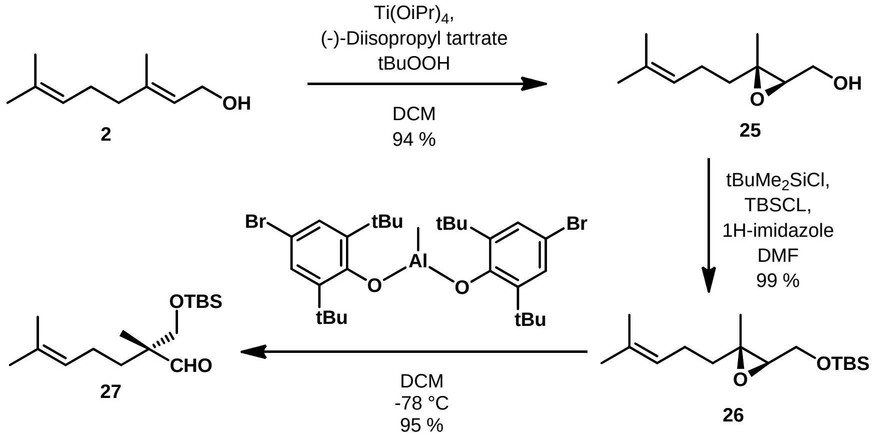
Scheme 7. Stereoselective Addition to Form Quaternary Center

In 2008, (+)-bakuchiol (**1**) was synthesized by the Fukuyama group using vinylcopper(I) reagents. Chiral Michael acceptor **23** was added to the copper lithium reagent made from vinyl tin in a diastereoselective manner to create the quaternary carbon center in **24** (Scheme 8). This method led to the total synthesis of (+)-bakuchiol with an overall yield of 20 % over ten steps.[36] This method required the purchase of chiral phenyl oxazolidinone auxiliary to form **23** and 1.9 equivalents of toxic (vinyl)$_4$Sn to set the desired stereochemistry. The asymmetric addition yielded the desired *R* enantiomer of **24** in a ratio of 95:5 with the less favored *S* enantiomer of **24** giving an enantiomeric excess (ee) of 90 %.



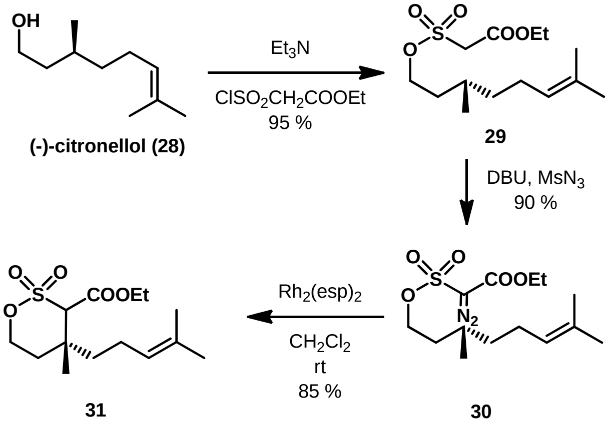
Scheme 8. Fukuyama Method of Establishing Chiral Center via Michael Addition

Independently, in 2008 the Li group synthesized (+)-bakuchiol (**1**) also in ten steps, with an increased yield of 51 %. This same group synthesized the non natural (*R*)-enantiomer of bakuchiol in 9 steps with an overall yield of 40 %.[37] The key steps in establishing the stereoselective center started off with geraniol (**2**) treated with Sharpless epoxidation reagents to form **25**. The molecule was then protected with a TBS group to form **26** followed by a rearrangement of the silyl ether to form **27** (Scheme 9). This method was done using a racemic starting material and only required 13 mole percent (-)-diisopropyl tartrate and only 5 mole percent $Ti(OiPr)_4$.



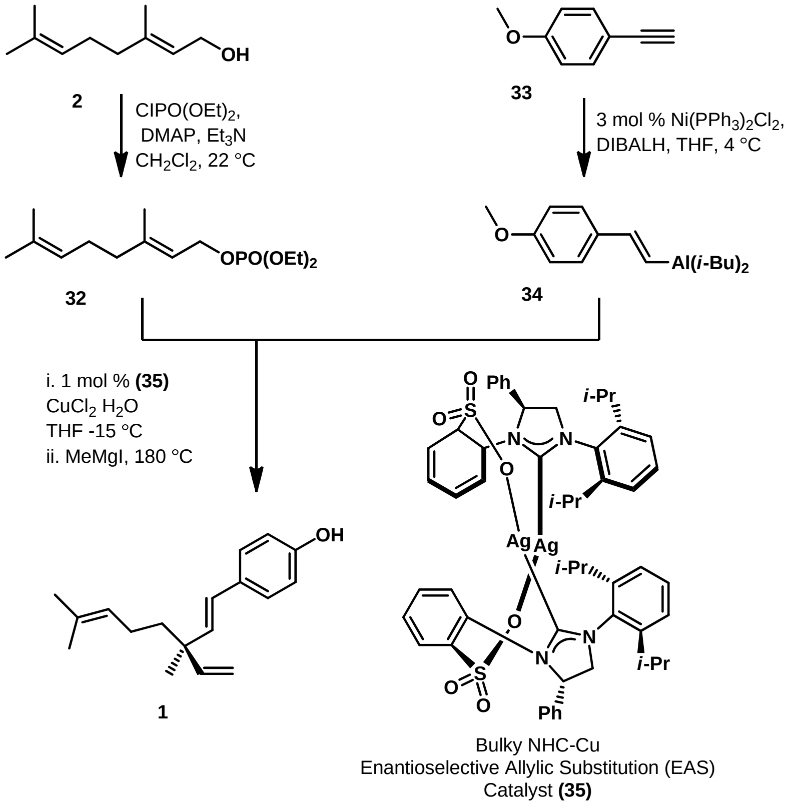
Scheme 9. Li Method of Chiral Center Installation

In 2009, another method for the enantioselective synthesis of (+)-bakuchiol (**1**) was developed by the Novikov group using diazosulfonate C-H insertion to install the quaternary center. This method started with (–)-citronellol (**28**) as the starting material and was converted to δ-sulfone **31** in 3 steps with high yields. The total synthesis gave **1** in 45 % yield over 10 steps, however, like many of the previous syntheses before it, it required the purchase of a chiral starting material. (Scheme 10)



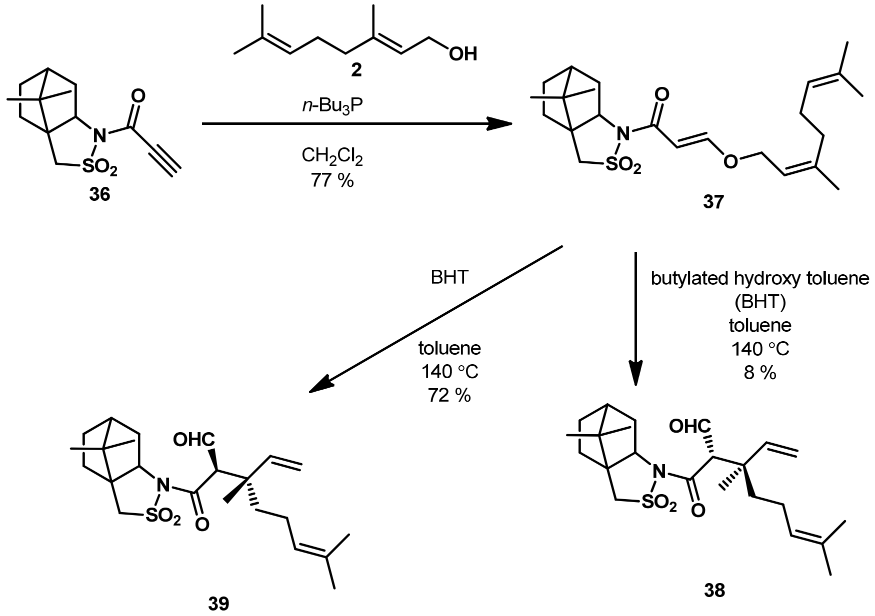
Scheme 10. Novikov Preparation of δ-Sultine From (–)-Citronellol by C-H Insertion

In 2010, the Hoveyda group was able to synthesize (+)-bakuchiol (**1**) in 3 steps with an overall yield of 72 %. This synthesis started with the phosphonation of geraniol (**2**) to yield alcohol **32**. In another pot, a β-selective Ni catalyst was attached to the terminal end of an alkyne **26** followed by a hydroalumination. The two products were then mixed together with a bulky catalyst **28** and the reaction proceeded via the use of a NHC-Cu catalyzed Enantioselective Allylic Substitution (EAS).[38] This efficient synthesis is shown in Scheme 11. While the yields were high, the NHC-Cu catalyst had to be prepared by another protocol that the Hoveyda group established.[39]



Scheme 11. Hoveyda Synthesis of (+)-Bakuchiol via Ni Catalyzed NCH-Cu EAS

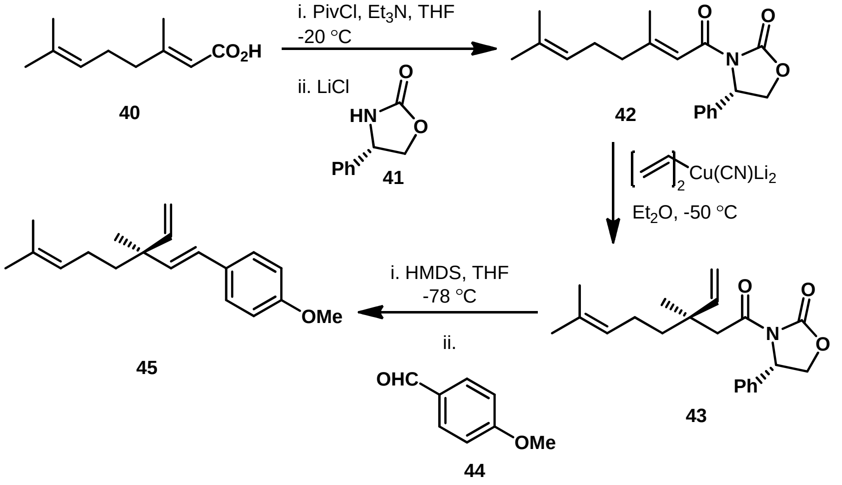
In 2012, a synthetic route was developed by the Tadano group which utilized an asymmetric Claisen rearrangement. The Tadano group designed novel substrate **36**, a β-(allyloxy)acrylate derivative which was mixed with geraniol (**2**) and underwent a oxy-Michael addition to form compound **37**. Compound **37** was heated with butylated hydroxytoluene to yield enantiomers **38** and **39** via Claisen rearrangement with the set stereocenter (Scheme 12). Enantiomer **39** was the desired enantioenriched material for the use of (+)-bakuchiol (**1**) synthesis. The overall synthesis was completed in 6 steps and gave a yield of 25 %.[40] This method required the synthesis of the starting material **36** and only yielded 72 % of the desired enantioenriched quaternary center for the manipulation to (+)-bakuchiol (**1**).



Scheme 12. Tadano Method for Asymmetric Claisen Rearrangement

The most recent synthesis of (+)-bakuchiol (**1**) was done in 2013, once again by the Fukuyama group. A geranic acid **40** was treated with pivaloyl chloride and triethylamine, then (2'*R*)-2'-phenyloxazolidinone (**41**) was used as a chiral auxiliary to form compound **42**. Compound **42** then underwent an asymmetric 1,4 addition to form compound **43** which was reacted with sodium hexamethyl disilazane (SHMDS), then p-methoxy benzaldehyde (**44**). The product after 3 steps was enantioenriched bakuchiol methyl ether (**45**) which was then demethylated using the previously established method.

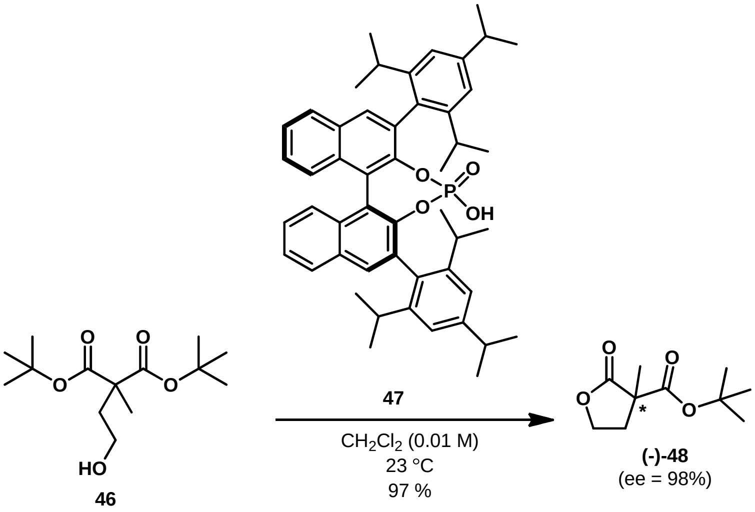
(+)-bakuchiol (**1**) was synthesized in four steps with an overall yield of 64 %.[41] This synthesis shown in Scheme 13 was short and efficient but used (2'*R*)-2'-phenyloxazolidinone as a chiral auxiliary.



