CHAPTER-III

Total synthesis of (-)-osmundalactone, it’s epimer and butyro-lactone moiety of angiopterlactone A
**Introduction:**

Natural products,\(^1\) due to their bioactivity and interesting complex structural features, have always fascinated the synthetic organic chemists throughout the world. Target oriented synthesis (TOS) of natural products is a very challenging yet very important task. This may be attributed to: a) the attractive structural features with diverse functional groups and number of asymmetric centres in them, b) due to their important biological activity and availability in minute quantities from natural sources and c) sometimes nature stops producing the natural products anymore, (for eg. Acutiphycin) so only the synthesis becomes the primary source (Figure 1).

![Figure 1](image)

Many of the biologically active natural products isolated from diverse sources such as plant, animal and microorganisms have asymmetric centres in their structures. Thus in the total synthesis of such natural products, the introduction of chirality is a major problem. In the earlier time, syntheses have mostly utilized reactions, that produced the products in racemic form,
which were later subjected to optical resolution to get optically pure compounds. Such approaches are not only laborious and wasteful only one of the two antipodes is biologically active, while the other isomer is not useful. Therefore, a synthetic strategy is preferred, wherein, such a wastage of optical isomers is avoided totally are excluded at the earlier stages of synthesis by the creation of chiral centres.

The successful synthesis of a molecule depends upon the analysis of the problem to design a better approach. Until the early 60’s, each of the tasks were addressed as special cases with a highly individualized analysis, whereby it lacked a general problem-solving feature. E. J. Corey by the mid 60’s, developed a systematic approach, known as “retrosynthetic or antithetic analysis” which transforms the structure of a complex target molecule into a sequence of simpler structures that ultimately would lead to simple or commercially available starting materials. With the advancement of instrumental techniques along with the development of a vast number of synthetic reagents and other operational and technical facilities at the disposal, the art of chemistry has become far superior, while doing away with traditional methods of resolution in synthetic schemes. The new approaches started devising strategies that utilize readily available and versatile optically active starting materials and reagents for the target oriented synthesis of natural products.

This development has broadly divided the modern synthetic organic chemistry into two inter-related yet independent branches, (1) the “asymmetric synthesis”, in which the emphasis is on chiral reagents and (2) the “chiron approach” in which starting materials are optically active. The evolution of asymmetric synthesis is unpredictable, but the dramatic progress will certainly persist. In chiron approach, readily available starting materials such as terpenes\(^2\), amino acids\(^3\), hydroxy acids\(^4\), carbohydrates etc., are used as starting materials for the construction of target molecules.

Carbohydrates are a group of versatile substances, which can be utilized as starting materials\(^5\) in the synthesis of natural products of varied structural complexity and containing predisposed centres of asymmetry. The organic chemist has discovered carbohydrates hopefully to maintain a long lasting and rewarding rapport for generations to come. Carbohydrates are relatively cheap and replenishable source of chiral compounds\(^6\) available in a variety of cyclic and acyclic forms, chain lengths and oxidation or reduction states. They are endowed with a plethora of functional, stereochemical and conformational features which lend themselves to
chemical exploitation. These very features also ensure a measure of regio and stereo control in bond forming reactions that are not easily matched by other class of organic compounds.

The annonaceae family has been well known for the frequent presence of isoquinoline alkaloids. Recently on the basis of the restrictive existence of a very active class of natural products, acetogenins are inhibitors of the mitochondrial respiratory chain complex I. However, this family also produces compounds belonging to various phytochemical groups like, terpenoid compounds co-occur with isoquinoline alkaloids in some genera. Styryllactones are secondary metabolites that have been isolated mainly from the genus Goniothalamus. The first styryllactone is goniothalamin 1, found within the annonaceae family, was isolated from several species of Goniothalamus.

Styryllactones are a new class of compounds both of natural and synthetic origin with potential cytotoxic activity including antitumour, antifungal and antibiotic properties. Most of these natural products are isolated from the genus Goniothalamus belonging to Annonaceae, which are widely distributed throughout Malaysia. Many of these species were used as traditional medicine to treat various ailments and had been claimed to have connection with an antifertility effects such as procurement of abortion, undefined post-natal treatments and low birth rate.

Goniothalamin 1 was isolated from barks, roots and the whole plant material of several groups of Goniothalamus and can be considered as a biogenetic precursor of the other groups of styryllactones. Styrylpyrones are the most important amongst the group of styryllactones. Some of the examples 1-10 are presented in Figure 2.

**Figure 2**

![Diagram of goniothalamine, goniothalamine oxide, and 7-epi-goniodiol](image-url)
The other class belonging to styryllactones is furano-pyrones. Altholactone 11 is the first example of this group was initially isolated from *Polyalthia* and later from the bark of *Goniothalamus giganteus*. All furanopyrones 11-15 (Figure 3) are biogenetically related to styrylpyrones, this class is the second most abundant class of styryllactones in *Goniothalamus*. All furanopyrones, including the main styryllactone of the genus, are characterized by the presence of α, β-unsaturated δ-lactone moiety.

**Figure 3**

Goniobutanolides-A 16 and B 17 are the two known butenolide class of compounds (Figure 4), originally isolated from *G. giganteus*. Recently both the metabolites 16 and 17 were isolated from the bark of *G. borneensis*.11
Many natural products containing lactone rings particularly the α,β-unsaturated lactone ring are isolated from nature, many of these possess diverse biological activities. Some examples of natural products with α,β-unsaturated δ-lactone such as phomalactone $^{18,13,14}$, acetylphomalactone $^{19,15,16}$, asperlin $^{20,13}$, olguin $^{21,17}$ and phomopsolide $^{22}$ are presented in Figure 5.$^{18}$
CHAPTER III: Total synthesis of (-)-osmundalactone, it’s epimer and butyro-lactone moiety of angiopterlactone A

Chapter III deals with total synthesis of (-)-osmundalactone, it’s epimer and butyro-lactone moiety of angiopterlactone A

Present work:

Introduction to osmundalactone:

These lactones are found as structural sub units and also these simple lactones have been used as intermediates for synthesis of biologically active molecules. Those $\alpha,\beta$-unsaturated lactone shows the pharmacologically/biologically active properties like anti-tumoural/else tumour promoting activity. (-)-Osmundalactone $23^{19}$ (Figure 6) is the aglycone part of the natural glycoside osmundalin $26^{19}$ and occurs also in the free form in the edible Japanese fern species Osmunda japonica. Carcinogenic properties have not been unequivocally established for the aforementioned compounds but osmundalactone $^{19}$ itself has been found to display antifeedant activity against larvae of some insect species. $^{20}$ (-)-Osmundalactone $23$ recently isolated $^{21}$ from rhizome of Angiopteris caudatiformis and having insect antifeeding activity against Plutella xylostella and Heliothis virescens. Its enantiomer, (+)-osmundalactone $24$ has also been reported as a natural product. $^{22}$ Osmudalactones $23$, $24$ and cis-diastereomer (4-Epi-osmundalactone $25^{19,23,24}$) used as O-substituted derivatives such as angiopterlactone A and B ($27$ and $28$) of several natural product $^{25-30}$

![Figure 6](image-url)
Previous approaches:

Murayama *et al.* approach:

Murayama *et al.*\(^{23}\) reported the synthesis of osmundalactones wherein, the C4 and C5 centers were generated by two different Grignard reactions with methyl magnesium iodide and 1-lithio-3-triethylsiloxy-1-propyne, followed by lactonization (Scheme 1).

