Intramolecular Vinyl Heteroatom Radical Additions

By

Eric Eisenhauer
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(Andrew G. Campbell), Dean of the Graduate School
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I would like to dedicate my thesis to my Father that has passed during my time at Brown University. I know you would have been proud to see what I have accomplished!

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Abstract

In 1970, G. Ohloff et al. (Helv. Chim. Acta. 1970) observed an unexpected product when preforming a Wharton reaction, i.e. reaction of an α,β-epoxy ketone with hydrazine. Instead of the desired allylic alcohol product, the major product was identified as a bicyclic allyl alcohol that formed via an intramolecular cyclization. The authors proposed that formation of this product occurred via a carbanion intermediate. This conclusion was later dismissed by Stork and Williard in 1977. These latter investigators proposed that olefinic α,β-epoxy ketones in the presence of hydrazine in methanol proceed to form product via an intramolecular vinyl radical cyclization. Stork and Williard’s research evokes the question of whether the same would be necessarily true for olefinic α,β-epoxy esters. After several unsuccessful attempts to observe the corresponding reaction of α,β-epoxy esters with hydrazine, we have shifted focus to prepare vinyl radicals by using vinyl dibromides as a means to form the desired vinyl radicals. We initiated these experiments to test the hypothesis whether α-halo and/or α-alkoyx vinyl radical will undergo the same intramolecular cyclization as their α-alkyl analogs.

Background and Significance

Atom Transfer Radical Addition (ATRA)

The addition of halogenated compounds to alkenes or alkynes via a radical process is a fundamental reaction in organic synthesis. In the 1940s, halogenated
methanes were directly added to olefinic bonds in the presence of radical initiators or light. Such addition reactions are known as the Kharasch additions, or more recently as atom transfer radical addition (ATRA) reactions.\textsuperscript{1} Early work in this field mostly involved the use of CCl\textsubscript{4} or CBr\textsubscript{4} in the presence of radical initiators such as 2,2’-azobis(2-methylpropionitrile) (AIBN). Very high yields of the monoadducts were obtained in addition to monosubstituted olefins, but yields are considerably decreased with more reactive olefins such as styrene or methyl acrylate. The foremost reason for the decrease in the yield is attributed to radical-radical coupling and repetitive radical addition to alkene to generate oligomers, i.e. polymerization.\textsuperscript{1b} Commercially this polymerization reaction is very important but it is most undesirable when these radical additions reactions are employed in organic synthesis. The radical-radical coupling, i.e. chain terminating reactions can be repressed by the decreasing concentration, but the formation of oligomers cannot be avoided due to the low chain transfer constant. As a result of these conflicting reaction pathways, research in this area focused on developing methodology to selectively control the product distribution.\textsuperscript{1}

In the 1960s, many groups started to use transition metal complexes to catalyze and influence the different reaction pathways. The idea behind this was to increase the chain transfer constant, where the chain transfer constant is the rate to transfer a halide (k\textsubscript{tr}) over the rate for polymerization (k\textsubscript{p}) which can be seen in
Figure 1. Transition metal complexes are much better halogen transfer agents than alkyl halides. Complexes of Cu, Fe, Ru, and Ni were found to be fairly active catalysts for ATRA reactions. Not only did the use of these complexes offered control of product selectivity, it also permitted the use of a wider variety of halogenated compounds such as alkyl and aryl halides such as, N-chloroamines, alkylsulfonyl halides, and polyhalogenated compounds. Furthermore, it permitted the use of a variety of alkenes such as, styrene, alkyl acrylates, and acrylonitrile, which were not previously useful.

Figure 1

Intramolecular transition-metal catalyzed radical additions, currently referred to as atom transfer radical cyclization (ATRC), are also very appealing since these reactions enables the synthesis of functionalized ring systems that can be used as precursors for the preparation of more complex molecules.
halogenated products formed in ATRC reactions are also useful because they can be easily reduced, eliminated, displaced, converted to a Grignard reagent, or can serve as precursors for further radical reactions. Figure 2 below shows some of the most well designed examples of ATRC that have been performed over the last three decades. Even with all the different carbon sources that have been used with the ATRA reactions, there are extremely few documented attempts to use vinyl halides as a synthetic precursors.

