The thesis entitled **"STUDIES TOWARDS THE SYNTHESIS OF BIOACTIVE LACTONES AND DEVELOPMENT OF NOVEL METHODOLOGY USING Fe/CITRIC ACID"** is divided into four chapters.

Chapter I: This chapter is divided into two sections;

> **Section A:** This section deals with the introduction and The total synthesis of antifungal Gamahonolide A.
>
> **Section B:** This section deals with the introduction, earlier synthetic approach and Stereoselective total synthesis of Lippialactone.

Chapter II: This chapter deals with the introduction, earlier synthetic approaches and Synthetic studies towards the Phostriecin.

Chapter III: This chapter deals with the introduction, synthesis and cytotoxic activities of (*S*)-Dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone and its analogues.

Chapter IV: This chapter deals with the introduction, earlier synthetic approaches and Green Approach for the Domino Reduction/Reductive Amination of Nitroarenes and Chemoselective Reduction of Aldehydes Using Fe/aq. Citric acid/Montmorillonite K10.

Chapter I: This chapter is divided into two sections.

Section A: This chapter describes the introduction and the Total synthesis of antifungal Gamahonolide A.

6-Substituted α,β-unsaturated δ-lactone moiety containing natural products attracted the attention of synthetic chemists due to their interesting structure and potential biological activities. The activities include antiviral, antifungal, antibacterial, growth inhibitory, antitumor and antileukemic properties. Gamahonolide A (**1**) is a δ-lactone, isolated from stromata of phytopathogenic fungus, *Epichloe typhina* on *Phleum pratense*. *E. typhina* causes choke disease to the pasture grass, timothy, *P. pratense*.

The Gamahonolide structure was determined by spectroscopic methods and the absolute configuration by its ORD spectrum and ^{1}H NMR shift difference between the diastereomeric pair of its *O*-methyl mandelate. To the best of our knowledge, the synthesis of Gamahonolide A (**1**) has not been reported to date. In continuation of our program on the total synthesis of bioactive *α,β*-unsaturated *δ*-lactone containing natural products, herein we report the first total synthesis of Gamahonolide A (**1**) by a simple synthetic strategy.
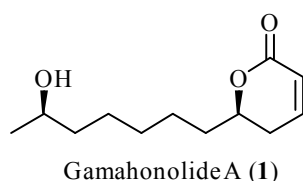

Gamahonolide A (**1**)

Figure 1

Retrosynthetic analysis of **1** is outlined in Scheme 1. Ring-closing metathesis reaction and removal of functional group in compound **2** would provide the target molecule. Whereas, RCM precursor **2** could be available from **3** by oxidation followed by Keck allylation and acryloylation. This, in turn, could be made from octane 1,8-diol via compound **4** by adopting *α*-aminoxylation reaction as a key step.
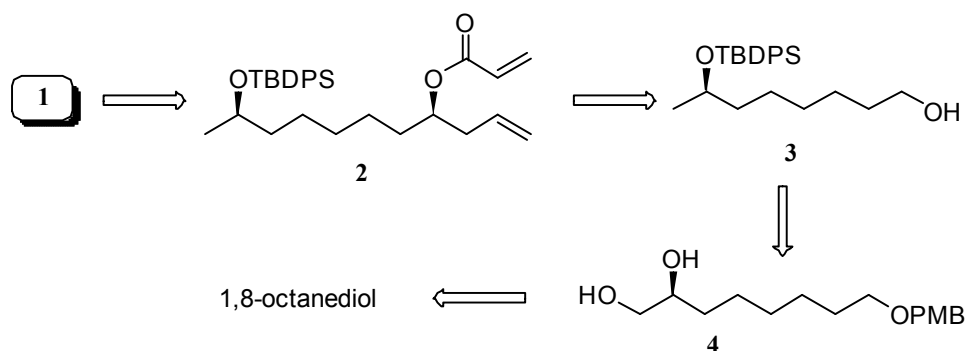
Scheme 1: Retrosynthetic analysis

To begin the synthesis, octane 1,8-diol was selectively monoprotected as its PMB ether **5** and the remaining hydroxyl group was oxidized to the corresponding aldehyde. The crude aldehyde without purification was subjected to the MacMillan *α*-

hydroxylation using nitrosobenzene and 40 mol% of D-proline in $CHCl_3$, followed by rapid reduction with sodium borohydride to furnish the unstable anilinoxy compound which was further treated with Zn in acetic acid at room temperature to cleave the O-N bond providing the diol **4** with high enantioselectivity (98.6% ee).
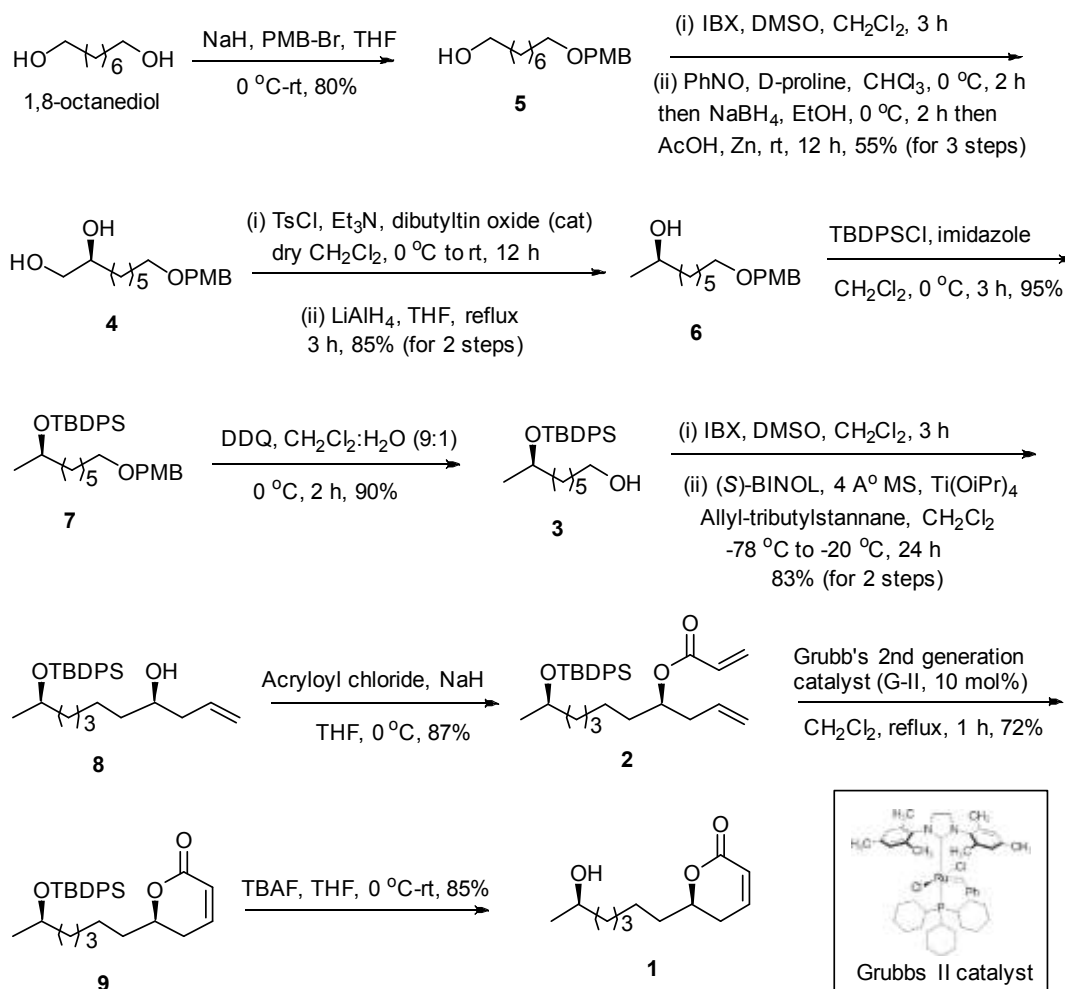
Scheme 2

This resulting 1,2-diol **4** on treatment with TsCl and Et_3N in the presence of dibutyltin oxide was monosilylated which on further reduction with $LiAlH_4$ in THF provided terminal methyl compound **6**. The secondary alcohol was silylated using TBDPSCl and imidazole to silyl ether **7** followed by removal of PMB group resulted in **3**. IBX oxidation of alcohol provided aldehyde which was allylated following Keck's protocol to give homoallyl alcohol **8** with high diastereoselectivity (83%, 98% *de*).

Acrylation of **8** was achieved by treatment with acryloyl chloride, NaH in THF to obtain diene **2** in 87% yield. Ring-closing metathesis of **2** proceeded well with 10 mol% of Grubbs-II to produce lactone **9** in 72% yield. Finally, desilylation with TBAF in THF afforded the target Gamahonolide A (**1**) in 85% yield. This compound is identical in all respects to the reported natural product including NMR, optical rotation.

