"Towards the total synthesis of 15-Hydroxygeldanamycin, KOSN-1633 and Herbimycin A."

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
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TO

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BY

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(Research Guide)

DIVISION OF ORGANIC CHEMISTRY
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INDIA

March 2009

DEDICATED
TO
MY PARENTS,
BROTHER & SISTER
my late aunt And
Jyothi …….

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Ex. Deputy Director and Head, Division of Organic Chemistry, National Chemical Laboratory, Pune - 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Division of Organic Chemistry
National Chemical Laboratory
Pune-411008
March 2009

(Rambabu Dakarapu)
Candidate

CERTIFICATE

The research work presented in thesis entitled **"Towards the total synthesis of 15-Hydroxygeldanamycin, KOSN-1633 and Herbimycin A."** has been carried out under my supervision and is a bonafide work of **Mr. Rambabu Dakarapu**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008 **(Dr. M. K. Gurjar)**

March 2009 **Research Guide**

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- *Rambabu Dakarapu.*

Contents

General Remarks

- ^{1}H NMR spectra were recorded on AV-200 MHz, MSL-300 MHz, AV-400 and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometers.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde inthanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

List of abbreviations

Ac	-	Acetyl
Ac_2O	-	Acetic anhydride
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
$H_3B{\cdot}SMe_2$	-	Borane-dimethyl sulfide complex
BnBr	-	Benzyl bromide
n-BuLi	-	*n*-Butyl lithium
m-CPBA	-	*m*-Chloroperbenzoic acid
DCC	-	Dicyclohexylcarbodiimide
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	-	Diisopropyl azodicarboxylate
DIEA	-	Diisopropyl ethylamine
2,2-DMP	-	2,2-Dimethoxypropane
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
DMAP	-	4-Dimethylaminopyridine
TEA	-	Triethylamine (Et_2N)
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
LiHMDS	-	Lithium hexamethyl disilazane
LDA	-	Lithium diisopropylamine
MeI	-	Methyl iodide
MsCl	-	Methanesulfonyl chloride
NaOAc	-	Sodium acetate
Pd/C	-	Palladium on Carbon
PivCl	-	Trimethylacetyl chloride

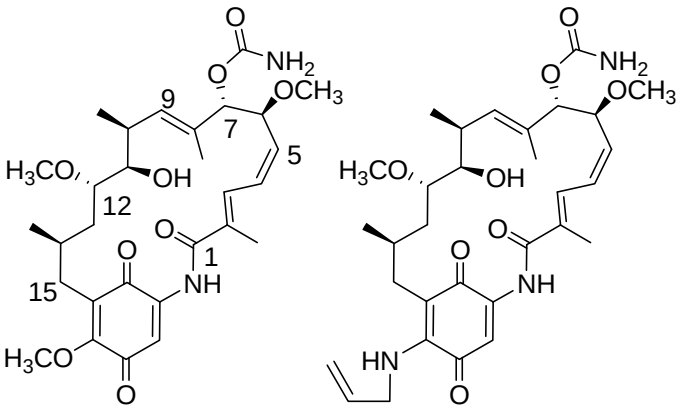
PMB-Cl	-	*p*-Methoxybenzyl chloride
Py	-	Pyridine
PPh_3 (TPP)	-	Triphenylphosphine
PPTS	-	Pyridinium *p*-toluenesulfonate
TBSCl	-	*tert*-Butyldimethylsilyl chloride
p-TSA	-	*p*-Toluenesulfonic acid
TBAF	-	Tetra-*n*-butylammonium fluoride
TBAI	-	Tetra-*n*-butylammonium iodide
Tf_2O	-	Trifluoromethanesulphonic anhydride

The thesis entitled **"Towards the total synthesis of 15-Hydroxygeldanamycin, KOSN-1633 and Herbimycin A."** consists of one chapter which is subdivided into 3 sections; section-I describes our approach towards the total synthesis of Herbimycin A.where as section-II describes our efforts towards the synthesis of 15-Hydroxygeldanamycin. The final section deals with synthetic approach for the key fragment of KOSN-1633.

Section-I: Towards the total synthesis of Herbimycin A:

Introduction

Geldanamycin was isolated (from streptomyces hygroscopicus var. geldanus) in 1970 by workers at Upjohn and the structure was determined by Rinehart and co-workers shortly thereafter. Geldanamycin belongs to benzoquinone anasamycin family. Benzoquinone containing ansa-bridged macrocyclic lactams have a significant range of antitumor, antibacterial, antifugal and antiprotozoa activies. Hsp90-geldanamycin complex were studied by X-ray crystallography, absolute stereochemistry was determined by its total synthesis by Andus *et.al*. The greatest drawback of biologically active geldanamycin is its cytotoxicity and low solubility in water for any formulation that can be used to administer it. To rectify this problem, derivatization of geldanamycin with ionisable or polar groups was explored. The 17-allyl amino geldanamycin prepared in this context, was currently in phase-II clinical trial.



Figures A and B

Other important members of this family are Herbimycin A, 15-Hydroxygeldanamycin and KOSN-1633 which exhibit reduced cytotoxicity against

SKBr3 cancer cells. Herbimycin A was isolated in 1979 from the fermentation broth of *streptomyces hygroscopicus* strain AM-3672, The 15-Hydroxygeldanamycin was formed as the major product when geldanamycin was added to the fermentation with *streptomyces hygroscopicus* AM-3672 and a minor compound, a tricyclic geldanamycin (KOSN-1633) was isolated. It has been established that the OH at 15-position of geldanamycin does not interfere in binding with Hsp90 but increase the lypophilicity of it. The structure of 15-hydroxy geldanamycin was elucidated by comparing the similarities of its spectral data with that of geldanamycin which are similar in all aspects (^{1}H, ^{13}C, HSQC, and COSY) except at the 15- position. The stereochemistry of 15 –OH group was assumed to be the same as in herbimycin A. The cytotoxicity of 15-hrdroxygeldanamycin is same as that of reblastatin and 20 times lower than that of geldanamycin. KOSN-1633 is two fold less cytotoxic than 15-hydroxygeldanamycin. The potential biological activity and interesting structural complexities of this class of compounds prompted us to under take the total synthesis of these target molecules.

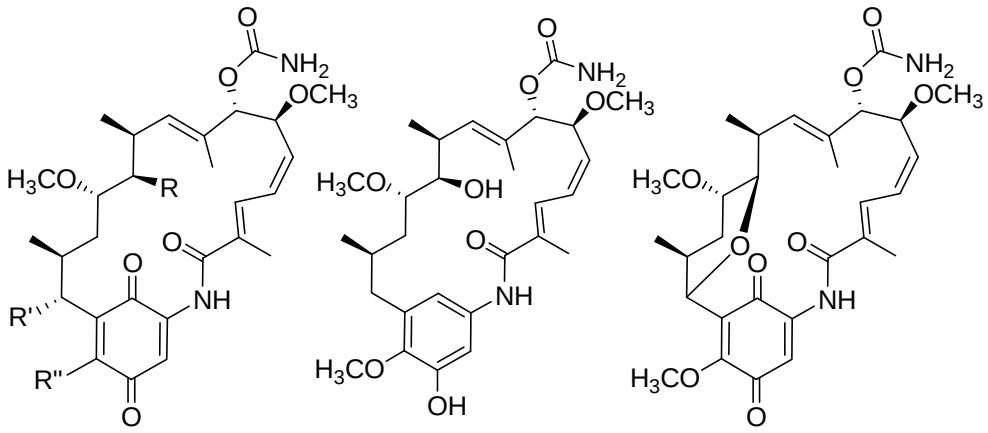
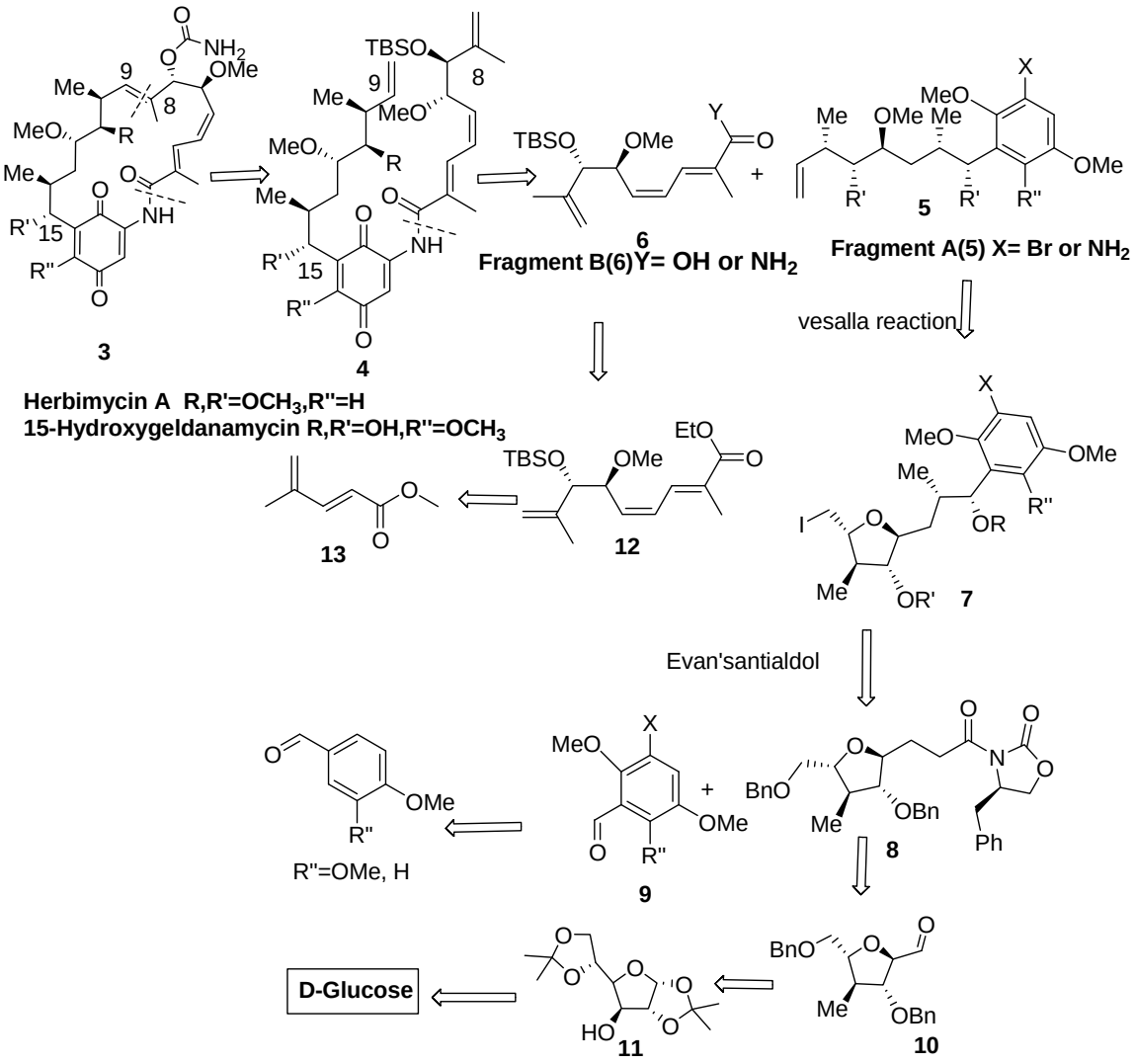