**Figure 2**
Vinyl Radicals

Radical cyclization is a good alternative for building all carbon or heterocyclic rings, and should be taken into account when devising a synthetic plan. Vinyl radicals are typically generated three ways: i) from vinyl halides through halogen abstraction; ii) by the addition to the alkyne of silicon-, tin-, carbon-, sulfur-, or selenium-centered radicals; or iii) by electrochemical or chemical reduction of vinyl bromides, e.g. by reaction with samarium(II) iodide. A common reaction that takes place with vinyl radicals is a 1,5-hydrogen atom transfer to generate a more stable alkyl radical, followed by an intramolecular radical cyclization (Figure 3). Some work on intramolecular vinyl radical cyclizations with alkynes is known, but very little has been documented on vinyl radical cyclizations with alkenes.

Figure 3

In 1970 Ohloff attempted the Wharton reaction, utilizing α-ionone in an attempt to convert it to the corresponding allyl alcohols 4 and 5 depicted below in Figure 4a. The unexpected product 3, the bicyclic allyl alcohol was formed along with the expected allyl alcohol in a 60:40 ratio, with a 1:1 ratio of cis/trans isomers.
of the expected product (Figure 4a). Ohloff believed that both products derived from the same intermediate, i.e. a vinyl anion, as this mechanism was proposed for the Wharton reaction (Figure 4b).

Figure 4

a)

b)

In 1977, Williard and Stork published a paper where they utilized the conditions of the Wharton reaction on various conjugated α,β-epoxy ketones with an additional olefin five to six carbons away from the ketone. Hence these
compounds reacted with hydrazine in methanol hoping to reproduce the same cyclization that Ohloff reported. Some of the complexes they have tried, are shown in Figure 5a. The cyclization showed a strong preference for the formation of the five member ring over the six, as can be seen with compound 6 going to 7 below. One example was reported which formed the six member ring when 3-methyl-4-isopropyl-2-cyclohexenone was the starting material. The authors suggested that the original mechanism, the addition of a vinyl carbanion, must be rejected since such a species could not survive in methanol and definitely would not be expected to add to an unactivated trisubstituted olefin. The authors suggested that there are two possibilities. Either a concerted collapse of the vinyldiazene or the decomposition of the diazene to afford a vinyl radical which adds to the olefin (Figure 5b).
Figure 5

a) 

b) 

Progress Report

Chapter 1

The results Williard and Stork published in 1977 led to the idea of heteroatom vinyl radical additions, since it was thought that conjugated α,β-epoxy ketone in the presence of hydrazine in methanol would result in a vinyl radical that adds to the olefin intramolecularly to form the cyclic compounds as depicted in
**Figure 5b.** Hence, I’ve proceeded to investigate the use of an α,β-epoxy ester in place of the α,β-epoxy ketone analogy with the original Ohloff result depicted in **Figure 4a.** The idea behind this was that α-ionone is known to form the bicyclic allyl alcohol and it seemed relatively simple to oxidize the methyl ketone of α-ionone to the corresponding carboxylic acid via a haloform reaction. Ultimately the plan was to synthesize the α,β-epoxy ester and to determine if in the presence of hydrazine and methanol the same radical reaction would occur to produce the compound depicted in **Figure 6.** We proposed to use the α,β-epoxy ester 14 depicted in **Figure 8** to determine whether a vinyl radical could be formed in the presence of a geminal heteroatom, in this case a methoxy group, analogously to the original Ohloff observations. We also predict that the α-alkoxy substituent may stabilize the very reactive vinyl radical as shown.

**Figure 6**

![Chemical Structure](image)