In conclusion, we have accomplished the first total synthesis of Gamahonolide A by a simple strategy involving α-aminoxylation, Keck allylation and Ring closing-metathesis as the key steps.

Section B: This section deals with the introduction, earlier synthetic approach and Stereoselective total synthesis of Lippialactone.

In 2013, Ree and co-workers isolated a new antimalarial Lippialactone **1** (Figure 1) from aerial parts of *Lippia javanica*, which is active against the chloroquine-sensitive D10 strain of *Plasmodium falciparum* with an IC_{50} value of 9.1 μg/mL and is known to show mild cytotoxicity. The relative stereochemistry of Lippialactone was determined by molecular modeling based on the determination of the relative configuration by quantum mechanical GIAO ^{13}C chemical shift calculations. Lippialactone (**1**) is structurally related to Synargentolide A (**2**) (Figure 1), whose structure was revised by us. To date, however, a single report appeared on the synthesis of **1**. In continuation of our interest in the synthesis of bio-active natural δ-lactones we herein describe a stereoselective total synthesis of Lippialactone.

Lippialactone **1**

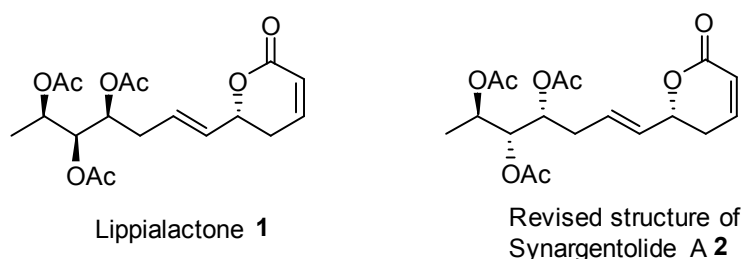Revised structure of
Synargentolide A **2**

Figure 1

Retrosynthetic analysis of Lippialactone (**1**) is summarized in Scheme 1. Lippialactone (**1**) could be accomplished from homoallyl alcohol **3** and vinyl lactone **4** *via* olefin cross-metathesis reaction. While the construction of three contiguous stereogenic hydroxyl groups in compound **3** could be achieved from commercially available D-mannitol. While vinyl lactone **4** could be prepared from a known chiral epoxide **12** by a new synthetic route.
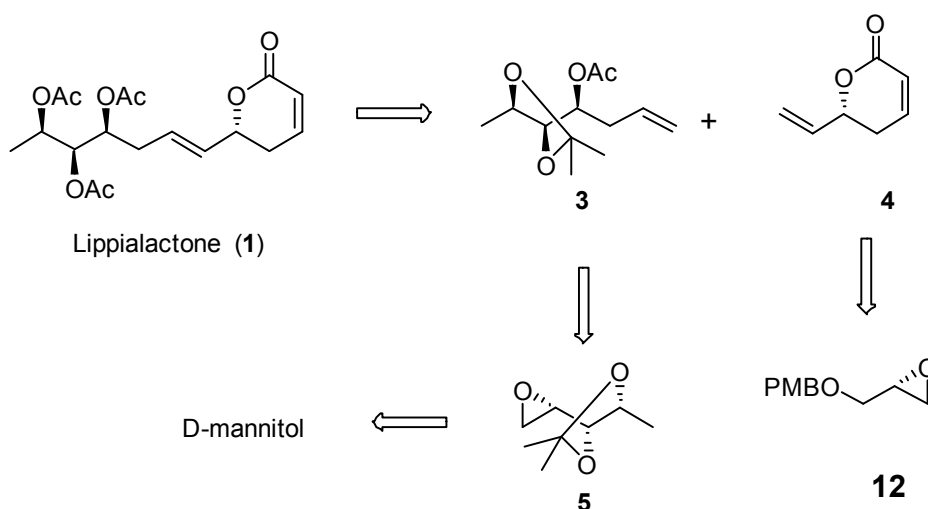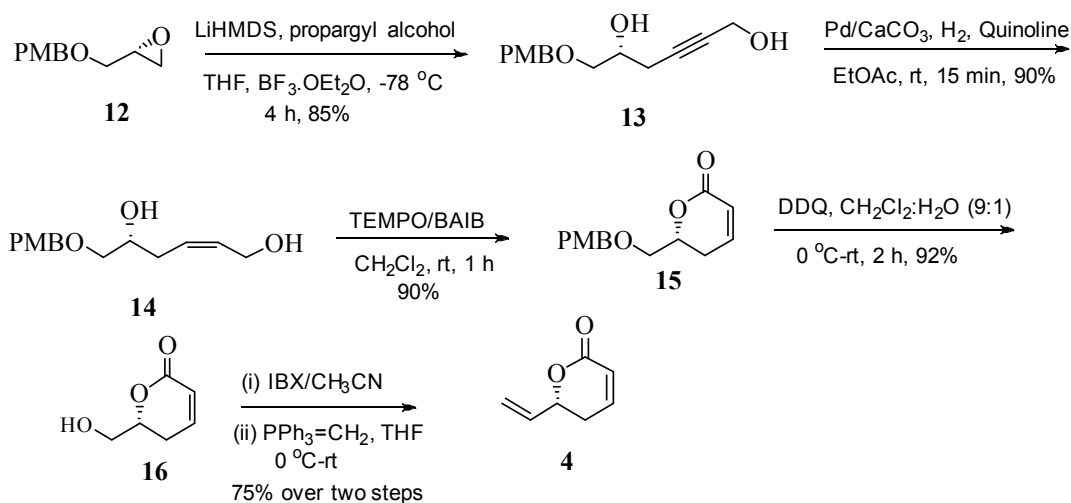

Scheme 1. Retrosynthetic analysis

The synthesis of fragment **3** (Scheme 2) commenced from a primary alcohol **6**, which was prepared from D-mannitol according to the reported procedure. Tosylation of the primary hydroxyl group in compound **6** with TsCl, Et_3N and DMAP in CH_2Cl_2 gave compound **7**, which on treatment with $LiAlH_4$ gave a terminal methyl compound **8**. Selective deprotection of the terminal acetonide with $CuCl_2.2H_2O$ in CH_3CN afforded diol **9**. Selective protection of the primary hydroxy group in **9** as the pivaloyl ester with PivCl, Et_3N and DMAP in CH_2Cl_2 gave compound **10**. Mesylation of secondary hydroxyl group in compound **10** with MsCl, Et_3N and DMAP in CH_2Cl_2 gave secondary mesylate, followed by the treatment with anhydrous K_2CO_3 in anhydrous CH_3OH at rt afforded epoxide **5** with the required stereocenter. The opening of epoxide **5** with vinylMagnesium bromide in the presence of CuI afforded homoallyl alcohol **11**. The resulting free secondary hydroxyl group was acetylated to give a mono acetate compound **3**.
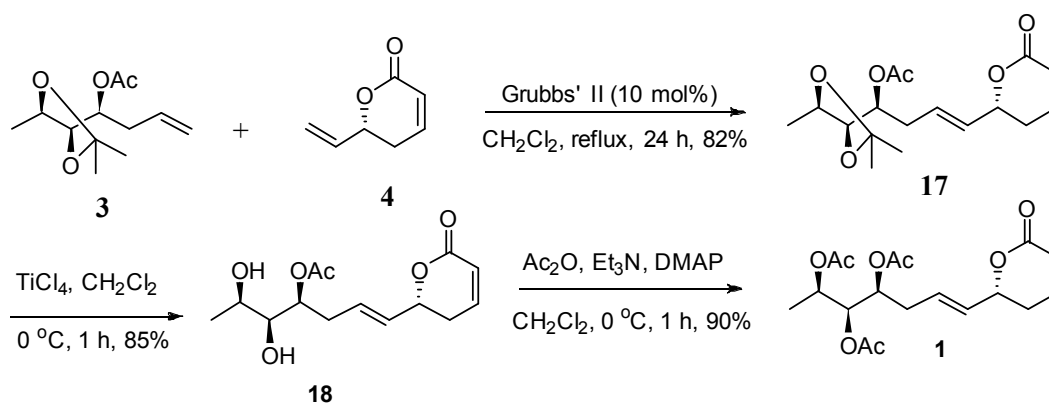
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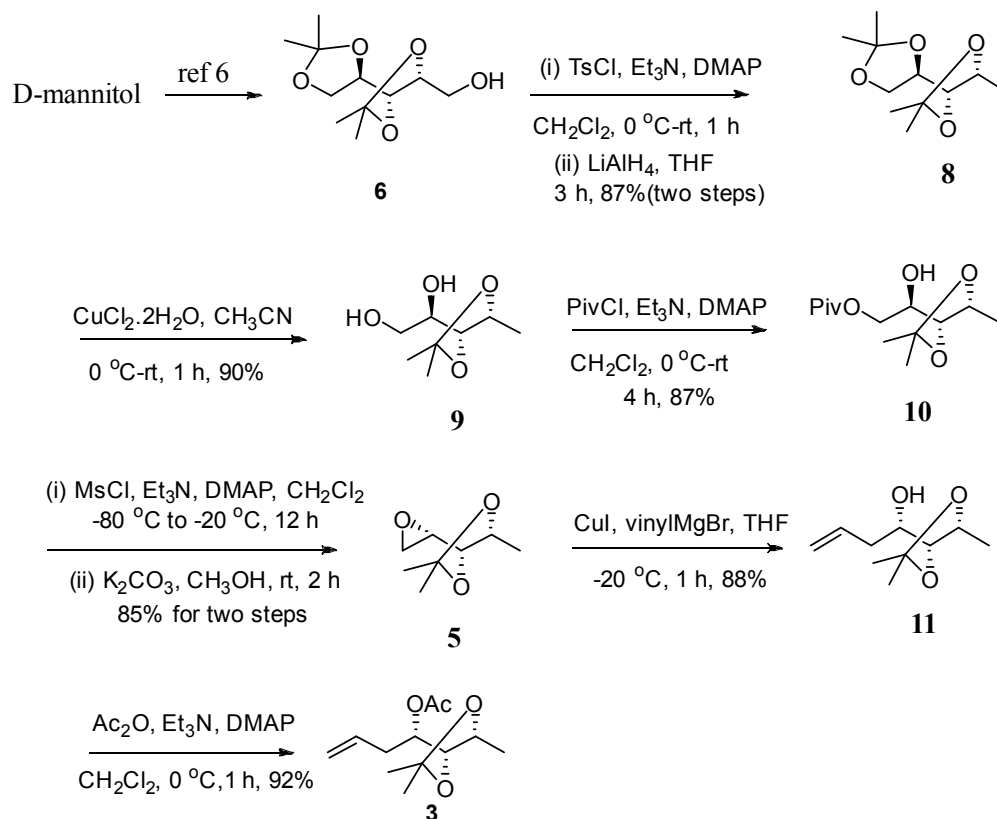
Scheme 2

