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Novel Strategy for the Synthesis of Allenes

A thesis

presented to

the Faculty of the Department of Chemistry

East Tennessee State University

In partial fulfillment

of the requirements for degree

Master of Science in Chemistry

by

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August 2009

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Keywords: Eschenmoser fragmentation, phloroglucinols, allenes, tosylhydrazones
ABSTRACT

Novel Strategy for the Synthesis of Allenes

by

Mark-Henry MbaMba Kamga

Allenes are very important chemical reagents in organic synthesis. Due to their high reactivity, they have been extensively used to carry out a variety of unique and effective chemical transformations including but not limited to ionic and free radical additions and transition metal catalyzed cyclizations. As the chemistry of this group of compounds is explored further and their applications expanded there is a need to develop alternative and cost effective methods for their synthesis. Our approach involves the synthesis of allenes from oxa-bicyclo-alkan-2-ones by methyllithium induced Eschenmoser fragmentation of the bicyclotosylhydrazone derivatives.
DEDICATION

This thesis is dedicated to my late father: Mr. Peters Meange Kamga. Your strength of character and dedication are my source of inspiration.
ACKNOWLEDGMENTS

I render immense thanks to God Almighty for seeing me through each day.

I would like to extend a heartfelt ‘thank you’ to my supervisor, Dr. David Young, for his patience and dedication. I have learnt so much from him in so little time and I am confident that his example of an excellent teacher would remain with me always. I am proud to have known him and been his student. I equally want to thank Dr. Jeffrey Wardeska and Dr. Yu-Lin Jiang for being on my committee and revising my thesis.

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<tr>
<td>Ac</td>
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<tr>
<td>AIBN</td>
<td>2,2’-azobisisobutyronitrile</td>
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<td>i-Pr</td>
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<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
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<tr>
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<td>lithium diisopropylamide</td>
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<tr>
<td>THF</td>
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CHAPTER 1

INTRODUCTION AND BACKGROUND

Introduction

In this thesis we shall discuss research attempts to synthesize allenes from tosylhydrazones with the aim of synthesizing hyperforin, a phloroglucinol. In order to provide the reader with enough background, we shall provide a brief introduction to the phloroglucinol family of biologically active molecules. Then, we shall discuss our approach toward the synthesis of hyperforin. Previous studies relevant to our approach will precede the discussion on the results obtained this far.

Introduction to Phloroglucinols: Structure and Biological Activity

The term phloroglucinols is used to describe a group of organic compounds having the phloroglucinol (1) moiety as the key structural feature. The molecule phloroglucinol (1) exists in two tautomeric forms: 1,3,5-trihydroxybenzene (1) and 1,3,5-cyclohexanetrione (2) that exist in equilibrium with each other.

The polyfunctionality of phloroglucinol makes it an important intermediate in the synthesis of pharmaceuticals.
Phloroglucinol based natural products have recently gained a lot of attention for their unique features and important medicinal properties. They have been isolated from natural sources including members of plant genus Hypericum and Garcinia. Many of the biologically active metabolites of these phloroglucinol based species are polycyclic polypropenylated acylphloroglucinol (PPAP) derivatives. These contain prenyl or geranyl appendages and have been characterized by a densely substituted bicyclo[3.3.1]nonane-2,4,9-trione. Let us examine some phloroglucinols.

Hyperforin

Interest in PPAP natural products increased when it was discovered that hyperforin (3) was the primary active ingredient in St. John’s wort, a drug used to treat depression. The structure of hyperforin was first elucidated by Gurevich and coworkers in 1971 who carried out X-ray diffraction and spectroscopic methods to analyze the structure.

Figure 1: Hyperforin
Hyperforin (3), which is found in some members of the *Hypericum* plant genus, has been shown to have multiple antibacterial properties. It is active against methicillin resistant *Staphylococcus aureus* and has also shown some anticancer activity.

The mechanism of action for biological activity of hyperforin (3) has been studied. Hyperforin (3) acts as a reuptake inhibitor in synapses by inhibiting monoamines such as dopamine, serotonin, and epinephrine. It also inhibits GABA and glutamate. Its mode of action differs from other antidepressants because instead of inhibiting proteins, it activates the transient receptor potential ion channel (TRPC6), inducing the entry of sodium and calcium into the cell. This changes intracellular H\(^+\) and Na\(^+\) concentrations that cause inhibition of monoamine reuptake.