The synthetic plan is shown in **Figure 8.** Hence formation of the α,β-epoxy ketone followed by conversion of this ketone to the ester via a two-step synthesis from the carboxylic acid. The carboxylic acid is esterified diazomethane.
Alternatively, we could also synthesize the ester before epoxidation followed by the formation of the epoxide as depicted in Figure 8. I began by synthesizing the epoxide using the procedure that was published by Ohloff. There was success forming the α,β-epoxy ketone. Once I formed the α,β-epoxy ketone, I planned to form the corresponding ester. It seemed that the simplest way to execute this was to perform the haloform reaction to produce a carboxylic acid followed by diazomethane to synthesize the ester. However, I encountered difficulty synthesizing the carboxylic acid in the haloform reaction. Although I was able to see the formation of the α,β-epoxy acid via NMR, the conversion was low. The low conversion was most likely due to the Favorskii Rearrangement, in which an α,β-epoxy ketone can be converted to β,γ-unsaturated carboxylic acid under basic conditions as shown in Figure 7. Turning to the alternative approach of forming the ester prior to the epoxidation, I found a paper by Oritani in which the corresponding ester of α-ionone was prepared. I repeated this results with great success in formation of the ester.
Williard and Stork predicted that the formation of the cyclic allylic alcohols were possibly formed via decomposition of the diazene to afford a vinyl radical, which was formed via an hydrazone intermediate. For the same reaction to occur for the α,β-epoxy ester, a hydrazimidate ester intermediate 16 would need to be formed as depicted in Figure 8. The reaction in which α,β-epoxy ester in presence of hydrazine would yield the corresponding α,β-epoxy hydrazide. To prepare the desired hydrazimidate ester, we proposed to utilize a method that has been utilized to form imidate esters from amides. Thus, alkylation of the silver salt of the amide by treatment of Ag₂O salt in a 1:1 ratio to the amide, followed by the addition of ethyl iodide was used to prepare imidate esters. The need to use a 1:1 ratio of amide to Ag₂O salt make this a very expensive reaction to run on anything larger than a milligram scale. Hence, an alternative method to form imidate esters is to react an ortho ester with an amine. This represents an entirely new synthetic plan to form the α,β-epoxy hydrazimidate esters.
In 1983, E.J. Corey et al. (Tetrahedron Let. 1983) develop a new synthetic route to a bridged carboxylic ortho esters.\textsuperscript{10} The general idea is that this could be a valuable synthetic protecting group for carboxylic acid during strong basic conditions. In Figure 9, the general mechanistic scheme is shown for how the ortho ester is formed and how under mild acidic conditions, the carboxylic acid can be regenerated.\textsuperscript{11} The five traditional synthetic routes for ortho esters are: the reaction of trihalogenated derivatives with alkoxides; the addition of alcohols to ketene acetals; the electrochemical oxidation of aldehyde acetals; the reaction of Grignard reactants with orthocarbonates or trialkoxyacetonitriles; and the reaction of nitriles with alcohols under acidic conditions followed by alcoholysis of the resulting imido ester, best known as the Pinner synthesis.\textsuperscript{12} Compared to those five methods of synthesizing ortho esters, the E.J Corey OBO protecting group best fits our synthetic plan since it can be formed directly from a carboxylic acid.\textsuperscript{10}
The synthetic plan for forming the OBO protected α-acid 17 can be seen in Figure 10. The first step is to form the carboxylic acid 17 from α-ionone via Bromoform reaction. The α-acid 17 then reacts with oxalyl chloride with a atalytic DMF to form α-acyl chloride 18. The α-acyl chloride 18 in the presence of 3-methylloxetan-3-yl methanol will form the corresponding ester 19 necessary for ortho ester formation. The need for an α,β-epoxy ortho ester is believed to be important intermediate during the radical cyclization. After many attempt of running the H₂O₂ with base epoxidation method for ketones and esters, the reaction was not successful and only starting material remained.⁴ Therefore a different direction was needed.
With the difficulties of forming the α,β- epoxy ester due to the epoxidation step, a new path with the idea of trying to avoid this step was conducted. In 1979, G. Ohloff et al. (Helv. Chim. Acta. 1979) developed a new synthesis for Exaltone and Muscone after Eshenmoser et al. in 1967 show the first examples of a C₃ ring expansion during the synthesis.¹³ The ring expansion step involves an α,β-epoxy ketone which goes through a alkynone fragmentation which can be seen below in **Figure 11**.¹³ The formation of epoxy ketones from sterically hindered enones is often too difficult and route without the epoxidation was sought after. G. Ohloff et al. develop a new method the uses ROH/acetone/NBS to avoid the epoxidation step, which is shown in **Figure 11**.¹³ The hope is that even without the α,β- epoxy ester the ring closing might be possible with method develop by G. Ohloff et al. (Helv. Chim. Acta. 1979).
As mentioned above, the hope is that even without the $\alpha,\beta$-epoxy ester the ring closing might be possible with the method develop by G. Ohloff et al. (Helv. Chim. Acta. 1979). The new plan was to synthesis 21 and see if it has the same reactivity to NBS or DBH. This can be seen in Figure 12. The $\alpha$-acyl chloride 18 was forms via a two-step synthesis from $\alpha$-ionone as mentioned before. The $\alpha$-acyl chloride 18 was then reacted with p-tosylhydrazide in the presence of Et₃N to form the $\alpha$-p-tosylhydrazide 21.\textsuperscript{14} The $\alpha$-p-tosylhydrazide 21 was reacted under the exact same conditions developed by G. Ohloff which resulted in not the desired reaction.
but a mixture of $\alpha$, $\beta$, $\gamma$ – carboxylic acids. This result left us hopeless with this direction and drove the project into a new path.