Another fragment, vinyl lactone **4** was prepared from a known epoxide **12** as shown in Scheme 3. The epoxide was subjected to regioselective ring opening with propargyl alcohol using LiHMDS, BF₃.OEt₂ at -78 °C to furnish alcohol **13** in 85% yield. Triple bond in **13** was reduced to *Z*-double bond using Lindlar's catalyst to afford **14** in 90% yield. Oxidative removal of PMB group (DDQ/CH₂Cl₂:H₂O, 9:1, 0 °C-rt, 92%) and oxidation of the resulting alcohol **16** to the corresponding aldehyde and subsequent treatment with one carbon Wittig reagent furnished vinyl lactone **4**.

Scheme 3

PMBO $\overset{O}{\triangleleft}$ **12**

LiHMDS, propargyl alcohol
THF, BF$_3$·OEt$_2$O, -78 °C
4 h, 85%

PMBO $\overset{OH}{\underset{}{}}$ ═══ OH   **13**

Pd/CaCO$_3$, H$_2$, Quinoline
EtOAc, rt, 15 min, 90%

PMBO $\overset{OH}{\underset{}{}}$ OH   **14**

TEMPO/BAIB
CH$_2$Cl$_2$, rt, 1 h
90%

PMBO—O ... **15**

DDQ, CH$_2$Cl$_2$:H$_2$O (9:1)
0 °C-rt, 2 h, 92%

HO—O ... **16**

(i) IBX/CH$_3$CN
(ii) PPh$_3$=CH$_2$, THF
0 °C-rt
75% over two steps

4

Scheme 3

With the two key fragments in hand, the CM reaction was planned. Olefin cross-metathesis between fragment **3** and vinyl lactone **4** was promoted smoothly by the second Oxidative cyclization of 1,5-diol **14** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene [(PhI(OAc)2) (BAIB)] produced the desired *δ*-lactone **15** in presence of Grubb's-II catalyst in CH$_2$Cl$_2$ under reflux, to yield the desired lactone **17** (82%) exclusively (Scheme 4).

3 + **4**

Grubbs' II (10 mol%)
CH$_2$Cl$_2$, reflux, 24 h, 82%

17

TiCl$_4$, CH$_2$Cl$_2$
0 °C, 1 h, 85%

18

Ac$_2$O, Et$_3$N, DMAP
CH$_2$Cl$_2$, 0 °C, 1 h, 90%

1

Scheme 4

In conclusion, the stereoselective synthesis of Lippialactone has been achieved by employing LiAlH$_4$ reduction, epoxide opening and olefin cross-metathesis reactions as the key steps.

CHAPTER II: This chapter deals with the introduction, earlier synthetic approaches and Studies towards the Synthesis of Phostriecin.

Phostriecin (**1**) (originally referred to as Sultriecin (**2**)) was isolated in 1992 from *Streptomyces roseiscleroticus* no. L827-7 (Figure 1). Structurally Phostriecin consists of a 4-hydroxy unsaturated lactone, a hydrophobic *Z,Z,E*-triene and a centered 1,3-diol unit. It is a C9 phosphate-monoester. Later, studies with authentic material established that Phostriecin, but not Sultriecin, is an effective and selective inhibitor of protein phosphatase 2A (PP2A) defining a mechanism of action responsible for its antitumor activity. This compound was identified as antitumor, antibiotic when isolated from Streptomyces sp.44 Phostriecin (renamed for Sultriecin) displayed moderate broad spectrum antifungal activity *in vitro*, moderate *in vitro* cytotoxic activity against human and murine tumor cell lines, and potent *in vivo* antitumor activity against P388 leukemia and B16 melanoma.

In continuation of our interest in the synthesis of biologically active δ-lactone containing natural products, we herein describe the synthetic studies toward Phostriecin (**1**).
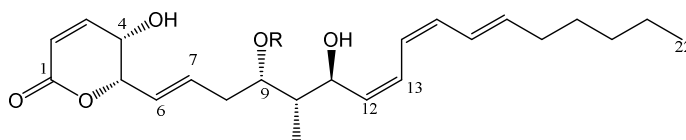

Phostriecin (**1**), R = PO$_3$H$_2$
Sultriecin (**2**), R = SO$_3$H

Figure 1

Our retrosynthesis is outlined in Scheme 1. It was envisaged that Phostriecin (**1**) could be obtained by cross metathesis of fragment **3** and fragment **4**. Fragment **3** could be synthesized from fragment **5** and **6** *via* a Sonogashira coupling. Fragment **5** could be generated by readily available ally bromide and propargylic alcohol by successive functional groups manipulation which includes alkyne and allyl bromide coupling, reduction, Sharpless epoxidation, Gilman's epoxide opening and Grignard reaction.

Whereas compound **6** obtained by Stork's protocol from the readily available aldehyde **10**. The 5-hydroxy vinyl lactone **4** could be obtained from readily available (+)-DET diol **11**.
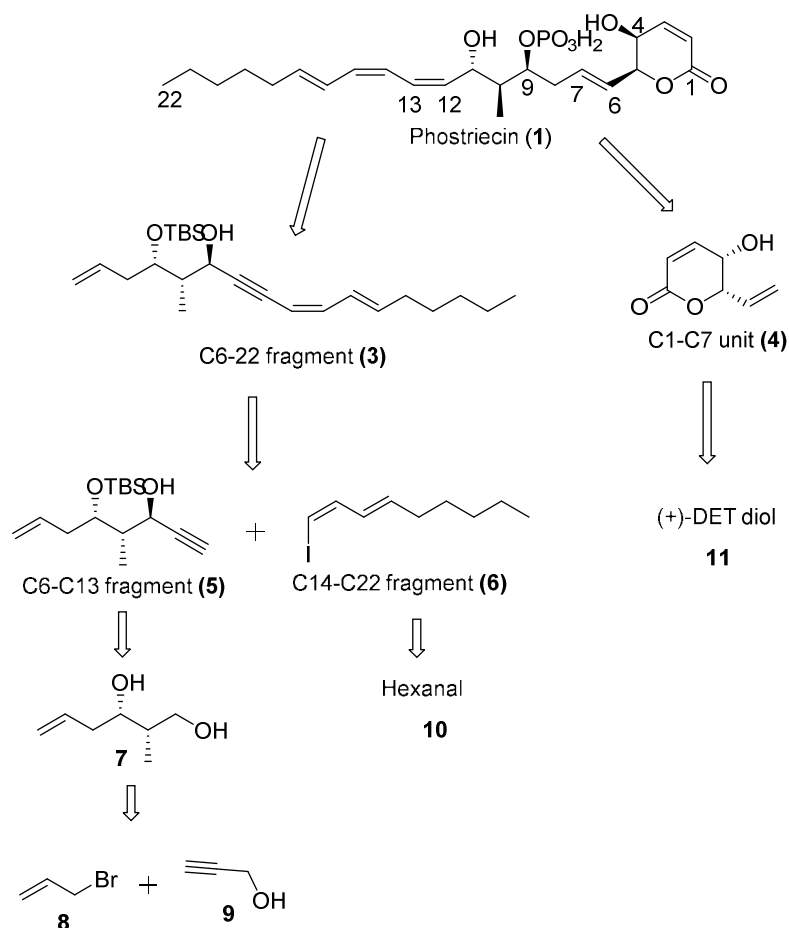
**Scheme 1. Retrosynthetic analysis**

