Total SynThesis of Syringolides 1 and 2

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TOTAL SYNTHESIS OF SYRINGOLIDES 1 AND 2

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2015
TOTAL SYNTHESIS OF SYRINGOLIDES 1 AND 2

by

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Sudhakar Kalagara
Abstract

The total synthesis of Syringolides is described. The synthetic pathway was designed in order to synthesize Syringolides in high yields using inexpensive starting materials. The synthesis strategy features a preparation of the linear tricarbonyl compound followed by intramolecular cyclization. The linear precursor is divided into two fragments, β-keto acid and protected D-xylulose, which are the key fragments and were synthesized from α,β-unsaturated compound followed by asymmetric dihydroxylation. The α,β-unsaturated compound was efficiently prepared by a Wittig reaction between aldehyde and ylide fragments. The butenolide derivative was also achieved by the Knoevenagel condensation of the tricarbonyl compound.
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ABBREVIATIONS

Ac     acetyl
aq     aqueous
avr D  avirulence gene D
Bn     benzyl
Bu     butyl
calcd  calculated
conc   concentrated
CSA    camphorsulfonic acid
DA     Diels-Alder Reaction
DBU    1,8-diazabicyclo[5.4.0]undec-7-ene
DCC    1,3-dicyclohexylcarbodiimide
DCM    dichloromethane
DDQ    2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP   4-(dimethylamino)pyridine
DMF    dimethylformamide
DMP    2,2-dimethoxy propane
equiv  equivalent
Et     ethyl
FDP    fructose 1,6-diphosphate
FTIR   Fourier transform infrared spectroscopy
HMPA   hexamethylphosphoramide
HPLC   high-performance liquid chromatography
HA     hydroxyacetone
HR     hypersensitive response
HRMS   high-resolution mass spectrometry
KHMDS  potassium hexamethyldisilazide
LDA    lithium diisopropylamide
lit    literature
Me  methyl  
min  minute(s)  
mp  melting point  
MOM  methoxymethyl  
MPM  p-methoxybenzyl  
Ms  methanesulfonyl  
MS  molecular sieves  
NMR  nuclear magnetic resonance  
PCC  pyridinium chlorochromate  
PDC  pyridinium dichromate  
Ph  phenyl  
PPTS  pyridinium p-toluenesulfonate  
Pr  propyl  
PTS  p-toluenesulfonic acid  
pv  pathovar  
soln  solution  
TBAF  tetrabutylammonium fluoride  
TBDMS or TBS  tert-butyldimethylsilyl  
TBDPS  tert-butyl diphenylsilyl  
TCDI  1,1’-thiocarbonyldiimidazole  
Tf  trifluormethanesulfonyl  
TFA  trifluoroacetic acid  
THF  tetrahydrofuran  
TIPS  triisopropyl silyl  
TMS  trimethylsilyl  
TLC  thin layer chromatography  
Ts  p-toluenesulfonyl
1.1 Isolation and structure determination of Syringolides

In the process of evolution, plants have adopted highly efficient chemical defense mechanisms against attacks by pathogens such as the hypersensitive response (HR). This active defense mechanism involves rapid and programmed localized cell death followed by the subsequent accumulation at the infection site of antimicrobial compounds called phytoalexins. Many resistant plants recognize specific elicitor molecules produced by the plant pathogens and thereby activate the hypersensitive response.

The first step in inducing the HR could be the recognition of the complementary avirulence gene (avr gene), produced by the pathogen, by the corresponding dominant plant resistance gene. This has driven attention on the chemical defensive compounds for plants, especially elicitors, which stimulate plants to produce phytoalexins.

The first report describing the gene for gene relationship between the host and the pathogen was published by Flor et al. in 1942. According to Flor, HR was found to occur only when the plant expresses a dominant resistance gene, and the pathogen expresses a complementary avirulence gene. If either the plant lacks the resistance gene or the pathogen lacks the avirulence gene, there will be no HR, and infection will not be prevented. During the process of HR, elicitors act as signal molecules produced either directly or indirectly by pathogens that are recognized by plants and thereby activate a defense response. Two types of elicitors are generally recognized, non-specific elicitors and specific elicitors. The non-specific elicitors do not exhibit differences in
cultivar responses within a plant species whereas the specific elicitors cause responses only in
cultivars carrying matching disease-resistance genes.

Syringolide 1 and 2 (Figure 1) are among the specific elicitors. They were reported to act as
bacterial signal molecules produced by the avirulence gene D (avr D) and invoke a
hypersensitive response in soybean plants having the Rpg4 disease resistance gene. These
non-proteinaceous elicitors were first isolated from bacterial plant pathogen pseudomonas
syringae pv. tomato in 1993 by Sims and co-workers.6,7 Both Syringolide 1 and 2 were extracted
from culture fluids of P. syringae pv. tomato or p.syringae pv. glycinea carrying plasmid
pAVRD12/519 or Escherichia coli carrying plasmid pAVRD12 using ethyl acetate.7,8 These
extracts were purified by HPLC with the guidance from the soybean HR assay and by using both
NMR spectroscopy along with X-ray crystallography, the structures of these two compounds
were confirmed (Figure 1).7

\[
\text{(-)-Syringolide 1 (1)} \quad \text{(-)-Syringolide 2 (2)} \quad \text{(-)-Syringolide 3 (3)}
\]

**Figure 1: Structures of Syringolide elicitors**

P. syringae pathavors consists of two distinct classes of functional alleles which are named as
class I and class II alleles.9,10 Class I alleles direct the production of two structurally related
molecules, Syringolide 1 and 2, whereas class II alleles lead to the production of only
Syringolide 1 and Syringolide 3. Even though the class II alleles are less homologous with the
class I alleles, functionally, they are unique as they direct the synthesis of *Escherichia coli* and *p. s. pv. glycinea* of different elicitors in the soybean hypersensitive response.\textsuperscript{11}

### 1.2 Binding of Syringolide elicitors

Soluble protein extracts from the leaves of soybean was reported to bind to the Syringolide elicitors in a ligand-specific manner.\textsuperscript{12} Several Syringolide derivatives of varying elicitor activities were synthesized including the radiolabelled with \textsuperscript{125}I.\textsuperscript{13} These derivatives were used in competitive binding assays, and the ability to elicit hypersensitive cell death in cultured soybean cells was investigated. It was found that compounds with reduced competitive binding activity gave very low or undetectable elicitor activity on *Rpg4* cells, which demonstrated a good correlation between competitive binding activity and elicitor activity. It was concluded that a free 3-hydroxyl group was required for both efficient Syringolide binding to the soluble protein fraction and elicitor activity.

\[
\text{4-(2-Iodo-3,4,5-trimethoxyphenylacetyl) syringolide1 (4a)}
\]

\[
\text{4-Succinyl syringolide 1(4b)}
\]
This proposal includes three main steps. The first step involved the acylation of D-xylulose with \( \beta \)-ketoacid 6 to provide the ester intermediate 7. Intramolecular condensation of 7 resulted in the formation of butenolide 8 which on further hemiketalization followed by Michael addition afforded the final Syringolide molecules 1, 2, and 3.
1.4 Previous reports of synthesis of Syringolides

Since 1995, there have been more than ten reports on the total synthesis of Syringolides 1 and 2,\(^{15-24}\) a report on Syringolide 3,\(^{25}\) and few reports on the formal synthesis of Syringolides.\(^{26,27}\) A concise review of previous approaches on the total synthesis of Syringolide 1, 2, and 3 is outlined below.

1.4.1 Wood's report on Total Synthesis of (+)- and (−)-Syringolides 1 and 2

The first total synthesis of Syringolides 1 and 2 was reported by Wood et al. in 1995 (Scheme 1.2).\(^{15}\) This synthetic path is based on the proposed biosynthesis of Syringolides.\(^{6,7}\) The synthesis started with protected L-threitol 11, a commercially available compound having prefixed chiral centers. The key step in this synthesis is the formation of butenolide 17 through the tricarbonyl 16 from 14. The removal of acetonide protection from 17 under acidic conditions followed by
intramolecular cyclization afforded Syringolide 1. However, this step resulted in only 15% of the product.