The mechanism for the biological synthesis of hyperforin (3) was proposed by Wolfgang and coworkers. They used carbon-13 labeling experiments to show that the core acylphloroglucinol 10 is prepared from pyruvate. Though some of the intermediates shown can be prepared from valine, self condensation of pyruvate (4) followed by decarboxylation to form \(\alpha\)-hydroxyketone 5 that transforms to ketocarboxylate 6 could explain the formation of 10. Oxidative decarboxylation of 6 affords acetyl-CoA (7) that condenses with three malonyl-CoA (8) units to generate the triketone 9. Intramolecular cyclization yields acylphloroglucinol 10.
Scheme 2: Proposed mechanism for the biological synthesis of hyperforin (3)
Guttiferone E

Guttiferone was first identified from a sample of *Garcinia ovalifolia* from Central African Republic in 1988.

![Guttiferone E](image)

Figure 2: Guttiferone E

Guttiferone (11) has been found to be active against HIV. It works by inhibiting the cytopathic effects of *in vitro* HIV infection. HIV causes the cytopathic effect by binding to and penetrating a helper T cell. When HIV replication is initiated, the helper T cell is destroyed and immunodeficiency results. Guttiferone inhibits HIV-1 reverse transcriptase that is responsible for transcribing RNA to DNA during reproduction.
Garsubellin A

The structure of garsubellin A (12) was first reported by Fukuyama and coworkers in 1997. Garsubellin A (12) is extracted from the wood of *Garcinia subelliptica* a tree that grows in Japan. It is a potent inducer of acetyltransferase (ChAT). This enzyme is responsible for the biosynthesis of the neurotransmitter acetylcholine (ACh).

![Garsubellin A](image)

**Figure 3: Garsubellin A**

One of the hypotheses proposed for the causes of Alzheimer’s disease is the reduced synthesis of acetylcholine. Therefore, garsubellin A (12) can be a potent candidate for the treatment of Alzheimer’s. Studies on rats has already shown that garsubellin A (12) increases ChAT activity by 154% at a 10 µM concentration.

Garsubellin A (12) has been successfully synthesized by Kuramochi and coworkers.
Garcinol

Garcinol (13) is extracted from *Garcinia indica*. It is a potent inhibitor of histone acetyltransferases (HATs) both *in vitro* and *in vivo*. The inhibition of this enzyme inhibits the acetylation of histones that is believed to directly facilitate DNA transcription. This process can be applied for the treatment of cancer. Studies have shown that garcinol (13) can cause apoptosis in HeLa cells by causing down-regulation of global gene expression. It also down-regulates several proto-oncogenes, therefore, it is potent for the treatment of cancer.

However, inhibition of histone acetylation has also been associated with other disease conditions such as AIDS and so further research still has to be done in order to find if garcinol (13) or its derivatives can be used for designing therapeutic agents for the treatment of other diseases.

![Garcinol](image)

Figure 4: Garcinol
The focus of our research is to synthesize hyperforin (3). Although this synthesis has been attempted by several research groups, there has been no published total synthesis of hyperforin (3). Our approach toward the synthesis of hyperforin (3) involves a nitrile oxide allene cycloadditions. We began with the following retrosynthetic analysis.

Scheme 3: Retrosynthetic analysis for hyperforin (3)
We projected that the nitrile oxide allene cycloaddition would take place regioselectively at the external $\pi$-bond rather than the internal. This is in line with previous studies by Young and Zeng$^1$ as seen below. The studies concluded that in the presence of a bulky group $\alpha$ to the allene, allene-intramolecular nitrile oxide cycloadditions would take place at the external $\pi$-bond.

Scheme 4: Allene-intramolecular nitrile oxide cycloadditions presence of bulky group

Scheme 5: Allene-intramolecular nitrile oxide cycloadditions in presence of bulky group
Scheme 6: Allene-intramolecular nitrile oxide cycloadditions in absence of bulky group

These results obtained seemed to be in disagreement with previous studies by Norman A. LeBel\textsuperscript{6} who showed that the product distribution seemed to follow the thermodynamics of ring formation. Formation of five and six-membered rings are favored and the formation of four and seven-membered rings are not observed suggesting that the internal π-bond of the allene is more reactive in many cases.

Scheme 7: Intramolecular nitrone-allene cycloadditions

Our objective, therefore, is to synthesize an allene similar in structure to 14. Let us first examine some of the current methods that have been used for the synthesis of allenes.
Current Methods of Allene Synthesis

Brummond and DeForrest from the University of Pittsburg published a comprehensive paper in 2007 detailing methods that have been used for the synthesis of allenes since 1982. Though their paper was not exhaustive, it gave an overall idea of the synthetic methods and protocols that have stood the test of time. We shall examine some of these general methods that have been employed and our classification of the methods shall be based on the initial material from which the allene is obtained.