Our synthetic studies started with the synthesis of the C6-C13 fragment. Accordingly, synthesis of alkyne fragment **5** was initiated by reacting allyl bromide **8** with propargylic alcohol **9** to give the compound **12**. Subsequently, triple bond was reduced to *cis* double bond using $Ni(OAc)_2/NaBH_4$ to furnish compound **13**. Sharpless asymmetric epoxidation of *cis* double bond using (-)-DIPT gave an epoxide **14** in 88% yield. Under Gilman reaction conditions, the epoxide yielded *syn* compound **7**. The contamination of the 1,2-diol was eliminated by exposing the crude reaction mixture to $NaIO_4$ followed by simple chromatography afforded 1,3-diol. Primary alcohol **16** was

obtained by di TBS protection of **7** and selective removal of primary TBS group with PPTS in ethanol. This compound (**16**) was converted into a mixture of alkyne (**5, 5a**) in two steps by oxidation (IBX) followed by Grignard reaction with ethynyl bromide. Conversion of **5a** under Mitsunobu conditions yielded alkyne **5**.
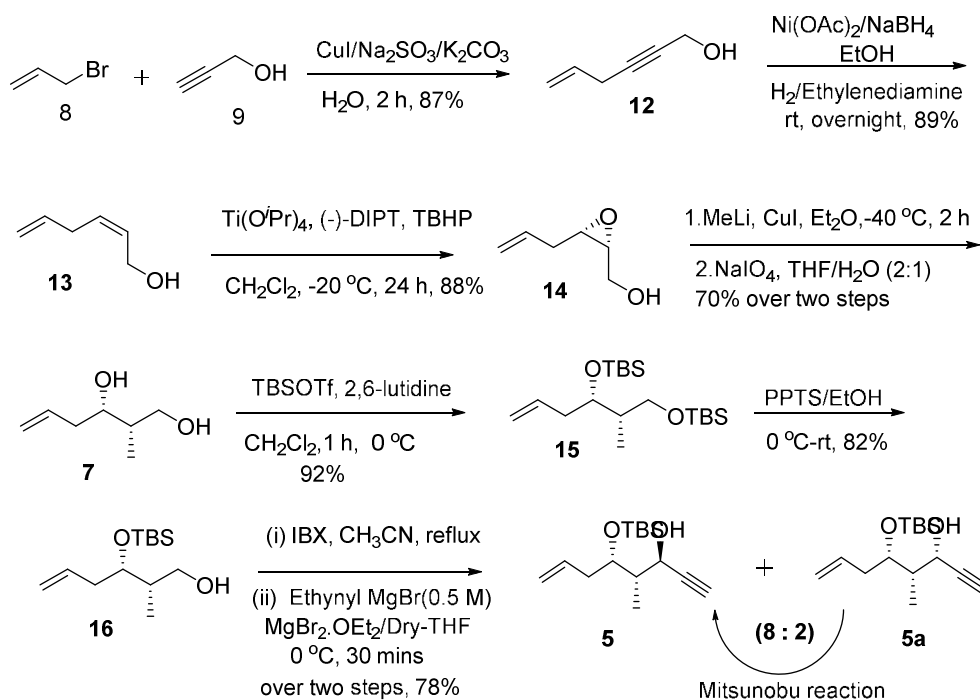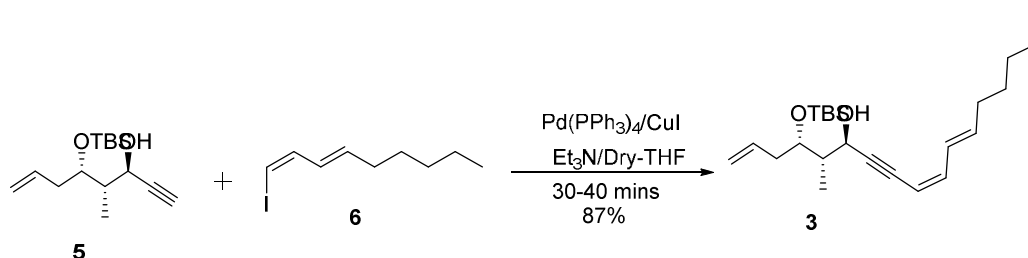

Scheme 2

Z,E-iododiene fragment (C14-C22) was produced from 1-hexanal (**10**) in 3 steps. Accordingly, hexanal was subjected to Wittig olefination with C2-ylide to yield unsaturated ester **17** that was reduced to the aldehyde by using DIBAL-H and the key intermediate *Z*-vinyl iodide **6** was obtained from aldehyde using Stork's protocol.
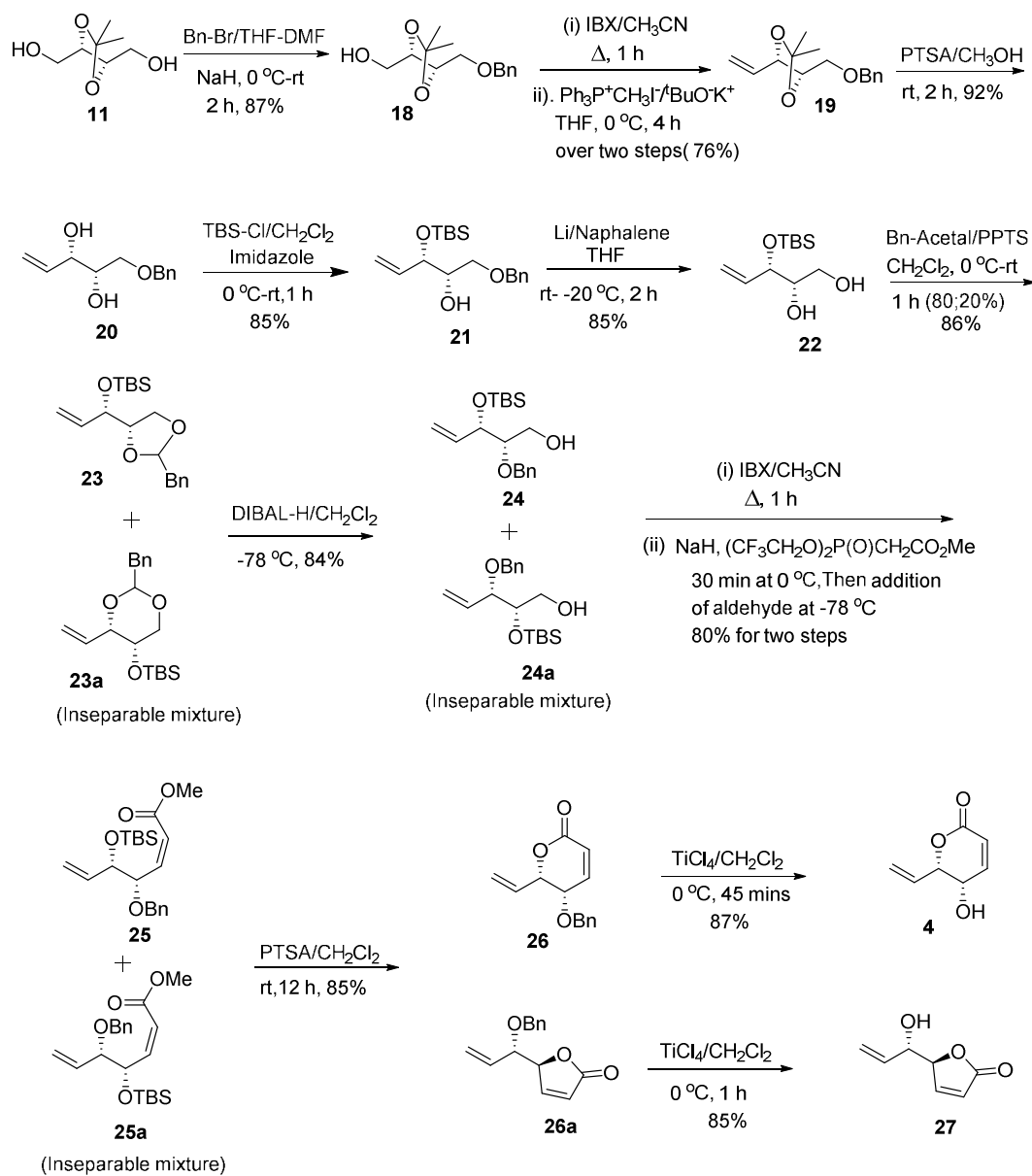