Scheme 13. Fukuyama Method of Asymmetric 1,4 Addition

1.4 Introduction to Desymmetrization

As shown above, (+)-bakuchiol (**1**) contains a chiral all carbon quaternary center. There have been multiple ways to set the stereocenter of (+)-bakuchiol (**1**). As shown in Scheme 14, an efficient and highly selective desymmetrization process was developed by the Petersen group that involves the reaction of a prochiral hydroxy diester **46**, with a bulky chiral Brønsted acid **47**, to form an enantioenriched γ-lactone (-)-**48**.



Scheme 14. Desymmetrization of Prochiral Hydroxy Diester **46** to Form Enantioenriched Lactone (-)-**48**

This process is unique because of the acid's ability to selectively form an enatioenriched lactone from a prochiral substrate. This method of desymmetrization was able to produce **(-)-48** with a 97 % yield and an enantiomeric excess (ee) of 98 %.[42] This lactone will be used as the key intermediate to set the absolute configuration of the all carbon quaternary center in (+)-bakuchiol (**1**).

1.5 Conclusion

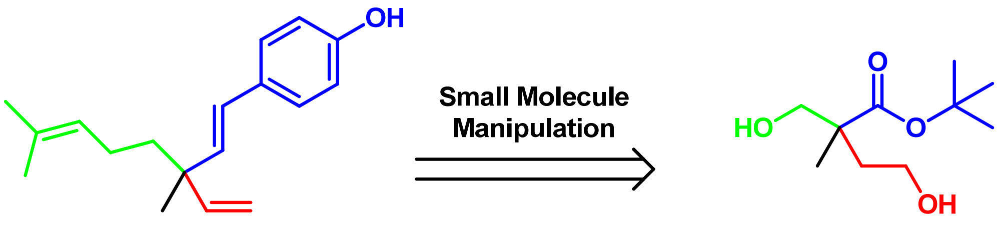
There are multiple syntheses of (+)-bakuchiol (**1**) that have been published. Most of the previous work makes use of chiral starting materials either by purchasing or synthesizing them. Some methods required stoichiometric quantities of reagents to be used as chiral auxiliaries in order to form the chiral center. There also has not been a serious synthetic approach to develop a plethora of analogs. This work is focused on developing a synthetic pathway for racemic bakuchiol (**12**). After the synthetic pathway has been refined, prochiral alcohol **46** will then be reacted with only 5 mole percent of commercially available chiral catalyst **47** to set the stereochemistry of the quaternary center. The use of the enantiomer of the phosphorous BINOL catalyst **47** could be used to synthesize the non-natural (–)-bakuchiol enantiomer. The final steps in the synthesis of (+)-bakuchiol (**1**) can then be manipulated to form various analogs using the developed pathway.

CHAPTER II

METHODOLOGY AND DEVELOPMENT OF THE SYNTHETIC PATHWAY

2.1 Retrosynthesis

The most challenging aspect in the syntheses of the (+)-bakuchiol (**1**) has been the installation of the quaternary center. Historically, the enantioenrichment of a racemic molecule has been achieved with the use of chiral starting materials (purchased or synthesized). The use of expensive reagents as chiral auxiliaries in stoichiometric ratios has also been used to achieve enantioenrichment by some research groups. Recently, the Petersen group synthesized a chiral lactone (**48**) using only 5 mole percent of a chiral BINOL phosphoric acid catalyst (**47**).[42] With this in mind, a retrosynthesis was designed around a quaternary center that had easily manipulated terminals. Scheme 15 shows the desired functional groups that would yield racemic bakuchiol (**12**).



racemic bakuchiol
12

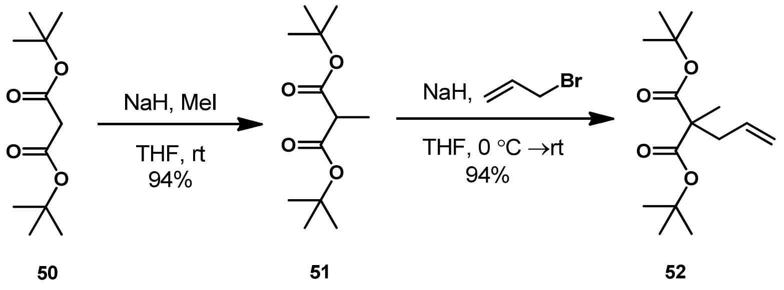
diol
49

Scheme 15. Retrosynthesis of Racemic Bakuchiol **12**

The methyl group is set during the lactonization. The primary alcohols require separate protecting groups in order to manipulate them individually. The ester would be converted to an aldehyde which can undergo a Horner-Wadsworth-Emmons reaction to install the phenyl functional group.

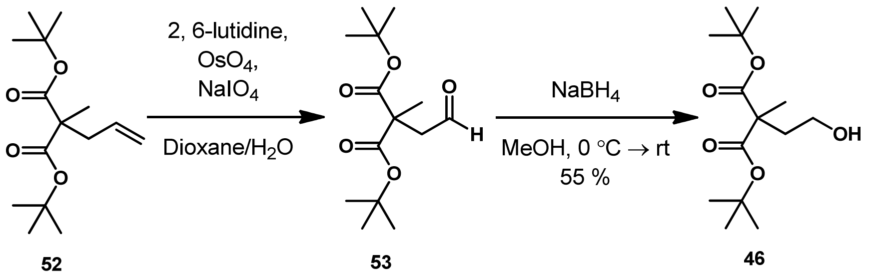
2.2 Results and Discussion

Our first step in the synthesis of racemic bakuchiol was the deprotonation of commercially available di-*tert* butyl malonate (**50**) using sodium hydride in THF. Methyl iodide was added and the reaction was quenched with aqueous ammonium chloride, producing the methyl malonate intermediate **51** with a 94 % yield. The methyl malonate intermediate **51** was again deprotonated with the use of NaH. Then, allyl bromide was added to install the allyl group. The reaction was then quenched with aqueous ammonium chloride to produce allyl methyl malonate intermediate **52** with a 94 % yield (Scheme 16).



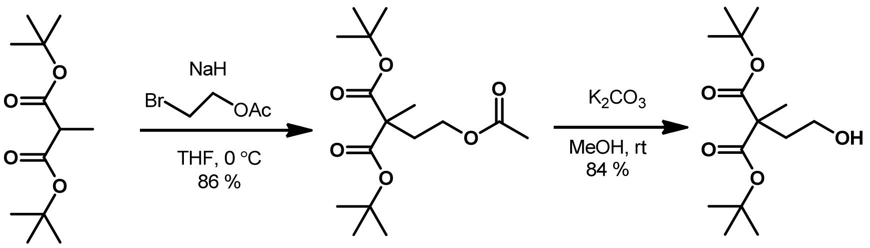
Scheme 16. Methylation and Second Alkylation of Di *Tert* Butyl Malonate

To the allyl methyl malonate intermediate **52** was added a mixture of dioxane/ H_2O, then 2,6-lutidine was added followed by OsO_4 and sodium periodate to form aldehyde **53**. The crude aldehyde intermediate **53** was dissolved in methanol and added to a sodium borohydride methanol solution. Prochiral hydroxy diester alcohol **46** was produced as a colorless oil with a 55 % yield. (Scheme 17)



Scheme 17. Formation of the Prochiral Alcohol

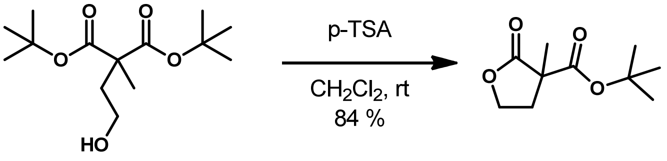
A new, more efficient synthesis of the prochiral diester alcohol **46** was refined for application.[43] This route, shown in Scheme 18, involved the addition of 2-bromo ethyl acetate to methyl malonate **51** in THF at 0 °C and slowly bringing the reaction to room temperature. The acetate protecting group was then cleaved using potassium carbonate in methanol to yield hydroxyl diester **46** in 3 steps with an overall yield of 70 %.



51 **54** **46**

Scheme 18. Formation of Prochiral Alcohol via More Efficient Pathway

The next step produced racemic lactone **55** and is shown in Scheme 19. It required only 5 mole percent of *para*-toluene sulfonic acid. This is the step that would produce the enantioenriched lactone **48** using the chiral BINOL catalyst **47**. However, for the racemic lactonization, *p*-toluenesulfonic acid was mixed with alcohol **46** in CH_2Cl_2 to yield lactone **55** in 84 % yield.

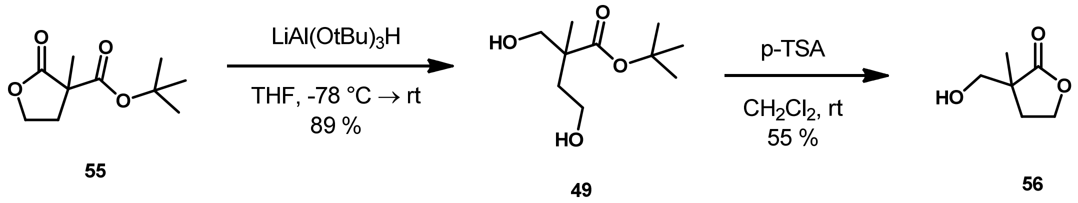


46 **55**

Scheme 19. Racemic Lactonization of Prochiral Alcohol

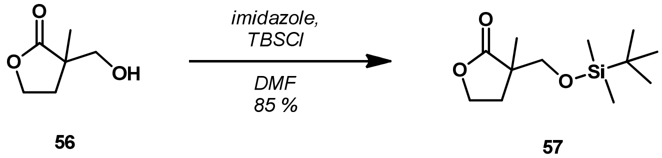
Racemic lactone **55** was added to $LiAl(OtBu)_3H$ and THF at -78 °C under argon. After 18 hours, potassium sodium tartrate was used to quench the reaction and produce diol **49** in 89 % yield. The selective protection of one terminal primary alcohol was required. In order to selectively protect one of the terminal alcohols, diol **49** was added to *p*-

toluenesulfonic acid in CH_2Cl_2 to yield the hydroxy lactone **56** with a yield of 55 % as shown in scheme 20.



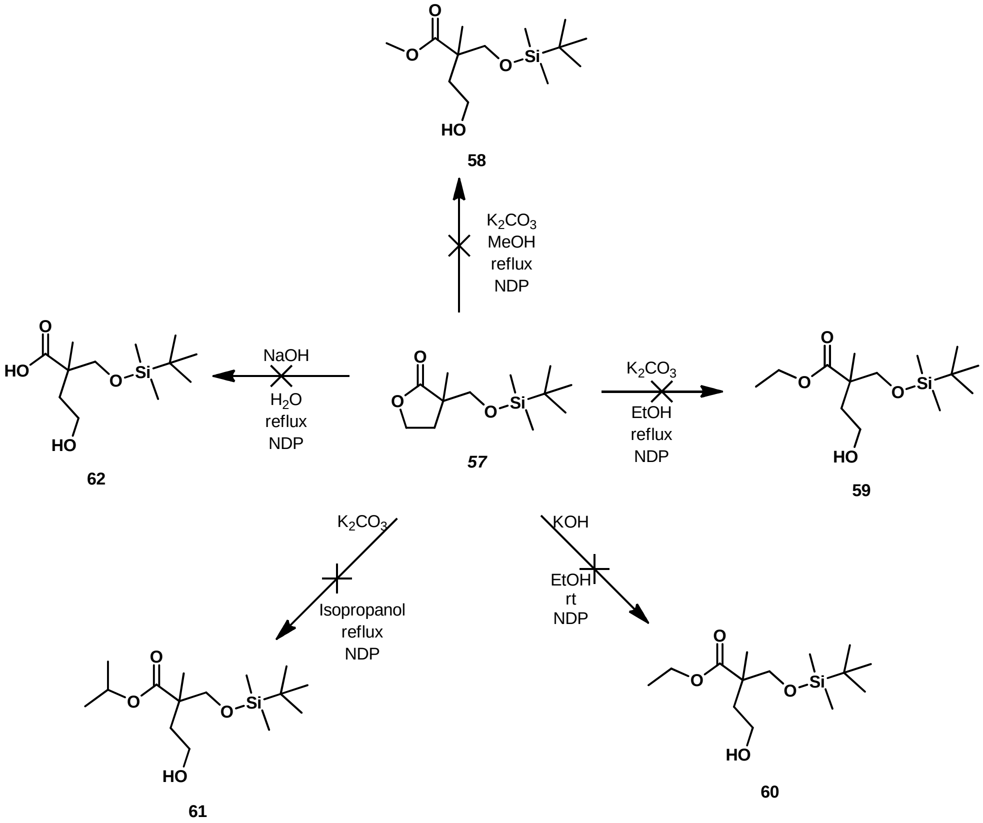
Scheme 20. Reduction to Diol and Subsequent Lactonization to Hydroxy Lactone

Once hydroxy lactone **56** was formed, a protecting group was required that would be readily added and easily cleaved. Many protecting groups were looked at but it was decided to use a bulky *tert*-butyl dimethyl silyl protection due to its ease of formation and relative size. As shown in scheme 21, hydroxy lactone **56** was mixed with imidazole and TBSCl in DMF to yield the desired TBS protected lactone **57** in 85 % yield.