Figure 2

Retrosynthetic analysis:



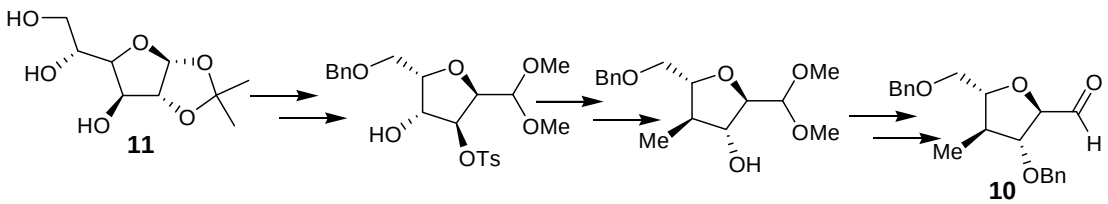
Scheme 1: Retrosynthesis of Herbimycin A and 15-hydroxy geldanamycin

As shown in the retrosynthetic scheme the critical fragment A can be prepared via Evan's anti aldol[3] protocol from aldehyde **9** and carbohydrate precursor **8**

Synthesis of fragment-A (5) for Herbimycin A:

Synthesis of aldehydes-10:

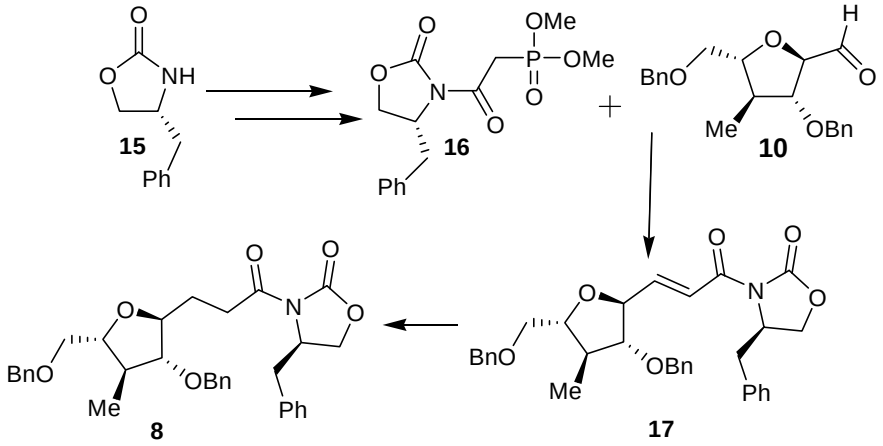
Scheme 2:



Synthesis of aldehyde-**10** started with triol-**11** obtained from D-glucose in two steps, followed by selective protection and acid catalyzed rearrangement ,which on epoxidation gave epoxide. Regioselective opening of this epoxide followed by protection and strong acid hydrolysis to afford required (carboaldehyde) compound **10**.

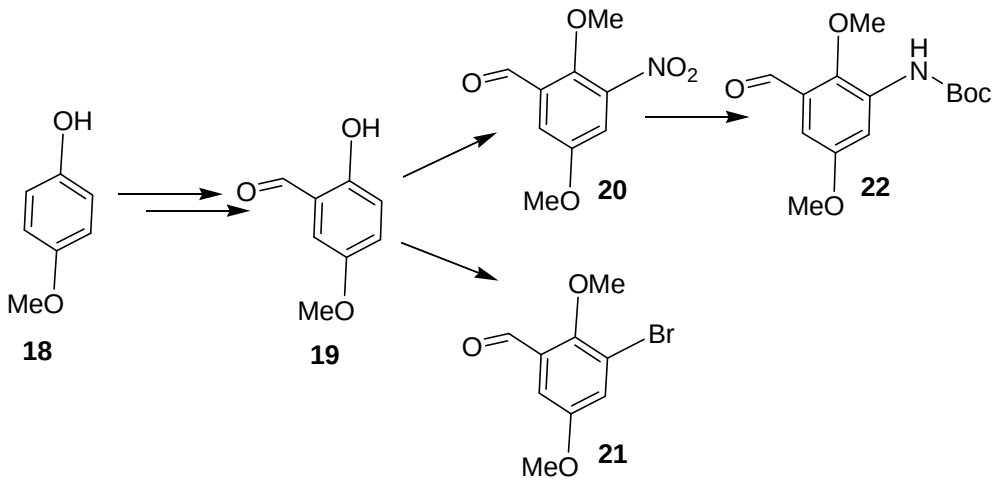
Conversion of aldehyde-10 to Oxazolidinone derivative- 8:

Scheme 3:



Chiral auxillary-**15** was acylated using chloroacetylchloride and subsequently converted to the wittig precursor-**16** . Olefination of aldehyde-**10** using this **16** afforded **17**, the double bond of which was reduced using 10% Pd/C to provide desired compound **8**.

Synthesis of the Masked Quinone fragment (compound 20 and 21):

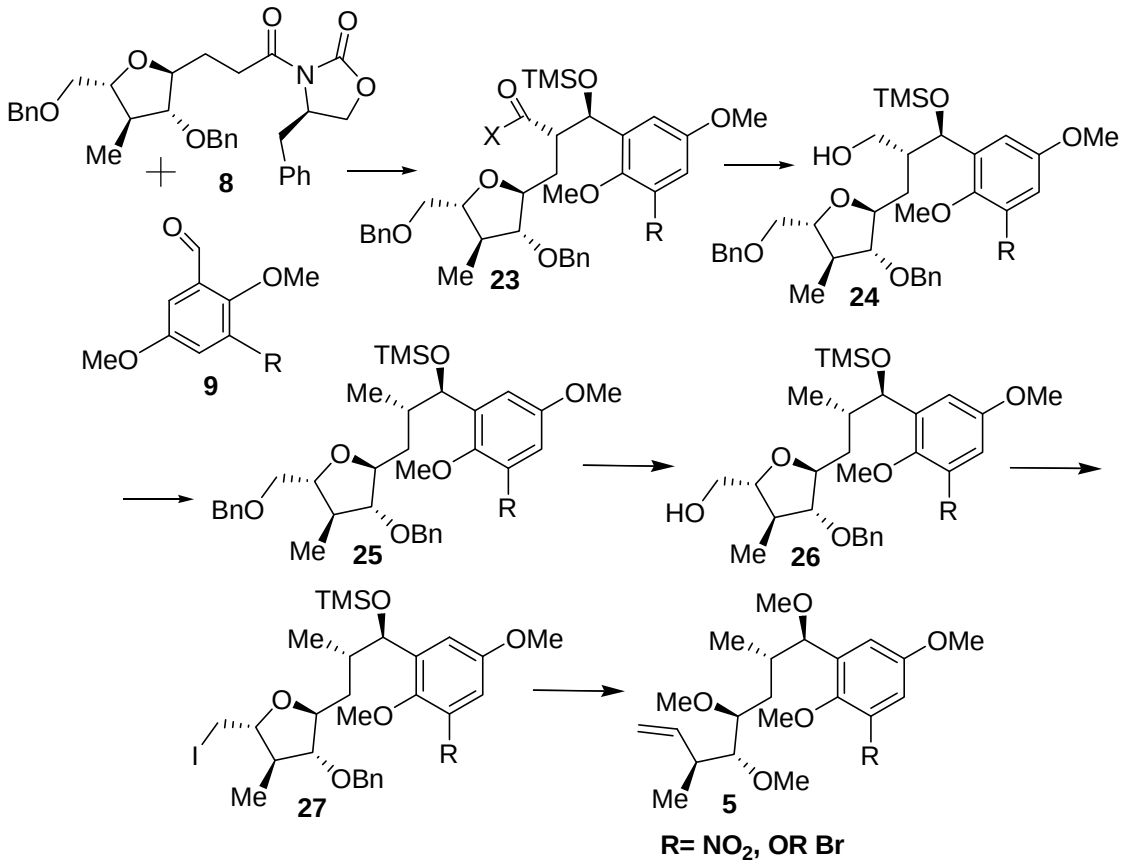


Compound **20** was prepared from 4-methoxyphenol in three steps, 4-methoxyphenol was on o-farmylation then on nitration followed by methylation give

nitroarylaldehyde **20** and the aldehyde **19,** which on bromination followed by methylation gives **21**. the nitro aldehyde (**20**) was reduced to give amino product **22.**

Evan's aldol and synthesis of intermediate 5:

Scheme 4:



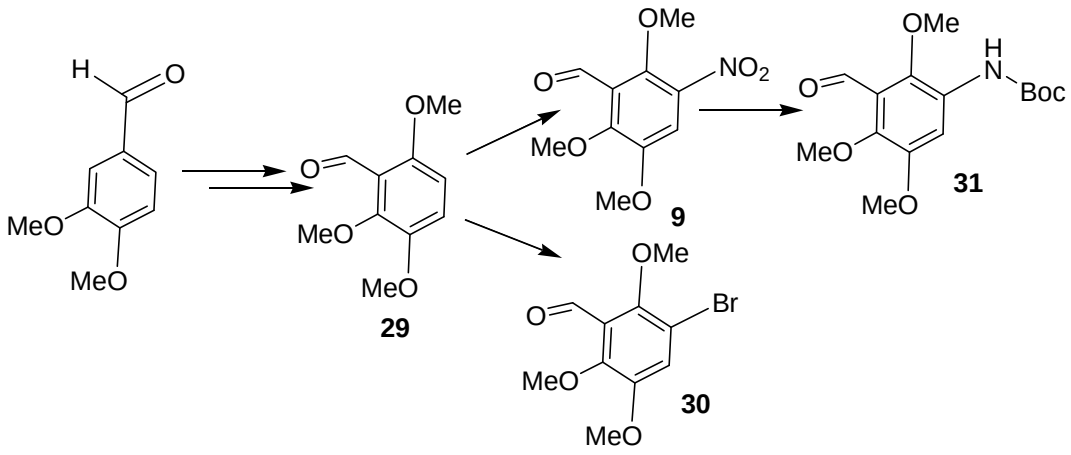
Evan's Aldol, using Oxazolidinone derivative **8** on aldehyde **9** afforded the condensed product **23**. Reductive cleavage of the chiral auillary followed by deoxygenation of the resulting alcohol provided the key intermediate **25**, which was subsequently manipulated to intermediate-**5**.

