# The Monoreduction of Diketones and its Application towards the Total Synthesis of Kalmanol

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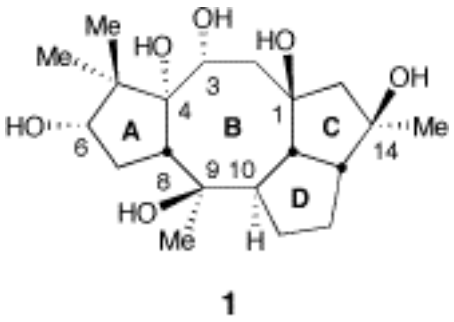
**Abstract**

Kalmanol exhibits a difficult to synthesize 5-8-5-5 ring structure with 10 stereocenters that have made it a popular target for total synthesis research for several years. The focus of current research has been on how to efficiently construct (*S*)-2,2-dimethyl-3-(tri-isopropylsilate)-cyclopentyl triflate, an enantiomerically pure five membered carbon ring required for the intramolecular [2+2] photocycloaddition key step from which the 8-membered ring structure is formed.

# 1 Introduction

In 1989, Burke et al. [2] reported the isolation of kalmanol from the leaves of *Kalmmia angustifolia L.* and determined its structure (Figure 1, **1**) by X-ray crystallography. A significant portion of early research on kalmanol focused on its structural similarities with the cardiotoxic grayanotoxins [3, 16, 17]. These toxins increase the permeability of sodium channels in certain excitable cell membranes. The structures of these molecules are lipid-soluble and can easily access the inner membrane portions of the sodium-channels. Once these channels are distorted, a large depolarization occurs and both gating and permeability are strongly affected. The resulting impact on nerve impulses is significant.




**1**

Figure 1: Structure of Kalmanol

The primary reason for selecting kalmanol as a target molecule for total synthesis, however, does not have to do with its biological activity. The difficulty of setting stereocenters, carbon atoms with four different substituents attached, is well known. The formation of structures containing eight-membered rings is often even more difficult. Kalmanol unites these two challenges with its 5-8-5-5 core structure and its 10 stereocenters, 6 of which are occupied by hydroxyl groups. Furthermore, kalmanol is a useful target molecule because it is capable of illustrating the effectiveness of the Snapper group's methodology for creating 5-8-5 ring structures. The group has developed a novel and efficient strategy towards a 22-step synthesis. The core of the molecule is reached in 6 steps using a

[2+2]-photocycloaddition/fragmentation methodology previously developed by the Snapper group [1, 6, 25]. These 6 steps will also simultaneously set 5 of the 10 stereocenters.

Previous attempts have been made to achieve the total synthesis of kalmanol. In 1996, Paquette [18–20] reported the synthesis of 7-oxy-5,6-dideoxykalmanol (Figure 2, **4**) from (4*R*)-silyloxycyclopentanone (Figure 2, **2**) in 25 steps utilizing a [3,3]-sigmatropic rearrangement of the tetrahydropyran (Figure 2, **3**), with a 1.6% overall yield. The only stereocenters that were missing were on carbons 3 and 4. It is estimated, however, that Paquette's strategy may require 30–40 synthetic steps to complete kalmanol. It has been ten years since this publication and the total synthesis of kalmanol still has not been reported by Paquette.