Scheme 1. 2 Total Synthesis of (+)- and (–)- Syringolides 1 and 2 by Wood et al.

The same strategy was applied in the synthesis of Syringolide 3 (Scheme 1.3). Using HF/H₂O/CH₃CN in the simultaneous deprotection–cyclization step gave only 7% of the Syringolide 3 along with side product 18a.
1.4.2 Kuwahara's report on Total Synthesis of (−)-Syringolides 1 and 2

Another total syntheses of (−)-Syringolides 1 and 2 were accomplished by Kuwahara and co-workers.\textsuperscript{16,17} This approach (Scheme 1.4) is also based on the proposed biosynthesis.\textsuperscript{6} The starting material 19 was prepared from diethyl D-tartrate. The important intermediate, protected D-xylulose 22, was successfully synthesized. The reaction of 22 with 23 gave tricarbonyl compound 24. Deprotection of diol compound 25 resulted in the formation of acetal 26 which on further treatment with \( p \)-TsOH afforded the final Syringolide 1 and 2.
1.4.3 Rickards's reports on Total Synthesis of (−)-Syringolide 2 and (−)-Deuterosyringolide

Using D-xylulose 5 as starting material, Henschke and Rickards were successful in synthesizing the Syringolide 2 (Scheme 1.5). However, it was obtained in very low yield (6%) from 29a.
Scheme 1. 5 Total synthesis of \((-\))-Syringolide 2 by Rickards and Henschke

\[ \begin{align*}
5 \text{ (D-Xylose)} & \xrightarrow{\text{H}_2, \text{Pd(OH)}_2, \text{AcOH}} 29a \text{ (83\%)} \\
\xrightarrow{\text{AcOH}} 29 & \xrightarrow{\text{Basic Al}_{2}\text{O}_{3}, \text{THF}} 2 \text{ (6\%)}
\end{align*} \]

Scheme 1. 6 Total synthesis of \((-\))-Deuterosyringolide 2 by Rickards and Henschke

\[ \begin{align*}
27 & \xrightarrow{\text{THF, reflux}} 30 \\
& \xrightarrow{67\% \text{ aq TFA, THF}} 31 \text{ (38\%)} \\
32 \text{ (64\%)} & \xrightarrow{\text{Basic Al}_{2}\text{O}_{3}, \text{THF}} 33 \text{ (6\%)} \\
& \xrightarrow{\text{D}_2, \text{Pd(OH)}_2/\text{C}, \text{AcOH}} 34 \text{ (100\%)}
\end{align*} \]
As a modification of their previous approach, Rickards and Henschke were also able to obtain deuterated Syringolide 34. The key of this modification involves the introduction of the terminal olefin to the Meldrum's acid derivative 30. Saturation of the olefin with D₂ in the final step gave product 34 in quantitative yield.

1.4.4 Honda’s report on Total Synthesis of (−)-Syringolide 1 and 2

Additionally, Sharpless asymmetric dihydroxylation was used to introduce the chirality in the total synthesis of Syringolide 1 and 2, reported by Honda et al. (Scheme 1.7). However, removal of the protecting groups by either HCl/THF or Dowex 50W-X8/MeOH followed by intramolecular cyclization resulted in low yields of Syringolide 1 and 2.

Scheme 1.7 Total synthesis of (−)-Syringolides 1 and 2 by Honda et al.
1.4.5 Zeng's report on Total Synthesis of (−)- and (+)-Syringolide 1 and (−)-∆7-Syringolide 1

Using D-xylose 44 as the starting material, the acetonide protected D-xylulose 45 was obtained to use for the total synthesis of (−)-Syringolide 1 (Scheme 1.8). In addition, when L-xylose was used as a starting material, the unnatural (+)-Syringolide 1 was afforded and showed the same specific activity as elicitors of the hypersensitive response on soybean plants harboring the Rpg4 gene. Although this is a shorter approach compared to the previously reported syntheses, the final step for the tricyclization resulted in low yield.
An unsaturated analog of 1, (−)-Δ7-Syringolide 1 (33a), was also synthesized in order to prepare tritium-labeled Syringolides for the identification and purification of the Syringolide receptor. In this approach, acetonide protected D-xylulose 45 was treated with β-ketoacid 46 instead of 23a. The unsaturated syringolide analog 33a was hydrogenated to obtain Syringolide 1 in quantitative yield or was reduced by using 3H to afford tritium labeled Syringolide 1.

An alternate route for the synthesis of Syringolide 1 was also introduced (Scheme 1.9). To improve the preparation of the primary ester, D-xylulose acetonide 45 was treated with trityl chloride followed by BnCl/NaH and 2N HCl. The product 49 was subjected to esterification reaction with Meldrum’s acid derivative 28b to obtain the ester 50. Removal of acetonide protection followed by tricyclization and debenzylation formed Syringolide 1.
1.4.6 Murai's report on Total Synthesis of (−)-Syringolide 1

Instead of D-xylulose or D-xylose, a commercially available compound, 2-acetyl-4-butenolide 55 was also effectively used for the total synthesis of Syringolide 1 (Scheme 1.10). 21,29 1,4-addition of organocuprate reagent 60 to the enone 59 afforded olefin 61 in 49% yield. Reduction of keto carbonyl group using NaBH₄ resulted isomers 63a and 63b which were protected with 4-methoxybenzyl group to result 64a and 64b. Diolization of 64 using Sharpless asymmetric
dihydroxylation resulted in four isomers. Desilylation of butenolide 69 by p-TsOH-H₂O followed by cyclization gave Syringolide 1 in low yield (16%) along with the by-product 18b in 23% yield.

Scheme 1. 10 Total Synthesis of (−)-Syringolide 1 by Murai
1.4.7 Yoda's report on formal synthesis of (–)-Syringolide 1

A formal synthesis of Syringolide 1 was accomplished using commercially available 1,2-O-isopropylidene-D-xylofuranose 70 as the source of asymmetry (Scheme 1.11). Benzyl protection was used during the synthesis of 26a, which is an important precursor in the synthesis of Syringolide 1 and 2 reported by Kuwahara and co-workers.
1.4.8 Wong's report on the Synthesis of (–)-Syringolides and X-ray Structural Characterization of (–)-Syringolide 1

During the synthesis of Syributins and Secosyrins, Wong and co-workers obtained butenolide derivative 40,30 which was later used as an intermediate for the synthesis of Syringolide 1 and 2 (Scheme 1.12).22 As a modification of Honda's method,19 10% HF in MeCN in 1:1 ratio was
used to improve yield in the final step; and Syringolide 1 and 2 were obtained in 56% and 52%, respectively. Moreover, the side product 18 in the reaction was again converted into Syringolides 1 and 2 by reacting with $p$-TsOH.

Scheme 1. Total Synthesis of (−)-Syringolides 1 and 2 by Wong and co-workers
1.4.9 Total Synthesis of (−)-Syringolide 2 by Chênevert and Dasser

D-Arabinose was also effectively used as a starting material as reported by Chênevert and Dasser (Scheme 1.13). Chiral precursor 85 was prepared from D-arabinose in three steps as a skeleton for synthesizing Syringolide 2. The acetyl group of 90 was selectively removed by transesterification with ethanol in the presence of Candida antarctica lipase. The target molecule 2 was successfully obtained in 55% yield from 94.