Allenes from Alkynes

Reduction of Propargyl Electrophiles. Allenes have been synthesized from propargyl electrophiles such as ethers, alcohols, and epoxides by employing reducing agents such as lithium aluminum hydride (LiAlH₄) and diisobutylaluminum hydride. A hydride is delivered from the reducing agent to the electrophile via an S_N2' attack leading to a new carbon-hydrogen bond and generating a new carbon-carbon double bond. The mechanism is stereospecific and can lead to the syn or anti species depending on the identity of the substrate, reducing agent, and reaction conditions.

Scheme 8: Synthesis of allenes by reduction of propargyl electrophiles
Allenes from Reduction of Enynes. Conjugated enynes have also been converted to allenes by treatment with aluminum hydride reagents. This method has been used since 1973, and in 1988 Bovicelli and co-workers employed this method in the synthesis of β-allenyl alcohols by treating a variety of 1-silyl-enyne-ketones and esters with LiAlH₄.

Scheme 9: Allenes from oxygenated enynes

Allenes from Claisen Rearrangements. Allenes have been synthesized from the Claisen rearrangement and its variants such as the Claisen-Ireland and ortho-ester Claisen. The substrates for these rearrangements include molecules such as the propargyl vinyl esters, propargyl alcohols, and propargylic esters. The mechanism involves a [3,3]-sigmatropic rearrangement.

Scheme 10: Synthesis of an allene by Claisen-Ireland rearrangement
Allene Synthesis via Other [3,3]-sigmatropic Rearrangements. There exist other [3,3]-
sigmatropic rearrangements that can be employed for the synthesis of allenes from propargyl
substrates. Examples include the Saucy-Marbet rearrangement. Other methods include the metal
catalyzed [3,3]-sigmatropic rearrangements. This method has been done successfully with silver,
gold, platinum, and copper catalysts. A recent example is shown below where gold(III) chloride
is used to catalyze the [3,3] rearrangement of a propargyl ester.

Scheme 11: Metal catalyzed synthesis of allene by [3,3] rearrangement
Allenes from Ene Reactions. The ene reaction has been extensively used in the construction of carbon-carbon bonds and has now found application in the synthesis of allenes. Burger and co-workers showed that that trifluoropyruvate (44) can function as the enophile component in the carbonyl-ene reaction.

![Scheme 12: Allene synthesis by ene reaction](image)

Ene reactions have also been used by Buchwald who showed that titanocene catalyst systems can be used in the synthesis of allenes appended to a ring from acyclic dienynes. The reaction is an ene reaction in which the cycle begins with a loss of CO from the catalyst, then the reaction of the resulting species with a dienyne substrate (46). This results in a titanacyclopentane (47) that undergoes hydride elimination and subsequent reductive elimination to afford the allene (48).

![Scheme 13: Buchwald allene synthesis by ene reaction](image)
The Doering-Moore-Skatteböl Reaction

Reactions of geminal dibromocyclopropanes with alkyllithium reagents such as methyllithium and butyllithium produced the desired allene in high yields.

Scheme 14: Allene synthesis from carbene

Peterson Allenation (Allenes from Alkenyl Silanes)

In this procedure, a bromoalkenyl silane undergoes a halogen-metal exchange reaction to produce the vinyl carbanion by treatment with BuLi. Subsequent addition of a ketone results in a lithium alkoxide that undergoes rearrangement and elimination at moderate temperatures of about 50°C to yield the allene.

This reaction was found to be solvent sensitive because the yields obtained were higher when diethyl ether was used in contrast to tetrahydrofuran.
As shown in the scheme below, trisubstituted allenes have been successfully synthesized from β-ketosulfones. This method was developed by Satoh and co-workers. The sulfone is treated with lithium diisopropylamide and phenyl triflimide to obtain the enol triflate (60). Further treatment of the enol triflate (60) with n-butyllithium at low temperatures causes a sulfoxide-metal exchange to afford a reactive intermediate which undergoes β-elimination to produce a cyclic allene (62) in good yield.
Allene Synthesis via Radical Intermediates

Another method of allene synthesis based on β-elimination of sulfinyl radicals was designed by Malacria and co-workers. An allyl bromide is treated with excess amount of tris(trimethyl)silane (TTMS) and 2,2’-azobisisobutyronitrile (AIBN) to give a conjugated radical. Orbital rotation in the intermediate produces a species that undergoes β-elimination to afford the allene. When tin hydride is used in the place of TTMS, the final allene product obtained is contaminated with traces of tin hydride.
One of the most recent methods that has been used in the synthesis of allenes is the application of transition metal catalysts. Common metals used include palladium, indium, chromium, ruthenium, rhodium, zinc, titanium, and copper. Of all these, Pd is by far the most widely used. The reason for this is that Pd allows for the formation of allenes under very mild conditions.