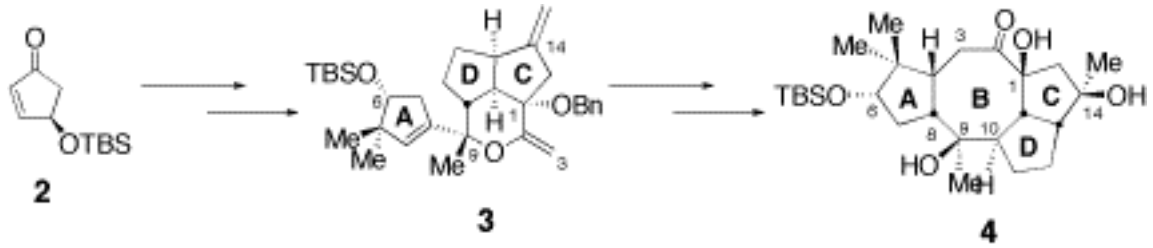



Figure 2: Paquette's synthesis of 7,oxy-5,6-dideoxykalmanol

The Snapper group's strategy for the synthesis of kalmanol, like Paquette's, employs (4*R*)-silyloxy-cyclopentanone as starting material. However, the Snapper group's strategy is capable of reaching the 5-8-5-5 ring structure in 6 steps compared to the 25 steps it takes Paquette's method. At the core of this novel synthetic method lies a [2+2] photocycloaddition/fragmentation technique which has often proven useful in the synthesis of systems containing eight-membered rings. Necessary for the [2+2]-photocycloaddition reaction is the enantiomerically pure (*S*)-2,2-dimethyl-3-(tri-isopropylsilate)-cyclopentyl triflate (Figure 3, **8**) that will be coupled with the tin-reagent (Figure 3, **7**). This five-membered ring was synthesized starting with 2,2-dimethyl-pentane-1,3-dianone and will eventually form the **A** ring in kalmanol. The two methyl groups found on the ring are also present on the target molecule. This paper will first discuss the enantiomerically pure synthesis of this key reagent

and will then proceed to describe its application within the broader context of the Snapper group's synthetic approach to the total synthesis of kalmanol.

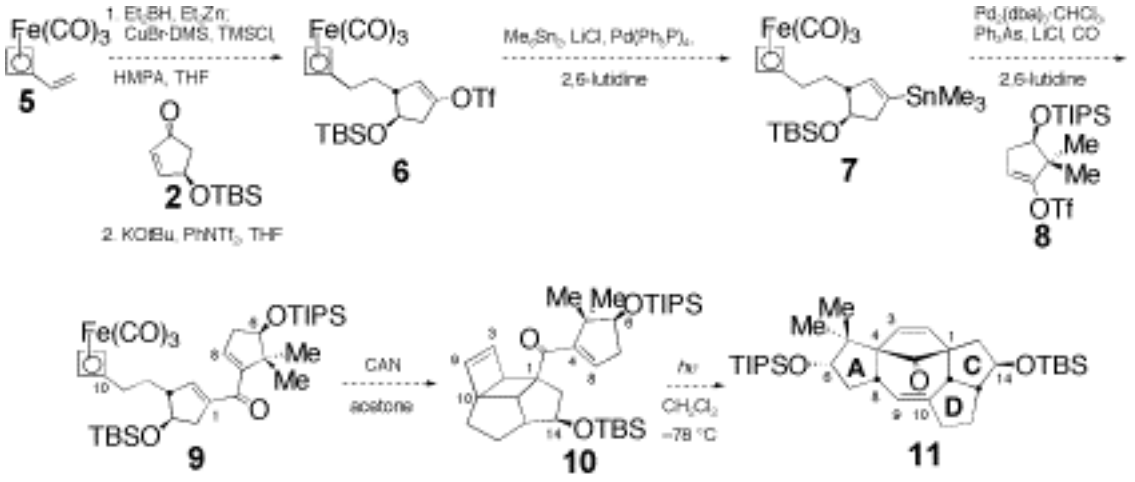



Figure 3: Snapper group's strategy for the core's synthesis

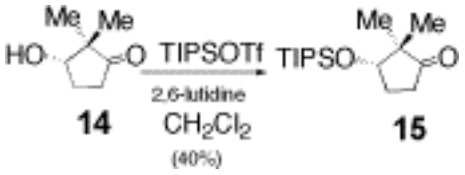
# 2 Methods and Materials

Proton nuclear magnetic resonance spectra ($^1$H NMR) were recorded on a Varian Gemini-400 instrument (400 Mhz). Analytical gas-liquid chromatography (GC) analyses were performed on a Hewlett Packard 5890 Level 4 Chromatograph, equipped with a split-mode injections system and a flame ionization detector. Fused silica capillary column (30 m x 0.32 mm) wall coated with DB-1 (J & W Scientific) was used with helium as the carrier gas (16 psi column head pressure). Liquid chromatography was performed using forced flow (flash chromatography) with the indicated solvent on 60-Å SiliTech silica gel ($SiO_2$). All reactions were performed under nitrogen atmosphere in oven-(135 °C) and flame-dried glassware using standard syringe/septa techniques. All reagents were used unpurified from the supplier. $CH_2Cl_2$ and THF were dried non-pyrophorically. All other solvents were dried and distilled unless otherwise stated.