Scheme 1.13 Enantioselective Synthesis of (−)-Syringolide 2 by Chênevert

![Scheme 1.13 Enantioselective Synthesis of (−)-Syringolide 2 by Chênevert](image-url)
As a shorter alternate pathway, the chemoenzymatic approach was developed to synthesize the protected D-xylulose 97 as an important precursor for Syringolide 2 (Scheme 1.14).24 The protected D-xylulose 97 was obtained by the enantiospecific condensation of aldehyde 95 and dihydroxyacetone phosphate 96 in the presence of fructose 1,6-diphosphate aldolase (FDP aldolase). The final step with p-TsOH in Acetone:H2O gave Syringolide 2 in 55% yield.

Scheme 1.14 Chemoenzymatic Synthesis of (−)-Syringolide 2 by Chênevert
1.4.10 Formal Synthesis of (–)-Syringolide 1 by Di Florio et al.

An intermediate 97 for the Syributin synthesis was also found to be the effective precursor to Syringolide 1 by Di Florio et al. (Scheme 1.5). Compound 97 was prepared from 95 and was subjected to desilylation to furnish butenolide 39. Utilizing the procedure reported by Honda et al. Syringolide 1 could be obtained from 39.

Scheme 1. 15 Formal synthesis of (–)-Syringolide 1 by Di Florio et al.
TBAF, 0 °C, 5 min → 39 (55%) → Ref. 21 → 1, R = n-C₆H₁₁
CHAPTER 2

Total Synthesis of Syringolides 1 and 2

2.1 Introduction

Syringolides attract considerable interests as they have features in common with the antigens that are recognized by the immune system of vertebrates. Their low abundance in natural sources and intriguing structures have made them the targets of several syntheses. Even though there were many existing reports on the total synthesis of Syringolides, those reports have limitations such as low yields\(^{15,19}\) and using an expensive starting material, D-xylulose\(^{18}\). Moreover, the isomerization of xylose to xylulose is also a tedious process\(^{31,32}\) resulting in low yields. We thus started to develop a new synthetic route from inexpensive and easily available starting materials, ethylene glycol and hydroxyacetone.

2.2 Retrosynthetic Analysis of Syringolides

Our retrosynthesis parallels to the biosynthetic pathway proposed by Sims and co-workers (Scheme 1.1).\(^{6,7}\) This involves the formation of tricarbonyl compound 7 from the esterification between the protected D-xylulose 100 and \(\beta\)-keto acids 23 (Scheme 2.1). Syringolides 1 and 2 can be prepared from 7 which undergoes intramolecular Knoevenagel condensation and results in the formation of butenolide intermediate 8. The final natural products can be achieved by the hemiketalization and Michael addition of 8. The highlight of our synthesis is the preparation of protected D-xylulose 100 by aldol reaction between the aldehyde 102 and dihydroxyacetone (DHA) 101.
Scheme 2. 1 Retrosynthetic analysis of Syringolides (through aldol reaction)

2.3 Synthesis of β-keto acid from Meldrum's acid

Initially, our synthesis was started with the preparation of β-keto acids. The 3-oxooctanoic acid 23a and 3-oxodeconoic acid 23b, were obtained from hexanoyl chloride 103a and octanoyl chloride 103b, respectively (Scheme 2.2). First, the acid chlorides were treated with Meldrum's acid 104, and the intermediate Meldrum's adducts 115 were refluxed in MeOH to get the corresponding β-keto esters 116 in decent yields.\(^{33,34}\) These esters 116 were hydrolyzed to β-keto acids in more than 80% yield of carboxylic acids 23.
2.4 Synthesis of the aldehyde fragment

To prepare the protected D-xylulose 100, we initially started with the mono-protection of ethylene glycol 105 with different groups such as TBDMS, benzyl, and TIPS (Scheme 2.3). All the three reactions afforded the products in good yields along with a little amount of the di-protected ethylene glycol.

Oxidation of the mono-protected ethylene glycol 106 was subjected to the oxidation using Dess-Martin periodinane (DMP) and SO₃•pyridine. Even though the reactions were successful and resulted in the corresponding aldehydes 102a and 102c, the yields were not satisfactory (40–60%). Later, Swern oxidation was found effective to obtain the aldehyde 102 in good yields (Scheme 2.3).
2.5 Synthesis of protected D-xylulose (through aldol)

After preparing the aldehydes 102, the synthesis of protected D-xylulose 100 was investigated with 102 and the dihydroxy acetone (DHA) 101 under base catalyzed aldol reaction conditions (Eq. 2.1). The control on the absolute configuration of the newly formed stereogenic centers has been a challenging goal in this step. Therefore, a number of reactions with different bases such as DBU, Et$_3$N, and DIPEA were used to prepare protected D-xylulose 100 (Eq. 2.1).
All these reactions resulted in complex mixtures, which indicates the formation of different compounds. It is speculated that hydroxy groups of DHA could be problematic under basic conditions, and we prepared TBDMS protected DHA 107. Aldol addition between 107 and aldehyde 102a was carried out using different bases to yield xylulose derivative 108. However, these reactions were also gave a complex mixture (Scheme 2.4).

**Scheme 2.4 Synthesis of protected D-xylulose**

![Scheme 2.4](image)

2.6 Retrosynthetic analysis of Syringolides (through Wittig reaction)

After many unsuccessful attempts to prepare the protected D-xylulose 100 through the aldol route, we designed a new synthetic pathway towards Syringolides 1 and 2 (Scheme 2.5). The key in this pathway is to synthesize the α,β-unsaturated compound 109 through Wittig reaction between the phosphonium salt 113 and the aldehyde 102. Diolization of 109 under Sharpless asymmetric dihydroxylation conditions would result in the protected D-xylulose 100.
2.7 Synthesis of α,β-unsaturated keto compound

In order to prepare the phosphonium salt 113, we began with an inexpensive starting material, hydroxyacetone 111 (Scheme 2.6). Protection of hydroxyacetone (HA) with TBDMS was successful in 74% yield. α-Bromination of resulting 112a was tried using different brominating agents such as Br₂, HBr, and NBS. All these attempts failed to give the corresponding bromo compound 110a. The acetyl protected 112b was then prepared, and bromination of 112b was successfully achieved by using Br₂ in CCl₄. Without any further purification, the crude 110b was treated with triphenyl phosphine to provide phosphonium salt 113 under reflux conditions.
Scheme 2. Synthesis of α,β-unsaturated ketone 114 by Wittig olefination

Wittig reaction between aldehyde 106b and the phosphonium salt 113 in the presence of 2N NaOH at 0 °C gave the enone 114b in 72% yield. Deacetylation of 114b under mild basic condition afforded the alcohol 109b in 60% yield. Esterification of 109b with 3-oxodeconoic acid 23a was investigated in different conditions such as Yamaguchi, Mitsunobu, Shiina, and Steglich esterification. All these reactions yielded complex mixtures, and none of them provided the tricarbonyl compound 117a. After several attempts of these procedures, we identified that the main problem is the instability of the 3-oxodeconoic acid 23a. The β-keto group of 23a lies more into the enol form (70%) than into the keto form (30%). As synthesizing
the tricarbonyl compound failed, we thus made Meldrum's adduct 115a which was prepared from the reaction between hexanoyl chloride 103a and Meldrum's acid 104 (Scheme 2.7). The tricarbonyl compound 117a was obtained in 75% yield when the alcohol 109 was treated with the Meldrums adduct 115a.\textsuperscript{18} Diolization of the corresponding tricarbonyl compound 117a was tried by using AD-mix-\(\beta\) reagent, but it resulted in a complex mixture. This is probably due to the lability of 117a. The enol might have formed in the keto-enol equilibrium of 117a. The enol would be oxidized faster than the target double bond at the \(\alpha\)-position of the keto carbonyl group, and the undesired oxidation might have occurred as proved previously.\textsuperscript{21}

**Scheme 2. 7 Synthesis of tricarbonyl compound 118**

\[
\begin{align*}
103a + 104 &\rightarrow \text{Pyridine, DCM} \rightarrow \text{115a (92\%)} \\
117a (75\%) &\rightarrow \text{AD-mix-\(\beta\), MeSO_2NH_2, t-BuOH-H_2O (1:1), 0 \(^\circ\)C, 3 days} \rightarrow \text{118}
\end{align*}
\]
2.8 Asymmetric dihydroxylation of \(\alpha,\beta\)-unsaturated compound

As our plan to oxidize the olefin in the tricarbonyl compound 117 did not work, we planned an alternate route to diolize the olefin of 114b before the esterification. Initially, we examined our plan by running a test reaction with OsO\(_4\) (Eq. 2.2). In this reaction, enone 114b was treated with OsO\(_4\) and NMO as a co-oxidant to afford the diol compound 119 in 70\% yield.