**Scheme 1**

Carda *et al.* approach:

Carda *et al.*\(^{31}\) reported the synthesis of 23 wherein, the C4 center was generated by Grignard reaction with vinylmagnesium bromide, while the lactonization was achieved by RCM reaction (Scheme 2).

**Scheme 2**
Ono et al. approach:

Ono et al.\textsuperscript{32} reported the synthesis of 23 by an enantioselective hydrolysis of 40 using the lipase ‘Amano P’ from \textit{Pseudomonas} sp. in phosphate buffer solution to gave 41 and 41a. The synthesis of 23 was achieved from 42 through the acid accompanied by trans-cis isomerization followed by lactonization (Scheme 3).

\textbf{Scheme 3}

\begin{center}
\begin{align*}
(\pm)-40 & \xrightarrow{\text{Lipase}} 41 + 42 \\
41 & \xrightarrow{\text{Yamaguchi conditions}} 43 \\
43 & \xrightarrow{\text{AlCl}_3/m\text{-xylene, CH}_2\text{Cl}_2, 0 ^\circ\text{C}}} 23 \\
\end{align*}
\end{center}

\textbf{Total synthesis of (-)-osmundalactone:}

The retrosynthetic strategy for 23 (Scheme 4), revealed that the lactone could be obtained by cyclization of \(\alpha, \beta\)-unsaturated ester 44. The requisite 4R, 5S-vic diol for 23 could be realized from C-3/C-4 of 45 derived from L-arabinose. Thus, the methyl side chain of the target 23 comes from C-5, C-4/C-5 stereocentres are correlated to C-3/C-4 of 45 respectively. The aldehyde generated from C-1/C-2 of 45 would be used for the homologation to introduce a two carbon chain. Thus the synthetic strategy could be: a) deoxygenate C-5 to methyl group, b) retention of C-3/C-4 for C-5/C-6 and c) extention of 2C with Wittig olefination.

\textbf{Scheme 4}

\begin{center}
\begin{align*}
23 & \xrightarrow{\text{L}(+)-\text{Ara}} 44 \\
44 & \xrightarrow{\text{PMBO}} 45 \\
\end{align*}
\end{center}

Accordingly, known silyl ether 46 was subjected to desilylation using TBAF in dry THF at 0 °C to room temperature for 14 h to give diol 46a in 82% yield (Scheme 5).
Diol 46a on reaction with p-toluenesulphonyl chloride, Et₃N and cat. DMAP in CH₂Cl₂ at room temperature for 2 h furnished monotosylate 47 in 75% yield (Scheme 6), along with ditosylate 47a (8%), which were separated by column chromatography. The ¹H NMR spectrum of 47 showed the expected signals corresponding to newly introduced tosyl group at δ 7.35 and 7.81 as doublets, while a singlet corresponding to Ar-CH₃ resonated at δ 2.45. In the IR spectrum of 47 the absorbance corresponding to sulfonate was observed at 1350 and 1150 cm⁻¹, further confirming the product.

Reductive deoxygenation of 47 using NaBH₄ in dry DMSO at 160 °C for 10 min under N₂ atmosphere gave 48 in 81% yield (Scheme 6). The ¹H NMR showed the disappearance of signals of tosyl group, while CH₃ protons resonated at δ 1.40 (J = 6.4 Hz) as a doublet. H-3a and H-6a resonated at δ 5.82 (J = 5.0 Hz) and δ 4.43 (J = 5.0 Hz) as two doublets, while H-5 and H-6 appeared at δ 4.02 as a multiplet respectively, besides the acetonide methyl protons resonating at δ 1.30 and δ 1.50 as two singlets. Further, M⁺+23 peak which appeared at m/z 197 in EIMS of 48 confirmed the structure.

Alcohol 48 on reaction with p-methoxybenzyl bromide in the presence of NaH in THF at 0 °C to room temperature for 4 h to furnish 45 in 95% yield (Scheme 7). ¹H NMR of 45 showed PMB proton signals at δ 3.78 for Ar-CH₂O as a singlet and aromatic proton signals at δ 6.82, 7.19 (J = 8.3 Hz) as two doublets, whereas, rest of the protons appeared at the expected chemical shifts. HRMS showed m/z 317.1355 for C₁₆H₂₂O₅Na (M+Na)⁺ confirming the product 45.
Further, hydrolysis of 1,2-acetonide in 45 on reaction with 60% aq. AcOH and catalytic amount of conc. HCl at room temperature for 18 h afforded the diol 49 in 75% yield (Scheme 7). In the $^1$H NMR of 49, the disappearance of isopropylidene protons was observed.

Oxidative cleavage of diol 49 with NaIO$_4$ and aq. NaHCO$_3$ in CH$_2$Cl$_2$ (5 mL) at room temperature for 3 h gave aldehyde 50, which on subsequent homologation with (methoxycarbonylmethylene)triphenyl phosphorane in MeOH at 0 °C to room temperature for 2 h furnished cis-ester as major product 51 in 77% yield (Scheme 8).

The newly created cis-olefinic protons in the $^1$H NMR spectrum of 51 resonated at $\delta$ 6.02-6.20 as a multiplet and ester -OMe protons at $\delta$ 3.72 as a singlet, while -CHO proton at $\delta$ 8.06 as a singlet. Rest of the protons at the expected chemical shifts. HRMS showed $m/z$ 331.11523 for C$_{16}$H$_{22}$O$_5$Na (M+Na)$^+$ confirming the structure.

Finally, hydrolysis of O-formyl in 51 with catalytic amount of conc. HCl in 1,4-dioxane:water (1:1) at room temperature for 18 h gave the required six-membered ring lactone 52 in 75% yield (Scheme 9), by hydrolysis of formyl, methyl ester and concomitant lactonization to give $\alpha,\beta$-unsaturated lactone 52.

In the $^1$H NMR spectrum of 52, the proton corresponding to O-formyl and ester -OMe groups were absent. The $\alpha$-olefinic proton resonated at $\delta$ 5.98 ($J = 1.7, 10.1$ Hz) as a doublet of doublet, while $\beta$-proton resonated at $\delta$ 6.84 ($J = 2.2, 10.0$ Hz) as a doublet of doublet. Rest of the protons were observed at the appropriate chemical shifts. HRMS (M+Na)$^+$ showed $m/z$ 271.09408 for C$_{14}$H$_{16}$NaO$_4$ (M+Na)$^+$ confirming the structure of 52.
Oxidative deprotection of the PMB group in 52 with DDQ in aq. CH₂Cl₂ at 0 °C to room temperature for 2 h gave osmundalactone 23 (Scheme 10). In ¹H NMR spectrum of 23, the methyl proton signals appears at δ 1.49 (J = 6.0 Hz) as a doublet, α- and β-protons at δ 6.00 and δ 6.82 (J = 2.0, 9.9 Hz) as two doublet of doublet, while C5-H and C6-H at δ 4.24 (J = 8.5 Hz) and δ 4.37 (J = 5.9, 12.9 Hz) as a broad doublet and a doublet of quintet. HRMS showed m/z 129.05481 for C₆H₉O₃ (M+H)⁺ confirming the structure of 23. The optical rotation value for 23 in H₂O are [α]D = -69.1 (c 0.38), was comparable with reported data [α]D = -68.4 (c 0.41, H₂O) in lit.⁵² The spectral and analytical data of 23 was in full accordance with literature data. Thus, the total synthesis of (-)-osmundalactone 23 was achieved in a simple and efficient route from L- (+)-arabinose as the starting material.