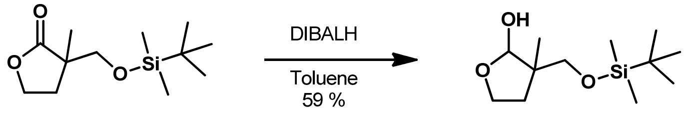
Scheme 21. Protection of Hydroxy Lactone with TBSCl

The next step in the synthetic plan was to open the ring in a controlled manor that would yield an aldehyde, an ester, or an alcohol. The TBS lactone **57** was combined with a variety of reagents and bases in different solvents to form the desired alcohol. Scheme 22 shows the reactions that were attempted with no success. First, **57** was refluxed with potassium carbonate in methanol in an attempt to form **58**. It was thought that the methyl group may not be a suitable protecting group for the ester so the next attempt involved potassium carbonate in ethanol in an attempt to form **59**. When no desired product was formed, it was thought that the base may not be strong enough, so **57** was added to potassium hydroxide in ethanol in an attempt to form **60**. With still no desired product, **57** was added to potassium carbonate in isopropanol in an attempt to form **61**. Finally **57** was added to sodium hydroxide in water in an attempt to form **62**. After this failed attempt, a new route was sought to open the ring.



Scheme 22. Attempted Ring Opening Reactions.

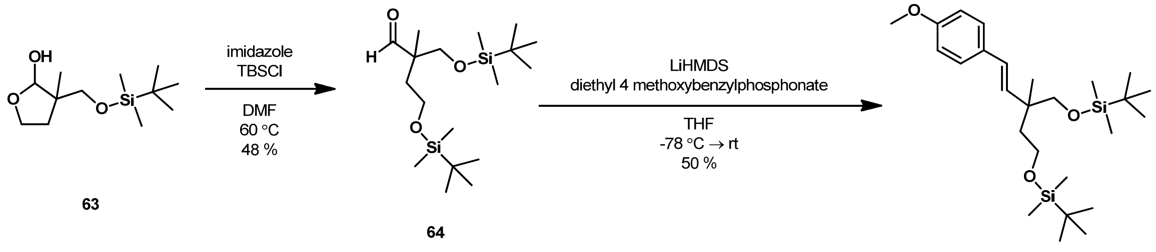
After these trials and failures, it was decided that there was too much functionality in the molecule and a protected alcohol was the more conservative approach. Scheme 23 shows the TBS lactone **57** was reduced to lactol **63** using DIBALH in toluene at -78 °C, which allowed easier access to the ester carbon.



57 **63**

Scheme 23. Reduction of TBS Lactone **57** to Lactol **63**

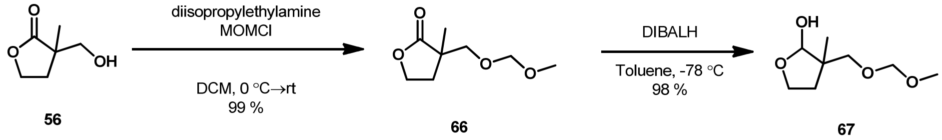
The TBS lactol **63** was then mixed with imidazole and TBSCl in DMF to test for the formation of an aldehyde. Gratifyingly, this yielded an aldehyde **64** but with two TBS groups that could not be manipulated independently. The aldehyde **64** was then used as a test substrate for the Horner-Wadsworth-Emmons reaction. It was combined with lithium hexamethyl disalizide and diethyl 4-methoxybenzylphosphonate in THF at -78 °C to form the desired HWE product **65** as shown in Scheme 24.



63 **64** **65**

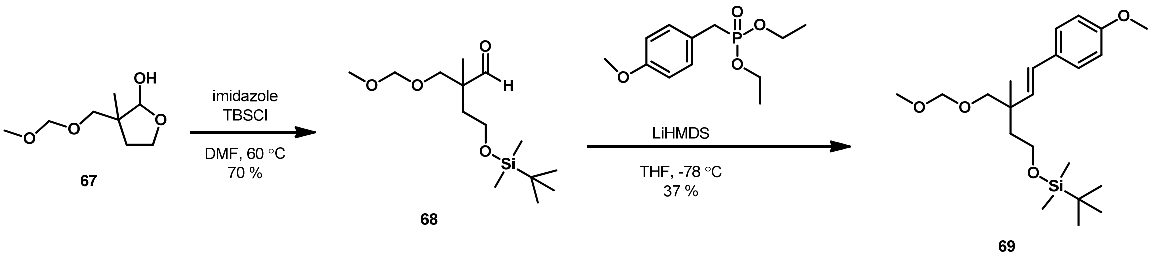
Scheme 24. HWE of TBS Lactol **63** to Form HWE Product **65**

With the Horner-Wadsworth-Emmons pathway set, a new protecting group was needed for the hydroxy lactone. This time, a methoxymethyl (MOM) protecting group was decided upon. The hydroxy lactone **56** was mixed with MOMCl and diisopropylethylamine in DCM at 0° C to yield a MOM protected lactone **66** in 99 % yield. The MOM lactone **66** was then reduced by adding it to DIBALH in toluene at -78 °C to produce to a MOM lactol **67** in 98 % yield, as seen in Scheme 25.



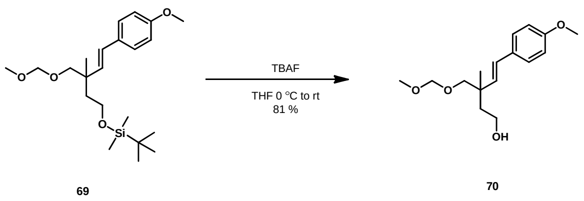
Scheme 25. Protection and Reduction of Hydroxy Lactone **56**

Scheme 26 shows the ring opening of the MOM lactol **67** using imidazole and TBSCl in DMF at 60 °C to form the reactive aldehyde **68**. Aldehyde **68** was then reacted with LiHMDS and diethyl-4-methoxybenzylphosphonate in THF at -78 °C to form the desired Horner-Wadsworth-Emmons product **69**.



Scheme 26. Ring Opening of MOM Lactol **67** and Subsequent HWE Reaction

The TBS group was then cleaved by using tetra-*n*-butylammonium fluoride (TBAF) in THF at 0 °C as shown in Scheme 27 to form alcohol **70** in a yield of 81 %. This alcohol can be manipulated later to form the desired vinyl group.



Scheme 27. Cleavage of TBS Group to Form Alcohol **70**

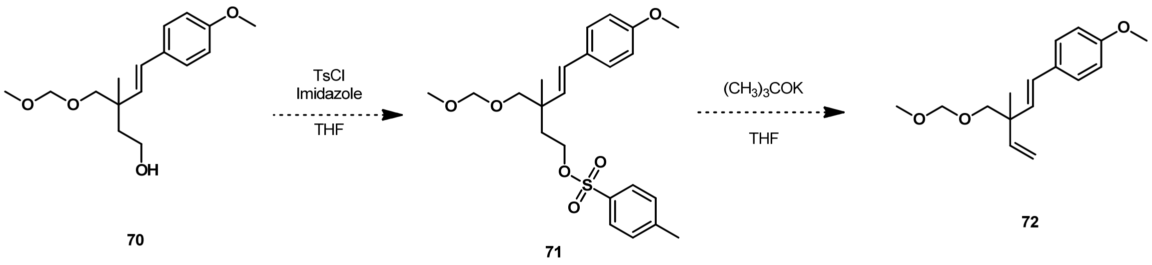
After the Horner-Wadsworth-Emmons reaction, two out of the four terminal ends were set in the pursuit of the racemic bakuchiol (**12**) synthesis. The next steps will involve an elimination of the alcohol to form a vinyl group followed by cleavage of the MOM protecting group in order to achieve the desired

CHAPTER III

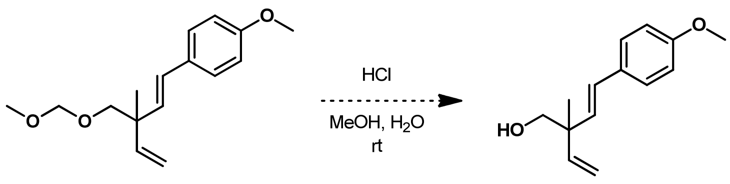
FUTURE WORK AND ANALOGS

3.1 Background and Discussion of Proposed Pathway

In order to manipulate the alcohol **70**, a tosyl group (good leaving group) will be added as seen in Scheme 28. The tosylate will then be eliminated with the use of potassium *tert*-butoxide, in order to form vinyl **72**. Once the elimination has occurred, the MOM protecting group will be cleaved using HCl in methanol and water to yield the neopentyl alcohol **73** (Scheme 29).[44]



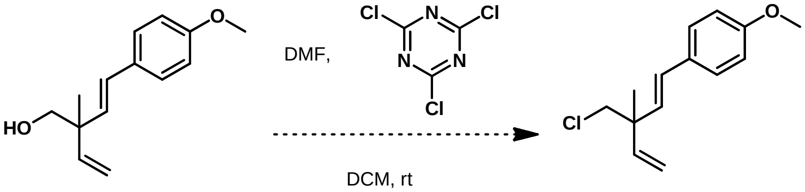
Scheme 28. Addition of Tosyl Group to Alcohol **70** and Elimination to Vinyl **72**



72 **73**

Scheme 29. MOM Cleavage of **72** to Form Neopentyl Alcohol **73**

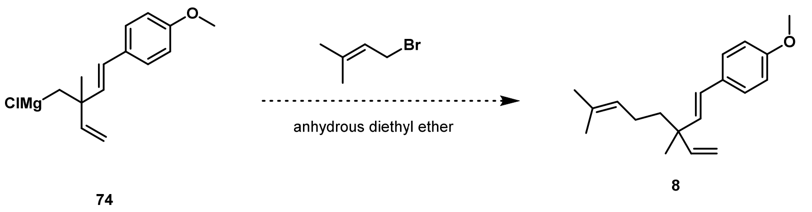
The neopentyl alcohol **73** will then need to be converted to alkyl chloride **74** by reacting it with cyanuric chloride and *N,N*-dimethyl formamide in methylene chloride (Scheme 30).[45]



73 **74**

Scheme 30. Conversion of Neopentyl **73** to Alkyl Chloride **74**

Once the alkyl chloride is formed, **74** can undergo a Grignard reaction with magnesium and 1-bromo-3-methyl-2-butene in anhydrous diethyl ether as shown in Scheme 31, in order to form the bakuchiol methyl ether (**8**).[46]



Scheme 31. Grignard Reaction of **74** to Form the Bakuchiol Methyl Ether (**8**)

Once synthetic pathway to **8** has been established, demethylation could occur with the use of MeMgI as shown in the literature. Since this has been established, the synthesis of **1** using the Petersen desymmetrization process will be the next project. Once **1** has been synthesized using this method, a library of analogs can be synthesized by manipulating the Grignard reagent in Scheme 31.

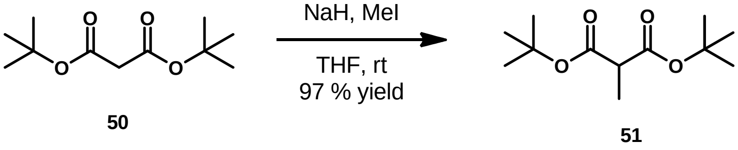
CHAPTER IV

EXPERIMENTAL

4.1 General Information

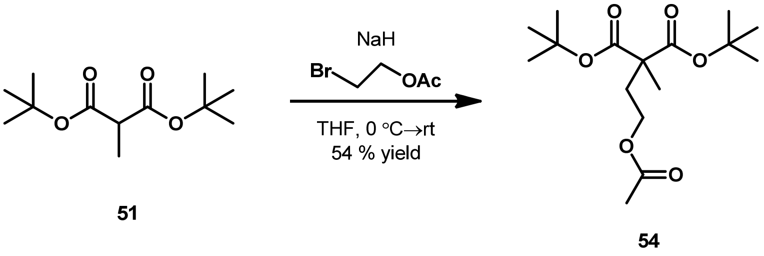
All anhydrous reactions were performed with dry solvents in oven dried glassware under an argon atmosphere. Most solvents and reagents were obtained from commercial sources and used without further purification. THF, DCM, and TEA were freshly distilled. MeOH was distilled over CaCl. Toluene was distilled over P_2O_5. Chromatographic purification was performed using silica gel (60 Å, 32-63 µm). NMR spectra were recorded using a JEOL ECA spectrometer (500 MHz for 1H, 125 MHz for 13C). Coupling constants, J, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of triplets (tt), multiplet (m), etc. The reactions were monitored by TLC using silica G F254 precoated plates. Flash chromatography was performed using flash grade silica gel (particle size: 40−63 µm, 230 × 400 mesh).