## 2.1 (*S*)-2,2-dimethyl-3-hydroxyl-cyclopentanone


A mixture of (2*S*,3*R*)-2-amino-3-(t-butyldimethylsiloxy)-1,1-di-phenylbutanol (172.2 mg, 0.465 mmol) and methylboronic acid (30.7 mg, 0.513 mmol) in THF (6 mL) was heated at 50 °C for 5 hours in the presence of 4-Å molecular sieves. The resulting mixture was then cooled to 0 °C and a mixture of the diketone (**12**, 58.7 mg, 0.465 mmol) and N,N-diethylaniline (32 $\mu$L) in THF (5 mL) was added. A solution of $BH_3$·THF (1.0 mL) was added to the mixture over a 45 minute period at 0 °C. After stirring for 19 hours at ambient temperature, the reaction was quenched by adding 2N HCl. The product was extracted using EtOAc (3 x 20 mL). The combined organic phases were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography (Hexanes to 50% EtOAc/Hexanes) to give a yellow oil. (26.8 mg, 60% yield, 96% ee)

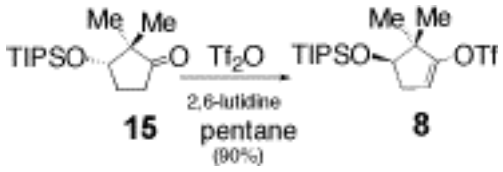
## 2.2 (*S*)-2,2-dimethyl-3-(tri-isopropylsilate)-cyclopentanone




To a solution of 2,2-dimethyl-3-hydroxyl-cyclopentanone (**14**, 70.0 mg, 0.545 mmol) in $CH_2Cl_2$ (5.6 mL) at ambient temperature was added 2,6 lutidine (93 $\mu$L, 0.816 mmol). TIPSOTf (293 $\mu$L, 1.09 mmol) was added dropwise to the solution. The reaction was stirred at ambient temperature for six hours. The reaction was then quenched with $NH_4Cl$ (3 mL).

The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography (Hexane). The product was a yellow oil (149.1 mg, 96% yield).

### 2.3 (*S*)-2,2-dimethyl-3-(tri-isopropylsilate)-cyclopentyl triflate




A solution of 2,2-dimethyl-3-(tri-isopropylsilate)-cyclopentanone (52.4 mg, 0.188 mmol) in freshly distilled pentanes (1 mL) was cooled 0 °C. To the mixture was added 2,6 lutidine (32 $\mu$L, 0.277 mmol). Triflic anhydride (47 $\mu$L, 0.277 mmol) was added dropwise to the solution. The reaction was stirred at ambient temperature for 19 hours. The reaction was then quenched with $NH_4Cl$ (3 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography (Hexane) to afford a yellow oil.

## 3 Synthesis of the Vinyl Triflate Reagent

As starting material for the synthesis of the vinyl triflate (Figure 3, **8**), 2,2-dimethylpentane-1,3-dianone (Figure 4, **12**) was used. Reducing the alcohol in a stereoselective manner was not trivial. Shimizu's [21] oxazoboralidine ligand (Figure 5, **16**) has been used in the past for the stereoselective mono-reduction of diketones. However, using it to reduce (Figure 5, **12**) would produce the enantiomer (Figure 5, **17**) instead of the desired (Figure 5, **14**). It was

hypothesized that if the diastereomer were constructed that it would be capable of reducing the diketone (Figure 4, **12**) to the correct enantiomer. Using a six-step synthetic pathway starting with the amino acid D-threonine, the diastereomer (Figure 5, **3**) was synthesized. As expected, it yielded the desired enantiomer with high stereoselectivity, but in moderate yield.