Section-II

Synthesis of fragment-A (5a) for 15-Hydroxygeldanamycin:

Synthesis of the Masked Quinone fragment (9):

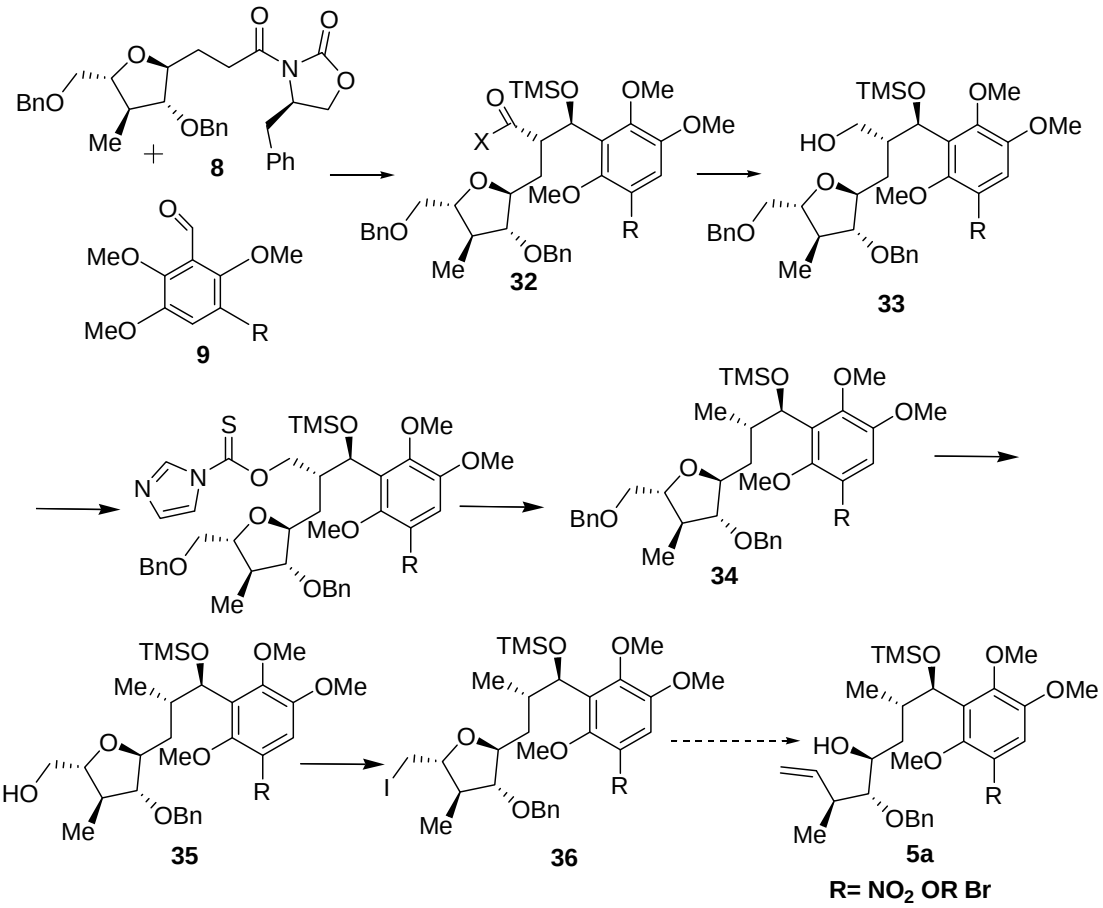
Scheme 5:



Compound-**9** was prepared from veratraldehyde in five steps; veratraldehyde was converted into phenol under acid catalysed Dakin reaction, which on methylation using dimethyl sulphate and base furnished trimethoxy compound. This was selectivily formylated, followed by nitration to give **9** in good yield, the compound **29** which was brominated to afford compound **30**. compound **9** was reduce to give Boc protected compound **31**.

Evan's aldol and synthesis of intermediate 5a:

Scheme 6:



Evan's Aldol, using compound **8** on aldehyde **9** afforded the condensed product **32** which shows a rare restricted conformational isomerism. Reductive cleavage of the chiral auillary followed by deoxygenation of the resulting alcohol provided the key intermediate **34**, which was subsequently manipulated to intermediate-**5a**.

Section-III

Synthesis of fragment-A (5b) for KOSN-1633:

Retrosynthetic analysis:

Scheme 7:

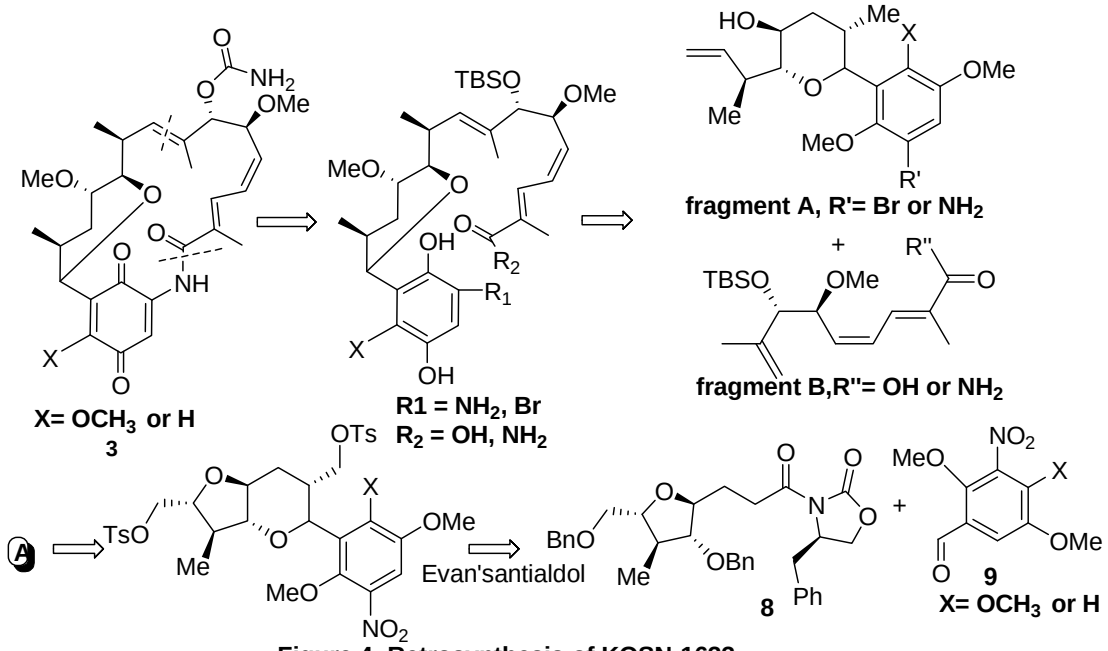
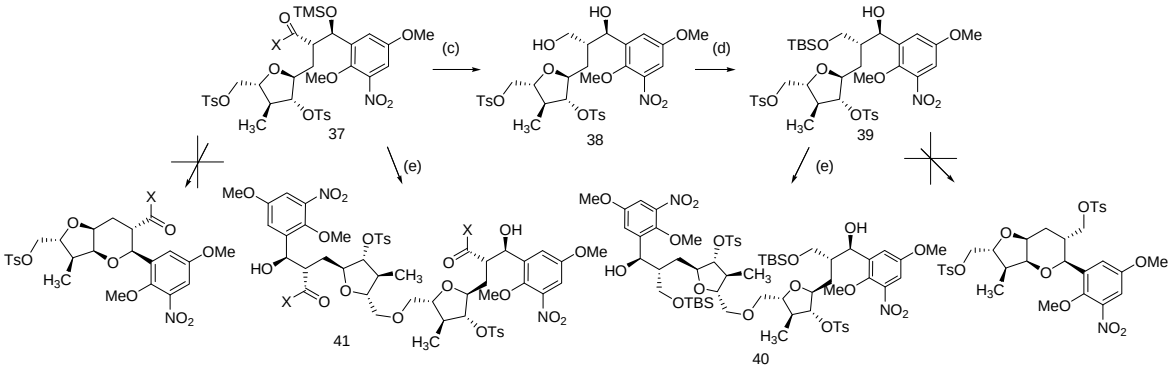


Figure 4: Retrosynthesis of KOSN-1633

As shown in the retrosynthetic scheme the critical fragment A can be prepared via Evan's anti aldol protocol from aldehyde **9** and carbohydrate precursor **8**

Evan's aldol and synthesis of intermediate 5b:

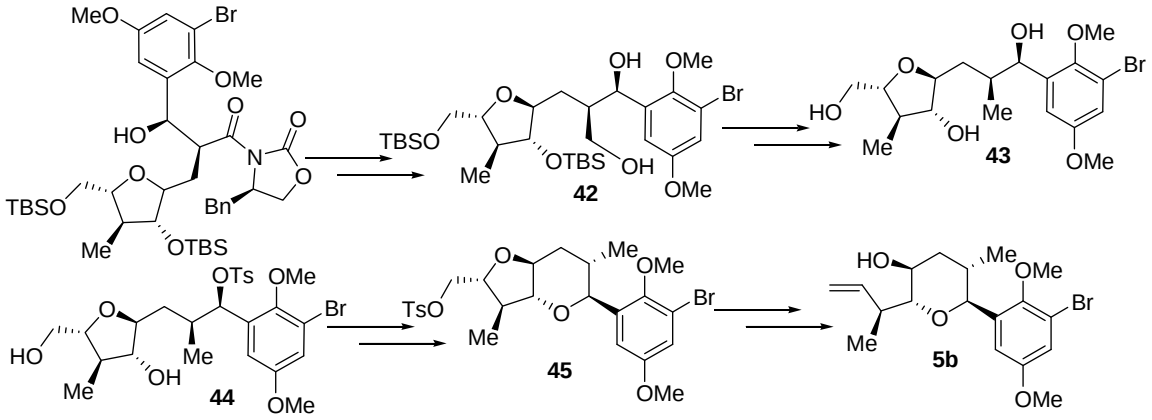
Scheme 8:



The Evan's anti aldol product under heating condition in HMPA to afford dimerized product. Reductive cleavage of the chiral auxillary followed by selective protection which was on heating condition to afford dimerised product **40** not a cyclized product .