4.2 Procedures



Scheme 32. Di-*t*-butyl 2-Methylmalonate (**51**)

Di-*t*-butyl 2-methylmalonate (51): To a clean flame dried round bottom flask with a magnetic stir bar was added a solution of sodium hydride (60 % in mineral oil, .92 g, 23.11 mmol) in THF (25 mL). Di-*tert*-butyl malonate (**50**) was added dropwise (5 mL, 23.11 mmol) and the solution was stirred for 30 min at rt. To the reaction mixture was added iodomethane (1.48 mL, 23.11 mmol) dropwise and the solution was stirred for 3 h at rt. The reaction was quenched with saturated NH_4Cl (10 mL) at 0 ºC, the phases were separated, the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10→30 % EtOAc in hexanes) to afford the di-tert-butyl 2-methylmalonate intermediate as a colorless oil (5.14 g, 97 % yield). The spectroscopic data matched the previously known compound reference.[42]

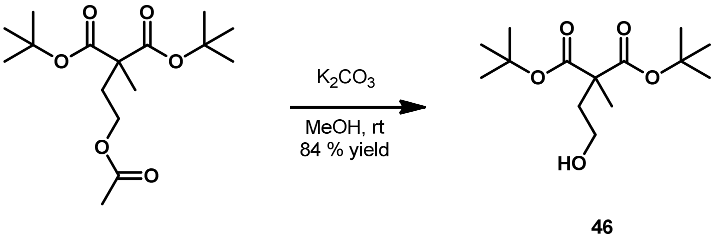


Scheme 33. Dialkylated Malonate Intermediate **54**

Dialkylated malonate intermediate 54: To a clean flame dried round bottom flask with stir bar was added a solution of sodium hydride (60 % in mineral oil, 4.47 g, 111.8 mmol in THF (75 mL) and di-*tert*-butyl 2-methylmalonate (**51**) was added dropwise (12.87 g, 55.9 mmol) and the solution was stirred for 30 min at 0 ºC . To the reaction mixture was added 2-bromoethyl acetate (15.46 mL, 139.78 mmol) dropwise and the solution was stirred for 3 h and warmed to rt. The reaction was quenched with saturated NH_4Cl (10 mL) at 0 ºC, the phases were separated, the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10→30 % EtOAc in hexanes) to afford the dialkylated malonate intermediate as a clear yellow oil (15.14 g, 86 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (t, $J = 5$ Hz, 2H), 1.98 (t, $J = 5$ Hz, 2H), 1.93 (s, 3H), 1.45 (s, 18H), 1.29 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 168.3, 81.8, 62.1, 50.0, 33.9, 27.9, 21.0, 19.9 ppm.

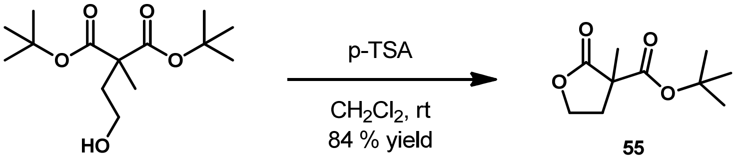


54

46

Scheme 34. Hydroxy Diester **46**

Hydroxy Diester 46: To a clean flame dried round bottom flask with stir bar was added a solution of the dialkylated intermediate **54** (2.50 g, 16.46 mmol) in MeOH (25 mL) was added H_2CO_3 and the solution was stirred at rt for 45 min. The reaction mixture was diluted with CH_2Cl and was extracted (3 x 30 mL) and H_2O (1 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vaccuo. The residue was purified via flash chromatography on silica gel (20→40 % EtOAc in hexanes with 0.1 % TEA) to afford the hydroxy diester (1.82 g, 84 % yield). The spectroscopic data matched the previously known compound reference.[42]

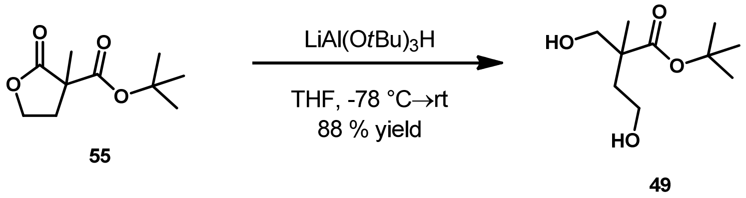


46

55

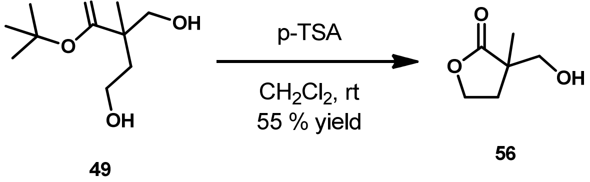
Scheme 35. Racemic Lactone 55

Racemic Lactone 55: To a clean flame dried round bottom flask with stir bar was added a solution of *para*-toluenesulfonic acid (0.07 g, .381 mmol) in CH_2Cl_2 (25 mL) at 0 ºC was added the hydroxy diester **46** (2.09 g, 7.62 mmol). The solution was stirred for 27 h and allowed to warm to rt. The reaction was extracted using H_2O (1 x 30 mL) and EtOAc (3 x 30 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10- 30 % EtOAc in hexanes) to afford the racemic lactone (1.28 g, 84 % yield) as a clear colorless oil. The spectroscopic data matched the previously known compound reference.[42]



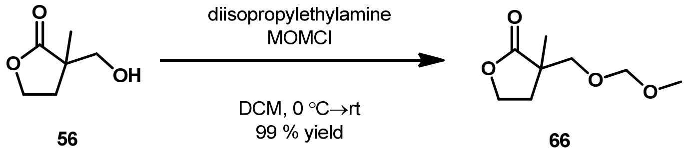
Scheme 36. Diol **49**

Diol 49: To a clean flame dried round bottom flask with stir bar was added LiAl(O*t*Bu)$_3$H (5.93 g, 23.35 mmol) in THF (18 mL) was cooled to -78 ºC. A solution of the racemic lactone **55** (1.17 g, 5.83 mmol in THF, 7 mL) was cooled to -78 ºC and added to the mixture. It was allowed to react overnight and warm to rt. The reaction was quenched with saturated potassium sodium tartrate and HCl. The phases were separated with CH_2Cl_2 (1 x 20 mL) and EtOAc (2 x 20 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo to yield the diol as a clear colorless oil (1.04 g, 88 % yield). The spectroscopic data matched the previously known compound reference.[42]



Scheme 37. Hydroxy Lactone **56**

Hydroxy lactone 56: To a clean flame dried round bottom flask with stir bar was added a solution of *para*-toluenesulfonic acid (10 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) at 0 ºC. Diol **49** (221 mg, 1.08 mmol) was added dropwise. The solution was stirred overnight and allowed to warm to rt. The reaction was extracted using H_2O (1 x 10 mL) and EtOAc (3 x 10 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10- 50 % EtOAc in hexanes) to afford the hydroxy lactone (165 mg, 55 % yield) as a clear colorless oil. The spectroscopic data matched the previously known compound reference.[47]

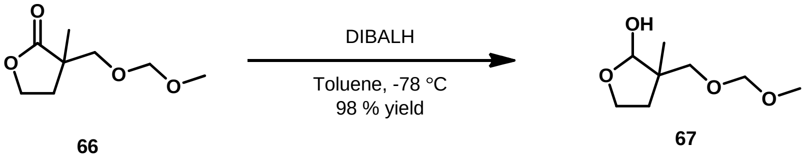


Scheme 38. MOM Lactone **66**

MOM Lactone 66: To a clean flame dried round bottom flask with stir bar was added a solution of the hydroxy lactone **56** (77 mg, 0.59 mmol) in CH_2Cl_2 (12 mL) at 0 ºC. Diisopropylethylamine (0.15 mL, 1.5 eq) and MOMCl (0.13 mL, 3 eq) were added dropwise. The reaction was stirred for 4 h then diisopropylethylamine (0.15 mL, 1.5 eq) and MOMCl (0.13 mL, 3 eq) were added. The reaction was stirred overnight and it was allowed to warm to rt. After, 14.5 h, diisopropylethylamine (0.15 mL, 1.5 eq) and MOMCl (0.13 mL, 3 eq) were added and the solution was allowed to stir for 24 h. The reaction was quenched with saturated sodium bicarbonate (10 mL). The organic phase was extracted with H_2O (1 x 10 mL) and EtOAc (3 x 10 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (30 - 60 % EtOAc in hexanes) to afford the MOM protected hydroxy lactone (103 mg, 99 % yield) as a clear yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 2H), 4.31 (m, 2H), 3.68 (d, *J* = 5 Hz, 1H), 3.45 (d, *J* = 5 Hz, 1H), 3.33 (s, 3H), 2.51 (m, 1H), 2.05 (m, 1H), 1.22 (s, 3H) ppm.

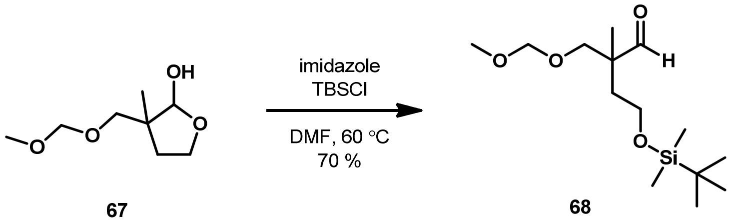
^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 96.6, 72.2, 65.6, 55.5, 43.7, 32.5, 20.3 ppm.



Scheme 39. Lactol **67**

MOM protected lactol 67: To a clean flame dried round bottom flask with stir bar was added a solution of the MOM protected lactone **66** (493 mg, 2.83 mmol) in toluene (8 mL) and the mixture was cooled to -78 ºC for 30 min. To this solution was added DIBALH (16.9 mL, 16.98 mmol) dropwise. This was allowed to react for 1 h. The reaction was quenched with H_2O (1 mL), 15 % saturated NaOH (1 mL) and H_2O (3 mL).

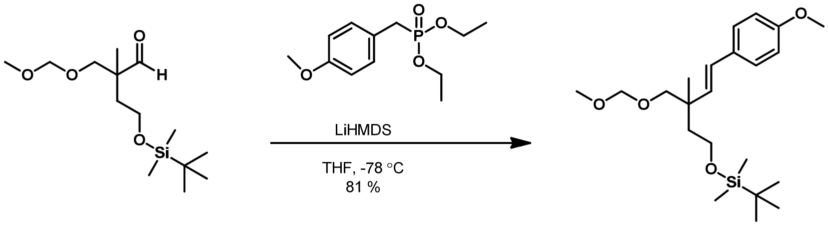
This solution was allowed to react for 1 h. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield the MOM protected lactol (0.49 g, 98 % yield).



Scheme 40. Aldehyde **68**

Aldehyde intermediate 68: To a clean flame dried round bottom flask with stir bar was added MOM Lactol **67** (96 mg, 0.54 mmol) in DMF (5 mL). To this solution was added imidazole (370 mg, 5.45 mmol) and TBSCl (410 mg, 2.72 mmol). The mixture was allowed to react at room temperature for 2 minutes then placed in an oil bath at 70 °C and allowed to react overnight. The organic layer was separated with H_2O and DCM, dried over MgSO4 and concentrated. The crude product was purified by flash chromatography in 0-15 % EtOAc in hexane to yield aldehyde **68** (111 mg, 70 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 4.58 (s, 2H), 3.64 (m, 3H), 3.51 (d, J = 10 Hz, 1H), 3.32 (s, 3H), 1.92 (m, 1H), 1.70 (m, 1H), 1.55 (s, 6H), 1.11 (s, 3H), 0.86 (s, 9H) ppm.



68

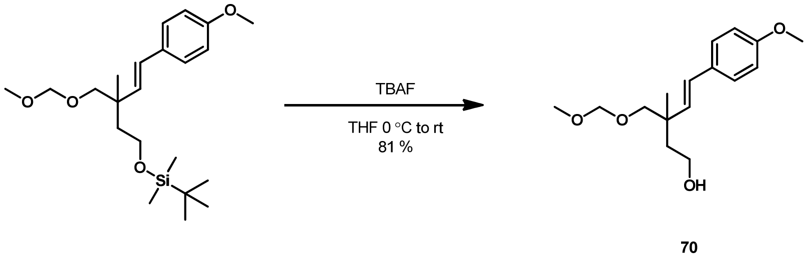
69

Scheme 41. Horner-Wadsworth-Emmons Product **69**

Horner-Wadsworth-Emmons Product 69: To a clean flame dried round bottom flask with stir bar was added diethyl 4-methoxybenzylphosphonate (0.21 mL, 1.22 mmol) and LiHMDS (1M in THF, 1.71 mL, 1.71 mmol) in THF (5 mL) at -78 °C. This solution was allowed to react for 30 min, then aldehyde **68** (198 mg, 0.68 mmol) was added and the mixture was allowed to react overnight. The reaction was quenched with saturated sodium bicarbonate (2 mL). The organic layer was separated with EtOAc, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography in 0 - 30 % EtOAc in hexanes to yield **69** (100 mg, 37 %) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 10 Hz, 2H), 6.83 (d, *J* = 10 Hz, 2H), 6.29 (d, *J* = 15 Hz, 1H), 6.10 (d, *J* = 15 Hz, 1H), 4.62 (s, 2 H), 3.80 (s, 3H), 3.67 (t, *J* = 5 Hz, 2H), 3.39 (s, 2H), 3.35 (s, 3H), 1.76 (dd, *J* = 10 Hz, 2H), 1.26 (s, 6H), 1.16 (s, 3H), 0.88 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 134.1, 130.6, 127.3, 127.4, 113.9, 96.8, 76.0, 60.1, 55.3, 40.9, 29.8, 29.5, 26.0, 21.9, -5.2 ppm.