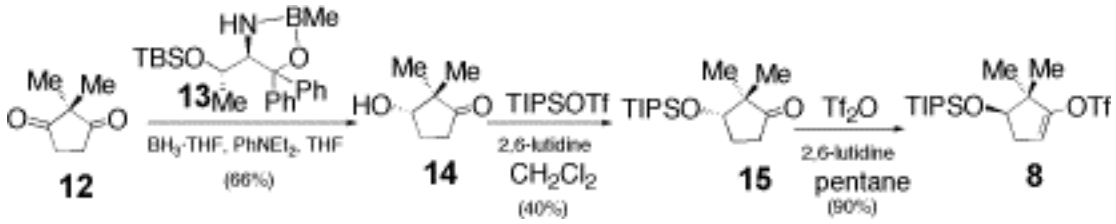



Figure 4: Synthesis of the triflate reagent

The mechanism behind this reaction is significant. First the $BH_3 \cdot$ THF complexes with the oxazoboralidine ligand. The unbonded electron pair in the ligand's nitrogen atom complex with the boron atom's empty orbital. This $BH_3 \cdot$ THF will serve as the hydride source during the reaction, donating its hydrogens to the ketone. The ligand complex then attaches itself to the diketone and forms a six-membered transition state (Figure 6, **18**). The hydrogen attaches itself to the ketone from behind. Depending on the orientation of the diketone, there are two possible transition states. However due to collision interactions between the methyl groups in the *R*-enantiomer forming transition state (Figure 6, **18**), the diketone rarely orients itself in that direction. The *S*-enantiomer forming transition state is favored.

The borane has gained a positive charge, but still retains two hydrogens capable of further reduction. Since approximately one equivalent of $BH_3 \cdot$ THF is added, if the reaction were to proceed past this point, overreduction of the alcohol (Figure 5, **14**) into the diol would occur at a large scale. In order to limit the effects of this overreduction, Shimizu [21] added $PhNEt_2$ to his reaction in the hope that the unbonded electrons on the nitrogen would complex with the oxidized borane and keep it from further reducing the alcohol. As

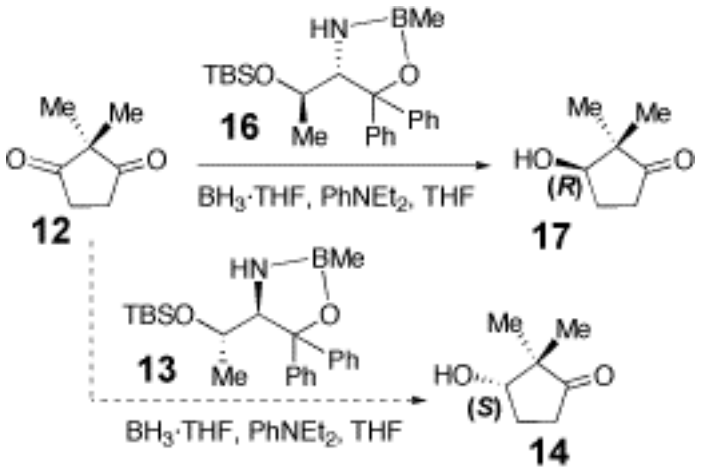



Figure 5: Shimizu's oxazoboralidine ligand and its diastereomer

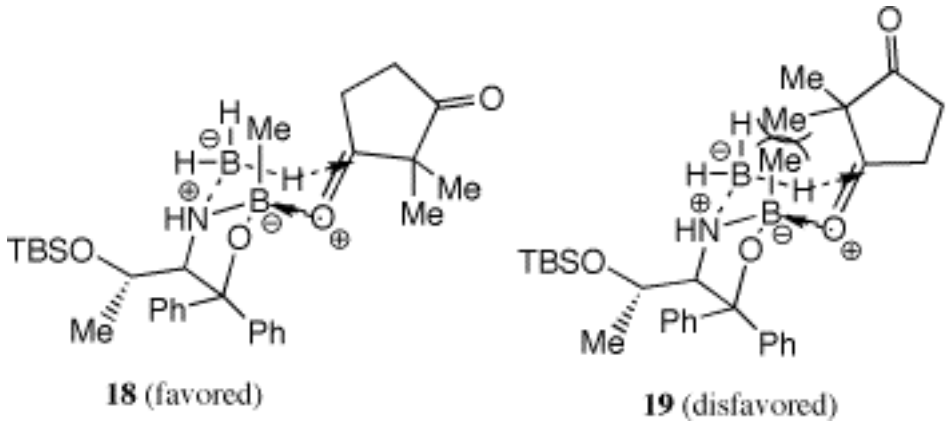



Figure 6: Transition states for the reduction using shimizu's oxazoboroalidine ligand