Scheme 10

Total synthesis of 4-Epi- (+)-osmundalactone:

Lactone natural products (+)-osmundalactone 24 and 4-epi- (+)-osmundalactone 25 are structurally related to (-)-osmundalactone 23. Lactone 24 is enantiomer to 23, while 25 is epimer to 24, while diastereomeric with 23. Having successfully synthesized 23 from L-Ara, it was then proposed to undertake the synthesis of 25 from D-Xylo. Since D-Xylo and L-Ara are C-4 epimers to each other, and as the C-4 stereocentre of L-Ara was correlated to the C-5 stereocentre of 23, the use of C-3/C-4 stereocentre in D-Xylo by the above strategy would result in an efficient synthesis of 4-epi-osmundalactone 25. Keeping the above strategy, similar synthetic strategy was planned for the synthesis of 25.

The retrosynthetic strategy for 25 as shown in the Scheme 11 revealed that the lactone could be obtained by lactonization of α,β-unsaturated ester 53, which inturn planned from 54, that could be prepared from D-xylose. The C-4 and C-5 stereocentres of 25 could be correlated to the C-3 and C-4 of D-xylose, while the aldehyde derived from oxidative cleavage of 1,2-diol in D-xylose after acetonide deprotection would be useful for two carbon chain elongation and introduction of α,β-unsaturated ester. In addition the deoxygenation C-5 hydroxy methyl group would introduce the requisite methyl side chain.
Accordingly, commercially available D-xylose was treated with acetone and catalytic amount of conc. H₂SO₄ at room temperature for 12 h to give 55 in 72% yield, which on hydrolysis with 5% aq. HCl at room temperature for 30 min afforded the diol 56 in 90% yield (Scheme 12).

Treatment of diol 56 with p-TsCl, Et₃N and cat. DMAP in CH₂Cl₂ at room temperature for 2 h furnished 57 in 75% yield (Scheme 13), along with ditosylate 57a (8%), as a separable mixture by column chromatography. The ¹H NMR spectrum of 57 showed the resonances for Ar-H at δ 7.35 and 7.81 (J = 4.7 Hz) as two doublets, while, Ar-CH₃ resonated at δ 2.45 as a singlet. HRMS showed m/z 367.0814 for C₁₅H₂₀O₇NaS (M+Na)⁺ confirming the structure of 57.

Reductive deoxygenation of 57 using LiAlH₄ in dry THF at 0 °C to room temperature for 18 h under nitrogen atmosphere gave alcohol 58 in 80% yield (Scheme 13). In the ¹H NMR spectrum of 58, CH₃ protons resonated at δ 1.36 (J = 6.2 Hz) as a doublet, while, H-3a and H-6a resonated at δ 5.82 (J = 3.0 Hz) and δ 4.46 (J = 3.0 Hz) as two doublets, while H-5 and H-6 appeared at δ 4.25 (J = 5.7, 6.2 Hz) as a doublet of quintet and δ 4.08 (J = 5.7 Hz) as a quintet respectively, besides the acetonide methyl protons resonating at δ 1.24 and 1.48 as two singlets. In EIMS, [M+Na]⁺ showed at m/z 199 confirmed the structure of 58.
Reaction of alcohol 58 with \( p \)-methoxybenzyl bromide in the presence of NaH in THF at 0 °C to room temperature for 4 h furnished 54 in 87% yield (Scheme 14). \(^1\)H NMR spectrum of 54 showed the -OCH\(_3\) signals of PMB at \( \delta 3.76 \) as a singlet and aromatic proton signals at \( \delta 6.81 \) and 7.20 \( (J = 8.3 \text{ Hz}) \) as two doublets, while, rest of the protons at the expected chemical shifts. HRMS showed \( m/z \) 317.1378 for C\(_{16}\)H\(_{22}\)O\(_3\)Na \((\text{M+Na})^+\) confirming the structure of 54.

**Scheme 14**

Further, hydrolysis of 1,2-acetonide in 54 on reaction with 60% aq. AcOH and conc. HCl (cat.) at room temperature for 18 h furnished 59 in 71% yield (Scheme 14). In the \(^1\)H NMR of 59, the expected disappearance of isopropylidene protecting group was observed.

Lactol 59 on oxidative cleavage with NaIO\(_4\) and aq. NaHCO\(_3\) in CH\(_2\)Cl\(_2\) (5 mL) at 0 °C to room temperature for 3 h gave aldehyde 60 in 82% yield (Scheme 15). Subsequently, Wittig olefination of aldehyde 60 with (ethoxycarbonylmethylene)triphenyl phosphorane in MeOH at 0 °C to room temperature for 2 h gave cis-ester as major product 61 in 78% yield (Scheme 15).

**Scheme 15**

In the \(^1\)H NMR spectrum of 61, the olefinic protons resonated at \( \delta 5.98 \) \( (J = 11.7 \text{ Hz}) \) and 6.11 \( (J = 11.7 \text{ Hz}) \) as two doublets and ester -OME at \( \delta 3.80 \) as a singlet. Rest of the protons resonated at the expected chemical shifts. HRMS showed \( m/z \) 345.13086 for C\(_{17}\)H\(_{25}\)O\(_6\)Na \((\text{M+Na})^+\) confirming the structure of 61.

Ester 61 was subjected to hydrolysis of O-formyl group with conc. HCl (cat.) in 1,4-dioxane:water (1:1) at room temperature for 18 h to give the lactone 62 in 82% yield (Scheme 16). During the hydrolysis reaction, the hydrolysis of O-formyl group followed by the concomitant cyclization occurred to give the lactone 62.
In the $^1$H NMR spectrum of 62, $\alpha$-olefinic proton resonated at $\delta$ 6.14 ($J = 10.0$ Hz) as a doublet, while the $\beta$-proton at $\delta$ 6.84 ($J = 4.9, 10.0$ Hz) as a doublet of doublet. Similarly, C6-H and C5-H protons resonated at $\delta$ 3.91 ($J = 3.8$ Hz) as triplet and $\delta$ 4.54 as multiplet respectively, while, the PMB protons appeared at the expected chemical shifts. HRMS showed $m/z$ 271.09408 (M+Na)$^+$ for $^{14}$C$_{14}$H$_{16}$NaO$_4$ (M+Na)$^+$ confirming the structure of 62.

Finally, oxidative removal of the PMB group in lactone 62, with DDQ in aq. CH$_2$Cl$_2$ at 0°C to room temperature for 2 h gave the lactone 25 in 74% yield (Scheme 17).

In $^1$H NMR spectrum of 25 showed the disappearance of signals corresponding PMB group, the $\alpha$-olefinic proton resonated at $\delta$ 6.14 ($J = 9.6$ Hz) as a doublet, while the $\beta$-proton at $\delta$ 7.01 ($J = 5.7, 9.6$ Hz) as a doublet of doublet. Similarly, C4-H and C5-H protons resonated at $\delta$ 4.04 as a broad singlet and $\delta$ 4.55 ($J = 2.8, 6.7$ Hz) as doublet of quintet respectively. HRMS showed $m/z$ 129.05505 for C$_6$H$_9$O$_3$ (M+H)$^+$ confirming the structure of 25. The optical rotation value for 25 in H$_2$O is $[\alpha]_D = -228.2$ (c 0.56), which was comparable with reported data $[\alpha]_D = -230.0$ (c 0.55, H$_2$O). The spectral and analytical data of 25 was in full accordance with literature data.

**Synthesis of butyro-lactone moiety of angiopterlactone A:**

Having successfully synthesized osmundalactone 23 and 4-epi-osmundalactone 25 with (4R,5S)- and (4R,5R) respectively, the study was then extended to the synthesis of butyro-lactone moiety of angiopterlactone A 27.\(^{21}\)
Angiopterlactone A 27\(^{21}\), a unique metabolite possessing dual-lactone skeletons, was isolated\(^{35}\) from rhizome *Angiopteris caudatiformis* and shown insect antifeeding activity against *Plutella xylostella* and *Heliothis virescens*, besides cytotoxic against HeLa cells, with an IC\(_{50}\) value of 68.8 µM. *Angiopteris caudatiformis* Hieron (Angiopteridaceae) is an ancient fern species that grows mainly in Asia.