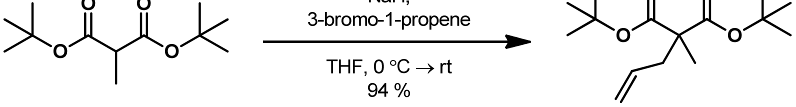


69 **70**

Scheme 42. Alcohol **70**

Alcohol 70: To a clean flame dried round bottom flask with stir bar was added the Horner-Wadsworth-Emmons product **69** (60 mg, 0.15 mmol) and 1.5 mL of THF. The solution was cooled to 0 °C for 40 min. TBAF (1 M in hexane, 0.31 mL, 0.31 mmol) was added and the mixture was allowed to react overnight. The mixture was diluted with EtOAc, washed w/ sodium bicarbonate and dried over $MgSO_4$. The crude product was purified by flash chromatography in 10-100 % EtOAc in hexanes to yield the alcohol (35 mg, 81 %).

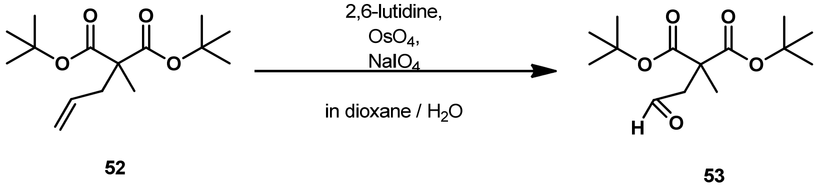
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 10 Hz, 2H), 6.85 (d, J = 10 Hz, 2H), 6.32 (d, J = 15 Hz, 1H), 6.10 (d, J = 15 Hz, 1H), 4.64 (s, 2 H), 3.80 (s, 3H), 3.72 (t, J = 10 Hz, 2H), 3.52 (m, 1H), 3.46 (d, J = 5 Hz, 1H), 3.42 (d, J = 5 Hz, 1H) 3.36 (s, 3H), 1.80 (m, J = 10 Hz, 2H), 1.17 (s, 3H) ppm.



51 **52**

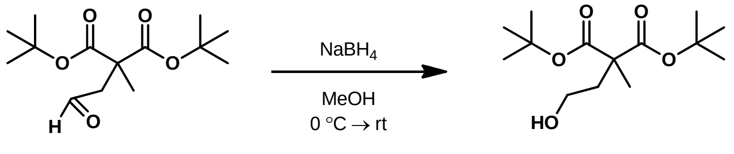
Scheme 43. Dialkyl Malonate **52**

Allyl Diester 52: To a clean flame dried round bottom flask with stir bar was added NaH (60 %, 1.83 g, 45.92 mmol) and methyl malonate (5.28 g, 22.96 mmol) at 0 °C. To the reaction mixture was added 3-bromo-1-propene (4.99 mL, 57.40 mmol). The reaction was allowed to react for 3 h then quenched with NH_4Cl at 0 °C. The organic layer was separated with EtOAc and dried over $MgSO_4$. The crude product was purified by flash chromatography 0-20 % EtOAc in hexanes to yield the allyl malonate **52** (5.82 g, 94 %). The spectroscopic data matched the previously known compound reference.[42]



Scheme 44. Aldehyde **53**

Malonate Aldehyde 53: To a clean flame dried round bottom flask with stir bar was added 7 mL of dioxane, 3 mL of deionized H_2O and allyl malonate **52** (1.20 g, 4.47 mmol). To the solution was added 2, 6 lutidine (1.04 mL, 8.94 mmol) followed by OsO_4 (2.5 %, 91 mL, .08 mmol) and $NaIO_4$ (4.55 g, 17.88 mmol). The organic layer was flushed through filter paper and separated with DCM and H_2O, then dried over sodium sulfate and concentrated in vaccuo to yield the crude malonate aldehyde **53** (1.35g).

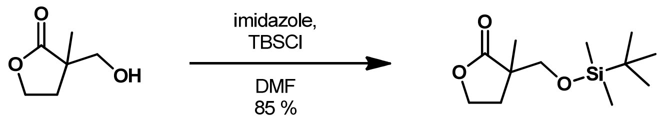


53

46

Scheme 45. Alcohol **46**

Alcohol 46: To a clean flame dried round bottom flask with stir bar was added a solution of $NaBH_4$ (.80 g, 21.24 mmol) in MeOH (20 mL) and cooled to 0 °C. To the solution was added aldehyde intermediate **53** (1.35 g, 5.31 mmol), and the mixture was allowed to react overnight. The reaction was quenched with 1 M HCl at 0 °C and the organic layer was extracted with DCM, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography in 20-60 % EtOAc in hexanes to yield prochiral alcohol **46** (.23g). The spectroscopic data matched the previously known compound reference.[42]



56

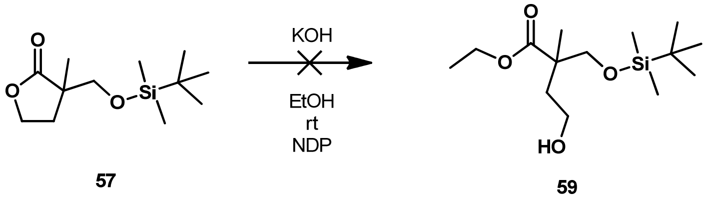
47

Scheme 46. TBS Lactone **57**

Silyl Lactone 57: To a clean flame dried round bottom flask with stir bar was added imidazole (0.19 g, 2.87 mmol) and 5 mL of THF. To the solution was added lactone **56** and the mixture was allowed to react for 22 h. The organic layer was rinsed with DCM (3 x 20 mL) then separated with H_2O and EtOAc. The organic layer was dried over $MgSO_4$

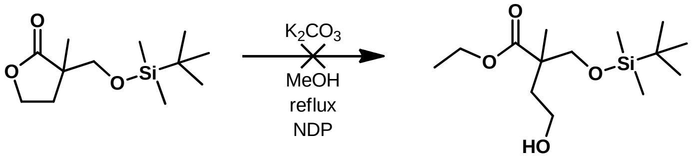
and concentrated in vaccuo. The crude product was purified by flash chromatography in 0-40 % EtOAc in hexanes to yield TBS lactone **57** (199 mg, 85 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (m, 2H), 3.78 (d, *J* = 10 Hz, 1H), 3.48 (d, *J* = 10 Hz, 1H), 2.50 (m, 1H), 2.03 (m, 1H), 1.16 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H) ppm.



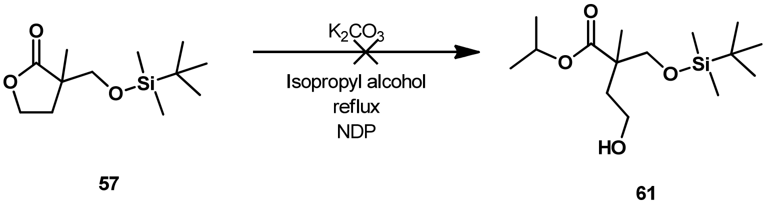
Scheme 47. Attempted Formation of **60**

Ethyl Ester Alcohol 60: To a clean flame dried round bottom flask with stir bar was added silyl lactone **57** (38.2 mg, 0.15 mmol) with EtOH (5 mL) and KOH (8.77 mg, 0.15 mmol). The mixture was allowed to react overnight. The organic layer was separated with EtOAc and H_2O, dried over $MgSO_4$ and concentrated. The crude product (50.2 mg) was analyzed with NMR. The desired product was not formed.



Scheme 48. Attempted Formation of **59**

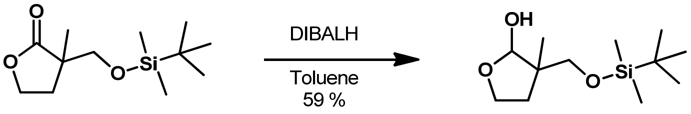
Ethyl Ester Alcohol 59: To a clean flame dried round bottom flask with stir bar was added silyl lactone **57** (36.5 mg, 0.14 mmol) and MeOH (5 mL). To the solution was added K_2CO_3 (3.7 mg, 0.02 mmol) and the mixture was refluxed 23 h. The solvent was removed under reduced pressure, and the residue was washed with H_2O (3 x 10 mL), EtOAc (3 x 10 mL) and dried over $MgSO_4$. The residue was concentrated to yield a crude residue (86.1 mg) which was analyzed with NMR. The desired product was not formed.



57 **61**

Scheme 49. Attempted Formation of **61**

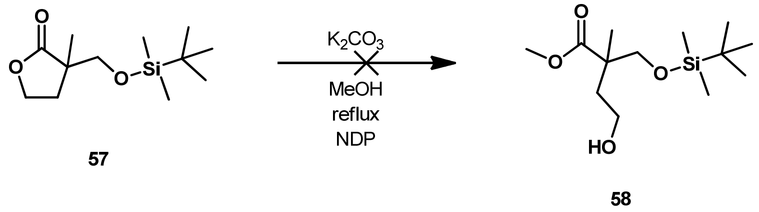
Isopropyl Ester Alcohol 61: To a clean flame dried round bottom flask with stir bar was added silyl lactone **57** and isopropyl alcohol (5 mL). To the solution was added K_2CO_3 (2 mg, 0.01 mmol) and the mixture was refluxed for 13 h. The solvent was removed under reduced pressure and the residue was washed with H_2O (3 x 10 mL), EtOAc (3 x 10 mL) and dried over $MgSO_4$. The residue was concentrated to yield a crude residue (87 mg), which was analyzed with NMR. The desired product was not formed.



57 **63**

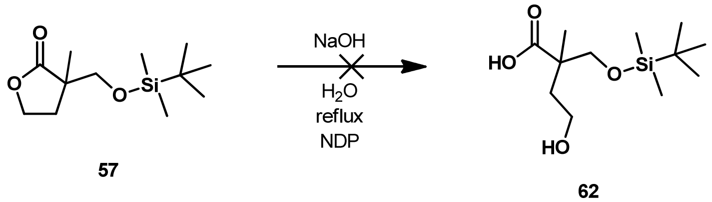
Scheme 50. Formation of Lactol **63**

Silyl Lactol 63: To a clean flame dried round bottom flask with stir bar was added dry toluene (10 mL) and silyl lactone **57** (100 mg, 0.40 mmol). The mixture was cooled to -78 °C and DIBALH (0.45mL, 0.45 mmol) was added drop wise. The mixture was allowed to react for 1 h then quenched with H_2O (0.1mL), 10 % NaOH (0.1 mL), H_2O_2 (0.2 mL) and allowed to react for 30 min. The organic layer was separated with diethyl ether (3 x 5 mL) dried over $MgSO_4$ and concentrated to yield silyl lactol **63** (56 mg, 59 %).



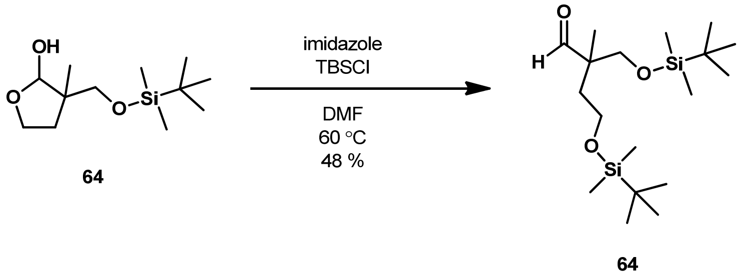
Scheme 51. Attempted Formation of Alcohol **58**

Methyl Ester 58: To a clean flame dried round bottom flask with stir bar was added K_2CO_3 (67.9 mg, 0.49 mmol) and MeOH (10 mL). To the mixture was added silyl lactone **57** (100mg, 0.40 mmol). The mixture was refluxed overnight and separated with EtOAc (3 x 10mL) and H_2O (10 mL). The organic layer was dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude product (30 mg) was analyzed via NMR. The desired product was not formed.



Scheme 52. Attempted Formation of Alcohol **62**

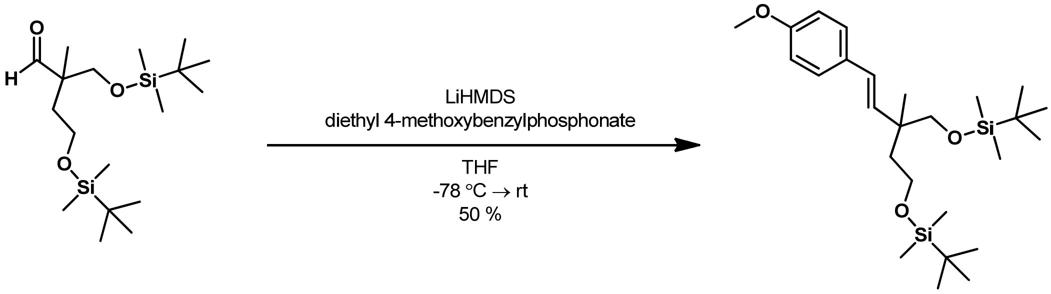
Alcohol 62: To a clean flame dried round bottom flask with stir bar was added silyl lactone **57** (47 mg, 0.19 mmol) in H_2O (5 mL) and NaOH (106 mg, 2.65 mmol). The mixture was allowed to react for 2 h then quenched with HCl. The organic layer was separated with EtOAc (3 x 10mL) and H_2O (10 mL), dried over $MgSO_4$ and concentrated and analyzed by NMR. The desired product was not formed.