Kinetic controlled on Evan's adduct for formation of intermediate 5b:

Scheme 9:



The Evan's anti aldol product on reductive cleavage of the chiral auxillary followed by functional group manipulation to afford compound **43.** this triol compound was selectivily monoprotected followed base catalysed cyclization to afford bicyclic product **45**, which was subsequently manipulated to intermediate **5b**.

Section-I: Towards the total synthesis of Herbimycin A

Section-I: Towards the total synthesis of Herbimycin A

INTRODUCTION :

ANTITUMOR ACTIVITIES:

Richert *et. al.* first found that the protease inhibitor N-a-tosyl-L-lysyl chloromethylketone (TLCK) inhibited $p60^{v\text{-}src}$ and induced the reversion of the cell morphology of avian sarcoma virus-transformed fibroblasts to normal. During the course of searching for natural products converting the morphology of Rous sarcoma virus-infected rat kidney cells to normal, an active constituent produced by Streptomyces sp. (MH237-CF8) was identified as herbimycin A [1], a benzoquinoid anasmycin which had previously been isolated as a herbicide.[2] Two other benzoquinoid ansamycins, macbecin and geldanamycin, were also found to induce the phenotypic change from src-transformed to normal morphologies, and to reduce the intracellular phosphorylation of $p60^{v\text{-}src}$ [3]. The immune complex formed by mixing the herbimycin-A treated cell extracts with monoclonal antibody against $p6O^{v\text{-}src}$ was inactive in vitro as measured by autophosphorylation. However, the immune complex produced from untreated cell extracts was active in vitro in the presence of herbimycin A, suggesting that the benzoquinoid ansamycins might not directly act on the $p60^{src}$ tyrosine kinase *in situ* .[3]

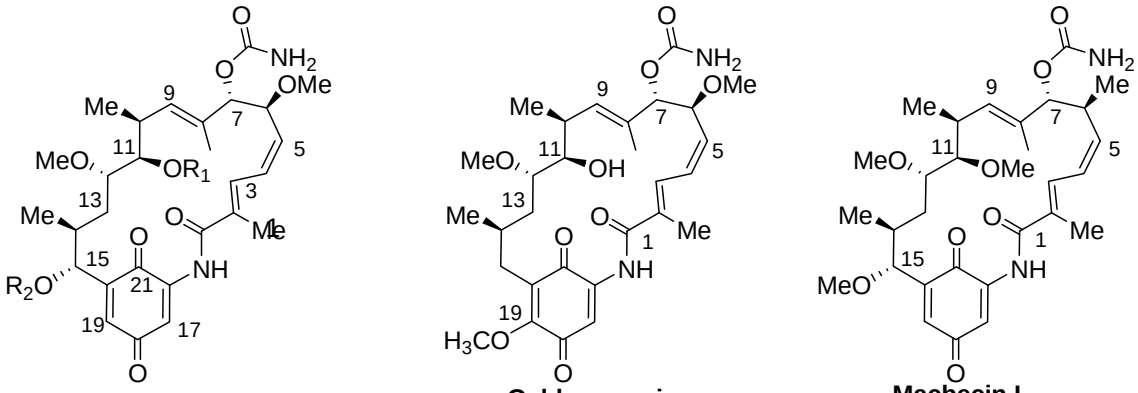


Figure 1. structure of novel natural products, Herbimycin (A-C), Geldanamycin, Macbecin I

In order to further probe the inhibitory specificity of tyrosine kinase oncogenes by herbimycin A, the effectiveness of herbimycin **A** to reverse the morphology of chicken and mammalian cells transformed by various oncogenes was investigated (Table 1).[4,5].

Oncogene	Cell Transformed [a]	Morphological reversion
Src……	NRK	+ +
	NIH/3T3	+ +
	3Y1	+ +
	Field vole	+ +
	DDD	+
Fps.....	3Y1	+ +
abl…….	NIH/3Y3	+
	Balb/c	+ +
raf……	NIH/3Y3	−
K-*ras*……...	NRK	±
H-*ras*……...	NIH/3Y3	−
	3Y1	−
myc…….	3Y1	−
	C3H10T1/2	±
	A431	+

[a]NRK, normal rat kidney; NIH/3Y3, Swiss mouse fibroblast; 3Y1, Fisher rat fibroblast; DDD, mouse fibroblast ascites tumor; Balb/c and C3H10T 1/2 , mouse embryonic fibroblast; A 43, human epidermoid carcinoma

Table1. Effects of Herbimycin A on the Morphology of Mammalian cells Transformed by variousOncogenes.[4]

It was demonstrated that this antibiotic was effective for cells transformed by the PTK oncogenes *src***,** *yes*, *fps***,** *ros***,** *abl*, *erb*B, and was unable to reverse the transformed morphologies induced by the non-PTK oncogenes *ras*, *raf* and *myc*. Herbimycin **A** also caused *src*-expressed cells to become sensitive to contact inhibition but did not affect *ras*-expressing cells.[6] Yamaki *et.al*. [7] found that geldanamycin and herbimycin **A** inhibited the expression of c-*myc* and stimulated the expression of the p53 tumor suppressor gene. Treatment of *src*-transformed cells with herbimycin A resulted in a reduction in the phosphotyrosine content of total cellular proteins, 36K protein phosphorylation, and autophosphorylation of the tyrosine-416 of p60 $^{v\text{-}src}$. [4,8] Measurement of the rate of p60 ^{src} synthesis and degradation showed that herbimycin A accelerated the degradation of p60 ^{src}.[8] In addition, herbimycin A was recently shown to inhibit p60 $^{v\text{-}src}$ irreversibly in an in vitro immune complex kinase assay (IC_{50} = 7 μg/ml). Addition of a sulfhydryl compound

abolished its inhibitory activity.[9] On the contrary, recent studies using the HT-29 human colon adenocarcinoma cell line showed that growth and p60 $^{v\text{-}src}$ inhibition were reversible following removal of herbimycin A .[10]

Induction Of Differentiation:

The human chronic myelogenous leukemic (CML) cell line K562 and leukemic cells of patients with CML with an accompanying chromosomal translocation (t9; 22) express a structurally altered c-*abl* protein (p120$^{c\text{-}abl}$) with elevated tyrosine kinase activity.[11,12] A non-cytotoxic concentration of herbimycin A was found to induce erythroid differentiation of K562 concomitant with a rapid reduction in the tyrosine phosphorylation of p120 $^{c\text{-}abl}$ but not of other human myeloid leukemia cell lines (HL-60, THP-1, and U937). In addition, K562 cells were the most sensitive to the cytotoxic effect of herbimycin A (IC50 = 9.5 x $l0^{-2}$ μM) among the human leukemia cell lines tested (IC_{5o} > 1 μM) .[13] Kondo *et al*. [14] also found that Herbimycin A could induce endoderm differentiation of murine embryonal carcinoma (F9) cells and terminal erythroid differentiation of murine erythroleukemia (MEL) cells. These results suggest that tyrosine phosphorylation may play an important role in the regulation of tumor cell differentiation. A non-toxic concentration of herbimycin A also enhanced the cytotoxicity of adriamycin or 1-β-D-arabinofuranosylcytosine against K562 cells.[13]

Heat shock proteins:

Cancer is a disease characterized by genetic instability. Although identification of novel therapeutic agents via molecular targeting offers the promise of great specificity coupled with reduced systemic toxicity, specific inhibition of individual proteins or signaling pathways faces the potential peril of being subverted by the inherent genetic plasticity of cancer cells. If one assumes that cancer cells are always under moderate to severe stress of one type or another, an approach to this apparent dilemma might be to target the basic machinery that allows cancer cells to adapt so successfully to stress. Cells respond to stress by increasing synthesis of a number of molecular chaperones (also known as heat shock proteins, or Hsps, because they were first observed in cells exposed to elevated temperature).

The heat shock response was first described in 1962 [15], and heat shock proteins (HSPs) are named for their increased synthesis after heat shock that is contrary to the reduced synthesis of most cellular proteins under these conditions. In addition to heat, these proteins are modulated by nutrient deprivation, and oxidative and other stresses where protein denaturation might otherwise occur.[16,17] Many HSPs form multimolecular complexes that act as molecular chaperones binding other proteins, denoted as client proteins. These complexes play a regulatory role in the fate of proteins in several different ways including: folding of proteins in the cytosol, endoplasmic reticulum and mitochondria; intracellular transport of proteins; repair or degradation of proteins partially denatured by exposure to various environmental stresses; control of regulatory proteins; and refolding of misfolded proteins.[18,19] HSPs differ in their cellular localization and functions and mammalian HSPs have been classified into several families according to their molecular size: Hsp90, Hsp70, Hsp60 and Hsp40, and the small HSPs such as Hsp27 [16,17] (Table 2).

Name	Localization	Function
Hsp104	Cytoplasm	Releases proteins from aggregates
Hsp90α,β	Cytoplasm	Prevents protein aggregation, helps protein stabilization and protein trafficking, facilitates activation of many regulated protein
GRP94	Endoplasmic reticulum	Quality control of protein processing in the endoplasmic reticulam.
TRAP/Hsp 75	Mitochondria	Unknown
Hsp70	Cytoplasm	Prevents protein aggregation, helps protein folding
GRP78,BiP	Endoplasmic reticulum	Protein import and folding in the endoplasmic reticulum
Hsp60, chaperonins	Cytoplasm and mitochondria	Prevents protein aggregation, helps protein folding
Hsp40/HDJ2	Cytoplasm	Helps protein folding as a co-chaperone of Hsp70
Hsp27	Cytoplasm	Prevents protein aggregation, may have role in cell growth and differentiation.

Table 2: The name, localization and function of some of the better characterized heat shock proteins.

Hsp90:

Hsp90 is one of the most abundant cellular chaperone proteins. It functions in a multi-component complex of chaperone proteins that may include p60/Hop, $p50^{cdc37}$, Hsp40/HDJ2, p23, Hsp70 and one of a variety immunophilins.[18,19] It accounts for 1–2% of total protein in unstressed cells and increases to 4–6% of cellular proteins under stress. Unlike other chaperones, Hsp90 distinguishes itself in that most of its known clients are protein kinases or transcription factors involved in signal transduction (Table 2).[18,19,20]

These include ligand-dependent transcription factors such as steroid hormone receptors, ligand-independent transcription factors such as *Myo*D, tyrosine kinases such as $p185^{erbB2}$ (Her-2/neu), serine/ threonine kinases such as *Cdk*-4 and *Raf*-1, and mutant transcription factors such as p53.