A major protocol used in Pd catalyzed allene formation is the $S_{N}2'$ substitution of conjugated dienes. The most common substrate used is 2-bromo-1,3-butadienes. The scope of this method was extended by Hayashi. He showed that hard nucleophiles tend to give the 1,3-
diene products and that a chiral palladium catalyst generates the allene product with high enantioselectivity.

This method was used in the asymmetric synthesis of methyl (R,E)-(−)-tetradeca-2,4,5-trienoate, a sex pheromone of male dried beans beetle.

Scheme 18: Allene synthesis by Pd catalyzed S\textsubscript{N}2΄ substitution of conjugated dienes

All these schemes designed for the synthesis of allenes proved to be insufficient in satisfying our objectives. The final allene products either do not have the desired functionality or do not provide efficient means of converting the allene product to the desired compound.

We, therefore, turned to the Eschenmoser fragmentation designed in 1967 and explored further by Masato and coworkers. Eschenmoser showed that fragmentation of α, β-epoxyketones by the reaction with p-toluenesulfonylhydrazine occurred readily to afford both terminal and internal acetylenic ketones.
Soon after Eschenmoser’s publication, Tanabe and coworkers explored this protocol for the synthesis of secosteroid acetylenic ketones and also showed that the mechanism is not limited to aromatic sulfonylhydrazone derivative.

This approach was used by Kane in the synthesis of (±)-zoapatanol. A mixture of diastereomeric epoxides was converted to the monocyclic ω-acetylenic ketone via tosylhydrazone by using an Eschenmoser fragmentation under acidic conditions. The intermediates and mechanism of interest are shown below.
Objective of the Research

Our research is focused on developing a novel method for the synthesis of allenes. In order to do this we have developed a theory and our objectives can be presented in two steps.

- Synthesize an oxa-bicyclo-alkan-2-ones and transform it to the corresponding bicyclotosylhydrazone
Convert the tosylhydrazone to the allene by the methyllithium induced nitrogen gas elimination and rearrangement reaction.

**Approach**

The first part of our approach was to synthesize an oxa-bicyclo-alkan-2-one.

![Model oxa-bicyclo-alkan-2-one](image)

The second part was to convert this ketone to the tosylhydrazone and do a methyllithium induced nitrogen gas elimination and rearrangement as shown below.

![Scheme 21: Novel strategy for allene synthesis](image)

We recognize that in Eschenmoser fragmentation, the ring strain in the three-membered epoxide ring enhances ring opening. However, our molecule contains a five-membered epoxide
ring that does not have as much ring strain and so our conjugated anion generated by base treatment may or may not open the epoxide ring. If the ring opens, then fragmentation should occur exactly as observed for the classic Eschenmoser reaction.

Based on this strategy, we designed an approach for the synthesis of our required allene.

Scheme 22: Strategy for allene synthesis
Scheme 22 (continued): Strategy for allene synthesis
CHAPTER 2

RESULTS AND DISCUSSION

Our overall objective is to synthesize hyperforin and our retrosynthetic analysis involves a step requiring an intramolecular nitrile oxide allene cycloadditions as seen in the scheme below. We hypothesized that we could synthesize 15 from 92 or 93. The objective of this study is aimed at synthesizing 92 and/or 93 by the application of Eschenmoser fragmentation.

Scheme 23: Retrosynthetic analysis for allene synthesis

Successful reactions carried out, together with reagents used in completing transformations are shown below (Scheme 24). The percentage yield in each reaction is also indicated.
a) 1.1 eq $p$-toluenesulfonic acid, 1 eq iodobenzene diacetate (b) Furan, CF$_3$CH$_2$OH, NEt$_3$

(c) LiAlH$_4$, anhydrous ether, 0°C (d) MOMCl, N(i-Pr)$_2$Et, CH$_2$Cl$_2$ (e) BnCl, NaH, THF, ∆ (f) MCPBA, NaHCO$_3$, CH$_2$Cl$_2$.

Scheme 24: Toward novel allene synthesis

Synthesis of Toluene-4-sulfonic acid 2-oxo-cyclohexyl ester (Tosyloxy cyclohexanone)

Toluene-4-sulfonic acid 2-oxo-cyclohexyl ester (78) was synthesized using a known procedure developed by Koser and co-workers. The reaction involves a two-step process. The first step is a ligand exchange process. Iodobenzene diacetate (77) reacts with tolenesulfonic
acid (76) and undergoes ligand exchange to generate (hydroxytosyloxyiodo)benzene (94) in a reaction whose mechanism is not fully understood.