Scheme 53. Formation of Aldehyde **64**

Silyl Aldehyde 64: To a clean flame dried round bottom flask with stir bar was added silyl lactol 63 (41 mg, 0.16 mmol) in DMF (5 mL) and imidazole (17.2 mg, 0.25 mmol). *Tert*-butyl silyl (38.07 mg, 0.25 mmol) was added and the mixture was allowed to react for 2 min, and then placed in an oil bath at 60 °C for 1 hr. Imidazole (11.5 mg, 0.16 mmol) and tosyl chloride (13 mg, 0.08 mmol) were added and the mixture was allowed to react overnight. The organic layer was separated with DCM (3 x 10 mL) and H_2O (3 x 10 mL), dried over $MgSO_4$ and concentrate. The crude product was purified by flash chromatography in 0-30 % EtOAc in hexanes to yield silyl aldehyde **64** (29 mg, 48 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 4.25 (m, 2H), 3.56 (d, *J* = 10 Hz, 1H), 3.48 (d, *J* = 10 Hz, 1H), 2.50 (m, 2H), 1.60 (s, 3H), 0.88 (s, 18 H), 0.04 (s, 12H) ppm.



64

65

Scheme 54. Formation of **65**

Silyl Phenol 65: To a clean flame dried round bottom flask with stir bar was added LiHMDS (1M in THF/ethyl benzene, 0.24 mL, 0.24 mmol) in THF (3 mL) and diethyl 4-methoxybenzylphosphonate (62.3 mL, 0.24 mmol). The mixture was cooled -78 °C and silyl aldehyde **64** (29 mg, 0.08 mmol) was added. After 3 h, the reaction was quenched with NH_4Cl at 0 °C. The organic layer was separated with EtOAc (3 x 10 mL), dried over $MgSO_4$, and concentrated. The crude residue was columned in 0-100 % EtOAc in hexanes to yield silyl phenol **65** (18.8 mg, 50 %).

REFERENCES

[1]Mukerji, B. The Chemistry of Psoralea corylifolia Linn and related species has been reviewed. *J. Sci. Ind. Res*. **1956**, *5*, 1.

[2] Kirtikar, K.; Basu, B. Indian Medicinal Plants.2nd ed. Mahendra publication. 994.p. 718.

[3] Rajpal V. Standardization of Botanicals. 2nd ed. Eastern Publisher. **2005**, 2005, 284.

[4] Marg, K. The Wealth of India. *CSIR*. **2003**, 423.

[5] Uniyal, R.; Ghandhak, J. The Ayurvedic Encyclopedia. 1st ed. Shri Satguru publication. **1998**, 76.

[6] Mehta, G.; Ramdas, U.; Dev, S. Bakuchiol, A Novel Monoterpenoid. *Tetrahedron Lett*. **1966**, *38*, 4561.

[7] Labbe, C.; Faini, F.; Coll, J. Bakuchiol derivatives from the leaves of Psorlea glandulosa. *Phytochemistry* **1996**, 42, 1299.

[8] Krenisky, J.; Luo, J.; Reed, M. Isolation and antihyperglycemic activity of bakuchiol from Otholobium pubescens (Fabaceae), a Peruvian medicinal plant used for the treatment of diabetes. *Biol. Pharm. Bull*. **1999**, 22. 1137.

[9] Lystvan, K.; Belokurova, V.; Sheludko, Y.; Ingham, J.; Prykhodko, V. Kishchenko, O.; Paton, E.; Kuchuk, M. Production of Bakuchiol by in vitro systems of Psoralea drupacea Bge. *Plant Cell, Tissue Organ Cult.* **2010**, 101, 99.

[10] Choi, S.; Lee, S.; Choi, W. Isolation and anti inflamatory acativity of Bakuchiol from Ulmus davidiana var. japonica. *J. Med. Food*. **2010**. 13. 1019.

[11] Ohno, O.; Watabe, T.; Nakamura, K.; Kawagoshi, M.; Uotsu, N.; Chiba, T.; Yamada, M.; Yamaguchi, K.; Yamada, K.; Miyamoto, K.; Uemura, D. Inhibatory effects of Bakuchiol, bavachin and Isobavachalcone isolated from Piper longum on melanin production in B16 mouse melanoma cells. *Biosci., Biotechnol., Biochem.* **2010**. 74. 1504.

[12] Rangari, V.; Agrawal, S. Chemistry and Pharmacology of Psoralea corylifolia. *Indian Drugs*. **1992**, 29, 668.

[13] Haraguchi, H.; Inoue, J.; Tamura, Y.; Mitzutani, K. Inhibition of mitochondrial lipid peroxidation by Bakuchiol, a meroterpene from Psoralea corylifolia. *Planta Med*. **2000**, 66, 569.

[14] Haraguchi, H.; Inoue, J.; Tamura, Y.; Mitzutani, K. Antioxidative components of Psoralea corylifolia (Leguminosae). *Phytother Res.* **2002**, 16, 539.

[15] Jiangning, G.; Xinchu, W.; Hou, W.; Qinghua, L.; Kaishum, B. Antioxidants from a Chinese medicinal Herb - Psoralea corylifolia L. *Food Chemistry*. **2005**, 91, 287.

[16] Adhikkari, S.; Joshi, R.; Patro, B. Antioxidant activity of Bakuchiol: experimental evidences and theoretical treatments on the possible involvement of the terpinoid chain. *Chem. Res. Toxicol*. **2003**. 16. 1062.

[17] Bapat, K.; Pandey, U. Preparation and invitro evaluation of radioiodinated bakuchiol as an antitumor agent. *Appl. Radiat. Isot*. **2005**, 389.

[18] Park, E.; Zhao, Y.; Kim, Y.; Sohn, D.Bakuchiol-induced caspase-3-dependent apoptosis occurs through c-Jun NH2-terminal kinase-mediated mitochondrial translocation of Bax in rat liver myofibroblasts. *Eur. J. Pharmacol*. **2007**, 559, 115.

[19] Chen, Z.; Jin, K.; Gao, L.; Lou, G.; Jin, Y.; Yu, Y.; Lou, Y. Anti-tumor effects of bakuchiol, an analogue of resveratrol, on human lung adenocarcinoma A549 cell line. *Eur. J. Pharmacol*. **2010**, 643, 170.

[20] (a) Sun, N.; Woo, S.; Cassady, J.; Snapka, R. DNA polymerase and topoisomerase II inhibitors from Psoralea corylifolia. *J. Nat. Prod*. **1998**, 61, 362. (b) Lee, S.; Nam, K.; Mar, W. Induction of quinone reductase activity by psoralidin isolated from Psoralea corylifolia in mouse hepa 1c1c7 cells. *Arch. Pharmacal. Res*. **2009**, 32, 1061.

[21] Mehta, G.; Nayak, U. R.; Dev, S. Bakuchiol, a novel monoterpene phenol. *Tetrahedron* **1973**, *29*, 1119.

[22] Katsura, H.; Tsukiyama, R.; Suzuki, A.; Kobayashi, M. In vitro antimicrobial activities of bakuchiol against oral microorganisms. *Antimicrob. Agents Chemother*. **2001**, 45, 3009.

[23] Matsuda, H.; Kiyohara, S.; Sugimoto, S.; Ando, S.; Nakamura, S.; Yoshikawa, M. Inhibitors from the seeds of Psoralea corylifolia on production of nitric oxide in lipopolysaccharide-activated macrophages. *Biol. Pharm. Bull.* **2009**, 32, 147.

[24] Choi, Y.; Yon, G.; Hong, K.; Yoo, D.; Choi, C.; Park, W.; Kong, J.; Kim, Y.; Ryu, S. In vitro BACE-1 inhibitory phenolic components from the seeds of *Psoralea corylifolia*. *Planta Medica*. **2008**, 74, 1405.

[25] Wall, M. E.; Wani, M. C.; Manikumar, G.; Abraham, P.; Taylor, H.; Hughes, T. J.; Warner, J.; McGivney, R. Plant Antimutagenic Agents, 2. Flavonoids. *J. Nat. Prod.* **1988**, 51, 1084.

[26] Cho, H.; Jun, J. Y.; Song, E. K.; Kang, K. H.; Baek, H. Y.; Ko, Y. S.; Kim, Y. C. Bakuchiol: a hepatoprotective compound of *Psoralea corylifolia* on tacrine-induced cytotoxicity in Hep G2 cells. *Planta Medica*. **2001**, 67, 750.

[27] Krenisky, J. M.; Luo, J.; Reed, M. J.; Carney, J. R. Isolation and antihyperglycemic activity of bakuchiol from Otholobium pubescens (Fabaceae), a Peruvian medicinal plant used for the treatment of diabetes. *Biol. Pharm. Bull.* **1999**, 22, 1137.

[28] H.-C. Lin, H.-Y. Ding,W.-L. Chang, C.-L. Chao, H.-W. Huang,U.S. Pat. US2005256208, 2005 (Chem. Abstr. 2005, 143, 466066).

[29] Chaudhuri, R. K.; Bojanowski, K. Bakuchiol: a reinol-like functional compound revealed by gene expression profiling and clinically provento have anti-aging effects. *Int. J. Cos. Sci.* **2014**, 36, 221.

[30] Cha, M.; Choi, C. W.; Lee, J. Y.; Kim, Y. S.; Yon, G. H.; Choi, S.; Ryu, S. Y. Anti-Proliferative Effect of Synthesized Bakuchiol Analogues on Cultured Human Tumor Cell Lines. *Bull. Korean Chem. Soc*. **2012**, *33*, 2378.

[31] Damodaran, N. P.; Dev, S. Synthesis of (+)-Bakuchiol Methyl Ether. *Tetrahedron Lett*. **1967**, *30*, 2897.

[32] Carnduff, J.; Miller, J. A. The Synthesis of (+)-Bakuchiol. *Chem. Commun*. **1967**, *4561,* 606.

[33] Takano, S.; Shimazaki, Y.; Ogasawara, K. Enantiocontrolled synthesis of natural (+)-bakuchiol. *Tetrahedron Lett*. **1990**, *31*, 3325.

[34] Araki, S.; Bustugan, Y. Short Synthesis of (f)-Bakuchiol *via* a Geranylindium Reagent. *J . Chem. Soc., Perkin Trans.* **1991**, 1, 2397.

[35] Sakurako, S.; Yamamoto, K.; Asaoka, M. A New Synthesis of (+)-Bakuchiol. *Nat. Prod. Lett*. **1998**, *14*, 1.

[36] Esumi, T.; Shimizu, H.; Kashiyama, A.; Sasaki, C.; Toyota, M.; Fukuyama, Y. Efficient Construction of a Chiral All-Carbon Quaternary Center by Asymmetric 1,4-Addition and its application to Total Synthesis of (+)-Bakuchiol. *Tetrahedron Lett*. **2008**, *49*, 6846.

[37] Du, X.; Chen, H.; Feng, H.; Li, Y. Stereoselective Total Synthesis of Natural (S)-Bakuchiol and Its Enantiomer. *Helv. Chim. Acta* **2008**, 91 371.

[38] Gao, F.; McGrath, K.; Lee, Y.; Hoveyda, A. Synthesis of Quaternary Carbon Strategic Centers through Enantioselective Cu-Catalyzed Allylic Substitutions with Vinylaluminum Reagents. *J. Am. Chem. Soc*. **2010.** 132, 14315.

[39] Brown, M.; May, T.; Baxter, C.; Hoveyda, A. All Carbon Quaternary Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene. *Angew. Chem. Int. Ed*. **2007**, 46, 1097.

[40] Takao, K.; Sakamoto, S.; Touati, M.; Kusakawa, Y,; Tadano, K. Asymmetric Construction of All-Carbon Quaternary Stereocenters by Chiral-Auxiliary-Mediated Claisen Rearrangement and Total Synthesis of (+)-Bakuchiol. *Molecules* **2012,** 17, 13330.

[41] Esumi, T.; Yamamoto, C.; Fukuyama, Y. A Short Synthesis of (+)-Bakuchiol. *Synlett* **2013**, 24, 1845.

[42] Qabaja, G.; Wilent, J. E.; Benavides, A. R.; Bullard, G. E.; Petersen, K. S.; Facile Synthesis of Versatile Enantioenriched α-Substituted Hydroxy Esters through a Brønsted Acid Catalyzed Kinetic Resolution. *Org. Lett*. **2013**, *15*, 1266.

[43] Wilent, J.; Petersen, K. Enantioselective Desymmetrization of Diesters. *J. Org. Chem*. **2014**, 79, 2303.

[44] Bernet, B.; Bishop, P.; Caron, M.; Kawamata, T.; Roy, B.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. Formal total synthesis of erythromycin A. Part I. Total synthesis

of a 1,7-dioxaspiro[5.5]undecane derivative of erythronolide A. *Can. J. Chem*. **1985**, 63, 2810.