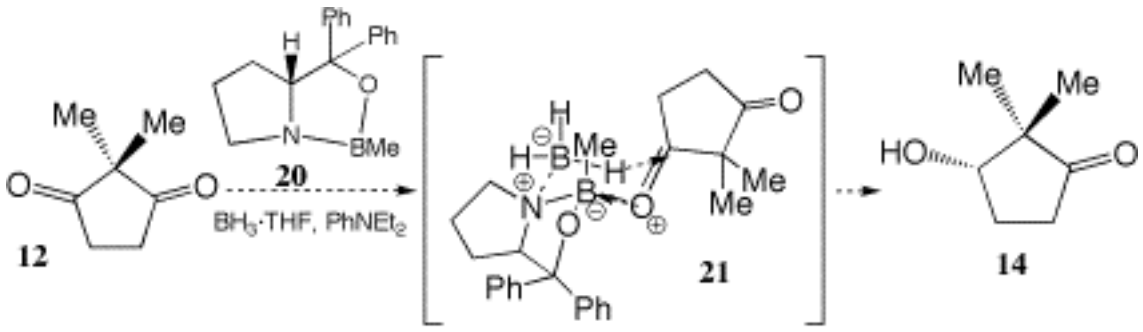



Figure 7: Transition States for the Reduction Using *R*-CBS Catalyst

expected, the yield increased significantly and the amount of diol that was formed decreased proportionately. Suprisingly, adding the $PhNEt_2$ also increased the enantioselectivity. One possible explanation for this phenomenon is that some of the $PhNEt_2$ complexes with the borane before it binds to ligand. The additional steric forces added by the bulky aromatic ring found in $PhNEt_2$ contribute to the collisions that drive the diketone from forming the *R*-enantiomer forming transition state (Figure 6, **19**).

To further expand our investigations into enantioselective mono-reductions of diketones, E. J. Corey's (*R*)-methyl-CBS catalyst (Figure 7, **20**) was employed. Structurally the *R*-CBS catalyst is very similar to the oxazoboralidine ligand (Figure 5, **13**) Shimizu employed. It has the same 5-membered ring structure and also contains the two phenol groups attached to the same carbon. The only difference lies its use of a second 5-membered ring to help generate steric forces rather than the TBS group the oxazoboralidine uses. The transition state (Figure 7, **21**) is nearly identical as well. However, since the CBS catalyst is commercially available, it offers the advantages of avoiding the six steps required to synthesize the oxazoboralidine ligand.

The reaction was performed several times using the *R*-CBS catalyst varying the proportions and reaction conditions. The procedure followed was identical to the one used for oxazoboralidine. The yields using the catalyst were much higher (80% compared to 60

The purpose of the next step was to protect the alcohol group from further reaction until the coupling and rearrangements were complete. The TIPS (triisopropylsilyl) group used to protect the alcohol is a large protecting group that remains stable until it is treated with acid. Previous attempts had been made to use TIPSCl to protect the alcohol. These attempts proved unsuccessful and only starting material was recovered. TIPSOTf was used instead and the reaction proceed successfully with 96% yield. One disadvantage to using this protective group is the possibility that it might collide with the TBSO group on carbon 14 during the photocycloaddition. If that occurs, a different protective group will have to be used. Finally, the vinyl triflate (Figure 4, **8**) was formed by treatment of (Figure 4, **15**) with triflic anhydride and 2,6-lutidine. A drawback to this strategy is the observed decomposition of the triflate at room temperature over a period of two hours. This is most likely due to triflic acid formed in the reaction due to water traces. The reaction must be run under very rigorous anhydrous conditions.