Scheme 25: First mechanistic step in the synthesis of tosyloxy cyclohexanone (78)

Under the reaction conditions, cyclohexanol undergoes tautomerization to the enol that reacts with the intermediate to form the tosyloxyketone (78) with yields ranging between 40%-50%.

Scheme 26: Second mechanistic step in the synthesis of tosyloxy cyclohexanone (78)
Synthesis of 11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-one

The cyclization reaction between tosyloxy cyclohexanone (78) and furan (79) is carried out in trifluoroethanol that enables the cyclization process. The reaction is done under kinetically controlled conditions involving dropwise addition of base to the ketone (78) at 0° C. The orientation of the molecules prior to the transition state of the cyclization, results in compound 80 as shown on the scheme below.

Scheme 27: Mechanism of cyclization
Synthesis of 11-Oxa-tricyclo[4.3.1.2,5]undec-3-en-10-ol

From the structure of 80, we expect that there are two modes of attack by the hydride ion from the reducing agent.

In a paper published by Camps, he observed that reduction of ketone 80 using LiAlH₄, would result in the stereoselective reduction to the syn-alcohol involving attack of the hydride ion from the less hindered side.

Scheme 28: Reduction of ketone 80 with lithium aluminum hydride

A solution of the ketone in anhydrous ether was added dropwise to a solution of the reducing agent in ether at 0°C. The reaction proved to be temperature sensitive because attempts
to run the reaction at room temperature were unsuccessful. The yields of this reaction were low. We registered a 40%-50% yield in most cases.

Alcohol 81 was used to synthesize two new compounds involving protection of the alcohol 82 and 83. Protection with MOMCl gave significantly higher yields (80%-95%). The benzyl ether had a characteristic bright yellow color and this was helpful in purification by chromatography because progress of the product could be visually monitored.

Scheme 29: Alcohol protection by MOMCl and BnCl

This product was characterized by $^1$H and $^{13}$C NMR, GC-MS and IR analysis and the results are recorded in the experimental section.

Attempts to convert 82 and 83 into alcohols by oxidation of the olefin with mercuric acetate failed to produce the desired product. The $^1$H NMR analysis showed alcohol coupling but the $^{13}$C was not consistent with structure 84 or 85. The first observation was that in both cases the protecting group was lost and the $^{13}$C NMR showed 10 peaks.
An IR spectrum showed that a cyclization process had occurred leading to an alcohol. We then hypothesized that the oxygen molecule from the protected alcohol was close enough to the mercurinium ion and opened this ion by neighboring group participation to generate the alcohol as shown in the scheme below. However, we are yet to prove the mechanism involved.

![Scheme 30: Proposed mechanism of reaction of 82 and 83 with mercuric acetate.](image)

Since the syn-alcohol was proving to be a problem, we tried to reduce ketone 80 by Wolf-Kishner reduction but the reaction failed to give the required product.

Rather than doing a direct oxidation to the alcohol, we attempted to convert the olefin to the epoxide 84 and then do a reduction of the epoxide 84 to the corresponding alcohol 84.
**Synthesis of Epoxide of 84**

Epoxide 84 was successfully prepared using a known procedure by adding *m*-chloroperoxybenzoic acid to a solution of 82 in dichloromethane and 0.5M NaHCO₃ as buffer. Epoxide 84 was obtained in moderate yields of 50%-70% with minimal purification.

![Scheme 31: Mechanism of synthesis of epoxide by MCPBA](image)

However, attempts to reduce 84 to the corresponding alcohol (86) were unsuccessful. The protecting group was lost and the ¹³C NMR did not correspond to the expected compound. The spectrum was similar to that obtained during oxymercuration, but the positions of the peaks were not exactly the same. We proposed that this difference could be as a result of the difference in the orientation of the alcohol function. We think the structure obtained during the reduction of the epoxide is actually:
Because the orientation of the alcohol was posing a problem, we decided to modify our procedure so as to change the orientation of the reduction of ketone 80. In the same paper by Camps mentioned earlier, he noted that in order to obtain the trans-alcohol by reduction of 80, aluminum triisopropoxide should be used in the place of LiAlH₄. The structure of the alcohol (99) would therefore not permit cyclization during oxymercuration or during epoxide reduction.

(a) 1.1 eq p-toluenesulfonic acid, 1 eq iodobenzene diacetate (b) Furan, CF₃CH₂OH, NEt₃ (g) Al(i-OPr)₃, xylene Δ (d) MOMCl, N(i-Pr)₂Et, CH₂Cl₂ (h) Hg(OAc)₂, THF:H₂O, NaBH₄

Scheme 32: Toward novel allene synthesis via trans-alcohol (99)
The *trans*-alcohol was successfully synthesized using the procedure published by Camps. We, however, noticed lower yields than those published.