With the successful result of the model study, asymmetric dihydroxylation reagent AD-mix-\(\beta\) was used in \(t\)-BuOH-H\(_2\)O at 0°C to diolize 114b. Contrary to the previous result (Eq. 2.2), with AD-mix-\(\beta\) reagent, the reaction was very slow, and some starting material was left unreacted even after five days. The crude NMR spectrum showed that both deacetylation and desilylation took place in the reaction (Eq. 2.3). We believe that fewer equivalents of OsO\(_4\) in purchased AD-mix-\(\beta\) could be the reason for the incomplete reaction.

In order to confirm our hypothesis, we tried the asymmetric dihydroxylation reaction again.
using the AD-mix-β that was prepared in our laboratory by taking 0.02 equivalents of OsO₄ and 0.01 equivalent of the chiral reagent (DHQD)₂PHAL. Although the starting material 114b was completely consumed in 48 h (Eq. 2.4), the reaction furnished a complex mixture, and the NMR analysis revealed the loss of both acetyl and TBDMS groups. We speculated it might be due to the basic condition: the presence of K₂CO₃ in the AD-mix-β reagent.

![Chemical Reaction Diagram]

**2.9 Synthesis of benzyl protected D-xylulose 100a**

In order to overcome undesired deprotection, we prepared the α,β-unsaturated compound 114a having a benzyl protection group which is stable under basic conditions (Eq. 2.5). Wittig reaction between aldehyde 106a and phosphonium salt 113 under basic conditions resulted in the enone 114a along with the deacetylated olefin 109a as a side product (Eq. 2.5). The enone 114a was able to be deacetylated to obtain the alcohol 109a in 69% yield under mild basic conditions. Diolization under Sharpless asymmetric dihydroxylation condition was carried out, and the desired protected D-xylulose 100a was obtained in 25% yield along with the aldehyde 106a in 27% yield (Eq. 2.6). Starting enone 109a was also recovered in 18% from the reaction. We believe that after the formation of the benzyl protected D-xylulose 100a, the retro-aldol reaction has happened in the reaction which finally resulted in the formation of aldehyde 106a.
2.10 Synthesis of TIPS protected D-xylulose

Modification of the protecting group was made to address the low yield. We synthesized α,β-unsaturated compound 114c having a TIPS group which is more stable under the basic reaction conditions than the TBDMS group. Wittig reaction between aldehyde 106c and phosphonium salt 113 gave the α,β-unsaturated ketone 114c in 47% yield along with the deacetylated compound 109c in 36% yield (Eq. 2.7). Enone 114c under basic conditions afforded deacetylated enone 109c in 74% yield. Asymmetric dihydroxylation of enone 109c was carried out by using our blended AD-mix-β reagent to prepare the TIPS protected D-xylulose 100c. The reaction proceeded smoothly with complete conversion of the starting material and yielded 78% of 100c (Eq. 2.8).
In order to determine the stereochemistry, D-xylulose 5 was synthesized from the protected D-xylulose 100a and 100c. Initially, we checked the optical rotation value of the benzyl protected D-xylulose 100a which matched with the previously reported value.\textsuperscript{37} Debenzylation of 100a was successful resulting 75% of the product 5 (Eq. 2.9). The NMR spectrum and optical rotation value of the product D-xylulose matched with the previously reported values.\textsuperscript{38}

The TIPS protected D-xylulose 100c was also deprotected by using TBAF. Although there was no starting material left after a few hours of reaction, the NMR spectrum of the crude reaction mixture indicated the presence of xylulose along with tertrabutyl ammonium salts originated from TBAF. Reported procedure for the desilylation using TBAF employing sulfonic acid resin DOWEX-50W-X8 and CaCO\textsubscript{3} was also proved ineffectual.\textsuperscript{39} Another attempt to desilylate 100c by using HF-Pyridine also encountered a problem with inseparable pyridinium salts from the
product. Finally, treating the protected D-xylulose 100c with 48% aqueous HF in the presence of THF at room temperature afforded the D-xylulose in 60% yield (Eq. 2.10). The NMR spectrum and optical rotation value of the resulted product is identical with the previously reported values of D-xylulose.\(^{38}\)

![Chemical Reaction](image)

Several reports have been described for the synthesis of D-xylulose in which most of them reported the synthesis through the isomerization of D-xylose. Both enzymatic and catalytic isomerization are well established in this process. Enzymatic isomerization of D-xylose to D-xylulose was achieved by using different enzymes including xylose isomerase,\(^ {40-43}\) galactose dehydrogenase,\(^ {44}\) glucose isomerase,\(^ {45,46}\) D-lyxose isomerases\(^ {47}\) and FDP aldolase\(^ {48}\). Synthesis of benzyl protected D-xylulose 100a from β-hydroxy pyruvic acid and 3-oxo-benzylglyceraldehyde using transketolase enzyme is notable.\(^ {49-53}\) A two-step microbial pathway from glycerol to D-xylulose via D-arabitol using *Gluconobacter oxydans* was also described.\(^ {54}\) In the last five years, prominent work has been reported on the catalytic isomerization of xylose to xylulose. This was accomplished using Lewis acid catalysts such as Sn-beta,\(^ {55-57}\) CrCl\(_3\),\(^ {58}\) Sn-MFI\(^ {59,60}\) MgF\(_2\)\(^ {61,62}\) and Al\(_2\)O\(_3\).\(^ {32}\)

Although there were many reports available based on enzymatic and catalytic isomerization process in synthesizing D-xylulose, the chemical pathways were very limited.\(^ {63,64}\) Our synthesis of D-xylulose 5 was achieved by using inexpensive starting materials, hydroxy acetone 111 and ethylene glycol 105, and can be performed in gram scale.
2. 11 Synthesis of Syringolide 1

Selective esterification on primary alcohol of 100c using the Meldrum's acid adduct 115 under thermal coupling conditions was not successful resulting the formation of primary ester, secondary ester, and diester. The starting material 100c remained intact when we tried the reaction at room temperature.
To avoid the complications with esterification, we protected the secondary alcohols by acetonide protection. Selective vicinal diol protection was successfully carried out with 2,2-DMP resulting in the acetonide 121 in 74% yield (Scheme 2. 8). It was treated with hexanoyl Meldrum's acid adduct 115 under reflux condition to yield the tricarbonyl compound 122 in 70% yield. The Knoevenagel condensation by simply mixing 122 with silica gel in EtOAc:hexanes (1:9) afforded butenolide 123 in 72% yield. The removal of both the silyl and acetonide protecting groups in a single step by treating 123 with 2N HCl resulted in the decomposition. The deprotection of TIPS group from 123 using TBAF will form the alcohol 124. Removing of acetonide group would result the triol 8a which on hemiketalization and intramolecular Michael addition sequentially will complete our target molecule Syringolide 1.
REFERENCES


EXPERIMENTAL

Materials and Methods
All reactions were carried out in oven or flame-dried glassware. Compounds were purchased from Sigma-Aldrich, Alfa Aesar, and Acros Organics. THF, CH$_2$Cl$_2$, and Et$_2$O were purified using solvent purification system (Mbraun SPS). Flash chromatography was performed using silica gel 60 Å (40–63 μm) purchased from Sorbent Technologies. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merk precoated silica gel 60 (particle size 0.040–0.063 mm). $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL 600 MHz spectrometer. $^1$H and $^{13}$C chemical shifts are referenced to internal solvent resonances and reported relative to SiMe$_4$ (0 ppm); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, $J$, are reported in Hertz. Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer. Infrared (IR) spectroscopy was performed on a Perkin Elmer Spectrum 100.