The CHCl\(_3\) and EtOAc extracts rhizomes of *A. caudatiformis* both exhibited significant insect antifeeding activity against *Plutella xylostella* and *Heliothis virescens*. Bioassay-guided fractionation of these extracts led to the isolation of two new metabolites, angiopterlactones A 27 and B 28, besides three known lactones, osmundalactone 23,\(^{19a}\) osmundalin 24,\(^{19a,19b}\) and 3,5-dihydroxy-γ-caprolactone.\(^{19c}\)

Angiopterlactone A 27 was obtained as colorless, transparent needles with a molecular formula determined as C\(_{12}\)H\(_{16}\)O\(_6\) by analysis of its HRESIMS (m/z 279.0844 (M+Na\(^+\)), indicating the presence of five degrees of unsaturation. The IR spectrum of 27 showed absorption bands at 3462 (OH), 1764 (C=O), 1712 (C=O), and 1633 (C=C) cm\(^{-1}\). An α,β-unsaturated-δ-lactone moiety in 27 was indicated by a carbonyl carbon signal at δ 162.9 (C-2) and two olefinic carbon signals at δ 122.6 and 144.6 in the \(^{13}\)C NMR spectrum. The NOESY correlation of H-3′ with H-5 suggested a cis-relationship between these protons.

Having synthesized the lactones 23 and 24, for the synthesis of 27, it was proposed to synthesize the appropriately functionalized butyrolactone 63 and couple with 23.

Accordingly, the retroanalysis of 27 revealed the fragmentation into two lactones 23 and 63, wherein, the butyrolactone 63 could be made from alcohol 64 (Scheme 18). Diol 65 could be the appropriate building block for the synthesis of 64, while 65 could be made from D-Mannitol. Thus, C-2, C-3 and C-4 of D-mannitol stereocentres retained for the synthesis of 27 correlated to inverted C-6′, C-2′ and C-3′, while C-1 on deoxygenation would give the methyl group, while, the C-5/C-6 diol would be converted into acetic acid moiety.
Thus, the known\textsuperscript{35} alcohol 66 on alkylation with benzyl chloride in the presence of NaH in THF at 0 °C to room temperature for 10 h gave 67 in 60\% yield (Scheme 19). \textsuperscript{1}H NMR spectrum of 67 showed the aromatic and Ar-H resonating at $\delta$ 7.46-7.21 (5H) as a multiplet and at $\delta$ 4.70-4.51 ($J = 11.7$ Hz) as two doublets respectively. Likewise, the methyl group resonated at $\delta$ 1.30 ($J = 6.4$ Hz) as a doublet, while the acetonide methyl’s appeared at $\delta$ 1.34, 1.36, 1.39, 1.41 as a singlets.

Acid mediated hydrolysis of 67 on reaction with 60\% aq. AcOH at room temperature for 5 h afforded the diol 65 in 57\% yield (Scheme 20). \textsuperscript{1}H NMR spectrum of 65 showed the disappearance of signals corresponding to acetonide group, while rest of the protons resonated at the appropriate chemical shifts.
Treatment of diol 65 with Ph₃P, imidazole and I₂ in CH₂Cl₂ at 0 °C to room temperature for 4 h furnished olefin 68 (Scheme 21). ¹H NMR spectrum of 68 showed the resonances for olefinic protons at δ 5.83-5.70 as a multiplet, δ 5.29 (J = 17.5 Hz) and δ 5.03 (J = 10.0 Hz) as a two doublets, whereas rest of the protons at the expected chemical shifts.

To convert the olefin into acetic acid moiety, olefin 68 was subjected to reaction with borane DMS in THF at 0 °C to room temperature for 10 h to afford 64 in 89% yield (Scheme 22). In the ¹H NMR spectrum of 64 the signals corresponding to olefinic protons disappeared, while, newly created -CH₂- and -CH₂OH resonated at δ 1.81 and δ 3.76 as two multiplets respectively. In ESIMS, (M+Na)⁺ appeared at m/z 303 gave further confirmation of the product.

Oxidation of alcohol 64 with TEMPO and BIAB in CH₂Cl₂:H₂O (1:1) at room temperature for 90 min afforded the acid 69 in 93% yield (Scheme 23). In the ¹³C NMR of 69, the acid carbonyl carbon resonated at δ 176.3. In the ¹H NMR spectrum of 69, the -CH₂- protons appeared at δ 2.62 (J = 3.5, 15.5 Hz) as a doublet of doublet. In ESIMS, (M+Na)⁺ observed at m/z 317 gave further confirmation of the product.
Acid catalyzed reaction of 69 with PTSA in MeOH at room temperature for 2 h, affected the acetonide hydrolysis and concomitant cyclization of the hydroxyl, acid to afford the lactone 63 in 63% yield (Scheme 24). In the $^1$H NMR of 63, the methyl group signals appeared at $\delta$ 1.37 ($J = 6.4$ Hz) as a doublet and -OH appears at $\delta$ 2.89 as a broad singlet, while -CH$_2$- at $\delta$ 2.60 as a doublet of doublet. In ESIMS, [M+Na]$^+$, peak observed at $m/z$ 259 gave confirmation for the product obtained.

Finally, having both the lactones, osmundalactone 23 and 63 in hand, the attempted etherification of 23 and 63 with BF$_3$.Et$_2$O in CH$_2$Cl$_2$ at 0 °C to room temperature for 4 h, met with failure to give 27a (Scheme 25). Other methods using various acid catalysts such as HF-Pyridine, PTSA and conc. HCl (cat.) also were not successful in giving the target molecule 27a. Hence, the work on the synthesis of 27 from 23 and 63 was abandoned at this stage.
Experimental Section:

**5-Hydroxymethyl-2,2-dimethyl-(3aR,5S,6S,6aR)-perhydrofurao[2,3-d][1,3]dioxol-6-ol (46a):** To a solution of silyl ether 46 (6.15 g, 14.33 mmol) in THF (20 mL), TBAF (3.74 g, 14.33 mmol) was added at 0 °C under N₂ atmosphere and stirred at room temperature for 14 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), brine (10 mL) and dried (Na₂SO₄). Solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 3:1) to afford diol 46a (2.25 g, 82%) as a colorless solid; m.p. 108 °C; [α]D = -14.8 (c 0.9, CHCl₃); IR (KBr): 3430, 2920, 1450, 1275, 1100 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.32 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 3.71 (m, 2H, H-5a, H-5b), 4.03 (m, 1H, H-6), 4.18 (br.s, 1H, H-5), 4.53 (d, 1H, J = 4.3 Hz, OH), 5.9 (d, 1H, J = 4.3 Hz, H-3a); (EI-MS): m/z 191 (M+H)+.