The alcohol (99) was successfully protected with MOMCl using the same procedure as for the *syn*-alcohol. We have equally succeeded in oxidizing the olefin to the alcohol (101) by oxymercuration and are currently attempting to oxidize the alcohol to the ketone. Our assumption that neighboring group participation would not work here due to orientational limitations is therefore true.

**Conclusion**

Despite the initial setbacks owing to the neighboring O-participation, we have made significant progress towards achieving our overall objective. The problem of this neighboring group participation has been resolved by synthesizing the *syn*-alcohol. This has led to the successful oxymercuration of the olefin to yield the alcohol. Oxidation of this secondary alcohol should not pose any real problem because several protocols exist for such reactions.

With the ketone produced, the tosylhydrazone can be generated and our hypothesis can be tested for the synthesis of allenes.
CHAPTER 3

EXPERIMENTAL SECTION

General Methods

$^1$H NMR and $^{13}$C NMR data were recorded on a JOEL Oxford AS 400 instrument. $^1$H NMR spectra are reported as follows: chemical shift [integration, multiplicity (s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet) coupling constants in hertz. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The Infrared data were obtained using a Fourier Transformed Infrared Resonance (FTIR) Spectrometer, Shimadzu (IRPrestige-21). A Shimadzu GCMS-QP2010 Plus instrument was used for all mass spectral analysis.

Analytical thin-layer chromatography was conducted using Whatman K5F 150Å 250µm silica gel plates. Column chromatography was performed in ICN Silitech silica gel (63-200 mesh, 60 Å).

All commercial grade reagents were used without further purification except as otherwise stated in the procedure. All reactions requiring inert conditions were carried out in flame-dried glassware under dry N$_2$(g) atmosphere. Tetrahydrofuran was dried by distillation from benzophenone ketyl.
Experimental Procedures

Toluene-4-sulfonic acid 2-oxo-cyclohexyl ester (78). Iodobenzene diacetate (7.13 g, 22.1 mmol), p-toluene sulfonic acid (4.42 g, 23.2 mmol) and cyclohexanone (2.28 g, 23.2 mmol) were ground for 20 min. Chromatography of the residue over 200 g of silica gel (eluted with EtOAc-hexane, 1:1), afforded a pale yellow oil that was subsequently recrystallized in hexane to afford 2.94 g (50%) of a white solid (78): $^1$H NMR (CDCl$_3$, 400MHz) $\delta$ 1.57-2.60 (m, 8H), 2.42 (s, 3H), 4.89 (dd, 1H, $J$ = 5.88 Hz), 7.32 (d, 2H, $J$ = 8.08 Hz), 7.82 (d, 2H, $J$ = 8.08 Hz); $^{13}$C NMR (CDCl$_3$, 100MHz) $\delta$ 21.78 (s), 23.23 (s), 27.01 (s), 34.71 (s), 40.67 (s), 81.91 (s), 128.03 (s), 129.82 (s), 144.99 (s), 202.86 (s).

11-Oxa-tricyclo[4.3.1.1$^{2,5}$]undec-3-en-10-one (80). To 5.36 g (20.0 mmol) of tosylxyketone 78 in 20.0 mL of furan at 0°C under nitrogen was added 20.0 mL of 2,2,2-trifluoroethanol. To the resulting solution was added dropwise 5.20 mL (37.5 mmol) of
triethylamine over 15 min. The reaction was warmed to room temperature, stirred for 4 h, diluted with 50.0 mL of water, and extracted with four 75-mL portions of ether. The combined organic layers were washed with 100 mL of saturated aqueous NaHCO$_3$, dried (MgSO$_4$), and concentrated. The residue obtained was chromatographed over silica gel (EtOAc-hexane, 1:1 as eluent). Concentration yielded 2.32 g (71%) of the cycloadduct 80 as a pale yellow oil: $^1$H NMR (CDCl$_3$, 400MHz,) δ 1.45-2.70 (m, 8H), 4.94 (s, 2H), 6.36 (s, 2H); $^{13}$C NMR (CDCl$_3$, 100MHz,) δ 215.13 (s), 135.54 (s), 83.63 (s), 53.15 (s), 31.15 (s), 20.92 (s).