Experimental Procedure:

Synthesis of 2-(benzyloxy) ethanol (106a): Ethylene glycol (5 g, 80.0 mmol) was taken into a round bottomed flask, and NaOH pellets (1.6 g, 40 mmol) were added at room temperature. To the above mixture benzyl chloride (5.06 g, 40 mmol) was added slowly at room temperature under stirring condition. The mixture was stirred at 55 °C for 1 h. TLC showed the consumption of starting material. To the reaction mixture, water was added, and the mixture was extracted with EtOAc three times (3 x 50 ml). The organic layers were combined and washed with brine and dried over Na$_2$SO$_4$. The mixture was evaporated under reduced pressure to give crude
compound which after silica gel column chromatography (EtOAc:hexanes, 1:9) gave 5.04 g (84%) of compound 106a as pale yellow liquid. \(^1\)H NMR(600 MHz, CDCl\(_3\)): \(\delta\) 3.15 (br, 1H), 3.54 (t, 2H), 3.69 (m, 2H), 4.52 (s, 2H), 7.28–7.34 (m, 5H). \(^1\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 137.8, 128.3, 127.4, 127.6, 73.1, 71.4, 61.6. HRMS (m/z): calcd [M+Na]\(^+\) for C\(_9\)H\(_{12}\)O\(_2\)Na\(^+\): 175.0735 found: 175.0788. IR (neat): 3404, 3064, 3031, 2862, 1604, 1496, 1453, 1357, 1312, 1267, 1206, 734, 696 cm\(^{-1}\).

**Synthesis of 2-[(tert-butyldimethylsilyl)oxy]ethanol (106b):** To a solution of ethylene glycol (3 g, 48.3 mmol) in DCM (150 ml), Et\(_3\)N (7 ml, 72 mmol) was added at 0 °C slowly under stirring condition. Catalytic amount of DMAP (0.06 g, 0.48 mmol) was also added at 0 °C. TBDMSCI (8.7 g, 58 mmol) was added portionwise at 0 °C, the resultant mixture was allowed to stir at room temperature for 12 h. The mixture was taken into water and extracted with DCM three times (3 x 60 ml). The combined organic layers were washed successively with sat. NaHCO\(_3\) aq., sat. NH\(_4\)Cl aq., H\(_2\)O, and brine. The organic layer was dried over Na\(_2\)SO\(_4\) and evaporated to get a crude compound which after silica gel column chromatography (EtOAc:hexanes, 1:9) gave 7.52 g (74%) of compound 106b as colorless liquid compound. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 3.70 (t, 2H), 3.63 (m, 2H), 2.13 (br, 1H, OH), 0.89 (s, 9H), 0.06 (s, 6H). \(^1\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 64.1, 63.7, 25.9, 18.4. HRMS (m/z): calcd [M+Na]\(^+\) for C\(_8\)H\(_{20}\)O\(_2\)SiNa\(^+\): 199.1130 found: 199.1100. IR (neat): 3327, 2974, 2889, 1657, 1380, 1087, 1045, 879 cm\(^{-1}\).

**Synthesis of 2-[(triisopropylsilyl)oxy]ethanol (106c):** To a mixture of ethylene glycol (18.8 g, 303 mmol) and pyridine (16.6 g, 210 mmol) triisopropyl chlorosilane (TIPSCI) was added dropwise (5.35 ml, 50 mmol) over 20 min at room temperature and the reaction mixture was left for stirring for 12 h at room temperature. The reaction was diluted with EtOAc and washed with
1N HCl aq. The aqueous layer was separated, and the organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and filtered, and solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc:hexanes, 2:8) to give 2-[(trisopropylsilyl)oxy]ethanol (5.15 g, 85%) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$): δ 3.15 (br, 1H), 3.79 (t, $J$ = 4.8 Hz, 2H), 3.67–3.64 (m, 2H), 2.28 (br, 1H), 1.18–1.02 (m, 21H).

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 64.3, 63.8, 17.9, 11.9. HRMS ($m/z$): calcd [M+Na]$^+$ for C$_{11}$H$_{26}$O$_2$SiNa$: 241.1599$ found: 241.1563. IR (neat): 3397, 2943, 2892, 2866, 1463, 1384, 1368, 1116, 1047, 933, 733 cm$^{-1}$.

**Synthesis of 2-(benzyloxy)acetaldehyde (102a):** To a solution of oxalyl chloride (1.83 g, 14.41 mmol) in DCM (30 ml) at –78 °C, DMSO (2.4 g, 31.44 mmol) was added dropwise. After stirring the mixture for 10 min, compound 106a (2 g, 13.1 mmol) was added which was diluted in DCM (15 ml) followed by the addition of Et$_3$N (3.9 g, 39.3 mmol) dropwise. The reaction mixture was warmed up to 10 °C over 5 min and maintained at this temperature for 20 min. After the complete consumption of the starting material, the reaction mixture was washed with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with DCM, and the combined organic layers were dried over Na$_2$SO$_4$ and evaporated to get crude compound which after silica gel column chromatography (EtOAc:hexanes, 2:8) gave 1.73 g (88%) of 102a as a syrupy liquid compound. $^1$H NMR (600 MHz, CDCl$_3$): δ 9.71 (s, 1H), 7.40–7.30 (m, 5H), 4.62 (s, 2H), 4.09 (s, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 199.2, 157.9, 129.5, 122.2, 114.9, 72.7. HRMS ($m/z$): calcd [M+Na]$^+$ for C$_9$H$_{10}$O$_2$Na$: 173.0578$ found: 173.0572. IR (neat): 3063, 3030, 2867, 1951, 1742, 1604, 1496, 1453, 1363, 1091, 1026, 909 cm$^{-1}$.

**Synthesis of 2-[(tert-butyldimethylsilyl)oxy]acetaldehyde (102b):** To a solution of oxalyl chloride (1.57 g, 12.4 mmol) in DCM (30 ml) at –78 °C, DMSO (2.11 g, 27 mmol) was added
dropwise. After stirring the mixture for 10 min, compound 106b (2 g, 11.3 mmol), which was diluted in DCM (10 ml), was added, followed by the addition of Et3N (3.44 g, 33.3 mmol) dropwise. The reaction mixture was warmed up to 10 °C over 5 min and maintained at this temperature for 20 min. After the complete consumption of the starting material, the reaction mixture was washed with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with DCM, and the combined organic layers were dried over Na2SO4 and evaporated to get crude compound which after silica gel column chromatography (EtOAc:hexane, 2:8) gave 1.5 g (76%) of 102b as a syrupy liquid compound. 1H NMR (600 MHz, CDCl3): δ 9.69 (s, 1H), 4.20 (s, 2H), 0.91 (s, 9H), 0.09 (s, 6H). 13C NMR (150 MHz, CDCl3): δ 202.4, 69.7, 25.8, 18.4, -5.3. HRMS (m/z): calcd [M+Na]+ for C8H18O2SiNa+: 197.0973 found: 197.0985. IR (neat): 2954, 2929, 2885, 2858, 1739, 1472, 1463, 1389, 1361, 1311,774, 667 cm⁻¹.