**6-Hydroxy-2,2-dimethyl-5-(4-methylphenylsulfonyloxymethyl)-(3aR,5S,6S,6aR)-perhydrofuro[2,2-d][1,3]dioxole (47):** To a solution of 46a (3.0 g, 15.78 mmol), Et₃N (7.48 g, 94.73 mmol) and catalytic amount of DMAP in CH₂Cl₂ (50 mL) at 0 °C, p-toluenesulphonyl chloride (3.0 g, 15.78 mmol) was added and the mixture stirred at room temperature for 2 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with saturated CuSO₄ solution (2 x 100 mL), brine (100 mL) and dried (Na₂SO₄). Organic layer was evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5). First eluted was 47a (1.17 g, 8%) as a yellow syrup. ¹H NMR (200 MHz, CDCl₃): δ 1.26 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 4.13 (m, 3H, H-5, H-5a, H-5b), 4.49 (d, 1H, J = 2.35 Hz, H-6a), 4.65 (s, 1H, H-6), 5.85 (d, 1H, J = 2.3 Hz, H-3a), 7.35 (d, 4H, J = 4.7 Hz, Ar-H), 7.81 (d, 4H, J = 4.7 Hz, Ar-H).

Second eluted was 47 (4.07 g, 75%) as a colorless solid; m.p. 128 °C; [α]D = -27.17 (c 0.9, CHCl₃); IR (neat): 3420, 2950, 1670, 1350, 1150 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.26 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 2.22 (br. s, 1H, OH), 2.45 (s, 3H, Ar-CH₃), 4.12 (m, 3H, H-5, H-5a, H-5b), 4.28 (s, 1H, H-6), 4.48 (d, 1H, J = 2.35 Hz, H-6a), 5.85 (d, 1H, J = 2.3 Hz, H-3a), 7.35 (d, 2H, J = 4.7 Hz, Ar-H), 7.81 (d, 2H, J = 4.7 Hz, Ar-H); (FABMS): m/z 367 (M⁺+Na).
Chapter III, Experimental Section

2,2,5-Trimethyl-(3aR,5S,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-6-ol (48): To a stirred solution of 47 (2.60 g, 7.55 mmol) in DMSO (20 mL) under N₂ atmosphere NaBH₄ (0.57 g, 15.10 mmol) was added at 0 °C and heated up to 160 °C for 10 min. The reaction mixture was cooled to room temperature and extracted into EtOAc (2 x 50 mL). It was washed with water (30 mL) and dried (Na₂SO₄). Solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether 1:3) to give 48 (1.04 g, 81%) in as a colorless solid; m.p. 78 °C; [α]D = -12.6 (c 0.65, CHCl₃); IR (KBr): 3420, 2950, 1670, 1350, 1140 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.30 s (3H, CH₃), 1.40 (d, 3H, J = 6.4 Hz, CH₃-5a), 1.50 (s, 3H, CH₃), 3.95-4.08 (m, 2H, H-5, H-6), 4.43 (d, 1H, J = 5.0 Hz, H-6a), 5.82 (d, 1H, J = 5.0 Hz, H-3a); (EI-MS): m/z 199 (M⁺+Na).

6-(4-Methoxybenzylxyloxy)-2,2,5-trimethyl-(3aR,5S,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxole (45): To a stirred suspension of NaH (0.16 g, 6.89 mmol) in THF (5 mL) at 0 °C, a solution of 48 (0.6 g, 3.44 mmol) in THF (5 mL) was added dropwise under nitrogen atmosphere and stirred for 30 min. It was treated with a solution of PMBBr (0.52, 3.78 mmol) in THF (3 mL) and stirred at room temperature for 4 h. The reaction mixture was diluted with saturated aq. NH₄Cl solution (10 mL) and extracted with EtOAc (2 x 25 mL). Combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. Solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether 1:9) to give 45 (0.97 g, 95%) as yellow syrup; [α]D = -27.25 (c 1.6, CHCl₃); IR (neat): 2940, 1450, 1080, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.32 (d, 6H, J = 6.7 Hz, 2CH₃), 1.49 (s, 3H, CH₃), 3.62 (d, 1H, J = 3.7 Hz, H-6), 3.78 (s, 3H, Ar-OCH₃), 4.03 (m, 1H, H-5), 4.40-4.56 (m, 3H, H-6a, -OCH₂Ar), 5.74 (d, 1H, J = 4.1 Hz, H-3a), 6.82 (d, 2H, J = 8.3 Hz, Ar-H), 7.19 (d, 2H, J = 8.3 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz): δ 159.3, 129.3 (3C), 113.8 (2C), 112.8, 105.3, 86.8, 85.6, 80.3, 71.4, 55.2, 27.1, 26.5, 19.9; HRMS (ESI): m/z calculated for C₁₆H₂₂NaO₅ (M⁺+Na) 317.1364, found 317.1355.

4-(4-Methoxybenzylxyloxy)-5-methyl-(3R,4S,5S)-2H,3H,4H-2,3-furandiol (49): To a stirred solution of 45 (0.99 g, 3.36 mmol) in 3:2 mixture of AcOH (12 mL) and H₂O (8 mL), catalytic conc. HCl was added and stirred at room temperature for 18 h. The reaction mixture was neutralized with solid NaHCO₃ (15 g) and extracted with EtOAc (3 x 100 mL). The combined
organic layers were washed with brine (50 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5) to afford diol 49 (0.64 g, 75%) as a yellow syrup; IR (neat): 3448, 2950, 1440, 1070, 750 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.26 (d, 3H, J = 6.9 Hz, CH₃), 2.57 (bs, 1H, OH), 3.33 (bs, 1H, OH), 3.67 (t, 1H, J = 5.9 Hz, H-5), 3.80 (s, 3H, Ar-OCH₃), 3.94 (m, 1H, H-4), 4.69-4.54 (m, 3H, H-3 and benzyl), 5.28 (d, 1H, J = 4.0 Hz, H-2), 6.88 (d, 2H, J = 7.0 Hz, Ar-H), 7.26 (d, 2H, J = 7.0 Hz, Ar-H).

2-(4-Methoxybenzylxoy)-1-methyl-4-[methylxocarbonyl]-(1S,2R,3Z)-3-butenyl formate (51): To a solution of 49 (0.3 g, 1.18 mmol) in CH₂Cl₂ (5 mL), NaIO₄ (0.378 g, 1.77 mmol) was added and stirred at room temperature for 3 h. Solvent was evaporated and the residue extracted with CH₂Cl₂ (3 x 10 mL) dried (Na₂SO₄) and evaporated to give aldehyde 50 as a yellow liquid, which was used as such for the next reaction.

To a stirred solution of aldehyde 50 (0.28 g, 1.11 mmol) in MeOH (6 mL), (methylxocarbonylmethylene)triphenyl phosphorane (0.55 g, 1.67 mmol) was added at 0 ℃ and stirred at the same temperature for 2 h. Solvent was evaporated and residue purified by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:4) to afford 51 (0.96 g, 77%) as a pale yellow syrup; [α]D = -103.5 (c 0.4, CHCl₃); IR (neat): 3403, 2926, 2864, 1764, 1706, 1451 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.26 (d, 3H, J = 6.0 Hz, CH₃), 3.72 (s, 3H, OCH₃), 3.80 (s, 3H, Ar-OCH₃), 4.49 (q, 2H, J = 11.3 Hz, -OCH₂), 5.16-5.25 (m, 2H, H-1 and H-2), 6.02-6.20 (m, 2H, α-H and β-H), 6.87 (d, 2H, J = 8.6 Hz, Ar-H), 7.22 (d, 2H, J = 8.6 Hz, Ar-H), 8.06 (s, 1H, -CHO); ¹³C NMR (CDCl₃, 75 MHz): 165.95, 160.47, 146.14, 145.42, 129.39, 123.40, 120.81, 113.70, 75.51, 71.65, 71.21, 55.23, 51.49, 15.73; HRMS (ESI): m/z calculated for C₁₆H₂₂O₅Na (M+Na)⁺ 331.11521, found 331.11523.