Syn-11-Oxa-tricyclo[4.3.1.1$^{2,5}$]undec-3-en-10-ol (81). To a slurry of 1.52 g (40.0 mmol) of lithium aluminum hydride in 100 mL of anhydrous ethyl ether was added dropwise 3.28 g (20 mmol) of the cycloadduct 80 in a solution of 100 mL of anhydrous ethyl ether at 0°C. The reaction was stirred 3 h. The reaction was quenched by careful addition of 25 mL of ethyl acetate and washed with five 100-mL portions of ammonium chloride and two 100-mL portions of water. The organic layer was dried (MgSO$_4$) in vacuo. The resulting residue was chromatographed over 160 g of silica gel (EtOAc-hexane, 1:1 as eluent) to afford 1.99 g (60%) of alcohol 81 as a colorless oil: $^1$H NMR (CDCl$_3$, 400MHz,) δ 1.45-1.51 (m, 2H), 1.76-2.11 (m, 4H), 2.32-2.55 (m, 2H), 2.72 (d, 1H, $J = 11.36$ Hz, O-H), 3.60 (d, 1H, $J = 10.64$ Hz), 4.76 (s, 2H), 6.65 (s, 2H); $^{13}$C NMR (CDCl$_3$, 100MHz,) δ 21.09 (s), 30.42 (s), 40.53 (s), 75.99 (s), 83.12 (s), 137.92 (s).
**Syn-10-Methoxymethoxy-11-oxa-tricyclo[4.3.1.12,5]undec-3-ene (82).** To a solution of 3.32 g (20.0 mmol) of alcohol 81 dissolved in 100 mL of dichloromethane was added 2.50 g (31.1 mmol) of chloromethyl methyl ether (MOMCl), followed by 3.88 g (30.0 mmol) of N,N-diisopropylethylamine over 5 min. The reaction was stirred 12 h. The reaction was quenched with 50 mL of water, the layers were separated, and the organic layer was dried (MgSO$_4$) and concentrated. Chromatography of the residue over 200 g of silica gel (EtOAc-hexane, 1:2 as eluent) afforded 4.02 g (95%) of a yellow oil: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.45-1.61 (m, 2H), 1.72-2.08 (m, 4H), 2.42-2.58 (m, 2H), 3.28 (s, 3H), 3.54 (s, 1H), 4.51 (s, 2H), 4.63 (s, 2H), 6.33 (s, 2H); $^{13}$C NMR (CDCl$_3$, 100MHz) $\delta$ 21.27 (s), 30.19 (s), 37.86 (s), 55.25 (s), 81.41 (s) 82.91 (s), 95.87 (s), 135.02 (s).

![Image of 82](image)

**10-Benzylxy-11-oxa-tricyclo[4.3.1.12,5]undec-3-ene (83).** To a solution of 100 mL of anhydrous THF, 0.58 g of sodium hydride and 3.17 g (25.0 mmol) of benzyl bromide was added 3.32 g (20.0 mmol) of alcohol 81 as a solution in 100 mL of anhydrous THF dropwise at room temperature. The resulting solution was heated under reflux for 20 h. The reaction was quenched by addition of 100 mL of saturated NH$_4$Cl, extracted with four 50-mL portions of ether, dried
(MgSO₄), concentrated in vacuo. Chromatography of the residue (Hexanes : EtOAc, 2:1 as eluent) afforded 3.07 g of benzylether 83 as a bright yellow oil (60%): ¹H NMR (CDCl₃, 400MHz) δ 1.45-1.61 (m, 2H), 1.72-2.08 (m, 4H), 2.42-2.58 (m, 2H), 3.48 (s, 1H), 4.41 (s, 2H), 4.69 (s, 2H), 6.39 (s, 2H), 7.20-7.40 (m, 5H); ¹³C NMR (CDCl₃, 100MHz) δ 21.55 (s), 30.24 (s), 36.58 (s), 66.99 (s), 82.48 (s), 83.07 (s), 127.24 (s), 127.36 (s), 128.40 (s), 135.10 (s), 139.17 (s).