Synthesis of 2-[(triisopropylsilyl)oxy]acetaldehyde (102c): To a solution of oxalyl chloride (1.9 g, 15 mmol) in DCM (30 ml) at –78 °C, DMSO (2.56 g, 32.8 mmol) was added dropwise. After stirring the mixture for 10 min compound 106c (3.0 g, 13.7 mmol) which was diluted in DCM (10 ml), was added, followed by the addition of Et3N (4.16 g, 41.2 mmol) dropwise. The reaction mixture was warmed up to 10 °C over 5 min and maintained at this temperature for 20 min. After complete consumption of the starting material, the reaction mixture was washed with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with DCM, and the combined organic layers were dried on Na2SO4 and evaporated to get crude compound which after silica column purification gave syrupy liquid compound 102c in 82% yield. 1H NMR (600 MHz, CDCl3): δ 9.74 (s, 1H), 4.26 (s, 2H), 1.02–1.17 (m, 2H). 13C NMR (150 MHz, CDCl3): δ 203.0, 69.7, 17.9, 11.9. HRMS (m/z): calcd [M+Na]+ for C11H24O2SiNa+: 239.1443 found: 239.1494. IR (neat): 2945, 2893, 2867, 2254, 1737, 1463, 1384, 1369, 1264, 1133, 733 cm⁻¹.
Synthesis of 2-oxopropyl acetate (112b): To a solution of hydroxyacetone 111 (5.0 g, 67.5 mmol) in 50 ml of ether at 0 °C, pyridine (5.6 g, 70.8 mmol) was added dropwise. To the above reaction mixture acetyl chloride (5.8 g, 74.2 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h. The light yellow precipitate solid was found during the course of reaction. The reaction mixture was filtered, and the solid was washed with ether three times. All the ether layers were combined and washed with water and brine. The organic layer was dried over Na₂SO₄ and evaporated to get crude compound which after silica gel column chromatography (EtOAc:hexanes, 1:9) gave 7.2 g (92%) of 112b as a pale yellow color compound. ¹H NMR (600 MHz, CDCl₃): δ 4.55 (s, 2H), 2.06 (s, 3H), 2.05 (s, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 201.5, 170.0, 68.25, 25.8, 20.3. HRMS (m/z): calcd [M+Na]⁺ for C₅H₈O₃Na⁺: 140.0507 found: 140.0699. IR (neat): 2936, 1730, 1419, 1374, 1271, 1233, 1177, 1069, 1002, 823 cm⁻¹.

Synthesis of 3-bromo-2-oxopropyl acetate (110b): The compound 112b (6.0 g, 51.6 mmol) was dissolved in 90 ml of CCl₄, and Br₂ (3.2 ml, 62 mmol) was added slowly at 0 °C. The reaction was stirred at room temperature for 1 h, and solvent was removed under reduced pressure to get 8 g of 110b as a red oily compound. The crude compound was taken directly to the next step without any further purification. The ¹H NMR of the crude product is given below. ¹H NMR (600 MHz, CDCl₃): δ 4.88 (s, 2H), 3.93 (s, 2H), 2.16 (s, 3H).

Synthesis of 2-oxo-3-(triphenylphosphoranylidene)propyl acetate (113): The crude bromo compound 112b (5 g, 25.7 mmol) was taken into THF (50 ml), and triphenylphosphine (7.4 g, 28 mmol) was added at room temperature. The reaction mixture was kept under reflux for 12 h.
The solvent was removed under reduced pressure to get the crude phosphonium salt 113. The $^1$H NMR of the crude product is given below.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.82–7.64 (m, 15H), 5.96 (s, 2H), 5.21 (s, 2H), 2.07 (s, 3H).

**Synthesis of (E)-5-[(tert-butyldimethylsilyl)oxy]-2-oxopent-3-en-1-yl acetate (114b):** Crude phosphonium salt 113 (5.2 g, 11.7 mmol) was taken into a round bottomed flask and was kept at 0 °C, and THF:H$_2$O (3:1) was then added. To the above reaction mixture 2M NaOH aq. was added (70.2 ml, 6 ml for 1 mmol of aldehyde) and stirred for 1 h at 0 °C. To this solution, aldehyde 106b (1.7 g, 9.7 mmol), which was dissolved in THF (50 ml), was added slowly at 0 °C. The reaction was kept under stirring condition at room temperature for 18 h until the starting material was consumed. The reaction mixture was quenched with H$_2$O and was extracted with EtOAc three times. The organic layers were combined and washed with brine, and solvent was evaporated. To remove the solid, the crude was dissolved in hexane and filtrated. The combined hexane fractions were evaporated under reduced pressure to get a crude oily syrup which on further purification on silica gel column chromatography (EtOAc:hexanes, 3:7) gave a 3.4 g (72%) of colorless oily compound 114b. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.98 (dt, $J_1 = 15.1$ Hz, $J_2 = 3.4$ Hz, 1H), 6.45 (dt, $J_1 = 15.7$ Hz, $J_2 = 2.5$ Hz, 1H), 4.82 (s, 2H), 4.35 (m, 2H), 2.16 (s, 3H), 0.90 (s, 9H), 0.066 (s, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 192.3, 170.5, 146.9, 123.4, 100.6, 77.1, 67.3, 61.9, 22.5, 20.6, 18.0, -3.5. HRMS (m/z): calcd [M+Na]$^+$ for C$_{13}$H$_{24}$O$_4$SiNa$: 295.1341$ found: 295.1372. IR (neat): 2954, 2930, 2886, 1746, 1639, 1472, 1463, 1439, 1374, 1231, 1134, 1101, 1050, 1015, 958, 939, 774, 695 cm$^{-1}$. 
Synthesis of (E)-5-[(tert-butyldimethylsilyl)oxy]-1-hydroxypent-3-en-2-one (109b):

The compound 114b (2.6 g, 9.6 mmol) was dissolved in dry 30 ml of dry MeOH, and KHCO₃ (3.37 g, 33.7 mmol) was added in portionwise at 0 °C. The reaction was stirred at room temperature until the starting material was completely consumed. The reaction was taken into minimum amount of H₂O and was extracted with EtOAc for three times. The organic layers were combined, and washed with brine, dried over Na₂SO₄, and concentrated to give colorless syrupy liquid. Purification of the crude on silica gel column (EtOAc:hexanes, 3:7) gave 1.31 g (60%) of pure 109b as a colorless oily compound. ¹H NMR (600 MHz, CDCl₃): δ 0.09 (s, 6H), 0.92 (s, 9H), 3.26 (t, J = 4.8 Hz, 1H), 4.39 (m, 2H), 4.43 (d, J = 4.86 Hz, 2H), 6.44 (dt, J₁ = 15.78 Hz, J₂ = 2.1 Hz, 1H), 7.01(dt, J₁ = 15.78 HZ, J₂ = 3.42 HZ, 1H). HRMS (m/z): calcd [M+Na]+ for C₁₁H₂₂O₃SiNa⁺: 253.1338 found: 253.1327.

Synthesis of (E)-5-(benzyloxy)-2-oxopent-3-en-1-yl acetate (114a) and (E)-5-(benzyloxy)-1-hydroxypent-3-en-2-one (109a):

Crude phosphonium salt 113 (18 g, 44.7 mmol) was taken into a round bottomed flask, and THF:H₂O (3:1) was added. To the above reaction mixture 2M NaOH aq. was added (223 ml, 6 ml for 1 mmol of aldehyde) and stirred for 1 h at room temperature. To this solution aldehyde 106a (5.6 g, 37.3 mmol), which was dissolved in THF (50 ml), was added slowly at room temperature. The reaction was kept under stirring condition at room temperature for 20 h until the starting material was consumed. The reaction mixture was quenched with H₂O and was extracted with EtOAc three times. The organic layers were combined and washed with brine, dried over Na₂SO₄, and evaporated to get crude compound. To remove the solid, the crude was dissolved in hexanes and filtrated. The combined hexane fractions were evaporated under reduced pressure to get a crude oily syrup which on further
purification on silica gel column (EtOAc:hexanes, 3:7) gave a colorless oily compounds 114a and 109a in 1.26 g (41%) and 0.97 g (38%), respectively.