[45] Luca, L.; Giacomelli, G.; Porcheddu, A. An Efficient Route to Alkyl Chlorides from Alcohols using the Complex TCT, DMF. *Org. Lett*. **2002**, 4, 553.

[46] Hoai, P.; Tsunoi, S.; Ike, M.; Inui, N.; Tanaka, M.; Fujita, M. Dicarboxylic degradation products of nonylphenol polyethoxylates: synthesis and identification by gas chromatography–mass spectrometry using electron and chemical ionization modes. *J. Chromatogr. A*. **2004**, 1061, 115.

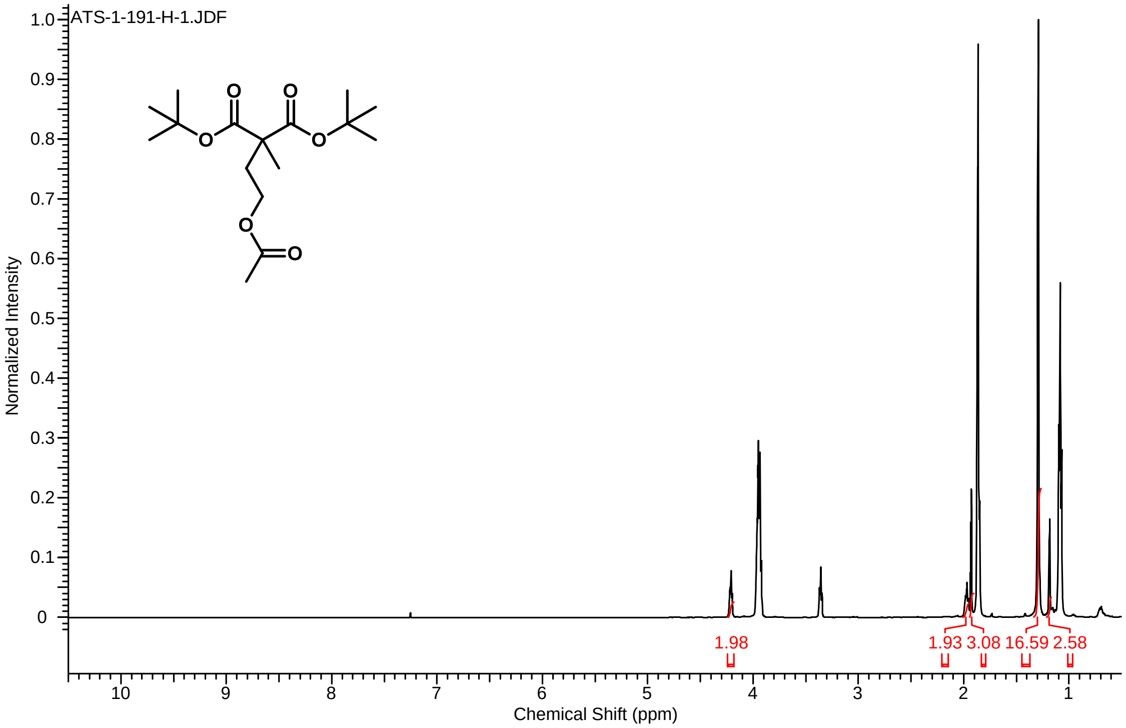
[47] Soengas, R.; Izumori, K.; Simone, M. I.; Watkin, D. J.; Skytte, U. P.; Soetaert, W.; Fleet, G. W. J. *Tetrahedron Lett.* **2005**, 46, 5755.

APPENDIX A

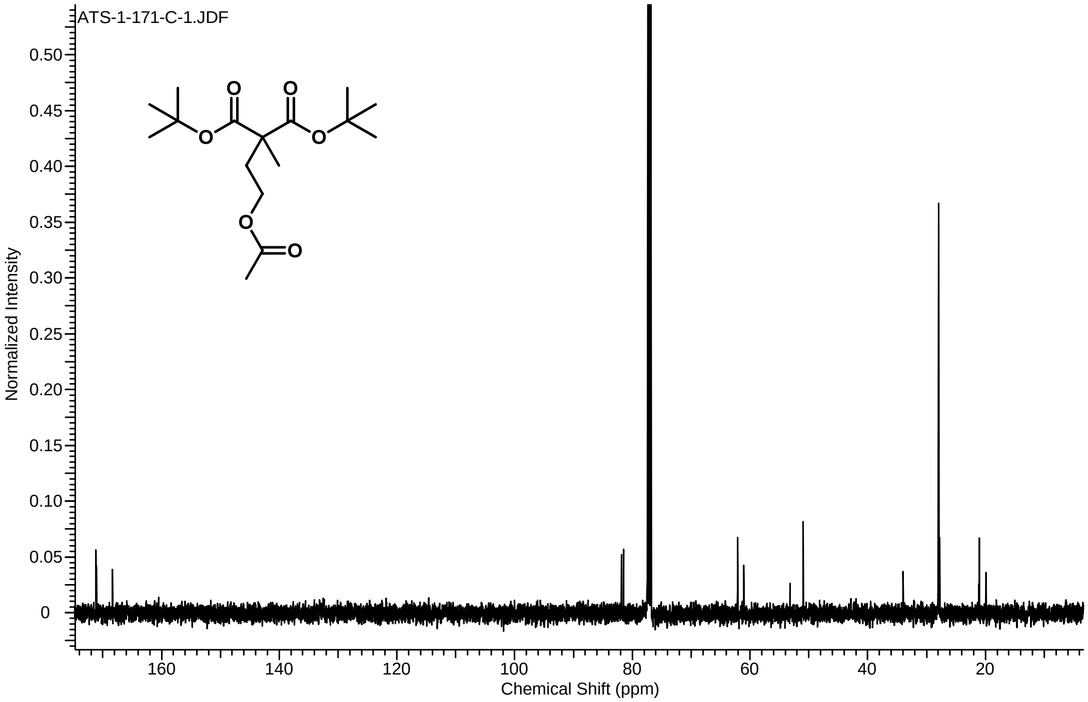
NMR SPECTRA OF COMPOUNDS

NMR spectra were recorded using a JEOL ECA spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). All spectra were taken at room temperature in $CDCl_3$.