In humans, there are two Hsp90 isoforms in the cytosol, Hsp90α and Hsp90β. These proteins are closely related. They are both induced by stress and no differences in their activities have been identified.[21] Hsp90 is a phosphorylated homodimer containing two to three covalently bound phosphate molecules on each monomer. Hsp90 contains a highly conserved ATP binding domain near its N-terminus and the chaperoning activity of Hsp90 requires both the binding and hydrolysis of ATP at this site.[22-24] A second nucleotide binding site appears to be present near the C-terminus, but this is less well characterized.[25-27] The C-terminus is also the main region for dimer interaction and for the binding of $p60^{HOP}$ and immunophilins. The binding of ATP at the N-terminal site alters the conformational state of Hsp90 and affects its interactions with client proteins and co-chaperones. Benzoquinone Ansamycin members compete with ATP/ADP in the nucleotide binding pocket, resulting in disruption of the Hsp90 function and degradation of Hsp90 client proteins by the ubiquitin-dependent proteasome pathway .[28,29]

Molecular chaperones are proteins that are responsible for maintaining the correct folding, function and stability of client proteins. Of these, heat shock protein 90 (Hsp90) has recently emerged as a focus of interest because of its role in regulating proteins that are responsible for malignant transformation

Regulation of Hsp90 function:

Functional analysis has revealed that the amino and carboxyl termini of Hsp90 are separated by a charged region. The dynamic interrelationship of these domains,

coordinated by nucleotide and co-chaperone binding, determines the conformation of the chaperone and, thus, its activation state. Association of Hsp90 with client proteins is regulated by the activity of the N-terminal ATPase domain, which binds and hydrolyses ATP to mediate a series of association–dissociation cycles between Hsp90 and client substrates. The activity of Hsp90 is further regulated by binding of co-chaperones, which promote the interconversion of the ATP- and ADP-bound states and modulate the formation of client-specific complexes.[31-33] Recent evidence suggests that in several tumor cell lines, Hsp90 might be exclusively complexed with co-chaperones in a state of high affinity for ATP/ADP or ligands of this regulatory pocket (i.e. ATPase inhibitor drugs), whereas in normal tissues, Hsp90 might exist primarily in a latent, uncomplexed, low affinity state.[34,35] Although no direct experimental evidence has yet been presented, post-translational modifications of Hsp90 might also regulate the 'activation' state of Hsp90 complexes. Overall, these observations suggest that Hsp90 is present in cells in equilibrium between a low chaperoning activity 'latent state' and an 'activated state', with increased chaperoning efficiency (see Figure 2). The shift in equilibrium might be dictated by the amount of 'stress' on the system, such as mutated and dysregulated proteins, hypoxia or a low nutrient concentration environment. Thus, the effects of inhibiting Hsp90 function could depend more on the 'activity' and degree of involvement of the co-chaperone–protein–Hsp90 complexes and less on its cellular levels. Collectively, the above data suggest that Hsp90 inhibitor concentrations can be identified that will disrupt crucial chaperone functions in a transformed cell but that might not be toxic to normal cells.

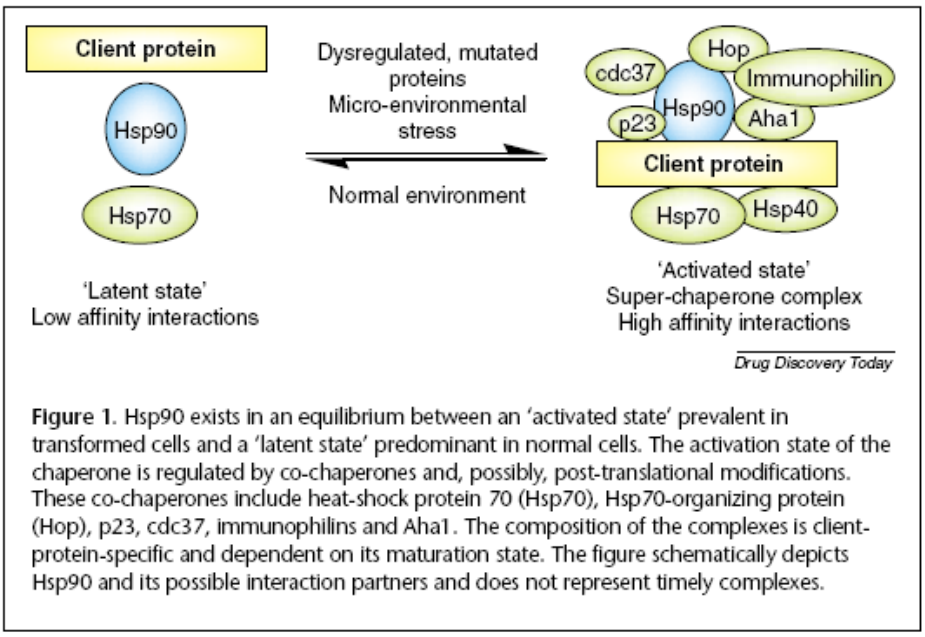


Figure 1. Hsp90 exists in an equilibrium between an 'activated state' prevalent in transformed cells and a 'latent state' predominant in normal cells. The activation state of the chaperone is regulated by co-chaperones and, possibly, post-translational modifications. These co-chaperones include heat-shock protein 70 (Hsp70), Hsp70-organizing protein (Hop), p23, cdc37, immunophilins and Aha1. The composition of the complexes is client-protein-specific and dependent on its maturation state. The figure schematically depicts Hsp90 and its possible interaction partners and does not represent timely complexes.

Identification of Hsp90 as a Target for Geldanamycin and Herbimycin:

v-Src is a tyrosine specific kinase that is involved in several signal transduction pathways that regulate cell growth and proliferation.[36] Geldanamycin (GDA, Fig. 1) and Herbimycin (HB) were shown to abolish Src kinase activity in whole cell assays,[37] but were unable to directly inhibit the kinase activity of the purified recombinant protein.[38] It was hypothesized that GDA and HB were inhibiting Src kinase activity indirectly by binding to a Src associating protein and thereby abolishing Src's activity in vivo. To identify this putative protein, Whitesell and Neckers[39] conducted an affinity isolation experiment using GDA immobilized on agarose beads. The beads were incubated with reticulocyte lysate, and a 90 kDa protein was isolated and shown to be specific for GDA binding. The protein identified was Hsp90. Upon further evaluation, these researchers demonstrated that Src protein levels decreased as the concentration of GDA was increased, which strongly correlated with the decrease in Src kinase activity previously observed in whole cell assays. Evidence gathered from this early experiment suggested that Hsp90 was interacting with Src and inhibition of Hsp90 by GDA disrupted its chaperone function for the maturation of not only Src but also other newly synthesized kinases. It was proposed that GDA could serve as a tool for studying other Hsp90-

dependent maturation processes. Since this seminal study, many researchers have sought to identify additional Hsp90 substrates by the use of GDA, which has led to elucidation of more than 100 Hsp90-dependent client proteins and partial characterization of the Hsp90-mediated protein folding process.

The Hsp90-Mediated Protein Folding Process:

Double-stranded DNA is transcribed into messenger RNA, which is then translated by the ribosome into single-stranded polypeptides containing the encoded amino acids. When nascent polypeptides exit the ribosome, the amino acid side chains have potential to interact with one another and cause aggregation, unless other proteins are present to prevent this process. Aggregation is prevented by the expression of chaperones, which bind to newly formed peptides and prevent deleterious interactions. In addition to their role as protein stabilizers, chaperones also facilitate the folding of nascent polypeptides into biologically active three-dimensional structures. As a result of their key role of transforming linear peptides into tertiary and quaternary structures, chaperones are considered essential for the second half of the genetic code.[40]

Cellular stresses, such as elevated temperatures, abnormal pH, nutrient unavailability, and malignancy, result in the denaturation of folded proteins as well as the increased synthesis of new proteins. Under these conditions, heat shock proteins (Hsps) are overexpressed to refold denatured proteins back into their biologically active conformation.[41–43] Some Hsps such as Hsp90 are expressed under normal conditions, but upon exposure to cellular stress they are overexpressed to assist in this renaturation process.[44] Thus, Hsps act as buffers to minimize the number of misfolded proteins and maximize the amount of functional proteins. Any alteration in this buffering capacity can have devastating effects on cell viability.[45,46]

The Hsp90-mediated protein folding pathway has not been fully resolved, but evidence suggests that a variety of co-chaperones, immunophilins, and partner proteins are involved in the conformational maturation of nascent polypeptides into biologically active native structures (Fig. 2). Hsp70 binds to and stabilizes newly synthesized proteins co-translationally or post translationally in an ATP- and Hsp40-dependent reaction to prevent aggregation.[40] Hsp70/ADP–protein complexes can be stabilized by the binding of

HIP (Hsp70 interacting protein) or dissociated by the interaction of BAG homologs, which stimulate exchange of ATP for ADP and polypeptide release. Hsp70–protein complexes then bind HOP (Hsp70-Hsp90 organizing protein). HOP contains highly conserved tetratricopeptide repeats (TPRs)[47,48] that are recognized by both Hsp70 and Hsp90, promoting the union of Hsp70–protein complexes and Hsp90 (2.1, Fig. 2).[49] In the case of telomerase[50] and steroid hormone receptors,[51] the client protein is transferred from the Hsp70 system to the Hsp90 homodimer (**2.2**) with concomitant release of Hsp70, HIP, and HOP. At this stage, co-chaperones and partner proteins in concert with immunophilins providing cis/trans peptidylprolyl-isomerase activity (FKBP51, FKBP-52, or CyP-40),[52,53] or protein phosphatase 5 bind to form a heteroprotein complex.