114a: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.37–7.28 (m, 5H), 6.98–6.94 (dt, $J_1$ = 15.5 Hz, $J_2$ = 3.6 Hz, 1H), 6.49–6.46 (dt, $J_1$ = 16.5 Hz, $J_2$ = 2.7 Hz, 1H), 4.83 (s, 2H), 4.57 (s, 2H), 4.21 (m, 2H), 2.17 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 192.0, 170.2, 144.1, 137.4, 128.5, 127.9, 127.6, 124.5, 68.6, 67.2, 20.5. HRMS ($m/z$): calcd [M+Na]$^+$ for C$_{14}$H$_{16}$O$_4$Na$: 271.0946 found: 271.0907. IR (neat): 3059, 2858, 1749, 1713, 1698, 1496, 1454, 1374, 1266, 1230, 1202, 1113, 1073, 732, 699 cm$^{-1}$.

109a: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.37–7.27 (m, 5H), 6.99–6.95 (dt, $J_1$ = 16.8 Hz, $J_2$ = 3.6 Hz, 1H), 6.47–6.43 (dt, $J_1$ = 15.5 Hz, $J_2$ = 1.8 Hz, 1H), 4.58 (s, 2H), 4.41 (s, 2H), 4.21 (m, 2H), 3.29 (br, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 192.6, 170.4, 147.7, 147.0, 123.0, 67.4, 62.6, 20.6, 20.0, 12.0. HRMS ($m/z$): calcd [M+Na]$^+$ for C$_{12}$H$_{14}$O$_3$Na$: 229.0840 found: 229.0823. IR (neat): 3464, 3058, 2859, 1682, 1639, 1496, 1454, 1361, 1265, 1207, 1115, 1076, 1027, 966, 918, 731, 698 cm$^{-1}$.

Synthesis of (E)-2-oxo-5-[(triisopropylsilyl)oxy]pent-3-en-1-yl acetate (114c) and (E)-1-hydroxy-5-[(triisopropylsilyl)oxy]pent-3-en-2-one (109c): Crude phosphonium salt 113 (7.5 g, 16.6 mmol) was taken into a round bottomed flask, and THF:H$_2$O (3:1) were added at room temperature. To the above reaction mixture 2M NaOH aq. was added (82.8 ml, 6 ml for 1 mmol of aldehyde) and stirred for 1 h at room temperature. Aldehyde 106c (3.0 g, 13.8 mmol) which was dissolved in THF (20 ml) was added slowly at room temperature. The reaction was kept under stirring condition at room temperature until the complete consumption of starting material. The reaction mixture was diluted with H$_2$O and was extracted with EtOAc three times. The organic layers were combined and washed with brine and evaporated to get syrupy crude
compound. To remove the solid, the crude compound was dissolved in hexanes and then filtrated. The combined hexane fractions were evaporated under reduced pressure to get a crude oily syrup which on further purification on silica gel column chromatography (EtOAc:hexanes, 3:7) gave a colorless oily compounds **114c** and **109c** in 0.98 g (47%) and 0.65 g (36%), respectively.

**114c**: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.03–7.00 (dt, $J_1 = 15.6$ Hz, $J_2 = 3.6$ Hz, 1H), 6.57–6.54 (dt, $J_1 = 15.6$ Hz, $J_2 = 1.8$ Hz, 1H), 4.84 (s, 2H), 4.47 (t, $J = 2.7$ Hz, 2H), 2.18 (s, 3H), 1.17–1.02 (m, 21H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 192.6, 170.4, 147.7, 123.0, 67.4, 62.6, 20.6, 18.0, 12.0. HRMS (m/z): calcd [M+Na]$^+$ for C$_{16}$H$_{30}$O$_4$SiNa$^+$: 337.1811 found: 337.1815. IR (neat): 2945, 2867, 1750, 1698, 1640, 1463, 1439, 1373, 1266, 1228, 1138, 1057, 1015, 995, 963, 919.799, 735, 685,661 cm$^{-1}$.

**109c**: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.00 (d, $J=15.6$ Hz, 1H), 6.48 (d, $J=15.6,1$H), 4.46 (s, 2H), 4.41 (s, 2H), 3.31 (br, 1H), 1.17–1.02 (m, 21H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 198.0, 147.6, 123.1, 66.7, 62.4, 17.9, 11.9. HRMS (m/z): calcd [M+Na]$^+$ for C$_{14}$H$_{28}$O$_3$SiNa$^+$: 295.1705 found: 295.1709. IR (neat): 3476, 2944, 2893, 2867, 1682, 1639, 1463, 1384, 1265, 1141, 1071, 1014, 996, 964, 910, 797, 733, 683,660 cm$^{-1}$.

**(3S,4R)-5-(benzyloxy)-1,3,4-trihydroxypentan-2-one (100a)**: K$_3$Fe(CN)$_6$ (6.47 g, 19.6 mmol) and K$_2$CO$_3$ (2.62 g, 19.6 mmol) were taken in a dry round bottom flask equipped with a stir bar. (DHQD)$_2$PHAL (5 mg, 0.06 mmol) and OsO$_4$ (16 mg, 0.06 mmol) were added to the dry mixture and was stirred until it appeared well mixed. A 1:1 mixture of a $t$-BuOH:H$_2$O (30 ml) was added, and the heterogeneous biphasic solution was stirred for 10 minutes and then cooled to 0 °C. Enone compound **109a** (1.35 g, 6.5 mmol) was added to the cooled heterogeneous solution using
a minimal amount of $t$-BuOH followed by the addition of MeSO$_2$NH$_2$ (0.62 g, 6.5 mmol). The resulting orange mixture was allowed to stir at 0 °C until all the starting material had been consumed by TLC analysis. Solid Na$_2$SO$_3$ was added at 0 °C until the yellow solution turned brown. The mixture was diluted with water and extracted with EtOAc three times. The organic layer was then washed with 0.1N KOH aq. and brine, dried over Na$_2$SO$_4$, and concentrated under vacuum to provide crude compound which on further purification on silica gel column chromatography (EtOAc:hexanes, 4:6) gave a colorless oily compounds **100a** in 0.39 g (25%) as a colorless oily liquid. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 7.51–7.32 (m, 5H), 5.40 (s, 1H), 4.48–4.35 (m, 4H), 4.22 (s, 1H), 4.03 (t, 1H), 3.51 (m, 1H), 3.48 (m, 1H), 3.22 (s, 1H). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 212.2, 138.2, 128.0, 127.5, 127.3, 75.8, 73.0, 70.7, 70.2, 66.5. HRMS ($m/z$): calculated [M+Na]$^+$ for C$_{12}$H$_{16}$O$_5$Na$^+$: 263.0998 found: 263.0964. IR (neat): 3476, 2944, 2893, 2867, 1682, 1639, 1463, 1384, 1265, 1141, 1071, 1014, 996, 964, 910, 797, 733, 683,660 cm$^{-1}$.

**$(3S,4R)$-1,3,4-trihydroxy-5-[(triisopropylsilyl)oxy]pentan-2-one (100c):** K$_3$Fe(CN)$_6$ (3.6 g, 11 mmol) and K$_2$CO$_3$ (1.5 g, 11 mmol) were added to a dry round bottom flask equipped with a stir bar. (DHQD)$_2$PHAL (30 mg, 0.03 mmol) and OsO$_4$ (10 mg, 0.03 mmol) were added to the dry mixture, and this mixture was stirred until it appeared well mixed. A 1:1 mixture of a $t$-BuOH:H$_2$O (16 ml) was next added, and the heterogeneous biphasic solution was stirred for 10 minutes and then cooled to 0 °C. Enone compound **109c** (1.0 g, 3.6 mmol) was added to this cooled heterogeneous solution using a minimal amount of $t$-BuOH, followed by the addition of MeSO$_2$NH$_2$ (1.0 eq). The resulting orange mixture was allowed to stir at 0 °C until all the starting material had been consumed by TLC analysis after 24 h. Solid Na$_2$SO$_3$ was added at 0 °C until the yellow solution turned brown. The mixture was diluted with water and extracted with EtOAc three times. The organic layer was then washed with 0.1N KOH aq. and brine, dried over
Na$_2$SO$_4$, and concentrated under vacuum to provide 100c in 0.87 g (78%) as colorless oily liquid. 