(5R,6S)-5-(4-Methoxybenzylxoy)-5,6-dihydro-6-methylpyran-2-one (52): To a stirred solution of 51 (0.40 g, 1.29 mmol) in 1,4-dioxane:H₂O (1:1; 14 mL), catalytic amount of conc. HCl was added and stirred at room temperature for 18 h. The reaction mixture was neutralized with solid NaHCO₃ (3 g) and extracted with EtOAc (2 x 50 mL). Combined organic layers were washed with brine (50 mL) and dried (Na₂SO₄). Evaporation of solvent and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5) furnished
52 (0.24 g, 75%) as a yellow syrup; [α]D = -97.05 (c 0.1, CHCl3); IR (neat): 3422, 2896, 2812, 1786, 1468, 745 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 1.44 (d, 3H, J = 6.4 Hz, CH₃), 3.81 (s, 3H, OCH₃), 3.96 (td, 1H, J = 1.9 Hz, H-5), 4.39-4.48 (m, H, H-6), 4.53-4.66 (dd, 2H, J = 11.3 Hz, OCH₂), 5.98 (dd, 1H, J = 1.7, 10.1 Hz, α-H), 6.84 (dd, 1H, J = 2.2, 10.0 Hz, β-H), 6.91 (d, 2H, J = 8.6 Hz, Ar-H), 7.28 (d, 2H, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl3, 75 MHz): δ 159.65, 146.15, 129.71 (2C), 120.80, 75.24, 73.49, 71.74, 55.27, 18.31; HRMS (ESI): m/z calculated for C₁₄H₁₆NaO₄(M⁺+Na) 271.09458, found 271.09408.

(5R,6S)-5,6-Dihydro-5-hydroxy-6-methylpyran-2-one (23): To a stirred solution of 52 (0.03 g, 0.10 mmol) in a 19:1 mixture of CH₂Cl₂:H₂O (5 mL) DDQ (0.04 g, 0.20 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was quenched with aq. saturated NaHCO₃ solution (0.6 mL) and extracted with CHCl₃ (2 x 10 mL). Combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and evaporated. Residue was purified by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5) to afford 23 (0.01 g, 72%) as a colorless solid; m. p: 83.1 °C; [α]D = -69.1 (c 0.38, H₂O); IR (neat): 3415, 2965, 2898, 1743, 1511 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.49 (d, 3H, J = 6.0 Hz, CH₃), 4.24 (bd, 1H, J = 8.5 Hz, H-5), 4.37 (dq, 1H, J = 5.9, 12.9 Hz, H-6), 6.0 (dd, 1H, J = 2.0, 9.9 Hz, α-H), 6.82 (dd, 1H, J = 2.0, 9.9 Hz, β-H); ¹³C NMR (CDCl₃, 75 MHz): 163.03, 148.39, 120.80, 78.96, 67.73, 18.13; HRMS (EI-MS): m/z calculated for C₆H₉O₃(M⁺) 129.05462, found 129.05481.

[(3aR,5R,6S,6aR)-6-Hydroxy-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-5-yl] methyl 4-methylbenzenesulfonate (57): To a stirred solution of diol 56 (3.00 g, 15.78 mmol), Et₃N (3.29 mL, 23.68 mmol) and catalytic amount of DMAP in CH₂Cl₂ (30 mL) p-toluenesulphonyl chloride (3.00 g, 15.78 mmol) was added at 0 °C and the mixture stirred at room temperature for 2 h. Worked up as described for 47 and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5). First eluted was 57a (1.17 g, 8%) as a yellow syrup. ¹H NMR (200 MHz, CDCl₃): δ 1.26 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 4.13 (m, 3H, H-5, H-5a, H-5b), 4.49 (d, 1H, J = 2.35 Hz, H-6a), 4.65 (s, 1H, H-6), 5.85 (d, 1H, J = 2.3 Hz, H-3a), 7.35 (d, 4H, J = 4.7 Hz, Ar-H), 7.81 (d, 4H, J = 4.7 Hz, Ar-H).
Second eluted was 57 (4.07 g, 75%) as a colorless solid. m.p. 128 °C; [α]D = -27.17 (c 0.9, CHCl3); IR (neat): 3420, 2950, 1670, 1350, 1150 cm⁻¹; 1H NMR (200 MHz, CDCl3): δ 1.26 (s, 3H, CH3), 1.36 (s, 3H, CH3), 2.22 (br. s, 1H, OH), 2.45 (s, 3H, Ar-CH3), 4.12 (m, 3H, H-5, H-5a, H-5b), 4.28 (s, 1H, H-6), 4.48 (d, 1H, J = 2.35 Hz, H-6a), 5.85 (d, 1H, J = 2.3 Hz, H-3a), 7.35 (d, 2H, J = 4.7 Hz, Ar-H), 7.81 (d, 2H, J = 4.7 Hz, Ar-H); HRMS (ESI-MS): m/z calculated for C15H20O7NaS (M+Na)+ 367.0827, found 367.0814.

(3aR,5R,6S,6aR)-2,2,5-Trimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (58): To a stirred suspension of LiAlH4 (0.57 g, 15.11 mmol) in THF (10 mL) at 0 °C, a solution of 57 (2.60 g, 7.55 mmol) in THF (20 mL) was added dropwise under N2 atmosphere and stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C, treated with saturated aq. Na2SO4 (5 mL) solution and filtered. The filtrate was dried (Na2SO4), evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:3) to give 58 (1.04 g, 80%) as a colorless solid; m.p. 78 °C; [α]D = -12.6 (c 0.65, CHCl3); IR (neat): 3420, 2950, 1670, 1350, 1140 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 1.24 (s, 3H, CH3), 1.36 (d, 3H, J = 6.2 Hz, CH3), 1.48 (s, 3H, CH3), 3.94 (d, 1H, J = 4.8 Hz, OH), 4.08 (q, 1H, J = 5.7 Hz, H-6), 4.25 (dq, 1H, J = 6.2, 5.7 Hz, H-5), 4.46 (d, 1H, J = 3.0 Hz, H-6a), 5.82 (d, 1H, J = 3.0 Hz, H-3a); (EI-MS): m/z 199 (M+Na)+.

(3aR,5R,6S,6aR)-2,2,5-Trimethyl perhydrofuro[2,3-d][1,3]-dioxol-6-yl-benzyl ether (54): To a stirred suspension of NaH (0.16 g, 6.89 mmol) in dry THF (5 mL) at 0 °C, a solution of 58 (0.6 g, 3.44 mmol) in dry THF (5 mL) was added dropwise under N2 atmosphere. After 30 min, PMBBr (0.51 g, 3.78 mmol) was added and stirred at room temperature for 4 h. Worked up as described for 45 and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:9) to give 54 (0.97 g, 87%) as yellow syrup; [α]D = -50.9 (c 0.5, CHCl3); IR (neat): 2978, 2920, 2870, 1453, 1064 cm⁻¹; 1H NMR (200 MHz, CDCl3): δ 1.26 (d, 3H, J = 6.2 Hz, -CH3), 1.28 (s, 3H, -CH3), 1.44 (s, 3H, -CH3) 3.63 (d, 1H, J = 3.1 Hz, H-6), 3.79 (s, 3H, Ar-OCH3), 4.20-4.29 (m, 1H, H-5), 4.42 (d, 1H, J = 12.1 Hz, Ar-OCH), 4.53 (d, 1H, J = 3.9 Hz, H-6a), 4.64 (d, 1H, J = 12.1 Hz, Ar-OCH), 5.81 (d, 1H, J = 3.9 Hz, H-3a), 6.84 (d, 2H, J = 8.6 Hz, Ar-H), 7.19 (d, 2H, J = 8.6 Hz, Ar-H); HRMS (ESI): m/z calculated for C16H22NaO5 (M+Na)+ 317.1364, found 317.1378.
(3R,4R,5R)-4-(4-Methoxybenzoyloxy)-tetrahydro-5-methylfuran-2,3-diol (59): A mixture of 54 (3.0 g, 10.27 mmol) in 3:2 mixture of AcOH (9 mL) and H2O (6 mL), was treated with catalytic conc. HCl and stirred at room temperature for 18 h. Worked up as described for 49 and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5) to afford diol 59 (1.91 g, 71%) as a yellow syrup.