# 4 Application to the Synthesis of Kalmanol

Now that the vinyl triflate (Figure 3, **8**) has been formed, future work will focus on its carbonylative Stille [7,9,11,14,21,22] coupling with the tin reagent (Figure 3, **7**) to produce the desired dianone (Figure 3, **9**). The product of that reaction will then undergo a intramolecular [2+2] photocycloaddition/fragmentation. It is generally accepted that intermolecular [2+2] photocycloadditions between two cyclobutenes favor the *cis,anti,cis*-polyfused products (Figure 8, **24**) over their *cis,syn,cis* isomers (Figure 8, **25**) [10]. The reason for this has to do with the limited space and high number of collisions that must be overcome to form the more compact *cis,syn,cis*-isomer. However, thermal (heat-induced) fragmentation of either of the structural isomers yield *cis,cis*-cyclooctadiene (Figure 8, **27**) via *cis,trans*-cyclooctadiene intermediates (Figure 8, **26**). It was hypothesized that the introduction of a

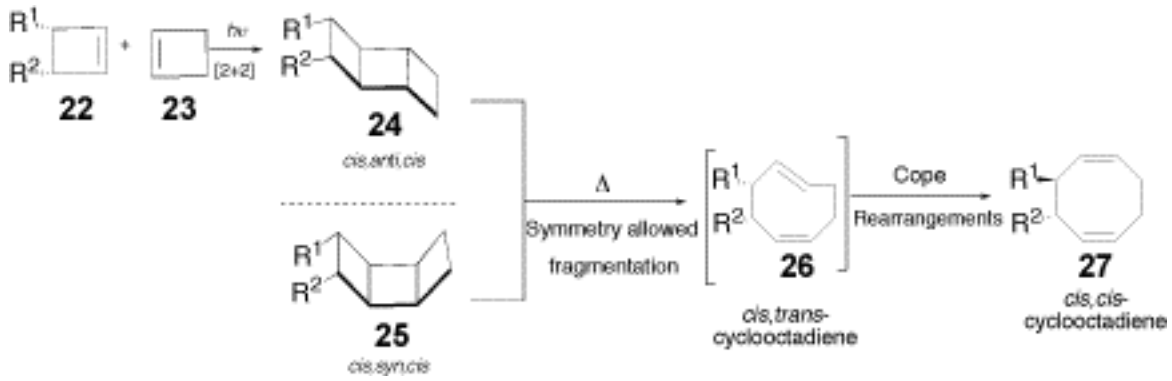



Figure 8: Intermolecular [2+2]-photocycloaddition/thermal fragmentation

tether between the two cyclobutenes would force the photocycloaddition to proceed in the *syn* fashion required for the core's synthesis. Futhermore it was expected that the tether would restrict the system during the thermal fragmentation so as to avoid the formation of the *cis,trans*-cyclooctadiene.

Indeed the Snapper group has already demonstrated the effectiveness of such a cycloaddition with other natural targets with 5-8-5 ring structures [8, 12, 13, 23]. The intramolecular [2+2]-photocycloaddition between the cyclobutene and the tethered cyclopentanone (**A** ring) proceeded to give the desired *cis,syn,cis* structure in a model study in which the functional groups were missing on carbons 6 and 14. In our case the [2+2]-photocycloaddition and thermal fragmentation should result in the direct formation of the fused 5-8-5-5 ring structure of kalmanol (Figure 3, **16**). Essential to this reaction is the vinyl triflate that was coupled. It contains one of the double-bonds used in [2+2] photocycloaddition and also sets the stereocenter at carbon 6. Note the similarity between this ring structure and kalmanol with the desired stereochemistry already set at carbons 6, 8, 13, 14, and 16. Equally important are the two double bonds which will serve as starting points for attaching additional functional groups.

A possible mechanism for the formation of this tetracyclic structure is a photo-mediated process (Figure 9). It is suspected that the ketone absorbs light at or near 280-300 nm.