**Figure 12**

After many attempts of trying to place the epoxide on the $\alpha$- methyl ester 14 as well as the $\alpha$- oxetane ester 19 and having no success, a different path needed to be derived. While looking for example of $\alpha,\beta$- epoxy esters with a second olefin in the structure, it came apparent the only successful method was to do a Darzen condensation reaction the form the desired product. If the $\alpha$-ionone scaffold was to be used, it would be formed from $\alpha$-cyclocitral and methyl bromoacetate. The methyl bromoacetate is commercially available but for $\alpha$-cyclocitral was needed to be synthesized. With the low yields (20%) of $\alpha$-cyclocitral and the difficulties of trying to avoid synthesizing the $\beta$-cyclocitral which is the thermodynamic product is almost impossible a simplest structure was found. The use of 6-methyl-5-hepten-2-one was used to form the $\alpha,\beta$- epoxy ester seen in **Figure 13**. The Darzen
condensation with 6-methyl-5-hepten-2-one and methyl bromoacetate was successful in forming the \( \alpha,\beta \)-epoxy ester 23 seen below. There is a mixture of the cis/trans isomers which should not be concerning for further reactions.

To finish off this project the \( \alpha,\beta \)-epoxy ortho ester has to be synthesized. This might be difficult to keep the epoxide during the next steps needed to form the ortho ester. The best route would most likely be to use the E.J. Corey OBO protecting group which is synthesized via an acyl chloride. The most concerning part is the \( \text{BF}_3 \) used to open up the oxetane ring and finish the OBO protecting group. I would be concerned that the \( \text{BF}_3 \) would also open up the epoxide which would be irreversible. For some reason the \( \alpha,\beta \)-epoxy ortho ester was successfully synthesized the final step would be to add hydrazine in methanol and see if the same reactivity occurs as the \( \alpha,\beta \)-epoxy ketone.

**Figure 13**
Chapter 2

After earlier complications arose in producing the α,β-epoxy ester, the plan was to try and find a simpler framework that utilized a vinyl halide to be used to form a vinyl radical. We felt that this would efficiently test the hypothesis of whether an α-halo substituted vinyl radical would undergo cyclization efficiently. It would be ideal to form a vinyl bromide with a methoxy group geminal to the bromide. This target is depicted below as the α-halo enol ether in Figure 14 to help stabilize the formation of a highly reactive vinyl radical.

Figure 14

Alternatively, the idea to utilize a vinyl dibromide complex where the bromines are geminal to one another seemed an even simpler precursor to prepare and to test the original hypothesis. Thus we turned out attention to convert 6-methyl-5-hepten-2-one and convert it to the 1,1-dibromo-2,6-dimethyl-1,5-heptadiene as seen below in Figure 15a. This conversion was performed by Köbrich in 1976. This compound seemed ideal because of the short number of steps to synthesize. Due to the fact that the compound had an olefin five carbons
away from the vinyl bromide, if a radical would form, it would react with the second olefin to form a five-membered cyclic compound. Importantly, this terminal dibromoolefin has a second bromine on the same carbon to help stabilize the formation of a vinyl radical. It was also noted in the original Köbrich paper that it is necessary to keep the dibromide away from light. This observation suggested to us a radical decomposition which seemed promising for formation of vinyl heteroatom radical. For these reasons, we were encouraged to synthesize this vinyl dibromide. Upon obtaining this simple vinyl dibromide, we can try various known techniques to form the vinyl radical to determine whether radical cyclization occurs. If successful, this observation strongly supports our original hypothesis that α-halo and perhaps even α-alkoxy substituted vinyl radicals lead to cyclization reactions compatible to the observations of α,β-epoxy ketone. Furthermore, we would be encouraged to proceed to develop an efficient synthesis of α,β-epoxy hydrazimidate esters and treat these with base that the mechanism depicted below would lead to a mild and efficient formation of a vinyl radical followed by intramolecular cyclization of this radical as shown in Figure 15b.
Figure 15

a)

b)


c)