Scheme 3

X
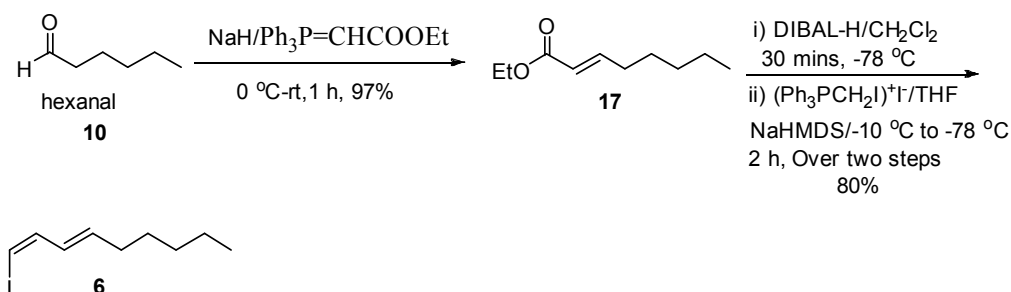
The alkyne **5** was subjected to coupling with *Z*-vinyl iodide **6** in the presence of Pd(PPh$_3$)$_4$/CuI in Et$_3$N/dry THF to obtain **3** in 85% yield, thus completing the synthesis of the C6-C22 fragment of Phostriecin.
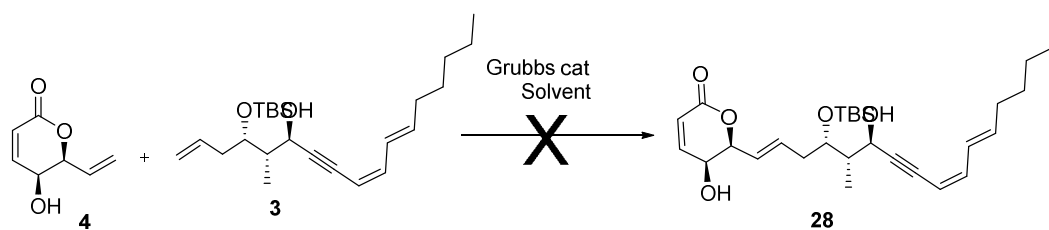

Scheme 4

Next, we turned our attention turned towards the synthesis of hydroxy vinyl lactone unit (**4**). This was started from a known DET diol **11** by protecting it as a mono benzyl ether **18**. Oxidation of alcohol using IBX in CH$_3$CN yielded the corresponding aldehyde, which was subjected to one carbon Wittig olefination using PPh$_3$P$^+$CH$_3$I$^-$ salt in the presence of ^{t}BuO$^-$K$^+$ in one-pot to give terminal alkene **19**. On acetonide deprotection using PTSA resulted in diol **20**, in which allylic alcohol was selectively protected as TBS ether with TBSCl at 0 ^{o}C to give compound **21**. Subsequently, benzyl group was removed using Li/Naphthalene in THF to yield a diol **22**. When 1,2-diol functionality in compound **22** was protected as the benzylidene acetal using benzaldehyde dimethyl acetal and catalytic PPTS in CH$_2$Cl$_2$ at 0 ^{o}C to rt for 1 h gave a mixture of 1,2 and 1,3-acetal as an inseparable mixture **23, 23a** in 80:20 ratio in an overall yield of 86%. Subsequent regioselective reductive ring-opening of the benzylidene acetals using DIBAL-H at -78 ^{o}C led to a mixture of inseparable alcohols **24, 24a**. Oxidation of the alcohol (mixture) with IBX followed by Still-Gennari of the resulting aldehyde gave an inseparable mixture of unsaturated esters **25, 25a** in 80% over all yield. When this mixture was treated with PTSA at room temperature for 12 h gave a mixture of lactones **26, 26a**. These two lactones were readily separated by column chromatography on silica gel to yield 6 and 5 membered lactones. Treatment of 6-membered lactone **26** and 5-membered lactone **26a** with TiCl$_4$ separately yielded 5-hydroxy vinyl lactone **4** and lactone **27**.

Scheme 5

Unfortunately, attempts to the coupling of these two fragments **4** and **3** failed to give the cross-coupled product under various Grubb's conditions. In Grubb's-I catalyst, there is no reaction between **3** and **4** and starting materials (SM) recovered. In case of Grubb's-II in CH_2Cl_2 or C_7H_8 at rt dimerization of compound **4** was obtained.

Entry	Reagent	Solvent	Yield (%)[b]
1	Grubbs cat-I	CH_2Cl_2	SM Recovered
2	Grubbs cat-I	C_7H_8	SM Recovered
3	Grubbs cat-II	CH_2Cl_2	Dimerisation of **4**
4	Grubbs cat-II	CH_2Cl_2	Dimerisation of **4**
5	Grubbs cat-II	C_7H_8/Δ	Decomposed SM

Scheme 6

We have developed a highly stereoselective synthetic route for C1-C22 fragment **28** of Phostriecin (**1**). The key features of the developed strategy are Gilman, Stereoselective synthesis, Stork's protocol, Sonogashira coupling, Cross-metathesis reactions.

CHAPTER III: This chapter deals with the introduction, synthesis and cytotoxic activities of (*S*)-dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone and its analogues.

Marine sponge-derived fungi are of rich and promising sources of novel and bioactive secondary metabolites. In 2002, Ghisalberti *et al.* isolated a butyrolactone from a fungal strain of *Acremonium* sp. The structure was established based on spectroscopic data and the relative stereochemistry (absolute configuration) was confirmed as (4*S*,5*S*) by a single-crystal X-ray study. This natural lactone was named as (*S*)-dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone (**1**) (Figure 1). Later, this butyrolactone has also been isolated from the fungus *Simplicillium* sp. YZ-11 by Xia et al. along with a diketopiperazine. γ-Substituted butenolides are important structural

motifs present in naturally occurring products and biologically active compounds. In continuation to our efforts and interest on the synthesis of γ-lactones, we herein report the first synthesis of (*S*)-dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone (**1**), its enantiomer (**2**) and natural lactone analogues (**6-11**) and further examined their cytotoxic activities.
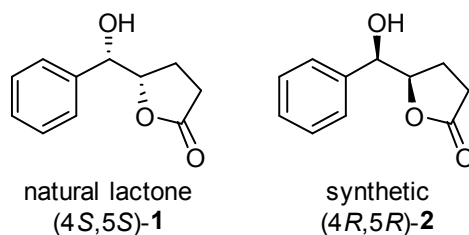

Figure 1

The synthesis of a natural lactone started by carrying out a Horner–Wadsworth–Emmons (HWE) olefination of triethyl phosphonoacetate with cinnamaldehyde (**3**) in the presence of NaH in THF which led to α,β-unsaturated ester (**4**) with highly selectively (99 : 1). Following Sharpless protocol for the dihydroxylation of **4**, diol **5** was provided in good yield and enantiomeric excess from the (DHQ)$_2$PHAL ligand system. Finally, selective reduction of double bond and lactonization of **5** using NiCl$_2$.6H$_2$O/NaBH$_4$ in CH$_3$OH for 6 h delivered the target butyrolactone (4*S*,5*S*)-**1** in 3 linear steps, with an overall yield of 64.6% (Scheme 1). We envisaged that this approach would be amenable to the synthesis of a number of modified aromatic/aliphatic analogues and its enantiomer. Thus, applying the same reaction conditions to a selection of aryl and heteroaryl aldehydes, enabled the synthesis of six structural analogues of the lead natural product (Scheme 1).
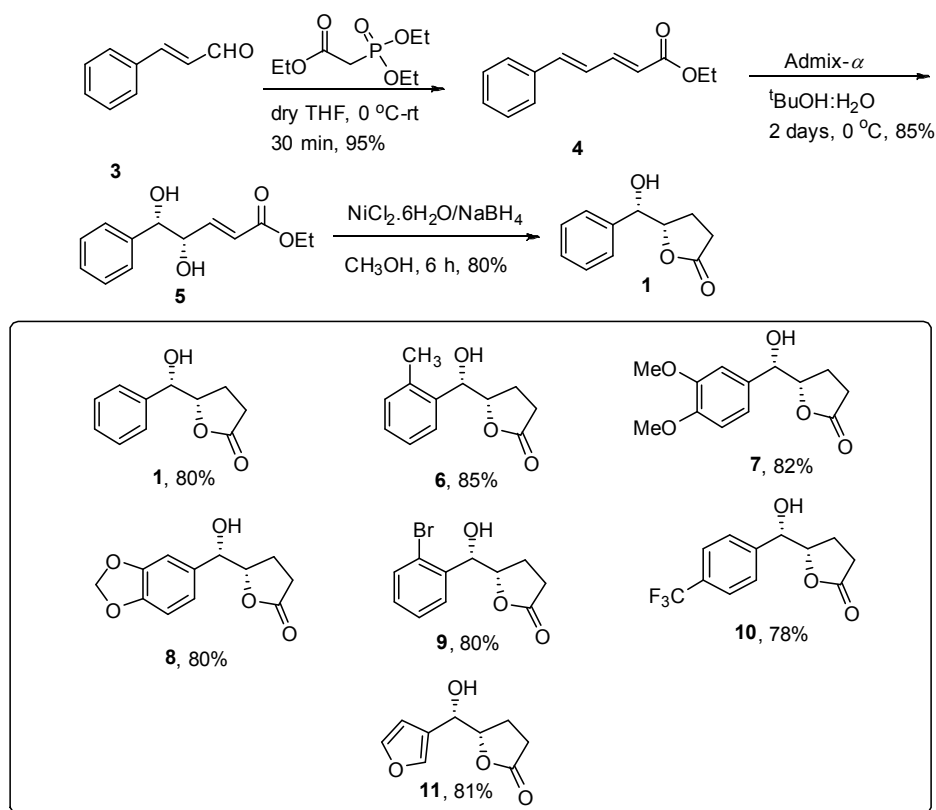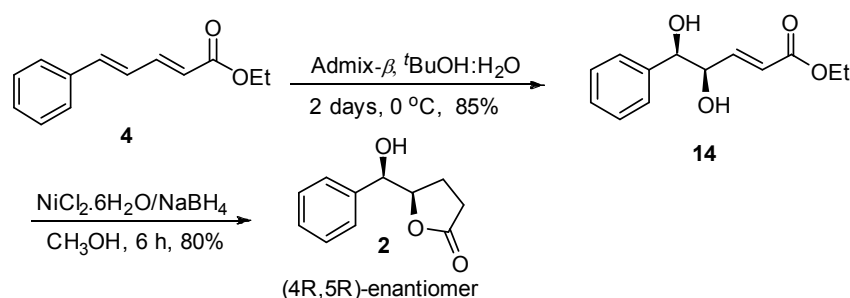
Scheme 1