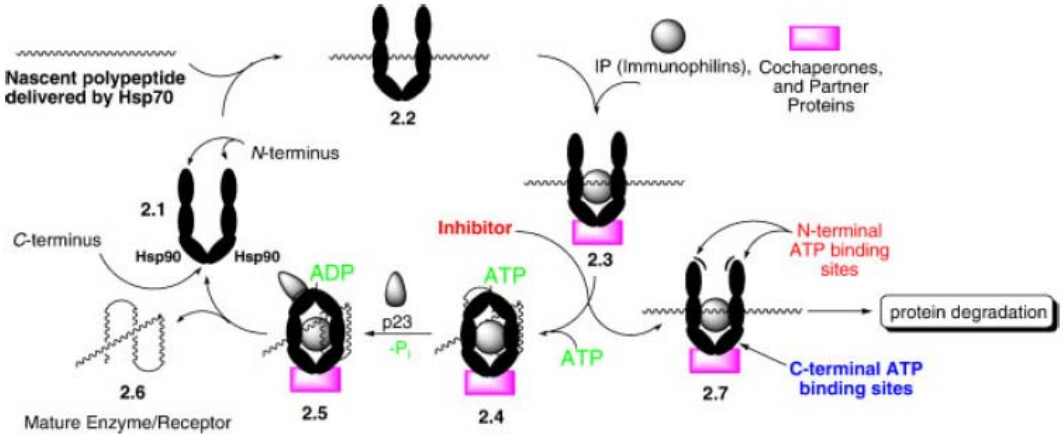


Figure3. The Hsp90-mediated protein folding process

(**2.3**). The activated multiprotein complex binds ATP to the N-terminus of Hsp90, and the ATPdependent dimerization of the N-terminal domains results in the ‘‘clamping’’ of Hsp90 around the bound client protein (**2.4**).[54,55] The proto-oncogenic protein Cdc37 is present in Hsp90 complexes containing protein kinase clients, but rather than being released, it remains associated with the kinase client after Hsp90’s ATP-dependent N-terminal clamping.[56] The co-chaperone p23 is also recruited to Hsp90 at this stage, which promotesATP hydrolysis and stabilization of Hsp90’s ‘‘clamped’’ highaffinity client-bound conformation (**2.5**). The ensemble of Hsp90 and its cohorts promote the folding of the bound client into its three-dimensional structure, and subsequently release the protein (**2.6**) through an as yet uncharacterized process that appears to be stimulated by p23.[57]

The model represented above reflects a simplified account of the Hsp90 protein folding process; however, it should be pointed out that more than 20 associated proteins have been shown to be involved in some aspect of the maturation process for various client proteins.

Hsp90 expression is upregulated in tumor cells[58,59] and mutational analyses of Hsp90 havedemonstrated eukaryotic organisms to be dependent upon Hsp90 for survival. Moreover, cancer cells have been shown to be particularly sensitive to molecules that inhibit Hsp90 function.[60] Consequently, Hsp90 has emerged as an exciting target for the development of cancer chemotherapeutics. Most inhibitors of Hsp90 exert their activity by binding to the N-terminal ATP binding pocket and inhibiting Hsp90's ATPase activity. The energy normally derived from ATP hydrolysis is used to elicit a conformational change within Hsp90 that clamps Hsp90 around the bound client protein, and facilitates proper folding of the protein substrate. However, when a non-hydrolyzable inhibitor is present, Hsp90 is unable to clamp around the bound client protein, which usually results in ubiquitination of the protein substrate and subsequent proteasome-mediated hydrolysis of the client.[61] In addition, some Hsp90-dependent proteins such as erbB2, telomerase, and constitutively activated forms of Hck, Lck, and v-SRC are unstable in their mature conformation. These proteins require Hsp90 function to maintain their active conformation, and inhibition of Hsp90 stimulates their rate of turnover.

Proteins that rely on Hsp90 for stability, such as erbB2, are generally degraded much more rapidly (~2 hr) than those that interact with Hsp90 transiently during conformational maturation such as AKT, which requires ≥24 hr before knockdown of the client protein is observed.[62] GDA-induced depletion of protein kinases, which require Hsp90 during their initial maturation, is primarily because of the rapid turnover of nascent kinase chains that are unable to properly fold.

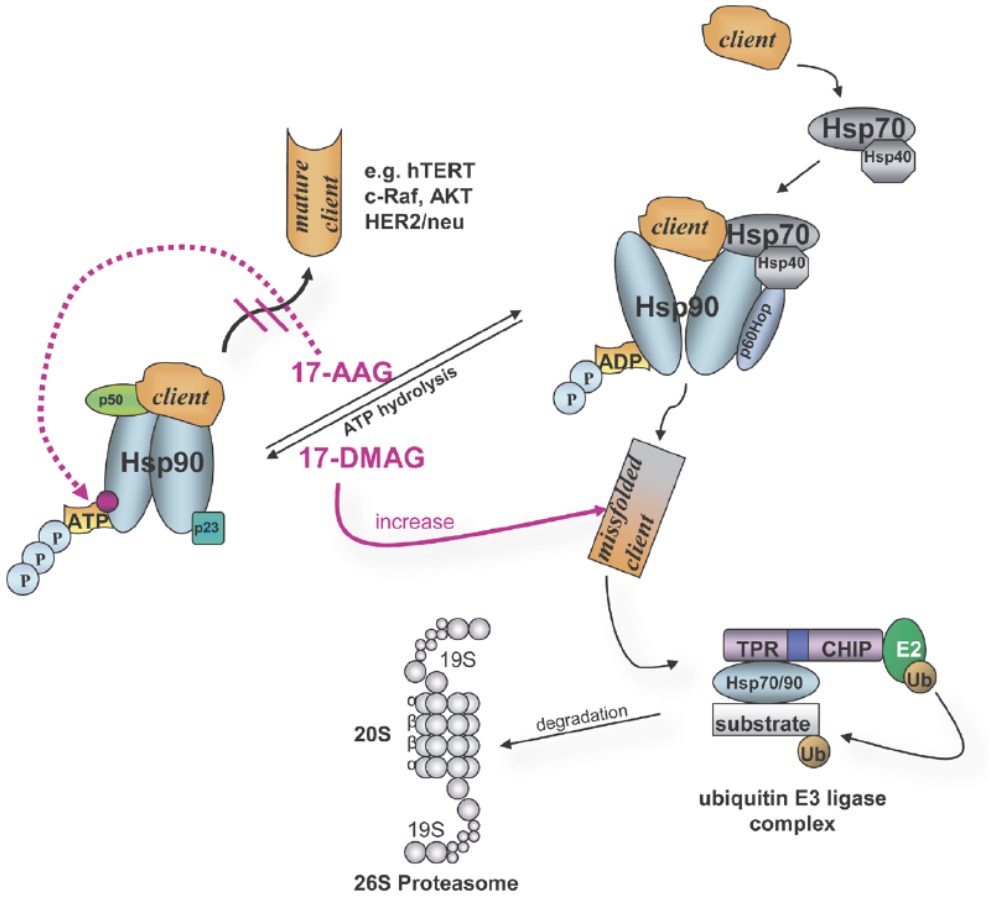


Figure4: Proposed mechanism of Hsp90-mediated activation, its inhibition by geldanamycin, and protein degradation in the U-PS. The Ubiquitin-proteasome system is exemplified by the U-box E3 ubiquitin ligase CHIP, which is complexed with a chaperone bound substrate and an E2ubiquitin conjugating enzyme. An important substrate of CHIP is the oncogenic growth factor receptor HER2. After ubiquitin-tagging substrates are degraded in the 26S proteasome. The proteasome consists of a catalytic core 20S, and two 19S regulatory units. Hsp90, heat shock protein 90; Hsp70, heat shock protein 70; Hsp40, heat shock protein 40; p50cdc 37, heat shock protein 90 binding protein ;23, Hsp binding protein; TRP, tetratrico peptide repeat, a protein domain that binds Hsp90; CHIP, carboxyl terminus of Hsc70-interacting protein= U-box type E3 UBIQUITIN LIGASE; Ub, ubiquitin; ATP, adenosine triphosphate; Raf-1, HER2/NEU, AKT and hTERT are Hsp90 client proteins.

INHIBITORS OF THE *N* –TERMINAL ATP BINDING DOMAIN:

Originally, GDA was believed to be a peptide mimic of a protein substrate bound to Hsp90 when the first co-crystal structure was solved.[63] Although this interpretation was later determined incorrect, key interactions between GDAand bovine Hsp90 were

observed, and subsequent studies by Pearl and co-workers[64] with yeast Hsp90 confirmed that GDA was binding to an ATP binding pocket in the N-terminus of Hsp90.[64] Confusion over the presence of an ATP binding pocket was the result of mammalian Hsp90's low ATPase activity,[65] which was not observed prior to solution of the first cocrystal structure. [64] Later studies confirmed that mammalian Hsp90 did in fact have inherent ATPase activity, albeit a low rate of hydrolysis.[66] The yeast homolog, Hsp82, produces a substantially higher rate of enzyme-catalyzed hydrolysis[67] and consequently has been used for high-throughput screening to identify new Hsp90 inhibitors that decrease Hsp90's inherent ATPase activity.

Geldanamycin and Radicicol Bind to the Hsp90 N-Terminal ATP Binding Domain:

Although the entire three-dimensional structure of Hsp90 remains unknown, the N-terminal ATP binding pocket was found to have strong similarity to the ATP binding region of DNA gyrase,[68,69] based upon the ''compacted'' conformation of the bound nucleotide diphosphate and complimentary amino acids. The highly conserved N-terminal region of Hsp90 contains an ATP binding motif, which is unique compared to other ATP-dependent enzymes because ATP is bound to Hsp90 in a bent conformation as opposed to the typical extended conformation (Fig. 5).[64,70] Only eukaryotic enzymes MutL[71] and histidine kinase[72] are known to bind ATP in this manner. In addition, type II

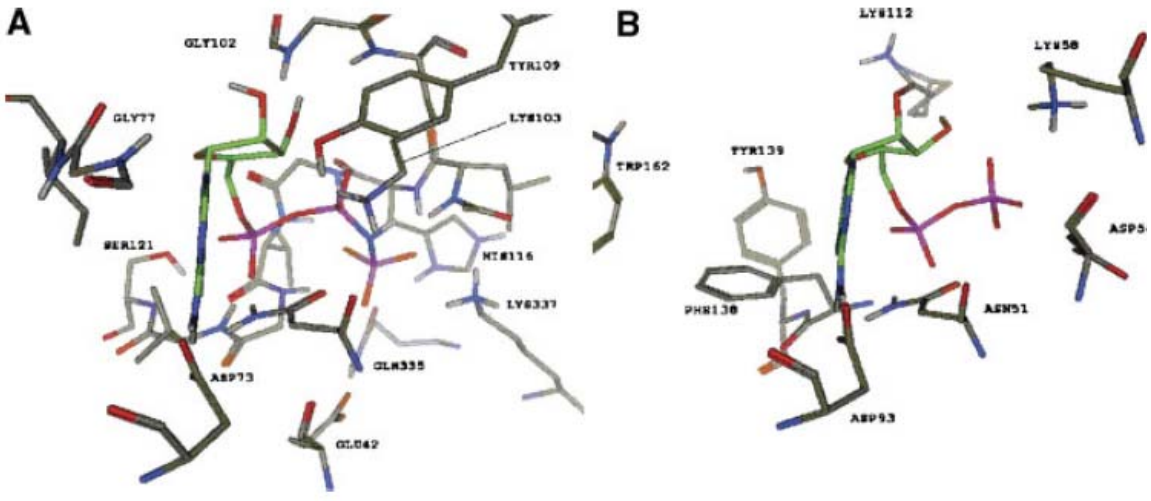


Figure 5 A: Co-crystal structure of ADPNP(green) bound to DNA gyrase. B: Co-crystal structure of ADP(green) bound to the Hsp90 *N*-terminal domain.