1) LDA, CH₂Br₂, 2) TMSCl
-100°C

"Trapp Mixture"
Presently the 1,1-dibromo-2,6-dimethyl-1,5-heptadiene was synthesized via two-steps (Figure 15c), with step one being the addition of dibromomethane to the carbonyl carbon to form the dibromosilylether. This was followed by the addition of LDA to form the vinyl dibromide. I have been able to successfully synthesize the dibromosilylether complex in 48.1 % yield.\textsuperscript{17} I plan to synthesize the vinyl dibromide and to purify this compound to determine whether it is possible to generate the vinyl radical and complete the cyclization.

To finish up this project I have is to successfully synthesize the vinyl dibromide using the synthesis procedure of Köbrich.\textsuperscript{17} If the synthesis does not work, an alternative method is to synthesize the vinyl dibromide complex via the use of bromoform instead of dibromomethane in the first step of the synthesis. The second step could be accomplished by the addition n-butyl lithium to form the vinyl dibromide complex instead of using LDA.\textsuperscript{18}

Once the vinyl dibromide is synthesized, I plan to try various techniques to form the cyclic compound as seen below in Figure 16. It has been shown that vinyl bromides in the presences of SmI\textsubscript{2} or AIBN form vinyl radicals. These methods will be attempted.\textsuperscript{2-3} Previous publications show that SmI\textsubscript{2} forms a vinyl radical followed by intramolecular reaction with an alkyne to form a new vinyl radical.\textsuperscript{2} These precedents provide optimism that vinyl radicals will be formed and that the subsequent cyclization will be successful as shown. Another method to try
and generate the vinyl radical is to attempt to use the ATRA catalyst that have been successful in forming radicals from alkyl and acyl halides.\textsuperscript{1} Lastly, a fellow group member is working on a gold(I) catalyst to form radicals, and on testing out the vinyl dibromides to see if the gold catalyst will be effective.

**Figure 16**

![Chemical structure](image)

### Supporting Information

**General Procedures:** NMR spectra were recorded on either Bruker Avence 400 (400MHz) or Bruker Avence 600 (600MHz) spectrometer. GC-MS were recorded on Hewlett Packard 6890 Series II Gas chromatography using a flame ionization detector. TLC was run on Kieselgel 60 F-254 precoated silica gel plates. ICN (70-220 mesh) or Kieselgel (230-240 mesh) was used for column chromatography. All experiments run under nitrogen were placed in flames dried flasks and degassed on a Schlenk line.
**Epoxidation Reaction:** Into a solution of 5.75 ml of 30% $\text{H}_2\text{O}_2$ with 20 ml of methanol, 3.845 g $\alpha$-ionone was added and stirred vigorously at ambient temperature. To the solution, 1.65 ml of 6M NaOH was added over 3 hr using a syringe pump. The reaction continued to stir for 1 hr after the addition was complete. The reaction was then worked up with water and extracted by ethyl ether. Purification was done by column chromatography and gave a 73.1 % yield based on recovered starting material. $^1\text{H}$ NMR (400MHz, CDCl$_3$) $\delta$ 5.49 (s, 1H), $\delta$ 3.12 (d, 1H, $J$ = 2.16 Hz), $\delta$ 2.82 (dd, 1H, $J$ = 9.29 Hz and 1.73 Hz), $\delta$ 1.97 (s, 3H), $\delta$ 1.70 (s, 3H), $\delta$ 1.08 (s, 3H), $\delta$ 0.92 (s, 3H). $^{13}\text{C}$ NMR (600MHz, CDCl$_3$) $\delta$ 24.46, $\delta$ 26.87, $\delta$ 27.33, $\delta$ 31.66, $\delta$ 32.61, $\delta$ 50.60, $\delta$ 52.46, $\delta$ 58.68, $\delta$ 59.18, $\delta$ 65.82, $\delta$ 124.64, $\delta$ 130.29, $\delta$ 206.13.