The reduction of α,β-unsaturated double bond in compound **5** using Pd/C in EtOAc was found to give similar results. However, it was noticed that the reduction reaction of furan compound **12** gave reduced compound **13** (Scheme 2). The structure of **13** was confirmed based on the spectral data.
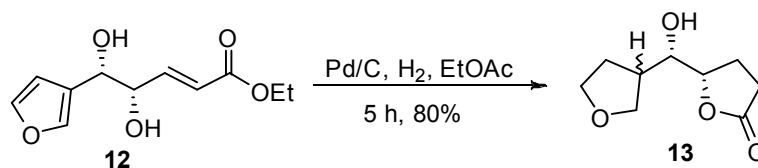
Scheme 2

Using Admix-β in place of Admix-α gave rise to diol **14**, which upon reduction with $NiCl_2.6H_2O/NaBH_4$ furnished (4R,5R)-**2** enantiomer (Scheme 3).

Scheme 3

In the present study, the synthesized (*S*)-dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone and its analogues were subjected to cytotoxicity evaluation against MDA-MB-231, HeLa, A549 and IMR-32 cell lines using MTT colorimetric assay and the quantified IC_{50} values are summarized in Table 1.

Table 1. Cytotoxicity of the synthesized natural dihydrofuranone and its analogues.

Test Compound	IC_{50} values (in µM)			
	MDA-MB-231	HeLa	A549	IMR32
1	24.19 ± 1.29	14.71 ± 0.72	11.60 ± 0.31	10.58 ± 0.61
6	25.87 ± 0.96	16.50 ±0.56	9.27 ± 1.08	12.49 ± 0.85
7	22.47 ± 0.87	13.75 ± 0.54	10.73 ± 1.06	12.12 ± 0.46
8	13.22 ± 0.78	15.82 ± 0.44	15.18 ± 0.70	14.18 ± 0.26
9	19.81 ±1.32	14.82 ± 0.76	10.76 ± 0.86	9.27 ± 0.98
10	23.36 ± 0.98	11.85 ± 0.58	10.58 ± 1.06	10.73 ± 0.23
11	23.50 ± 0.61	16.69 ± 0.51	12.49 ± 0.92	15.18 ± 0.76
13	19.36 ± 0.63	17.80 ± 0.49	12.12 ± 0.65	11.03 ± 0.84
Doxorubicin	0.89 ± 0.02	1.68 ± 0.24	2.06 ± 0.09	0.23 ± 0.76
Nocodazole	0.14 ± 0.01	1.35 ± 0.90	1.82 ± 0.20	1.52 ± 0.62

The synthesized natural dihydrofuranone exhibited good cytotoxic effect against these cancer cells at a micromolar range of 10.58-24.19, µM, while the dihydrofuranone

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analogues proved more promising with IC$_{50}$ values ranging between 9.27-25.87 µM. Based on the structure-activity relationship (SAR) study, it was observed that compounds **6, 7, 9** and **10** were quite promising since they possessed different substitutions such as ortho-methyl group, 3,4-dimethoxy moiety, 2-bromo and 4-trifluoromethyl groups, respectively, on the aromatic lactone scaffold which played a significant role in exhibiting the cytotoxic effect in A549 and IMR 32 cell lines. Further, other compounds showed moderate cytotoxicity against different cell lines. These results suggest that the cytotoxicity of the synthesized furanone analogues against different cancer cell lines has provided substantial information on the structural requirements for further improving the potency and selectivity of these compounds.

Conclusion

In conclusion, this highly enantiocontrolled route to (*S*)-dihydro-5-[(*S*)-hydroxyphenylmethyl]-2(3*H*)-furanone (**1**) and its analogues (**6-12**), along with the enantiomer **2** illustrates the utility of HWE olefination, Sharpless asymmetric dihydroxylation and NiCl$_2$ or Pd/C reduction reaction sequence. These dihydrofuranones showed good cytotoxicity against different cancer cells at a micromolar range of 10.58-24.19, µM, while the analogues (**6, 7, 9** and **10**) proved more promising with IC$_{50}$ values ranging between 9.27-25.87 µM and were considered as potential leads.

Chapter IV: This chapter deals with the introduction, earlier synthetic approaches and Green Approach for the Domino Reduction/Reductive Amination of Nitroarenes and Chemoselective Reduction of Aldehydes Using Fe/aq. Citric acid/Montmorillonite K10

Domino reactions have emerged as highly effective strategies in organic synthesis and they are referred as multi-step one-pot reactions. In these reactions, multiple transformations can be carried out in a single operation without isolating the intermediates and thus reducing the reaction time and energy, making them prime examples of green chemistry. Secondary amines are key building blocks and important intermediates for the chemical, pharmaceutical and agrochemical industries. *N*-

Benzylanilines or secondary anilines were prepared by reductive amination of carbonyl compounds with amines or in a single-pot synthesis by reduction of nitrobenzenes followed by reductive amination with carbonyl compounds.

To the best of our knowledge, this type of domino transformation is scarcely known. Even though, these methods are encouraging, most of them suffer from drawbacks such as high pressure reactions, reductive etherification, debenzylation, reduction of isolated double bonds, high temperature, long reaction times, expensive reducing agents and use of molecular hydrogen as the hydrogen source, which requires a specific equipment. Therefore, there is a need to develop a simple and efficient method for the three step one-pot reaction of reductive amination of nitroarenes with aldehydes. Recently, a combination of Fe/aq. citric acid/montmorillonite K10 was reported for the domino reduction/imine formation/aza-Diels-Alder reaction for the synthesis of tetrahydroquinolines from nitroaromatics. Herein, we report a domino reduction/reductive amination of nitroarenes and hetero nitroarenes and a chemoselective reduction of aldehydes using Fe as a reductant in aqueous citric acid in the presence of montmorillonite K10 catalyst at room temperature.
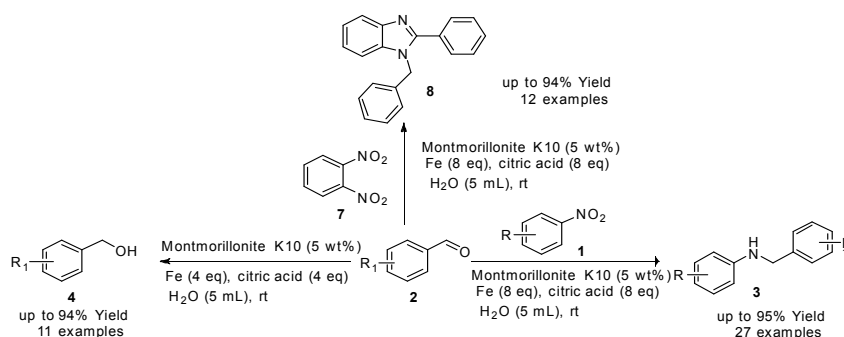

Scheme 1

Attempts of initial reaction with the nitrobenzene **1a** and benzaldehyde **2a** using 4 equiv of Fe, 4 equiv of citric acid and 5 wt% montmorillonite K10 clay in 5 mL of H_2O resulted in a clean conversion to *N*-benzylamine **3a** (Scheme 2) in 45% yield upon stirring for 5 h at room temperature. In this protocol, the reduction of the nitro group, followed by imine formation with the aldehyde and further reduction gave secondary amine in a domino fashion.