To a solution of protected alcohol 82 (2.10 g, 10.0 mmol) in 100 mL of CH₂Cl₂ and 20 mL of 0.5 M aqueous NaHCO₃, was added 1.08 g (5.0 mmol) of m-chloroperoxybenzoic acid. Additional m-chloroperoxybenzoic acid and 0.5 M aqueous NaHCO₃ was added after 9 h (1.08 g, 5.0 mmol) and after 18 h (0.54 g, 2.5 mmol). The mixture was stirred for 48 h and the two phases were separated. The organic portion was washed with three 50.0-mL portions of 1 M NaOH and one 100-mL portion of H₂O and dried (MgSO₄). Concentration by rotary evaporation followed by high vacuum to give a 1.72 g of a colorless oil (76%): IR (acetone): 2935 cm⁻¹ (m), 1033 (m); ¹H NMR (CDCl₃, 400MHz) δ 1.40-1.51 (m, 2H), 1.77-2.08 (m, 4H), 2.32-2.51 (m, 2H), 3.31 (s, 3H), 3.48 (s, 1H), 3.60 (s, 2H), 4.14 (s, 2H), 4.56 (s, 2H); ¹³C NMR (CDCl₃, 100MHz) δ 20.77 (s), 30.72 (s), 35.74 (s), 54.13(s), 55.62 (s), 76.84 (s), 79.16 (s), 95.34 (s).
trans-11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-ol (99). A mixture of ketone 80 (25.0 mmol), aluminum triisopropoxide (12.24 g, 60.0 mmol), and 200 mL of o-xylene was heated to reflux in a moisture free atmosphere, then 0.5 mL of acetone was added and heating continued for 12 h. The reaction was quenched by addition of 100 mL of 10% NaOH and stirred for a further 30 min. The layers were separated, the aqueous layer extracted with 100 mL of o-xylene, dried (MgSO₄), and concentrated in vacuo. The o-xylene solvent was distilled at reduced pressure and the crude product was chromatographed over 200 g of silica gel (EtOAc-hexane, 1:4 as eluent) to afford 2.99 g (70%) of alcohol (99) as a yellow oil: ¹H NMR (CDCl₃, 400MHz,) δ 1.41-1.74 (m, 2H), 1.90-2.11 (m, 4H), 2.15, (s, 1H), 2.22-2.41 (m, 2H), 3.98 (s, 1H), 4.75 (s, 2H), 6.22 (s, 2H); ¹³C NMR (CDCl₃, 100MHz) δ 19.73 (s), 21.14 (s), 34.20 (s), 66.26 (s), 83.86 (s), 132.65 (s).

trans-10-Methoxymethoxy-11-oxa-tricyclo[4.3.1.12,5]undec-3-ene (100). To a solution of 3.32 g (20.0 mmol) of alcohol 99 dissolved in 100 mL of dichloromethane was added 2.50 g (31.1 mmol) of chloromethyl methyl ether (MOMCl), followed by 3.88 g (30.0 mmol) of N,N-diisopropylethylamine over 5 min. The reaction was stirred 12 h. The reaction was quenched
with 50 mL of water, the layers were separated, and the organic layer was dried (MgSO₄) and concentrated. Chromatography of the residue over 200 g of silica gel (EtOAc-hexane, 1:2 as eluent) afforded 4.02 g (95%) of 100 as a yellow oil: IR (acetone): 3942 cm⁻¹ (m), 1041 (m); ¹H NMR (CDCl₃, 400 MHz) δ 1.41-1.60 (m, 2H), 1.91-2.05 (m, 4H), 2.22-2.48 (m, 2H), 3.31 (s, 3H), 3.80 (t, 1H, J = 4.4 Hz), 4.57 (s, 2H), 4.70 (s, 2H), 6.21 (s, 2H); ¹³C NMR (CDCl₃, 100MHz) δ 20.09 (s), 21.95 (s), 32.85 (s), 55.46 (s), 72.02 (s) 83.87 (s), 94.62 (s), 132.78 (s); GCMS (m/z) 210, 148, 81.

To 0.21 g (1.0 mmol) of olefin 100 was added a solution of mercuric acetate (0.38g, 1.2 mmol) in a 1:1 mixture of THF:H₂O (4.0 mL). The mixture was stirred for 48 h, diluted with 3.0 mL of 15% KOH, and treated with 0.04 g NaBH₄ in 3.0 mL of 15% KOH. After 1 h the mixture was filtered and the aqueous layer was extracted with three 10-mL portions of CH₂Cl₂, dried (MgSO₄), and chromatographed (Hexane:EtOAc as eluent) to afford the alcohol 101 as a colorless oil (60%): IR (acetone): 2943 cm⁻¹, 1036 cm⁻¹; ¹H NMR (CDCl₃, 400MHz,) δ 1.35-1.45 (m, 2H), 1.55-1.65 (m, 2H), 1.67-1.85 (m, 2H), 2.21-2.40 (m, 2H), 2.18 (d, 1H) 3.36 (s, 3H), 3.54 (t, 1H), 4.16 (s, 1H), 4.28 (s, 1H), 4.53 (td, 1H), 4.75 (s, 2H); ¹³C NMR (CDCl₃, 100MHz,) δ 94.38 (s), 88.85 (s), 81.15 (s), 74.59 (s), 69.82 (s), 55.59 (s), 41.47 (s), 37.91 (s), 36.54 (s), 23.16 (s), 19.65 (s); GCMS (m/z) 228, 71, 57.
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APPENDIX

$^1$H NMR and $^{13}$C NMR of Compounds Prepared

Solvent: d-CDCl$_3$/ TMS
VITA

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