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 4.51 (dd, $J = 12.2$ Hz, 2H), 4.37 (s, 1H), 4.00 (s, 1H), 3.83 (d, $J = 5.5$ Hz, 2H), 3.62 (br, 1H), 3.17 (br, 1H), 2.89 (br, 1H), 1.14-1.03 (m, 21H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 211.98, 76.28, 71.79, 66.95, 64.72, 17.93, 11.83. HRMS ($m/z$): calcd [M+Na]$^+$ for C$_{14}$H$_{30}$O$_5$SiNa$: 329.1760$ found: 329.1754. IR (neat): 3471, 2943, 2892, 2866, 1743, 1682, 1639, 1383, 1281, 995, 680 cm$^{-1}$.

**D-Xylulose (5):** Compound 100a (55 mg, 0.2 mmol) was taken into a round bottomed flask, and 4 ml of ethanol was added. To the above compound, Pd/C (10 mg) was added at room temperature, and the reaction was kept under H$_2$ gas using balloon. The reaction was allowed to stir at room temperature for 24 h. The reaction mixture was filtered on a celite bed, and the filtrate was concentrated under reduced pressure to give 5 in 25 mg (75%) as a pale yellow sticky compound. $[\alpha]^{25}_D = -32.2^\circ$ (c = 2, H$_2$O). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 4.50–4.35 (q, 2H), 4.29 (s, 1H), 4.22–4.00 (q, 1H), 4.12–4.00 (m, 3H), 3.92 (d, 1H), 3.87 (d, 1H), 3.55–3.39 (m, 4H) . $^{13}$C NMR (150 MHz, D$_2$O): $\delta$ 212.98, 105.74, 102.93, 80.5, 76.23, 75.85, 75.33, 74.87, 71.98, 71.91, 69.82, 66.04, 62.97, 62.42, 61.87.

**D-Xylulose (5):** Compound 100c (55 mg, 0.17 mmol) was taken into a round bottomed flask, and 6 ml of THF was added. To the above reaction mixture 1 ml of aq-HF (48%) was added at 0 $^\circ$C. The reaction was allowed to stir at room temperature for 4 h. The solvent was removed under reduced pressure to give crude compound 5 in 16 mg (60%) as pale yellow sticky compound. $[\alpha]^{25}_D = -31.9^\circ$ (c = 2, H$_2$O). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 4.52–4.36 (q, 2H), 4.29 (s, 1H), 4.29–4.09 (q, 1H), 4.12–4.02 (m, 3H), 3.92 (d, 1H), 3.87 (d, 1H), 3.59–3.36 (m, 4H) . $^{13}$C NMR (150 MHz, D$_2$O): $\delta$ 214.39, 107.64, 104.37, 77.64, 77.28, 76.75, 76.3, 73.4, 73.3, 71.2, 67.4, 64.41, 63.3.
2-hydroxy-1-[(4S,5R)-2-methyl-5-[(triisopropylsilyl)oxy]methyl]-1,3-dioxolan-4-yl] ethanone (121): Compound 100a (0.1 g, 0.32 mmol) was taken in 4 ml of DCM. To the above reaction mixture CSA (0.09 g, 0.39 mmol) was added at 0 °C followed by the addition of 2,2-DMP (0.2 ml, 0.64 mmol). The reaction mixture was allowed to stir at room temperature for 4 h. The reaction was taken with H₂O and was extracted with EtOAc three times. The organic layers were combined and washed with brine solution. The organic layer was dried over Na₂SO₄, and solvent was removed under reduced pressure. The crude compound was purified by silica gel column chromatography (EtOAc:hexane, 4:6) to give pure 0.08 g (74%) of 121 as a colorless sticky compound. ¹H NMR (600 MHz, CDCl₃): δ 4.61 (d, 1H), 4.57 (m, 1H), 4.10 (m, 1H), 4.05 (dd, J = 7.2 Hz, 1H), 3.86 (dd, J = 5.5 Hz, 1H), 3.11 (br, 1H), 1.46 (s, 3H), 1.419 (s, 3H), 1.16–1.07 (m, 21H). ¹³C NMR (150 MHz, CDCl₃): δ 209.75, 111.26, 79.44, 79.23, 66.39, 62.66, 26.80, 26.37, 17.88, 11.85.

2-[(4S,5R)-2,2-dimethyl-5-[(triisopropylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-2-oxoethyl-3-oxohexanoate (122): Compound 121 (0.07 g, 0.2 mmol) was taken and 5 ml of THF was added. Compound 115 (0.077 g, 0.32 mmol) which was already dissolved in 5 ml of THF was added to the above reaction. The reaction was kept under reflux condition for 6 h. The solvent was removed under reduced pressure and crude compound was purified by silica gel column chromatography (EtOAc:hexanes, 3:7) to give pure 0.064 g (70%) of 122 as a colorless sticky compound. ¹H NMR (600 MHz, CDCl₃): δ 5.18 (d, 1H), 4.97 (d, 1H), 4.56 (d, 1H), 4.16 (m, 1H), 3.99 (dd, J = 5.5 Hz, 1H), 3.82 (dd, J = 7.2 Hz, 1H), 3.55 (s, 2H), 2.6 (t, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.14-1.05 (m, 21H), 0.89 (t, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 202.53, 180.4, 166.6, 111.31, 79.51, 79.12, 67.04, 62.42, 48.76, 42.85, 31.2, 26.77, 26.37, 23.17, 22.44, 17.98, 13.98, 11.96.
3-butyryl-4-[(4R,5R)-2,2-dimethyl-5-[(triisopropylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]
furan-2(5H)-one (123): Compound 122 (0.040 g, 0.08 mmol) was taken in to 5 ml of EtOAc:hexane (1:9), and silica gel (0.9 g) was added to the solution at room temperature. The reaction mixture was allowed to stir at room temperature for 24 h. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give 0.027 g (72%) of 123 as a colorless sticky compound. $^1$H NMR (600 MHz, CDCl$_3$): δ 5.51 (d, 1H), 5.07 (d, 1H), 4.9 (d, 1H), 4.16 (m, 1H), 3.99–3.93 (m, 2H), 2.94 (t, 2H), 1.45 (s, 3H), 1.42–1.26 (m, 4H), 1.25 (s, 3H), 1.14–1.04 (m, 21H), 0.89 (t, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 196.42, 173.11, 170.46, 137.95, 128.3, 111.0, 82.92, 73.54, 69.27, 63.8, 48.76, 42.04, 31.2, 27.0, 22.8, 22.54, 17.9, 13.81, 11.92.
APPENDIX (NMR SPECTRA)
CURRICULUM VITA

Sudhakar Kalagara was born in Rajahmundry, Andhra Pradesh, India. He got his bachelor's degree in chemistry from Andhra University, Visakhapatnam. After his bachelor's degree, he worked in Aurobindo Pharmaceuticals as a production chemist for one year. Later, he moved to Nagpur for higher education. He earned his master's degree in organic chemistry from RTM Nagpur University in 2005 and continued to work as a research associate in Chembiotek Research International, Kolkata. In spring 2010, he came to the U.S to pursue his Ph.D. under the guidance of Dr. Shizue Mito at The University of Texas at El Paso.

As a graduate student, Dr. Kalagara enjoyed working on projects to develop new methods and synthetic routes to synthesize organic molecules. He was awarded the Cotton Memorial Scholarship in 2011. While pursuing his degree, he worked as an Assistant Instructor for both organic and general chemistry labs. Dr. Kalagara has presented his research at international conferences such as the American Chemical Society, and in several seminars at UTEP. He received his Ph.D. degree in Chemistry in May 2015 with the Academic and Research Excellence award from the Chemistry Department.

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