2-(4-Methoxybenzoyloxy)-1-methyl-4-[ethyloxycarbonyl]-(1R,2R,3Z)-3-butenyl formate (61): To a solution of 59 (0.50 g, 1.96 mmol) in CH2Cl2 (5 mL) was added NaIO4 (0.63 g, 2.95 mmol) and stirred at room temperature for 3 h. Solvent was evaporated and residue extracted with CH2Cl2 (3 x 30 mL). It was dried over Na2SO4 and evaporated to give aldehyde 60 as a yellow liquid, which was used as such for the next reaction.

To a stirred solution of aldehyde 60 (0.65 g, 2.58 mmol) in MeOH (8 mL), (ethyloxycarbonylmethylene)triphenyl phosphorane (1.36 g, 3.87 mmol) was added at 0 °C and stirred at the same temperature for 2 h. Solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:4) to afford 61 (0.65 g, 78%) as a pale yellow syrup; [α]D = -101.5 (c 0.4, CHCl3); IR (neat): 3403, 2926, 2864, 1706, 1451 cm-1; 1H NMR (500 MHz, CDCl3): δ 1.23 (d, 3H, J = 6.4 Hz, -CH3), 1.31 (t, 3H, J = 6.8 Hz, -CH3), 3.80 (s, 3H, OCH3), 4.02 (t, 1H, J = 5.6 Hz, H-1), 4.21 (q, 2H, J = 6.8, 14.1 Hz, OCH2), 4.36-4.60 (dd, 2H, J = 11.7 Hz, Ar-OCH2), 5.10-5.15 (m, 1H, H-2), 5.98 (d, J = 11.7 Hz, α-H), 6.11 (d, 1H, J = 11.7 Hz, β-H), 6.89 (d, 2H, J = 8.4 Hz, Ar-H), 7.23 (d, 2H J = 8.4 Hz, Ar-H), 8.04 (s, 1H, CHO); 13C NMR (CDCl3, 75 MHz): 165.81, 160.38, 146.40, 143.36, 129.47, 124.74, 123.52, 113.93, 78.38, 71.40, 70.90, 60.75, 55.22, 15.66, 14.18; HRMS (ESI-MS): m/z calculated for C17H22O6Na (M+Na)+ 345.13172, found 345.13086.

(5R,6R)-5-(4-Methoxybenzoyloxy)-5,6-dihydro-6-methylpyran-2-one (62): To a stirred solution of 61 (0.30 g, 0.93 mmol) in 1:1 aq. 1,4-dioxane (10 mL), catalytic amount of conc. HCl was added and stirred at room temperature for 18 h. Worked up as described for 52 and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5) to furnish 62 (0.19 g, 82%) as yellow syrup; [α]D = -164.5 (c 0.7, CHCl3); IR (neat): 3443, 2945, 2839, 1721, 1498, 768 cm-1; 1H NMR (300 MHz, CDCl3): δ 1.48 (d, 3H, J = 6.6 Hz, CH3), 3.81 (s, 3H, OCH3), 3.91 (t, 1H, J = 3.8 Hz, H-5), 4.54 (m, 3H, OCH2 and H-6), 6.14 (d, 1H, J = 10.0
(5R,6R)-5,6-dihydro-5-hydroxy-6-methylpyran-2-one (25): To a stirred solution of 62 (0.05 g, 0.20 mmol) in a mixture of 19:1 aq. CH$_2$Cl$_2$ (4 mL), DDQ (0.09 g, 0.40 mmol) was added and stirred at room temperature for 2 h. Worked up as described for 23 and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:1.5) to afford 25 (0.02 g, 74%) as a colorless solid; m.p. 51.5 °C; [α]$_D$ = -228.2 (c 0.56, H$_2$O); IR (neat): 3403, 2926, 2864, 1706, 1451 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 1.52 (d, 3H, J = 6.8 Hz, -CH$_3$), 4.04 (bs, 1H, H-5), 4.55 (dq, 1H, J = 2.8, 6.7 Hz, H-6), 6.14 (d, 1H, J = 9.6 Hz, α-H), 7.01 (dd, 1H, J = 5.7, 9.6 Hz, β-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): 163.79, 144.46, 122.76, 77.08, 62.98, 15.74; HRMS (ESI-MS): m/z calculated for C$_6$H$_9$O$_3$ (M+Na)$^+$ 129.05462, found 129.05505.

(4R,5R)-4-((S)-1-(Benzyloxy)ethyl)-2,2-dimethyl-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dioxolane (67): To a stirred suspension of NaH (1.46 g, 36.59 mmol) in THF (14 mL) under N$_2$ atmosphere at 0 °C, a solution of 66 (4.50 g, 18.29 mmol) in THF (30 mL) was added. After 10 min BnCl (2.61 g, 21.95 mmol) was added to the reaction mixture and stirred at room temperature for 10 h. It was quenched with sat. NH$_4$Cl (20 mL) at 0 °C, added water (60 mL) and extracted with EtOAc (100 mL). Organic layers were washed with brine (40 mL) and dried (Na$_2$SO$_4$). Solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.5:9.5) to afford 67 (3.50 g, 60%) as a pale yellow oil; [α]$_D$ = +75.2 (c 0.69, CHCl$_3$); IR (neat): 3412, 2954, 2832, 1721, 1698, 1490, 1154, 1076, 754, 681 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 1.30 (d, 3H, J = 6.4 Hz, CH$_3$), 1.34 (s, 3H, CH$_3$), 1.36 (s, 3H, CH$_3$), 1.39 (s, 3H, CH$_3$), 1.41 (s, 3H, CH$_3$), 3.75-3.64 (m, 1H, CHOBN), 4.20-3.85 (m, 5H, OCH$_2$, 3 x OCH), 4.51 (d, 1H, J = 11.7 Hz, benzylic), 4.70 (d, 1H, J = 11.7 Hz, benzylic), 7.46-7.21 (m, 5H, Ar-H).

(R)-1-((4R,5R)-5-((S)-1-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (65): A solution of 67 (3.50 g, 10.42 mmol) in 60% aq. CH$_3$COOH (25 mL) was stirred at room
temperature for 4 h. The reaction mixture was neutralized with solid NaHCO₃ (65 g) and extracted with EtOAc (3 x 75 mL). It was dried (Na₂SO₄), evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 4.5:5.5) to afford 65 (1.75 g, 57%) as a colorless syrup; [α]D = +24.1 (c 0.50, CHCl₃); IR (neat): 3523, 2987, 2812, 1757, 1691, 1436, 1253, 1108, 1056, 887, 751, 649 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.30 (d, 3H, J = 6.4 Hz, CH₃), 1.37 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 2.93-2.22 (brs, 2H, 2 x OH), 4.06-3.56 (m, 6H, OCH₂, 4 x OCH), 4.52 (d, 1H, J = 11.7 Hz, benzylic), 4.72 (d, 1H, J = 11.7 Hz, benzyl), 7.42-7.23 (m, 5H, Ar-H).