topoisomerases (DNA gyrase)[73] found in bacteria also bind ATP in this bent conformation(Fig. 3A).[65] The co-crystal structure of GDA bound to yeast Hsp90 revealed the Guinine moiety of GDA to occupy the phosphate region of the binding pocket and to facilitate five hydrogen bonding interactions with the protein (Fig. 4A).[64] Another compound, radicicol (RDC), was also found to be an Hsp90 inhibitor,[74] and when the co-crystal structure of this molecule bound to yeast Hsp90 was solved (Fig. 4B),[64] it was observed that the resorcinol ring of RDC did not bind to the diphosphatebinding region. Instead, the 2,4-diphenol occupied the region that normally bound the adenine ring of ATP, producing three important hydrogen-bonding interactions with the binding pocket. In contrast to the Guinine ring ofGDA, only one hydrogen bond was formed between the oxirane of radicicol and the peptide pocket. Pearl and co-workers determined the Kd of GDA and RDC to be 1,200 and 19 nM, respectively.[64] Data obtained from isothermal titration calorimetry showed that binding of GDA to Hsp90 resulted in an entropic penalty, whereas binding of RDC elicited a favorable entropic change. The entropic penalty exhibited by GDA is believed to result from the bending of GDA in the active site which is distorted from that of GDA in its native crystallographic form.[75,76] In contrast, RDC binds in the same conformation as its native crystal structure.[77]

Geldanamycin Derivatives:

The co-crystal structure of GDA bound to Hsp90 suggested that the 17-methoxy group pointed away from the chaperone's binding pocket and that modification of this molecule at the 17-position would likely have little effect on the binding of GDA to Hsp90. This fortuitous observation paved theway for the development of two GDA analogs that are currently in clinical trials. Although GDA produced promising biological responses in a number of cancer cell lines, this molecule was found to produce toxicity unrelated to Hsp90 inhibition.[78] Additionally, GDA was poorly water soluble and new derivatives of GDAwere difficult to prepare since the total synthesis of this natural product had not yet been reported. Studies by Dikalov and co-workers [79] showed that GDAwas a substrate for flavin-dependent reductases and upon incubation with these enzymes, the GDAquinone was transformed into a semiquinone. Semiquinones are known to react with molecular oxygen to produce superoxide radicals that can cause

toxicity or even cell death in a mechanism completely independent of Hsp90 inhibition.[80] In order to stabilize the quinone and reduce its redox-active potential, investigators incorporated stronger electron-donating groups into the 17-position of GDA. Derivatives of GDAwere prepared

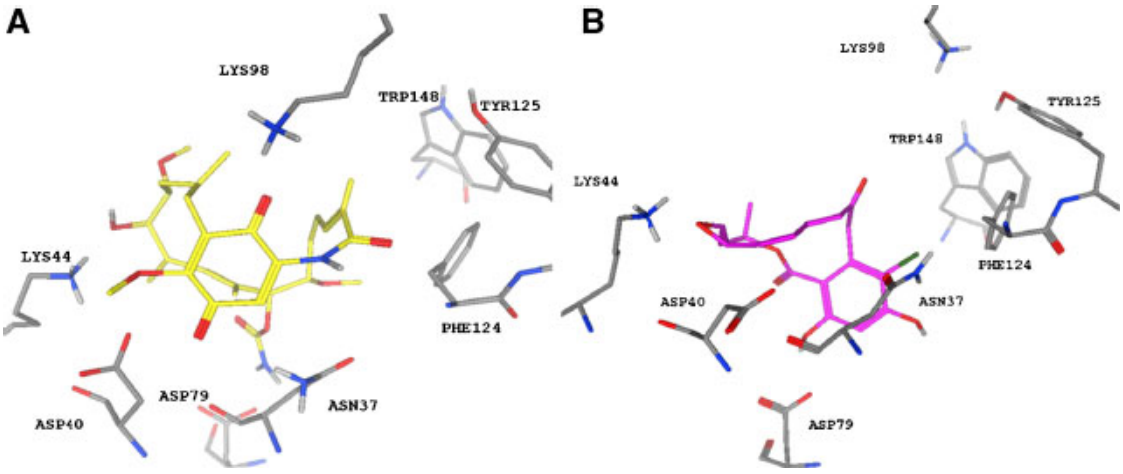


Figure 6 : Co-crystal structure of GDA (yellow) and radicicol (RDC) (magenta) bound to yeast Hsp90.

and evaluated in several murine xenograft models to determine that 17-allylamino-17-desmethoxygeldanamycin (17-AAG, Fig. 5) behaved significantly better than GDA.[81] However, this molecule still produces hepatotoxicity and has serious formulation difficulties.[82] Initial clinical studies with 17-AAG have been very promising and early data suggests that Hsp90 inhibitors can be administered without severely compromising the patients health by undesired side effects.[83,84] Additional derivatives of GDA incorporating various linkers and attachments to the 17-position were recently reported by scientists at Conforma Therapeutics, but no in vivo data has been reported.[85] Researchers at Kosan Biosciences hoped to improve the solubility of 17-AAG by incorporation of an extra tertiary amine, which led to the development of 17-desmethoxy-17-N,N-dimethylaminoethylaminogeldanamycin (17-DMAG, Fig. 5). 17-DMAG has demonstrated activity against mouse-human xenografts, and is reported to be more potent and more soluble than 17-AAG with excellent oral bioavailability.[86] Clinical studies with 17-DMAG are currently underway and preliminary results are expected in the very near future.

Development of second generation Hsp90 inhibitors:

On the basis of more recent clinical experience, the limited efficacy observed in the initial phase 1 trials of 17AAG was probably due to a lack of patient enrichment for those most likely to benefit and suboptimal target inhibition due to the requirement for intravenous dosing and the off-target toxicities of 17AAG and its DMSO formulation. These findings have catalyzed future efforts directed at both improving the delivery of 17AAG and identifying novel scaffolds with improved pharmacologic and toxicity profiles.

17-AAG and 17-DMAG Binding Studies:

One of the most intriguing observations made by researchers who solved the first co-crystal structure of GDA bound to Hsp90 was the fact that the amide bond resided in the cis-orientation[63] and that GDA did not bind Hsp90 in a conformation similar to its native crystal structure.[75,76] Instead, GDA bound to Hsp90 in a ‘‘cup’’ shaped conformation that projected the carbamate and quinone ring away from the apex of the bound molecule (Fig. 6). In its native crystalline state, GDA is found in an extended and relatively planar conformation containing a trans amide bond.[75]

Computational studies by researchers atKosan Biosciences suggested that uponGDAbinding to Hsp90, the quinone ring is folded over to fit into the phosphate binding site, which then stimulates isomerization of the amide bond from *trans* to *cis*.[82] Based on these studies, they suggested that a GDA analog containing a predisposed cis-amide bond in the ground state would result in a cup shaped molecule that could more easily bind to the open form of Hsp90 without substantial energy loss resulting from isomerization of the amide bond. They propose that a molecule containing a conformationally biased cis-amide bond could enhance Hsp90 binding more than 1,000-fold. Subsequent computational and experimental studies by researchers at the National Institutes of Health led to identification of two amino acids that are in close proximity to the amide bond and are believed to be responsible for Hsp90-catalyzed isomerization of GDA’s amide bond.[87] In these studies, they mutated Lys112 and Ser113 to alanine, and determined whether GDA could displace Hsp90 immobilized on an ATP-Sepharose column. The rationale for these two mutants is based on the hypothesis that both Lys112 and Ser113 can hydrogen bond with the amide oxygen of trans-GDA.

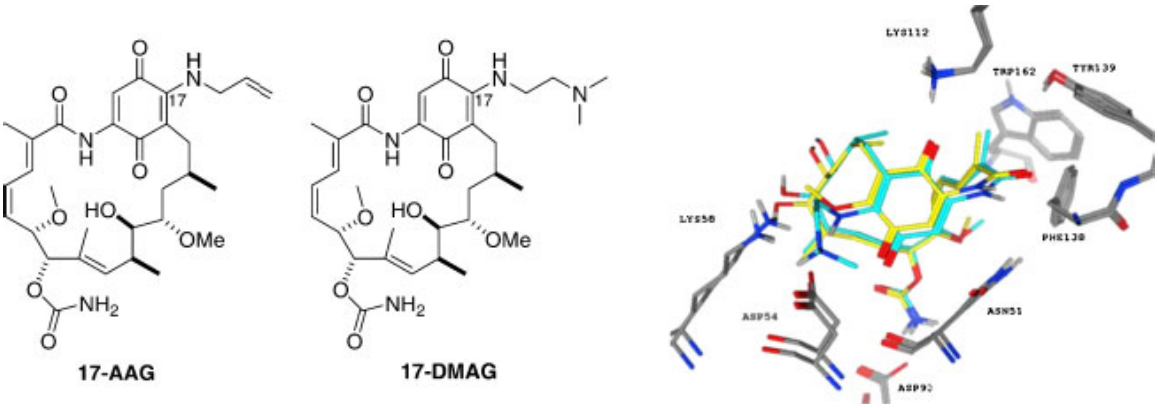


Figure 7: The chemical structuresof17-AAG and DMAG. Superimposed co-crystal structures of 17-DMAG (cyan) and GDA (yellow) bound to human Hsp90.