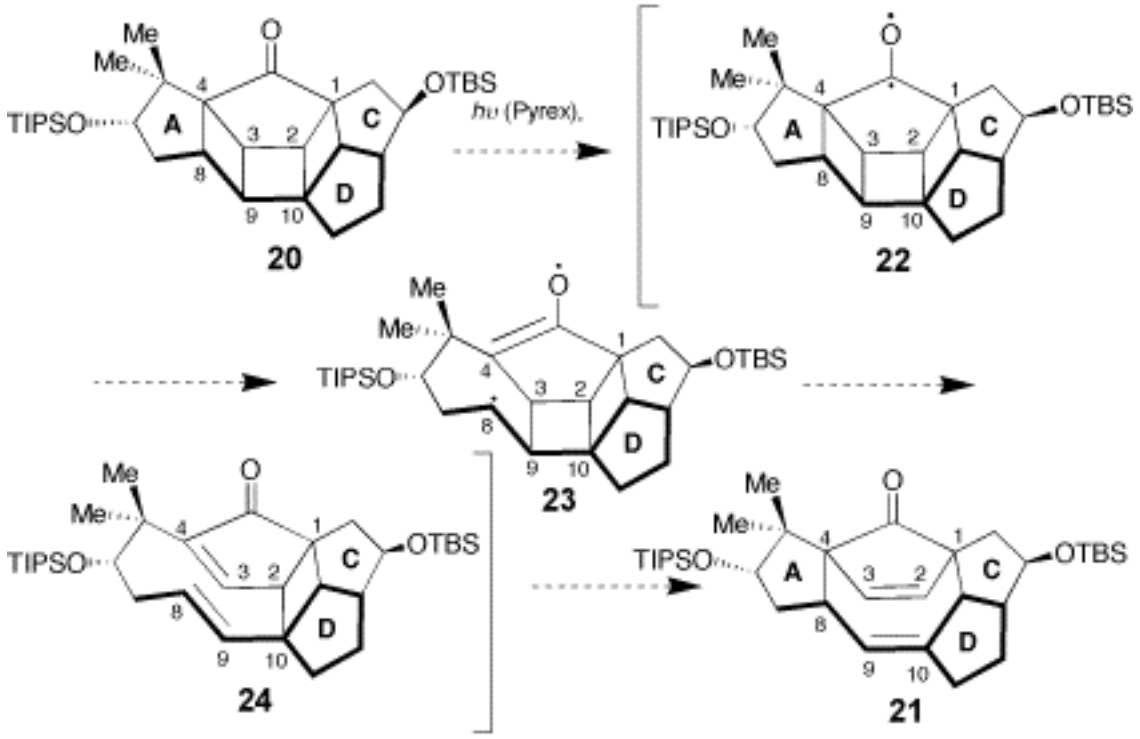



Figure 9: Proposed mechanism for the intramolecular photocycloaddition/fragmentation

The electrons in the double bond separate (Figure 9, **22**), which allows the bonds to shift locations (Figure 9, **23**). Additional fragmentation of the bond between carbons 3 and 9 yields a diene (Figure 9, **24**) which then goes through a Cope rearrangement of the double bonds to yield the tetracyclic structure. After the core of kalmanol has been reached, a series of manipulations are made to assign stereochemistry and add some functional groups.

The most important step that is made after the photocycloaddition is a Woodsward's oxidation that assigns the two stereocenters that Paquette was missing in his synthesis. The remaining alcohols at carbons 3 and 4 will be installed using the double bond found between carbons 3 and 4. Employing the more commonly used $OsO_4$ or $MnO_4$ for adding the two hydroxyl groups is impossible in this case. These two compounds would bind to the convex (facing out) side of the molecule and give the undesired stereochemistry. Subjecting the double bond between carbons 3 and 4 to the Woodwards oxidation method of AgOAc and

$I_2$, however, should result in the introduction of the hydroxyl groups at carbons 3 and 4 with the appropriate stereochemistry. It has been demonstrated that silver acetate with $I_2$ results in the formation of iodoacetate (IOAc) and in the presence of an alkene yields the trans-iodoacetate (Figure 10, **32c**). Subsequent treatment with silver acetate and water provides the *cis*-orthoacetate (Figure 10, **32d**) which opens in the presence of potassium hydroxide and methanol to yield the dihydroxylated product (Figure 10, **33**) with the two alcohols with the correctly assigned stereochemistry that Paquette was unable to add. The steps from this stage until kalmanol consist solely of converting the protected groups into their correct functional groups.