(4R,5R)-4-((S)-1-(Benzyloxy)ethyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane (68): To a stirred solution of 65 (1.75 g, 5.91 mmol), Ph₃P (6.20 g, 23.65 mmol) and imidazole (1.61 g, 23.65 mmol) in CH₂Cl₂ (25 mL), I₂ (4.51 g, 17.74 mmol) was added at 0 °C and stirred at room temperature for 4 h. Then sat. aq. NaOH solution was added to the reaction mixture and extracted with CHCl₃ (50 mL). Organic layer was washed with sat. aq. hypo (20 mL), brine (20 mL) and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.3:9.7) to afford 68 (0.50 g, 32%) as a pale yellow oil; [α]D = +55.6 (c 0.60, CHCl₃); IR (neat): 2933, 2857, 1744, 1665, 1434, 1356, 1212, 1124, 1064, 856, 716, 658 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.20 (d, 3H, J = 6.5 Hz, CH₃), 1.40 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 3.58 (m, 1H, OCH), 3.69 (dd, 1H, , J = 5.0, 8.0 Hz, OCH), 4.28 (t, 1H, J = 7.5 Hz, OCH), 4.52 ((d, 1H, J = 12.0 Hz, benzylic), 4.66 (d, 1H, J = 12.0 Hz, benzyl), 5.03 (d, 1H, J = 10.0 Hz, olefinic), 5.29 (d, 1H, J = 17.5 Hz, olefinic), 5.83-5.70 (m, 1H, olefinic), 7.36-7.27 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 138.5, 135.9, 128.2 (2C), 127.7 (2C), 127.5, 118.5, 109.0, 83.8, 78.5, 73.2, 71.0, 27.0, 26.9, 16.1.

2-((4R,5R)-5-((S)-1-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (64): To a solution of cyclohexene (0.59 mL, 5.73 mmol) in THF (2.5 mL), BH₃.Me₂S (0.26 mL) was added at 0 °C and stirred for 1 h. A solution of 68 (0.50 g, 1.91 mL) in THF (5 mL) was added and stirred for 3 h. Then reaction mixture was quenched with 2M NaOH (2 mL) and 30% H₂O₂ (1 mL) at 0 °C and stirred the mixture for 12 h. It was diluted with EtOAc (30 mL), washed with water (15 mL), brine (10 mL) and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by flash column chromatography (60-120 Silica gel, ethyl
acetate: pet. ether, 1:4) to afford 64 (0.47 g, 89%) as a colorless oil; [α]D = +57.5 (c 0.70, CHCl3); IR (neat): 3554, 2945, 2812, 1736, 1658, 1424, 1357, 1221, 1156, 1008, 856, 761, 632 cm⁻¹; ¹H NMR (500 MHz, CDCl3): δ 1.23 (d, 3H, J = 6.5 Hz, CH3), 1.40 (s, 3H, CH3), 1.41 (s, 3H, CH3), 1.92-1.71 (m, 2H, CH2), 2.39 (brs, 1H, OH), 3.68 (m, 1H, OCH), 3.76 (m, 3H, OCH2, OCH), 4.10 (m, 1H, OCH), 4.55 (d, 1H, J = 12.0 Hz, benzylic), 4.69 (d, 1H, J = 12.0 Hz, benzyl), 7.34-7.25 (m, 5H, Ar-H); ¹³C NMR (CDCl3, 75 MHz): δ 138.2, 128.2 (2C), 127.7 (2C), 127.5, 108.7, 83.0, 75.9, 73.4, 71.1, 60.6, 35.8, 27.2, 26.8, 15.3; (ESI-MS): m/z 303 (M+Na)⁺.

2-(((4R,5R)-5-((S)-1-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetic acid (69): To a stirred solution of 64 (0.43 g, 1.54 mmol) in 1:1 ratio of CH₂Cl₂:H₂O (8 mL), TEMPO (0.07 g, 0.46 mmol) and BAIB (1.48 g, 4.61 mmol) were added at 0 °C and stirred at room temperature for 1.5 h. The reaction mixture was diluted with CHCl₃ (2 × 30 mL), washed with sat. aq. hypo (15 mL), brine (10 mL) and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by flash column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 3:1) to afford 69 (0.42 g, 93%) as a pale yellow solid; mp 62-64 °C; [α]D = +42.2 (c 0.75, CHCl3); IR (neat): 3532, 2986, 2812, 1745, 1681, 1492, 1257, 1086, 889, 757, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.22 (d, 3H, J = 6.5 Hz, CH3), 1.38 (s, 6H, 2 x CH3), 2.51 (dd, 1H, J = 8.5, 16.0 Hz, CH), 2.62 (dd, 2H, J = 3.5, 15.5 Hz, CH₂), 3.79-3.64 (m, 2H, 2 x OCH), 4.39-4.29 (m, 1H, OCH), 4.48 (d, 1H, J = 12.0 Hz, benzyl), 4.65 (d, 1H, J = 12.0 Hz, benzyl), 7.31-7.23 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 176.3, 138.3, 128.3 (2C), 127.6 (2C), 127.5, 109.2, 82.1, 73.3, 72.8, 71.2, 39.0, 27.1, 26.9, 15.0; (ESI-MS): m/z 317 (M+Na)⁺.

(4R,5S)-5-((S)-1-(Benzyloxy)ethyl)-dihydro-4-hydroxyfuran-2(3H)-one (63): To a stirred solution of 69 (0.10 g, 0.34 mmol) in MeOH (4 mL), catalytic amount of PTSA was added and stirred at room temperature for 2 h. It was quenched with Et₃N, evaporated the solvent under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:2) to afford 63 (0.05 g, 63%) as a colourless solid; mp 90-92 °C; [α]D = +120.4 (c 0.95, CHCl₃); IR (neat): 3534, 2976, 2814, 1735, 1667, 1491, 1331, 1294, 1056, 854, 786, 659 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.37 (d, 3H, J = 6.4 Hz, CH₃), 2.50 (dd, 1H, J = 3.8, 17.6 Hz, CH), 2.70 (dd, 1H, J = 6.6, 17.6 Hz, CH), 2.89 (brs, 1H, OH), 4.03 (m, 1H, OCH),

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4.29 (t, 1H, $J = 4.9$ Hz, OCH), 4.60-4.48 (m, 2H, benzylic, CHOCO), 4.67 (d, 1H, $J = 11.5$ Hz, benzylic), 7.38-7.25 (m, 5H, Ar-H); (ESI-MS): $m/z$ 259 (M+Na)$^+$. 

References:


SPECTRA
Spectrum 1: $^1$H NMR Spectrum of compound 52 in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 52 in CDCl$_3$ (75 MHz)
Spectrum 2: $^1$H NMR Spectrum of compound 23 in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 23 in CDCl$_3$ (75 MHz)
Spectrum 3: $^1$H NMR Spectrum of compound 62 in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 62 in CDCl$_3$ (75 MHz)
Spectrum 4: $^1$H NMR Spectrum of compound 25 in CDCl$_3$ (500 MHz)

$^{13}$C NMR Spectrum of compound 25 in CDCl$_3$ (75 MHz)
Spectrum 5: $^1$H NMR Spectrum of compound 68 in CDCl$_3$ (500 MHz)

$^{13}$C NMR Spectrum of compound 68 in CDCl$_3$ (75 MHz)
Spectrum 6: $^1$H NMR Spectrum of compound 69 in CDCl$_3$ (500 MHz)
$^{13}$C NMR Spectrum of compound 69 in CDCl$_3$ (75 MHz)
Spectrum 7: $^1$H NMR Spectrum of compound 63 in CDCl$_3$ (300 MHz)