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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Master of Science

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2014

Approved by

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Date of Final Oral Examination
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<table>
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<tr>
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<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxy toluene</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-binaphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIBALH</td>
<td>Di-iso-butylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N, N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron-donating group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Eq</td>
<td>Equivalents</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron-withdrawing group</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>LG</td>
<td>Good leaving group</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner Wadsworth Emmons</td>
</tr>
<tr>
<td>im</td>
<td>Imidazole</td>
</tr>
<tr>
<td>MABR</td>
<td>Methylaluminum bis(4-bromo-2,6-di(tert-butyl)phenoxide</td>
</tr>
<tr>
<td>MOMCl</td>
<td>Chloromethyl methyl ether</td>
</tr>
<tr>
<td>MsCl</td>
<td>Mesyl chloride</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>Pf</td>
<td>Protection Factor</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>pKa</td>
<td>Acid dissociation constant</td>
</tr>
<tr>
<td>PPG</td>
<td>Primary protecting group</td>
</tr>
<tr>
<td>pTSA</td>
<td><em>para</em>-Toluenesulfonic acid</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SHMDS</td>
<td>Sodium hexamethyl disilazane</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-<em>n</em>-butylammonium fluoride</td>
</tr>
<tr>
<td>TBSCI</td>
<td>t-Butyldimethylchlorosilane</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
<tr>
<td>TsCl</td>
<td>Toluensulfonyl chloride</td>
</tr>
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</table>
CHAPTER I

INTRODUCTION TO BAKUCHIOL AND DESYMETRIZATION

1.1 Description

Bakuchiol (1), also known 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.
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, *Ottholobium pubescens* in 1999, *P. drupaceae* in 2010, *Ulmus davidiana* in 2010, and *Piper longum* in 2010.

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. 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.

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. 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)

<table>
<thead>
<tr>
<th>Concentration of I-bakuchiol (µM)</th>
<th>1.25</th>
<th>2.5</th>
<th>6.25</th>
<th>12.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% cell uptake</td>
<td>26.5 ± 1</td>
<td>39.5 ±1</td>
<td>40.5 ± 1</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>% Blank</td>
<td>2.4 ± .5</td>
<td>1.6 ± .4</td>
<td>1.1 ± .06</td>
<td>1.2 ± .04</td>
</tr>
<tr>
<td>Mean ± SD, n=3</td>
<td></td>
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</tbody>
</table>
Table 2. Uptake Studies of $^{125}$I-bakuchiol in Barcl-95 Cells (37 °C, 30 min)

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

Bakuchiol exhibits antibacterial activity notably against Staphylococcus aureus at only 2-4 µg/mL. 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.

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. It performed as a beta-site APP cleaving enzyme-1 (BACE-1) inhibitor in vitro. It also exhibits
antimutagenic activity\textsuperscript{25} and hepatoprotective activity in human liver cells with a dose of only 1.0 µg/ml.\textsuperscript{26} It exhibited an antidiabetic affect in rats with type 2 diabetes without affecting lean rats. It reduced blood glucose and triglyceride levels.\textsuperscript{27} It has also been shown to be effective against breast cancer.\textsuperscript{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.\textsuperscript{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\textsubscript{50} of 13.1 µM which, when compared to the ED\textsubscript{50} of (+)-bakuchiol of 36.2 µM, exhibits more of an inhibitory effect on the proliferation of human tumor cells.\textsuperscript{30} While this is still considered inactive, other analogs of bakuchiol may be more potent.
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 °C, aldehyde 5 was produced in 90 % yield via a Claisen rearrangement. It is important to note that when 4 was heated at 200 °C, 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 °C to form the bakuchiol methyl ether (8).\textsuperscript{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 \textit{p}-methoxyacetophenone diethyl ketal (9) and mercuric acetate in diglyme at 160 °C 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 °C 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 trifluoride 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.
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

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 %\(^3\).\(^5\) 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](image)

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\(^3\).\(^6\) 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 %.
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%. 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)$_4$.
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). 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.\textsuperscript{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 %. 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\%. 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 enantioenriched 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%. 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).

Scheme 15. Retrosynthesis of Racemic Bakuchioli
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$_2$O, 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. 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 %.
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 CH₂Cl₂ to yield lactone 55 in 84 % yield.

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$_2$Cl$_2$ 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 TBSCI in DMF to yield the desired TBS protected lactone 57 in 85 % yield.

Scheme 21. Protection of Hydroxy Lactone with TBSCI

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.

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.

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 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 TBSCI 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-\textit{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](image)

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).\textsuperscript{44}

![Scheme 28. Addition of Tosyl Group to Alcohol 70 and Elimination to Vinyl 72](image)
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

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 P₂O₅. 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-\textit{t}-butyl 2-Methylmalonate (51)

\textbf{Di-\textit{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-\textit{t}-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\textsubscript{4}Cl (10 mL) at 0 °C, the phases were separated, the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over MgSO\textsubscript{4} and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10→30 % EtOAc in hexanes) to afford the di-\textit{t}-butyl 2-methylmalonate intermediate as a colorless oil (5.14 g, 97 % yield). The spectroscopic data matched the previously known compound reference.\textsuperscript{42}
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 °C. 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 NH₄Cl (10 mL) at 0 °C, the phases were separated, the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over MgSO₄ 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 %).