**Bromoform reaction:** Into a solution of 16.5 g of sodium hydroxide in 140 ml of water was dropwise added 8 ml of bromine under stirring at 5°C. After stirring for 15 min, 10g of $\alpha$-ionone in 70 ml of dioxane was gradually added to the above solution at -7°C with stirring. Stirring was continued for 2 hr at 0°C and for 12 hr at room temperature. Then, the solution was diluted with water and extracted with ether to remove the neutral substances. The aqueous solution was acidified with dilute sulfuric acid and extracted with ether. The solvents were evaporated leaving the product in a 60.1 % yield. $^1\text{H}$ NMR (400MHz, CDCl$_3$) $\delta$ 6.93 (dd, 1H, $J$ = 15.6 Hz and 10.2 Hz), $\delta$ 5.82 (d, 1H, $J$ = 15.6 Hz), $\delta$ 5.52 (s, 1H), $\delta$ 2.39 (d, 1H, $J$ = 9.85 Hz).
Hz), δ 1.59 (s, 3H), δ 0.94 (s, 3H), δ 0.88 (s, 3H). $^{13}$C NMR (400MHz, CDCl$_3$) δ 22.77, δ 23.00, δ 26.76, δ 27.76, δ 31.05, δ 32.51, δ 54.08, δ 121.56, δ 122.82, δ 131.61, δ 152.80, δ 171.26.

**Procedure for the α-cyclocitral:** To a 25 mL round bottom flask, 5.064 g (0.033 mol) of citral in 5 mL of diethyl ether was added. To the citral solution, 3.1001 g (0.033 mol) Aniline dissolved in 5 mL of diethyl ether was added dropwise over 30 minutes. The solution was dried with anhydrous Sodium Sulfate and then filtered to a dry solution. To a new 100 mL round bottom flask, 30 mL of concentrated sulfuric acid was added over 3 g of ice. The temperature was lowered to -20 C with the avoiding of freezing the acid solution. The Schiff base solution was added dropwise over 30 mins. The solution continued to stir for an additional 45 minutes after addition was complete at -20 C. The solution was poured carefully over excess ice, followed by a steam distillation to recover the cyclocitral. The distillate was washed with sodium bicarbonate and extracted with diethyl ether to give a 23% yield.

**Procedure for α-acyl chloride:** To a dry 25 mL round bottom flask under nitrogen, 1.3229g α-acid, 15 mL THF, and 0.8 mL of oxalyl chloride. To the solution, 2 drops of DMF were added and the reaction stirred for 3 hours under nitrogen. After the reaction was finished, the flask was placed under vacuum and the solvent and excess oxalyl chloride were removed to leave behind the product.
with a 73 % yield. $^1$H NMR (400MHz, CDCl$_3$) δ 7.07 (dd, 1H, $J = 15$ Hz and 10 Hz), δ 6.06 (d, 1H, $J = 15$ Hz), δ 5.57 (s, 1H), δ 2.37 (d, 1H, $J = 9.85$ Hz), δ 1.59 (s, 3H), δ 0.94 (s, 3H), δ 0.88 (s, 3H).

**Procedure for the α-3-methyloxetan-3-yl ester:** In a 25 mL round bottom flask, 1.050 g of α-acyl chloride was added to a solution of the 3-methyloxetan-3-yl methanol (0.500 g) and pyridine (0.400 g), in 2 mL of DCM at 0 C. The mixture stirred for 8.5 hours at 0 C. The solution was washed with sodium bicarbonate and extracted with DCM. The solvent was removed under vacuum to leave a brown oil with a yield of 81 %. $^1$H NMR (400MHz, CDCl$_3$) δ 6.87 (dd, 1H) δ 5.83 (d, 1H) δ 5.52 (s, 1H), δ 4.57 (d, 2H), δ 4.42 (d, 2H), δ 4.23 (s, 2H), δ 2.32 (d, 1H), δ 2.07 (s, 2H), δ 1.59 (s, 3H), δ 0.94 (s, 3H), δ 0.88 (s, 3H).

**Procedure for the α-methyl ester:** In a 25 mL round bottom flask, 2.2581 g of α-acyl chloride was added to a solution of MeOH (0.429 mL) and pyridine (0.882 g), in 4 mL of DCM at 0 C. The mixture stirred for 8.5 hours at 0 C. The solution was washed with sodium bicarbonate and extracted with DCM. The solvent was removed under vacuum to leave a brown oil with a yield of 74 %. $^1$H NMR (400MHz, CDCl$_3$) δ 6.81 (dd, 1H) δ 5.79 (d, 1H) δ 5.50 (s, 1H), δ 3.76 (s, 3H), δ 2.28 (d, 1H), δ 2.05 (s, 2H), δ 1.59 (s, 3H), δ 0.94 (s, 3H), δ 0.88 (s, 3H).