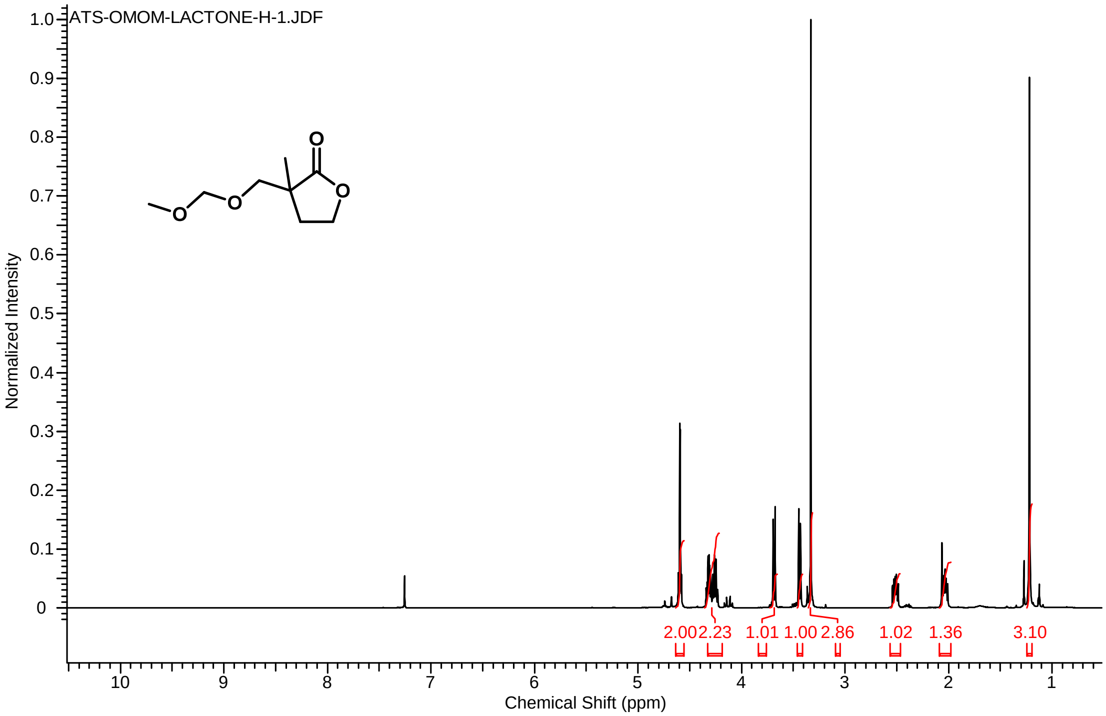
^{1}H NMR of **54**



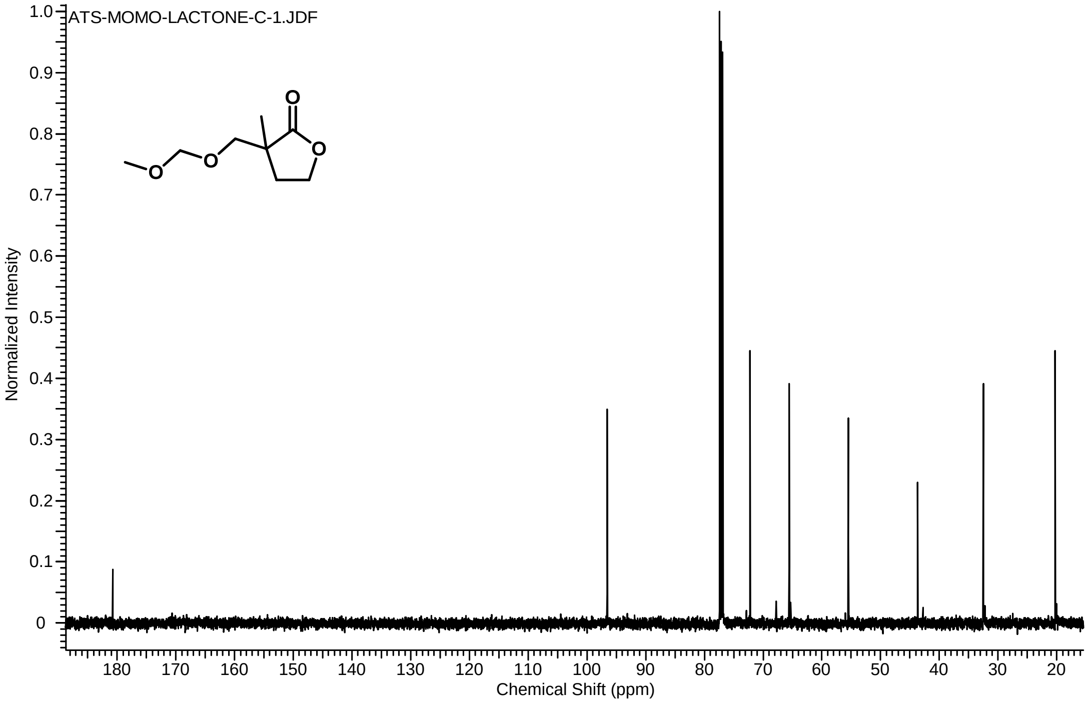
^{13}C NMR of **54**



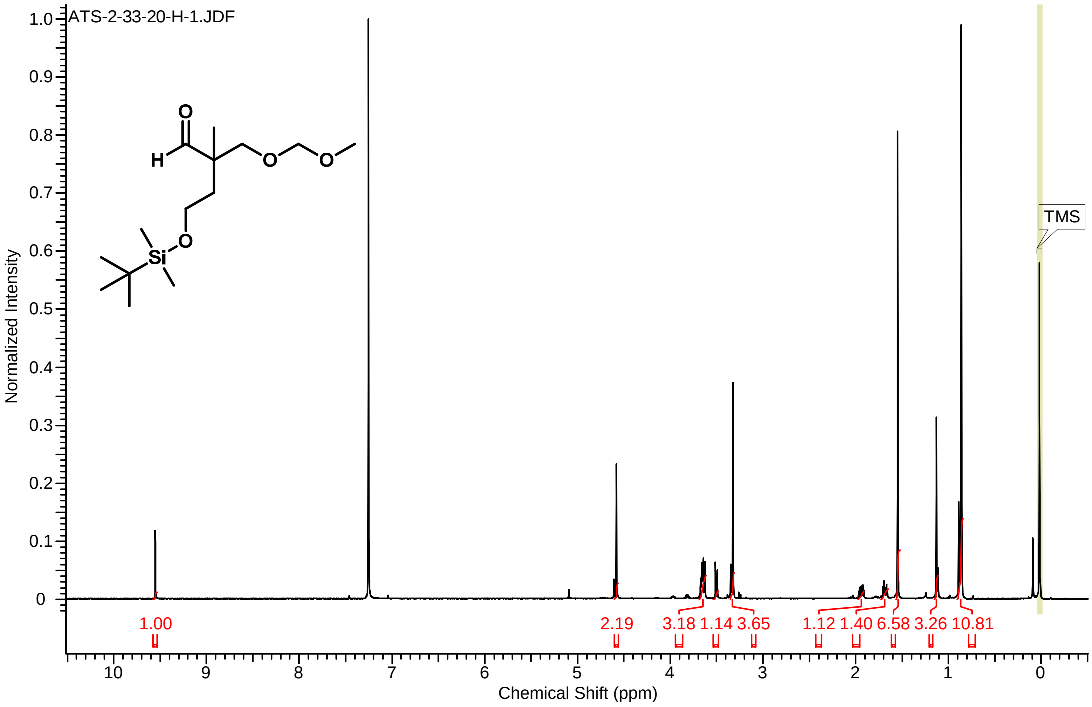
^{1}H NMR of **66**



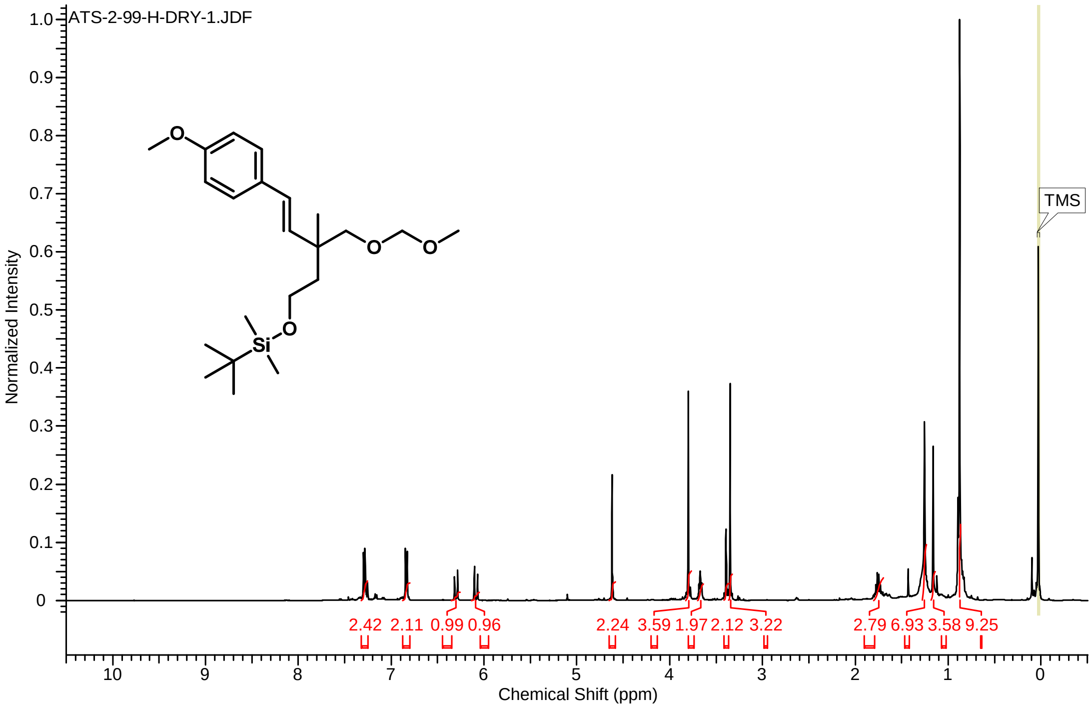
^{13}C NMR of **66**



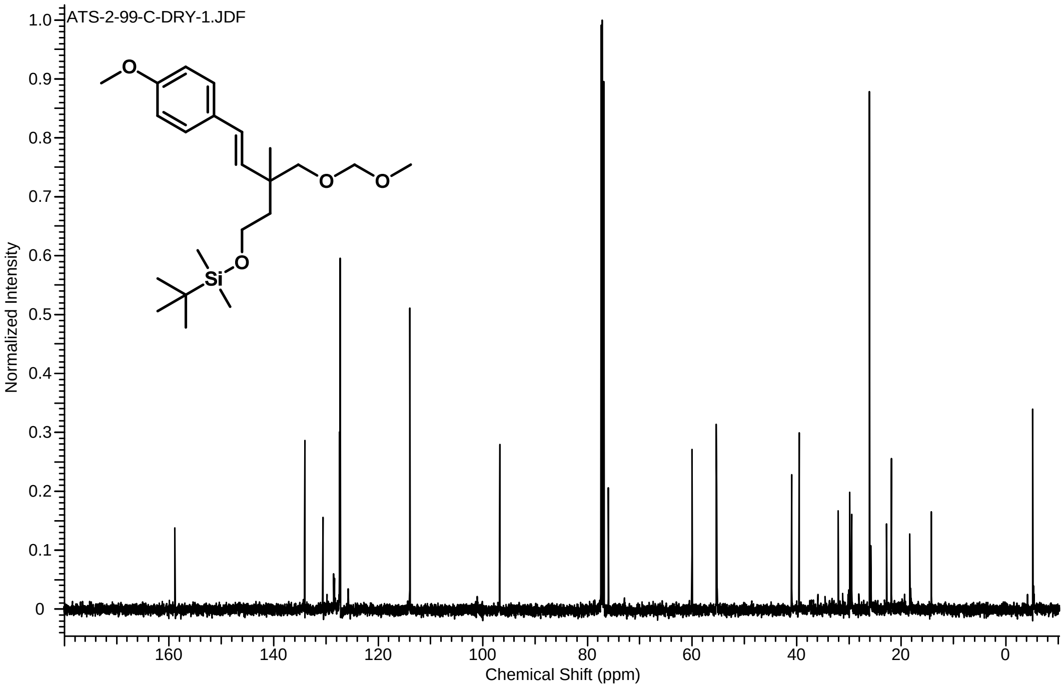
^{1}H NMR of **68**



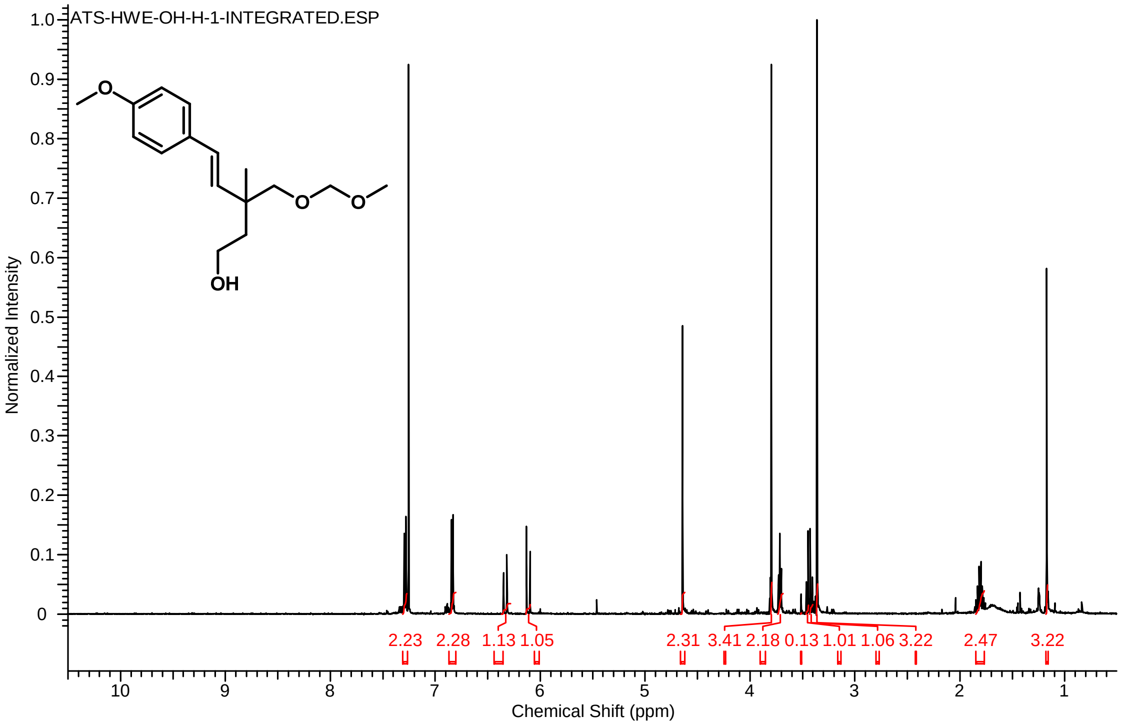
^{1}H NMR of **69**



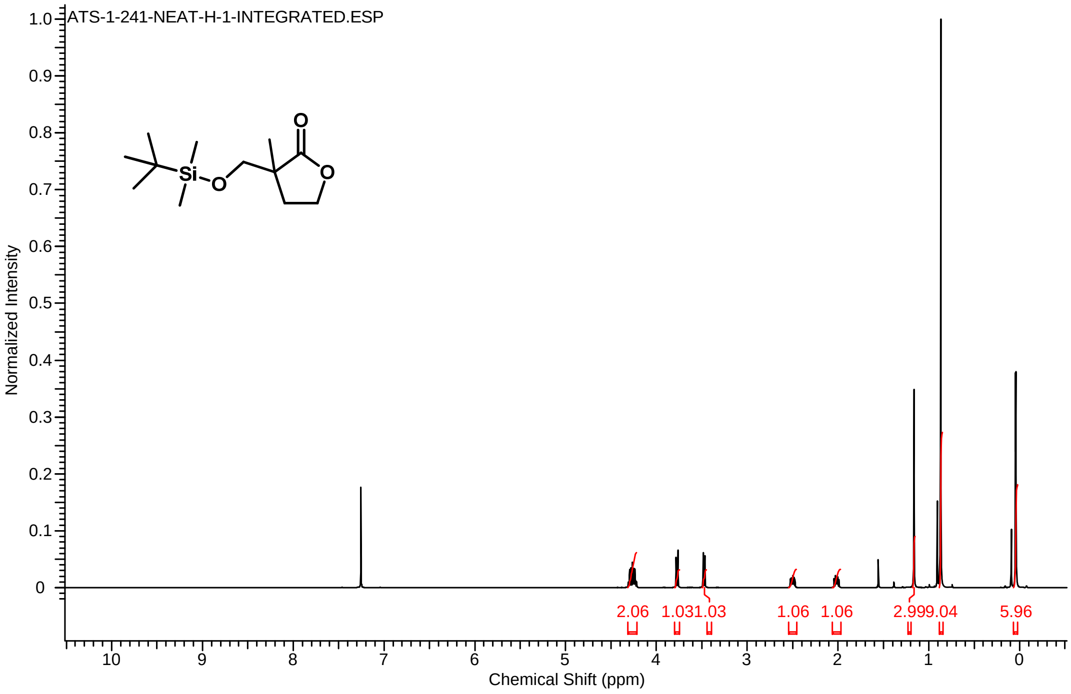
^{13}C NMR of **69**



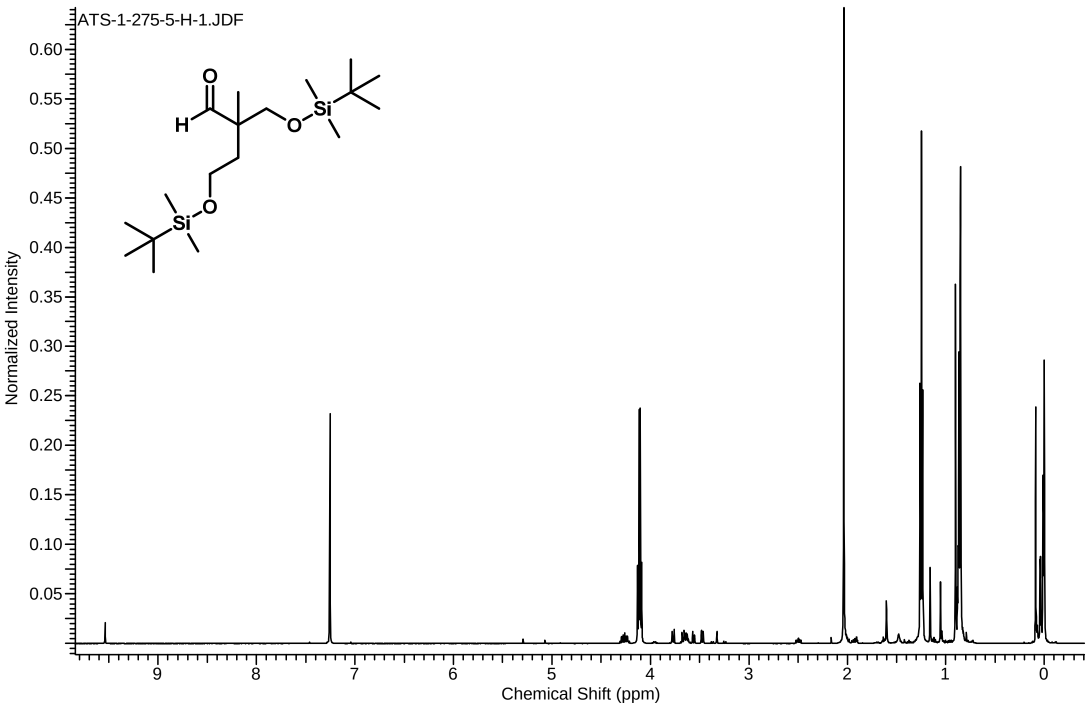
^{1}H NMR of **70**



^{1}H NMR of **47**



^{1}H NMR of **64**


ATS-1-275-5-H-1.JDF
Normalized Intensity
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
O
H
O
Si
O
Si