**¹H NMR** (500 MHz, CDCl₃) 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.

**¹³C NMR** (125 MHz, CDCl₃) δ 171.1, 168.3, 81.8, 62.1, 50.0, 33.9, 27.9, 21.0, 19.9 ppm.
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$_2$CO$_3$ and the solution was stirred at rt for 45 min. The reaction mixture was diluted with CH$_2$Cl and was extracted (3 x 30 mL) and H$_2$O (1 x 30 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. 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.$^{42}$

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$_2$Cl$_2$ (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 H₂O (1 x 30 mL) and EtOAc (3 x 30 mL). The organic phases were dried over MgSO₄ 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(OtBu)₃H (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 CH₂Cl₂ (1 x 20 mL) and EtOAc (2 x 20 mL). The organic phases were dried over MgSO₄ 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
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 CH₂Cl₂ (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 H₂O (1 x 10 mL) and EtOAc (3 x 10 mL). The organic phases were dried over MgSO₄ 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

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 CH₂Cl₂ (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 H₂O (1 x 10 mL) and EtOAc (3 x 10 mL). The organic phases were dried over MgSO₄ 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.

\[ ^1H \text{ NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta 4.60 \text{ (s, 2H)}, 4.31 \text{ (m, 2H)}, 3.68 \text{ (d, } J = 5 \text{ Hz, 1H)}, 3.45 \text{ (d, } J = 5 \text{ Hz, 1H)}, 3.33 \text{ (s, 3H)}, 2.51 \text{ (m, 1H)}, 2.05 \text{ (m, 1H)}, 1.22 \text{ (s, 3H) ppm.} \]

\[ ^{13}C \text{ NMR} (125 \text{ MHz, CDCl}_3) \delta 180.7, 96.6, 72.2, 65.6, 55.5, 43.7, 32.5, 20.3 \text{ ppm.} \]

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 °C 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 H₂O (1 mL), 15 % saturated NaOH (1 mL) and H₂O (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).

\[ \text{Scheme 40. Aldehyde 68} \]

**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\(_2\)O and DCM, dried over MgSO\(_4\) and concentrated. The crude product was purified by flash chromatography in 0-15 % EtOAc in hexane to yield aldehyde 68 (111 mg, 70 %).

\[ \text{\(^1H\) NMR (500 MHz, CDCl\(_3\) \(\delta\) 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.} \]
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 MgSO₄ 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\text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 7.28 (d, J = 10 \text{ Hz, 2H}), 6.83 (d, J = 10 \text{ Hz, 2H}), 6.29 (d, J = 15 \text{ Hz, 1H}), 6.10 (d, J = 15 \text{ Hz, 1H}), 4.62 (s, 2 \text{ H}), 3.80 (s, 3 \text{ H}), 3.67 (t, J = 5 \text{ Hz, 2H}), 3.39 (s, 2 \text{ H}), 3.35 (s, 3 \text{ H}), 1.76 (dd, J = 10 \text{ Hz, 2H}), 1.26 (s, 6 \text{ H}), 1.16 (s, 3 \text{ H}), 0.88 (s, 9 \text{ H}) \text{ ppm.} \\
\(^{13}\text{C NMR} (125 \text{ MHz, CDCl}_3) \delta 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 \text{ ppm.}
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 MgSO₄. The crude product was purified by flash chromatography in 10-100 % EtOAc in hexanes to yield the alcohol (35 mg, 81 %).

**1H NMR** (500 MHz, CDCl₃) 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.

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 NH₄Cl at 0 °C. The organic layer was separated with EtOAc and dried over MgSO₄. 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 H₂O 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 OsO₄ (2.5 %, 91 mL, .08 mmol) and NaIO₄ (4.55 g, 17.88 mmol). The organic layer was flushed through filter paper and separated with DCM and H₂O, then dried over sodium sulfate and concentrated in vacuo to yield the crude malonate aldehyde **53** (1.35 g).
Alcohol 46: To a clean flame dried round bottom flask with stir bar was added a solution of NaBH₄ (.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 MgSO₄ 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

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 H₂O and EtOAc. The organic layer was dried over MgSO₄
and concentrated in vacuo. The crude product was purified by flash chromatography in 0-40 % EtOAc in hexanes to yield TBS lactone 57 (199 mg, 85 %).

\[ ^{1}H \text{ NMR (500 MHz, CDCl}_3 \text{)} \delta 4.26 (m, 2H), 3.78 (d, J = 10 \text{ Hz}, 1H), 3.48 (d, J = 10 \text{ Hz}, 1H), 2.50 (m, 1H), 2.03 (m, 1H), 1.16 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H) \text{ ppm.} \]

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 H₂O, dried over MgSO₄ 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$_2$CO$_3$ (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$_2$O (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.

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$_2$CO$_3$ (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$_2$O (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.

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 H₂O (0.1mL), 10 % NaOH (0.1 mL), H₂O₂ (0.2 mL) and allowed to react for 30 min. The organic layer was separated with diethyl ether (3 x 5 mL) dried over MgSO₄ 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 K₂CO₃ (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 H₂O (10 mL). The organic layer was dried over MgSO₄ 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$_2$O (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 10 mL) and H$_2$O (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$_2$O (3 x 10 mL).
mL), dried over MgSO₄ 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).

¹H NMR (500 MHz, CDCl₃) 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.

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 NH₄Cl at 0 °C. The organic layer was separated with EtOAc (3 x 10 mL), dried over MgSO₄, and concentrated. The crude residue was columned in 0-100 % EtOAc in hexanes to yield silyl phenol 65 (18.8 mg, 50 %).
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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
$^{13}\text{C NMR of 66}$

$^{1}\text{H NMR of 68}$
$^1$H NMR of 69

$^{13}$C NMR of 69
$^{1}$H NMR of 70

$^{1}$H NMR of 47
\(^1\text{H NMR of 64}\)