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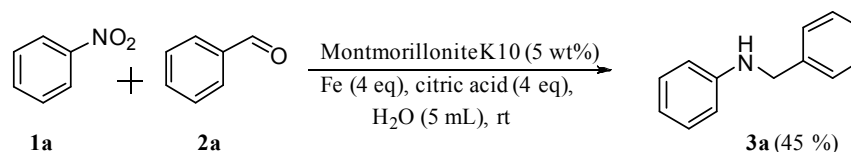
Scheme 2

Following this initial success, experiments were conducted to optimize the reaction protocol (Table 1). Nitrobenzene **1a** and benzaldehyde **2a** were chosen as the model substrates and Fe loading and citric acid equiv, were increased to 6, 8, 10 and then to 12 equiv. Faster reaction rates and high product yields were observed with 8 eq and the results are shown in Table 1. Final conditions were set at 1.0 M nitroarene, 8 equiv of Fe powder, 8 equiv of citric acid, 5 wt% of montmorillonite K10 clay and 5 mL of H_2O.
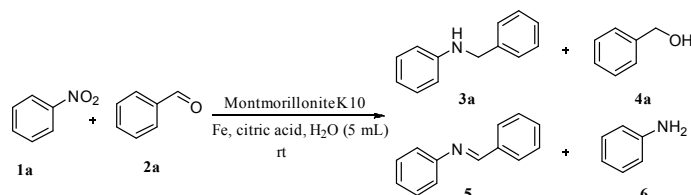
Entry	Reductant [equiv]	Clay [wt %]	Time [h]	Conversion of 1a [%]	Selectivity [%]			
					3a	4a	5	6
1	Fe [04], Citric acid [04]	5	Upto 24	>99	45	---	52	---
2	Fe [04], Citric acid [04]	10	Upto 24	>99	48	---	50	---
3	Fe [06], Citric acid [06]	5	Upto 24	>99	76	---	21	---
4	Fe [06], Citric acid [06]	10	Upto 24	>99	75	---	20	---
5	Fe [08], Citric acid [08]	5	4	>99	>95	---	<2	---
6	Fe [10], Citric acid [10]	5	3-4	>99	78	5	---	8
7	Fe [12], Citric acid [12]	5	3	>99	62	10	---	15
8	Fe [10], Citric acid [10]	---	Upto 24	>99	---	---	66	10
9	Fe [10], Citric acid [---]	5	Upto 24	40-50	8-10	---	5-8	20-25

Table 1

Using the optimized conditions, the applicability of this one-pot reduction/reductive amination of nitrobenzenes with aldehydes was explored on several substrates. Irrespective of the electronic nature of the substituents, either an electron-withdrawing or electron-donating groups present on nitroarenes, domino reactions

proceeded smoothly to give the corresponding *N*-benzylamines in excellent yields. Functional group tolerance was shown to include ketones, esters, olefins, and various halogens suggesting the selective nitro group reduction. In contrast to classical hydrogenation, no complications were encountered due to the presence of other reducible functionalities, including alkenes, and keto groups. Some heteroaromatic nitro compounds were also subjected to reductive amination with the benzaldehyde and found to be successful yielding the clean amino derivatives (Table 2, 3y, 3z).
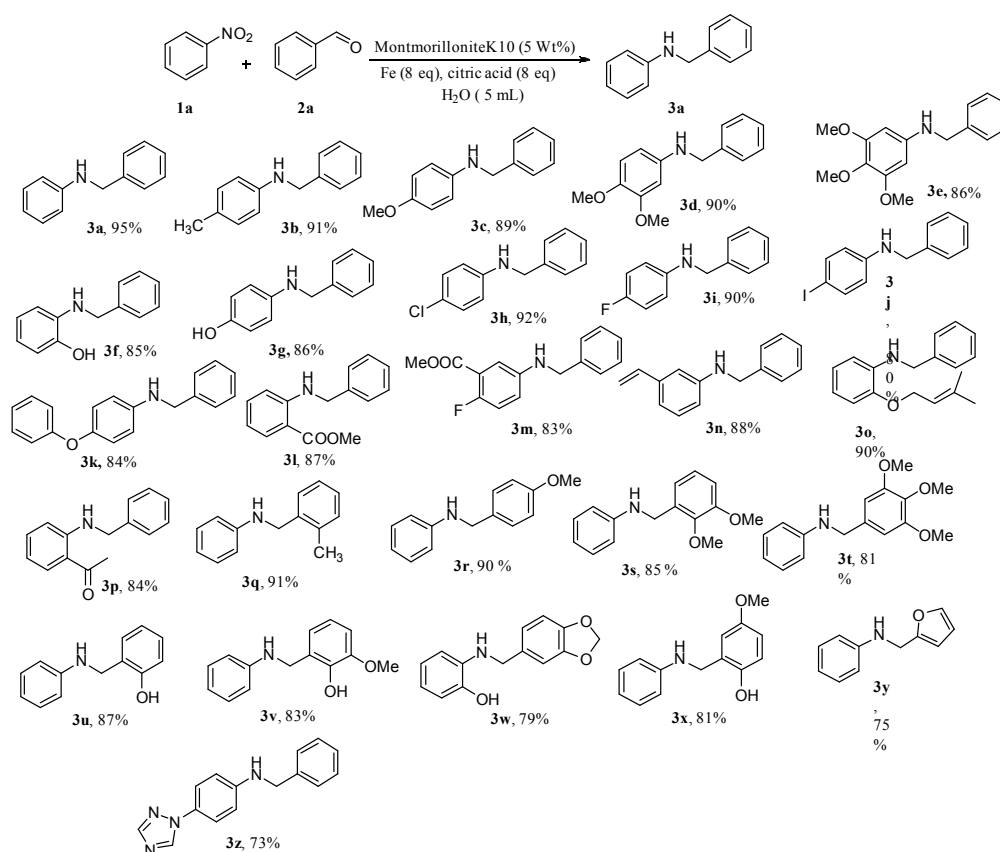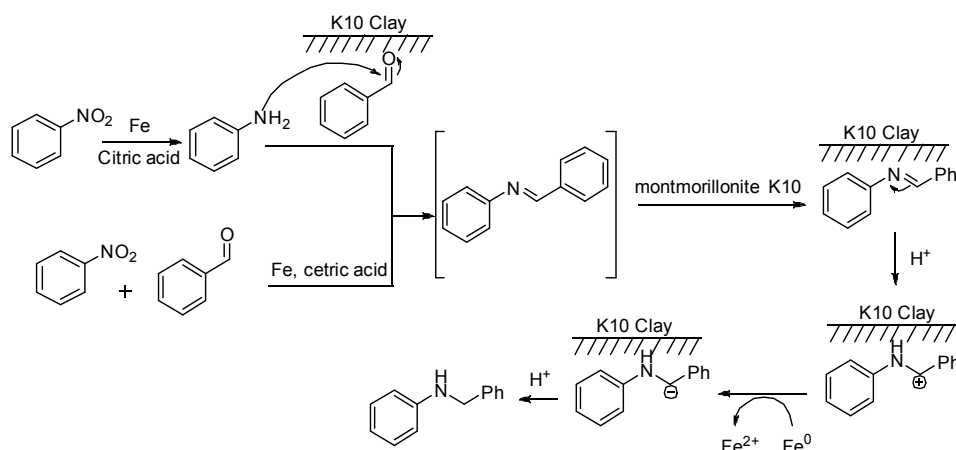

Table 2

Demonstrating its potential utility in pharmaceutical or natural product synthesis or other heteroaromatic targets of interest. It is important to note that ketones remained essentially inert under the same reaction conditions (**3p**). Whereas aliphatic aldehydes did not participate in the reductive amination reaction, however, hexanaldehyde with nitrobenzene gave the corresponding *N*-alkyl benzene in 30% yield. It is important to

note that no product was formed when the reaction of reductive amination of nitroarenes was run in absence of the catalyst.

It is plausible to assume that the Montmorillonite K10 driving the electron migration towards the nitrogen, Umpolung or polarity inversion is taking place with the help of Fe which leads to the required secondary amines as final products.

Plausible reaction Mechanism:

While optimizing the reductive amination procedure, we noticed that the aldehyde was partially reduced giving alcohols in 5% and 10% yields respectively (Table 1, entries 6 & 7). These observations using Fe/aq. citric acid/montmorillonite K 10 catalytic system led to the discovery of a mild, simple procedure for the reduction of aldehydes to alcohols. The scope of the reduction was surveyed with other aldehydes, and the products and isolated yields from these experiments are shown in Table 3.