**Procedure for α- p-tosyl hydrazide:** The excess Et$_3$N was added dropwise to a solution of α-acyl chloride (4.00mmol), p-tosyl hydrazide (4.00mmol), in 25 mL
of THF under nitrogen. After the reaction stirred at ambient temperature for 2 hours, the mixture was washed with water and extracted with diethyl ether. The organic layer was than washed two more time with water followed by one wash of brine. The organic layer was dried and the solvent was removed under vacuum to give a yield of 27%. $^1$H NMR (400MHz, CDCl$_3$) δ 7.81(d, 2H) δ 7.29 (d, 2H) δ 6.56(dd, 1H) δ 5.73 (d, 1H) δ 5.47 (s, 1H), δ 2.20 (d, 1H), δ 2.01 (s, 2H), δ 1.51 (s, 3H), δ 0.89 (s, 3H), δ 0.76 (s, 3H).

Procedure for epoxy ester via Darzen condensation: To a dry round bottom flask, 2mmol of LiHMDS was added to 0.22mL methyl bromoacetate in 10mL THF at -78 C under N$_2$. 1mmol of the Ketone was added to the flask dropwise slowly and stirred at -78 and allowed to warm up to room temperature slowly. The mixture was then washed with water and extracted with Et$_2$O. The organic layer was washed with 1M HCl and then 2 washed of water. The dried organic phase was then passed through a short plug of silica. The solvent was pumped off to leave an oil. $^1$H NMR (400MHz, CDCl$_3$) δ 5.10(t, 1) δ 3.80 (s, 2H) δ 3.37(s, 1H) δ 2.13 (m, 2H) δ 1.71 (s, 3H), δ 1.62 (s, 3H), δ 1.37 (s, 3H).

Procedure for the dibromosilylether: To 5:50 g of dry diisopropylamine (55 mmol) in 200 ml of “Trapp-mixture”* is added at -5 to 0 °C 50 mmol of n-BuLi (1.6- 1.8 M in n-hexane), with stirring for 1 h - slight yellowing. After cooling to -100 °C, over a period of 45 minutes 13.5 g of dibromomethane (50% excess) in 30
ml of anhydrous ether is added and the mixture stirred for a further hour. Then, the light yellow suspension of bromomethyl lithium (6) is formed. After the addition of 50 mmol of 6-methyl-5-hepten-2-one in 50 ml ether the suspension soon turns into a clear yellow solution. It is mixed at the same temp with 100 mmol trimethylchlorosilane and warmed slowly to room temperature. After washing with water it is worked normally (i.e. normal work-up with water). Final purification of the compounds was carried out with 20% H20 deactivated silica gel (deactivate by adding 20% water) gave the product with 48.1 % yield. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 5.64 (s, 1H), $\delta$ 5.09 (tt, 1H, $J = 7.05$ Hz and 1.50 Hz), $\delta$ 1.80-2.10 (m, 4H), $\delta$ 1.67 (s, 3H), $\delta$ 1.60 (s, 3H), $\delta$ 1.49 (s, 3H), $\delta$ 0.16 (s, 9H). $^{13}$C NMR (600MHz, CDCl$_3$) $\delta$ 2.32, $\delta$ 17.65, $\delta$ 21.87, $\delta$ 23.73, $\delta$ 25.69, $\delta$ 39.47, $\delta$ 47.96, $\delta$ 57.11, $\delta$ 123.52, $\delta$ 132.15.

**Procedure for the tribromosilyl ether:** To a dry round bottom flask, 2.10mL of bromoform and 8 mL was added at -78 C under N$_2$. To the flask 16mmol of LiHMDS which was dissolved in 16 mL THF was added dropwise slowly. To the mixture, 9 mmol of the carbonyl in 4 mL DMF was added in dropwise. 3 mL of TMSCl was added to the flask. The flask was then allowed to warm to room temperature slowly. The mixture was then washed with water and extracted with Et$_2$O. The organic layer was washed with 1M HCl and then 2 washed of water. The dried organic phase was then passed through a short plug of silica. The solvent was
pumped off to leave an oil. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 5.16 (s, 1H), $\delta$ 1.80-2.10 (m, 4H), $\delta$ 1.67 (s, 3H), $\delta$ 1.60 (s, 3H), $\delta$ 1.49 (s, 3H), $\delta$ 0.16 (s, 9H).

References