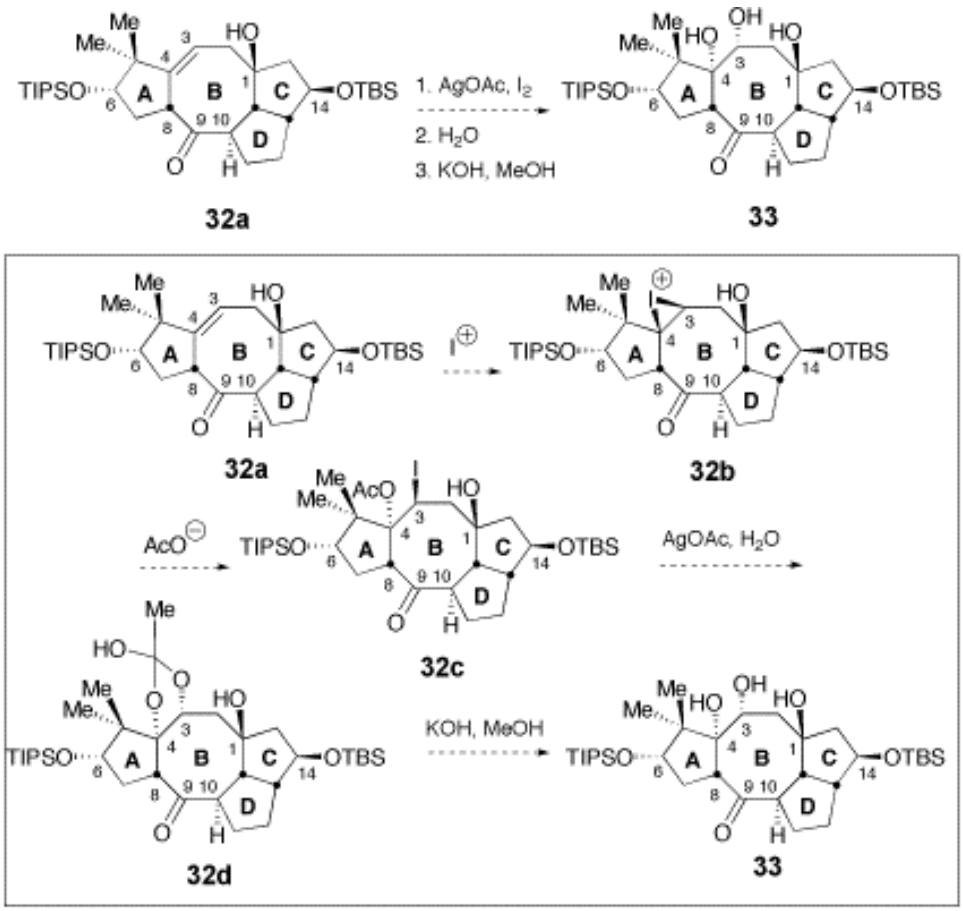



Figure 10: Woodward's Oxidation

# 5 Conclusion

Kalmanol is an ideal target for total synthesis because of its cardiotoxic biological activity, and complicated core structure with many stereocenters. A key reagent for this total synthesis is the vinyl triflate which was successfully synthesized in an enantiomerically pure manner.

# 6 Acknowledgments

I'd like to thank my previous mentor Merritt B. Andrus for allowing me to work in his lab and gain many of the skills I used while working on this project. I'd also like to thank Dr. Marc Snapper for allowing me to come and work for him. The person who has helped me the most on this project however is Dr. Claudia Lucero, the post-doctoral researcher under whose direction I worked. My sincere thanks to the RSI staff who read my paper especially Alli Gillmore, Luyi Zhao, and Shantanu Gaur. I also want to express my gratitude to my parents for their continued love and support.

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