Despite the importance of aldehyde reduction in organic chemistry, surprisingly few generally applicable. Manufacturing methods are available for this transformation, reduction of **2** through the use of hydride reagents (e.g., $LiAlH_4$, $NaBH_4$ etc.). Unfortunately, hydride reducing agents are moisture-sensitive reagents that are not economically attractive for manufacturing since they are employed in stoichiometric quantities and generates substantial quantities of waste (boron or aluminum salts). Numerous heterogeneous catalysts, such as PtO_2, Raney Ni and Pd/C, can catalyze the hydrogenation of aldehydes. However, heterogeneous catalysts generally do not actuate hydrogenation of aldehydes with a high degree of chemical selectivity (e.g., other

sensitive groups such as oxime, ketone, aryl halide, benzyloxy etc. also are reduced). Another serious problem encountered when reducing aromatic aldehydes using heterogeneous catalysts is that any formed hydroxymethyl group may be further reduced to a methyl substituent.
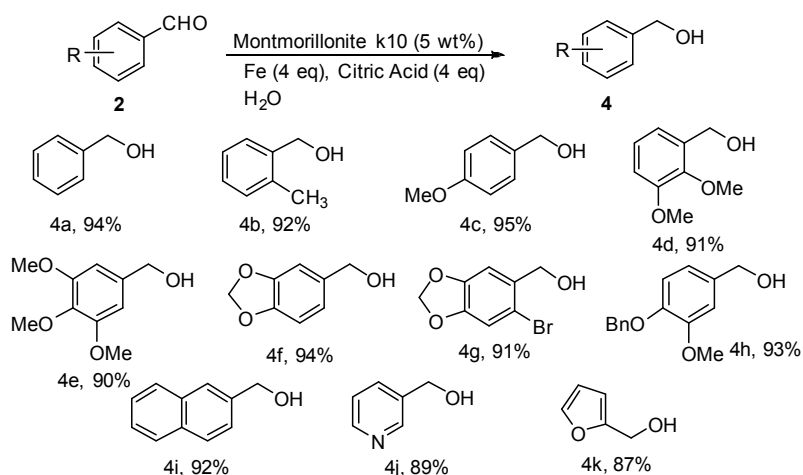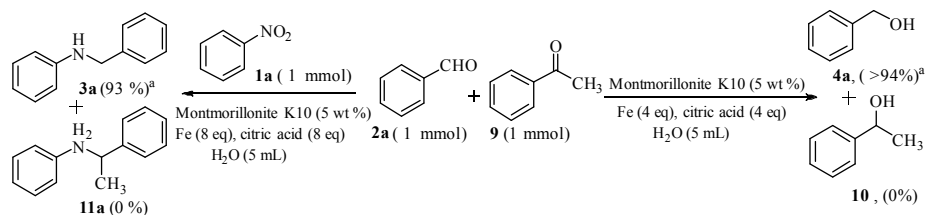

Table 3

When a mixture of equal amounts of benzaldehyde **2** and acetophenone **9** was treated with the present catalytic system, Fe (4 eq)/citric acid (4 eq)/5 wt% montmorillonite K 10/5 mL H_2O, reduction of benzaldehyde occurred to give benzyl alcohol **4** in excellent yield (>94% by NMR analysis) along with unreacted acetophenone **9** (Scheme 3). As shown in Scheme 3, the reported method is highly selective for the preparation of secondary amines from aldehydes in the presence of ketones *via* reductive amination. Generally, aromatic ketones are poor substrates for reductive amination protocols. Acetophenone alone as a ketone was also used for the one-pot reductive amination with nitrobenzene under the present catalytic system, Fe (8 eq)/citric acid (8 eq)/5 wt% montmorillonite K 10/5 mL H_2O and found to be intact at room temperature as well as at 80 ^{o}C. The result is, however, interesting because acetophenone has shown to be an inert or a difficult substrate for reductive amination reactions. This result clearly indicates that the reduction is chemoselective and explains the mild reactivity of the present catalytic system.

3a (93 %)[a]

11a (0 %)

1a (1 mmol)

Montmorillonite K10 (5 wt %)
Fe (8 eq), citric acid (8 eq)
H₂O (5 mL)

2a (1 mmol)

9 (1 mmol)

Montmorillonite K10 (5 wt %)
Fe (4 eq), citric acid (4 eq)
H₂O (5 mL)

4a, (>94%)[a]

10 , (0%)

[a]Yield was determined by ^{1}H NMR analysis

Scheme 3

We also explored the applicability of this catalytic system for the synthesis of 1,2-disubstituted imidazoles from 1,2-dinitrobenzene in a domino fashion. Benzimidazoles and their derivatives are an important heterocyclic compounds which are recently known to exhibit interesting pharmacological properties such as ischemia-reperfusion injury, hypertension, obesity and their wide range of biological activities including anti-ulcer, anti-hypertensive, anti-viral, anti-fungal, anti-cancer, and anti-histamine. Generally, a direct one-pot condensation–aromatization reaction of *o*-phenylenediamines and aldehydes under the oxidative condition is documented for the synthesis of 1,2-disubstituted benzimidazoles. However, many of these methods have several drawbacks such as expensive reagents, oxidation processes, and prolonged reaction times. In some cases, 2-substituted and 1,2-disubstituted benzimidazoles were generated simultaneously with poor selectivity. The broad range of biological activities of 1,2-disubstituted benzimidazole moiety makes them highly sought as synthetic targets. To the best of our knowledge, there is no report exist using 1,2-dinitrobenzenes as starting materials. Herein, we report for the first time the synthesis of 1,2-disubstituted benzimidazoles by the reaction of 1,2-dinitrobenzenes and aldehydes in a domino fashion. As an initial experiment, 1,2-dinitrobenzene **7a** was treated with benzaldehyde **2a** (Table 4) in the presence of 8 eq of Fe/aq. citric acid/5 mol% of montmorillonite K10 catalytic system at room temperature. It was observed that under these conditions, the starting materials were completely disappeared on TLC after 5 h to give compound **8a** exclusively in 94% yield.
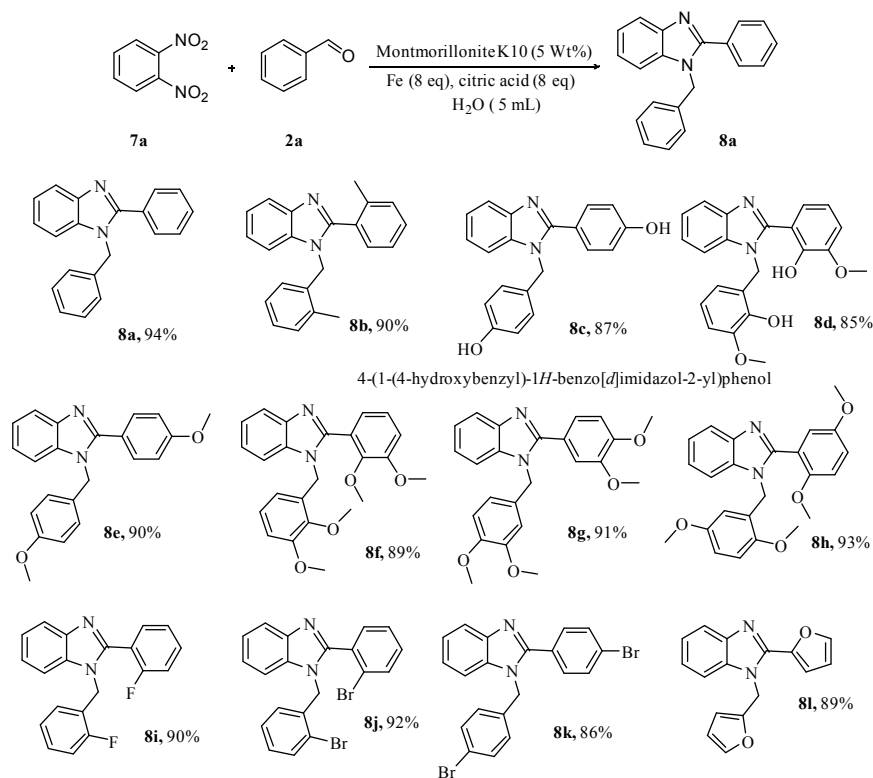
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Table 4

We then explored the generality of the method for the synthesis of 1,2-disubstituted benzimidazoles by employing differently substituted aromatic aldehydes and the results are summarized in Table 4. This method was found to be equally effective for aldehydes bearing either electron-donating (Table 4, entry) or electron-withdrawing substituents (Table 4, entries).

Conclusion

We have reported a one-pot reaction of reduction/reductive amination of nitroarenes with aldehydes to form secondary aniline derivatives in a domino fashion using a Fe/aq. citric acid/montmorillonite K10 clay catalytic system. In addition, chemoselective reduction of aromatic aldehydes to benzyl alcohols is reported in the presence of ketones. The domino reaction can be performed with numerous nitrobenzenes and aromatic, heteroaromatic aldehydes and is characterized by a high functional group tolerance.