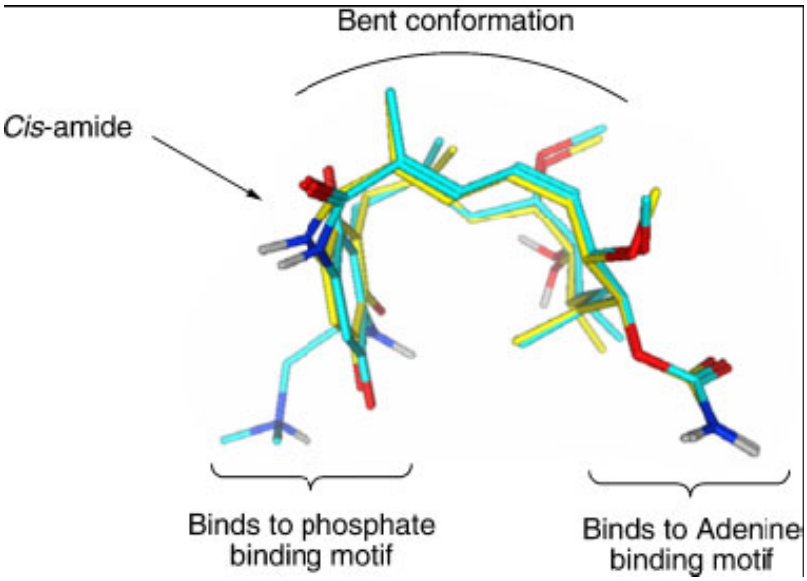


Figure 8: Superimposed bound conformations of 17-DMAG (teal) and GDA (yellow).

and that isomerization occurs through a mechanism similar to keto-enol tautomerization. Binding studies confirmed that GDA had low affinity for the Hsp90 S113A mutant, whereas radicicol could bind with equal affinity when compared to the wild-type chaperone. It is proposed that in the normal Hsp90-catalyzed reaction with ATP that both Lys112 and Ser113 bind to the a-phosphate of ATP and act as a ‘‘gatekeeper’’ to restrict access to particular conformations of ATP into the Hsp90 binding pocket.

Application of Hsp90 inhibitors in the treatment of cancer patients :

Though useful as biologic probes for studying the role of Hsp90 in mediating transformation, the natural products Geldanamycin (GDA) and radicicol (RD) have several pharmacologic limitations, including poor solubility, limited in vivo stability, and off-target toxicities that have precluded their use as drugs.[88] GDA proved too toxic for human use [89] but 17-AAG, a carbon-17 substituted derivative, retains activity against Hsp90 but with a more favorable toxicity profile.[90] 17-AAG entered human clinical testing in 1999 and has been evaluated in phase 1 trials using weekly, twice weekly (days 1, 4), daily x5 (21 day cycle), and daily x3 (14 day cycle) schedules.[91-95] In these trials, the toxicity of 17-AAG was dose dependent and schedule dependent with hepatic toxicity being more prominent with daily administration schedules. 17-AAG has limited solubility and, therefore, in order to formulate this drug for human use, the Cancer Therapy Evaluation Program (CTEP) that sponsored the initial phase 1 trials developed a dimethyl sulfoxide (DMSO), egg-phospholipid vehicle. Notably, many of the toxicities (anorexia, odor) observed in the phase 1 setting were probably attributable to the DMSO in this formulation. Pharmacokinetic studies incorporated into these phase 1 trials suggest that serum concentrations significantly greater than those required for depletion of Hsp90 clients in cell culture and xenograft model systems could be achieved with acceptable toxicity. Peripheral blood mononuclear cell studies and limited tumor biopsies showing degradation of Raf-1 and upregulation of Hsp70 suggest that at least partial target modulation was achieved.[91-95] However, minimal efficacy (primarily stable disease in melanoma, renal, and prostate cancers) was observed in the phase 1 trials and no patients in these trials achieved either a complete or partial response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Notably, these phase 1 trials were not enriched with those patients predicted by the preclinical experience to be most likely to respond (for example, patients with HER2-amplified breast cancer).[95]

Drug	Sponsor	Adminstration	Status
17AAG (DMSO/EPL formulation)	NCI/Kosan	Intravenous	Phase 1/2
KOS-953 17AAG, tanespimycin)	Kosan	Intravenous	Phase 1/2
CNF-1010 (17AAG)	Biogen Idec	Intravenous	Phase 1
IPI-504	Infinity	Intravenous	Phase 1
KOS-1022 (17DMAG, alvespimycin)	Kosan	Intravenous	Phase 1
KOS-1022 (17DMAG, alvespimycin)	Kosan	Oral	Phase 1
CNF-2024	Biogen Idec	Oral	Phase 1
SNX-5422	serenex	Oral	Phase 1

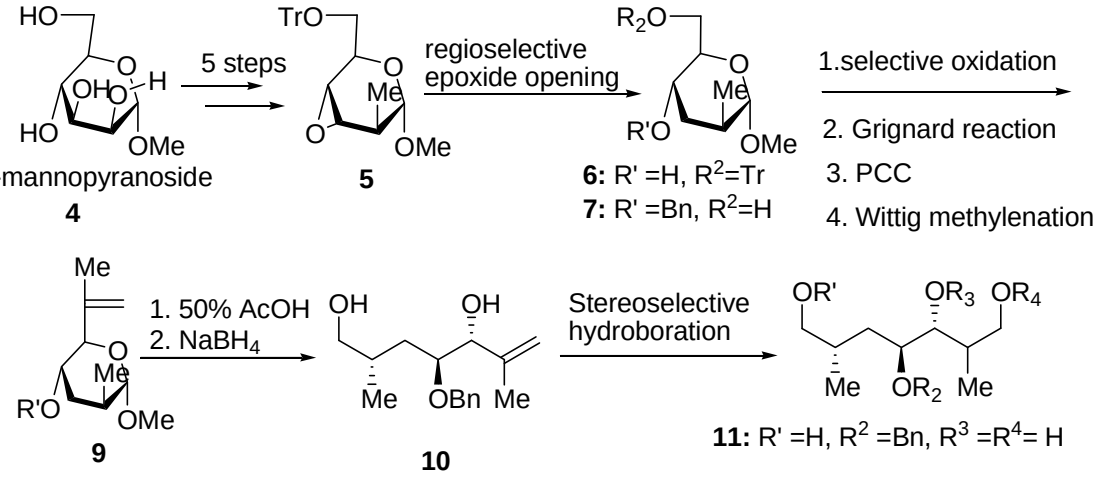
Table 3: Hsp90 inhibitor trials in cancer

Previous synthesis:

Kuniaki Tatsuta. *et.al.* approach for the total synthesis of Herbimycin

A: First total synthesis of Herbimycin A was reported by Kuniaki Tatsuta *et.al*. in 1991;[96] by assembling ansa fragment **2** lithiated chellated controlled with aryl aldehydes **3**, in which the ansa fragment was prepared from methyl α- D -mannopyranoside **4**.

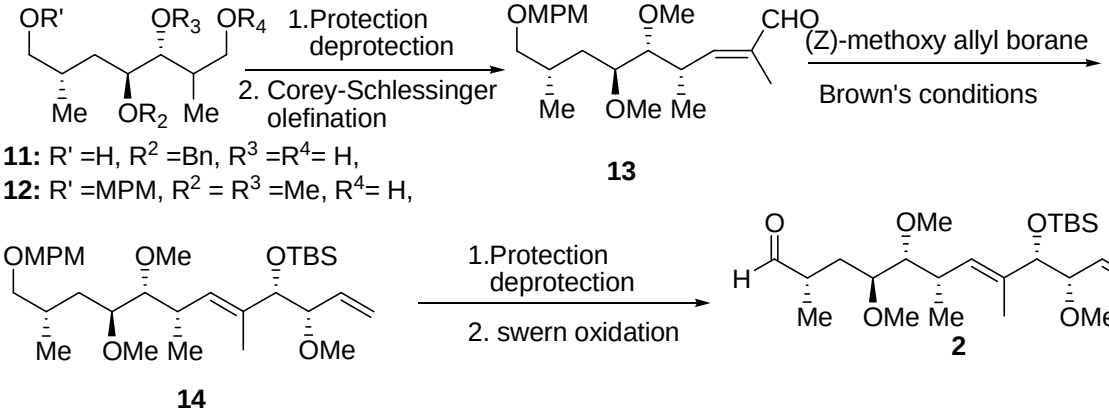
Scheme 1



The epoxide **5** was prepared from methyl–D-mannopyranoside in five steps sequence. The crucial step for the synthesis for ansa chain was the regioselective epoxide-ring opening by using disiamylborane-$NaBH_4$ system which gave regioisomers in required isomers 6:1 in ratio. After benzylation of free hydroxyl, de-*O*-tritylation gave primaryalcohol **7**, which on swern oxidation and Grignard reaction (MeMgBr, -78 ^{o}C) in one pot and subsequent oxidation gave the methyl ketone.

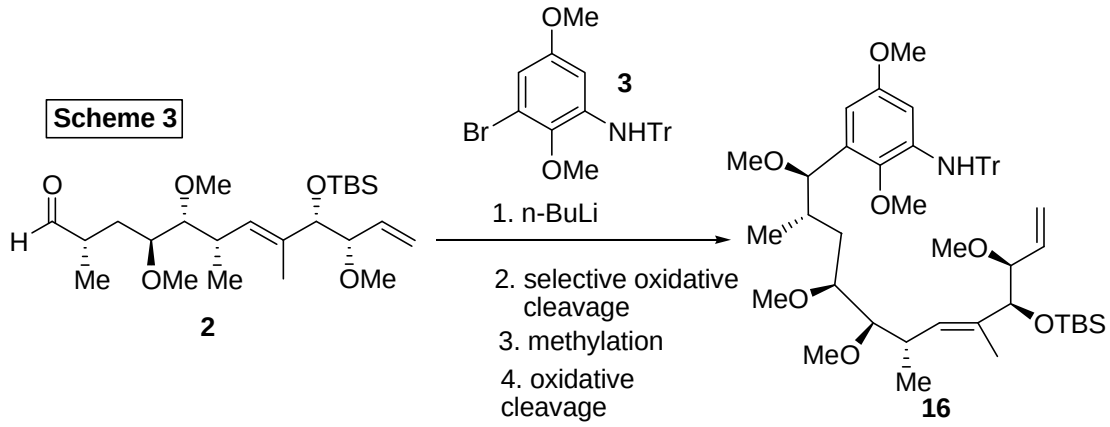
After Wittig methylation of methyl ketone, the resulting Olefin-**9** underwent smooth hydolysis and reduction to afford diol **10**. The diol **10** was stereoselectively hydroborated to afford required triol **11** in 83% along with 16 % yield of the C10 epimer (Scheme 1). After benzylidenation of resulting triol was transformed into **12** in a regular protection deprotection sequence followed by Dess-Martin oxidation to provide the C9-aldehyde, which was subjected to the Corey-Schlessinge olefination conditions followed by oxalic acid work up to give the (E)-unsaturated aldehyde **13**.

Scheme 2

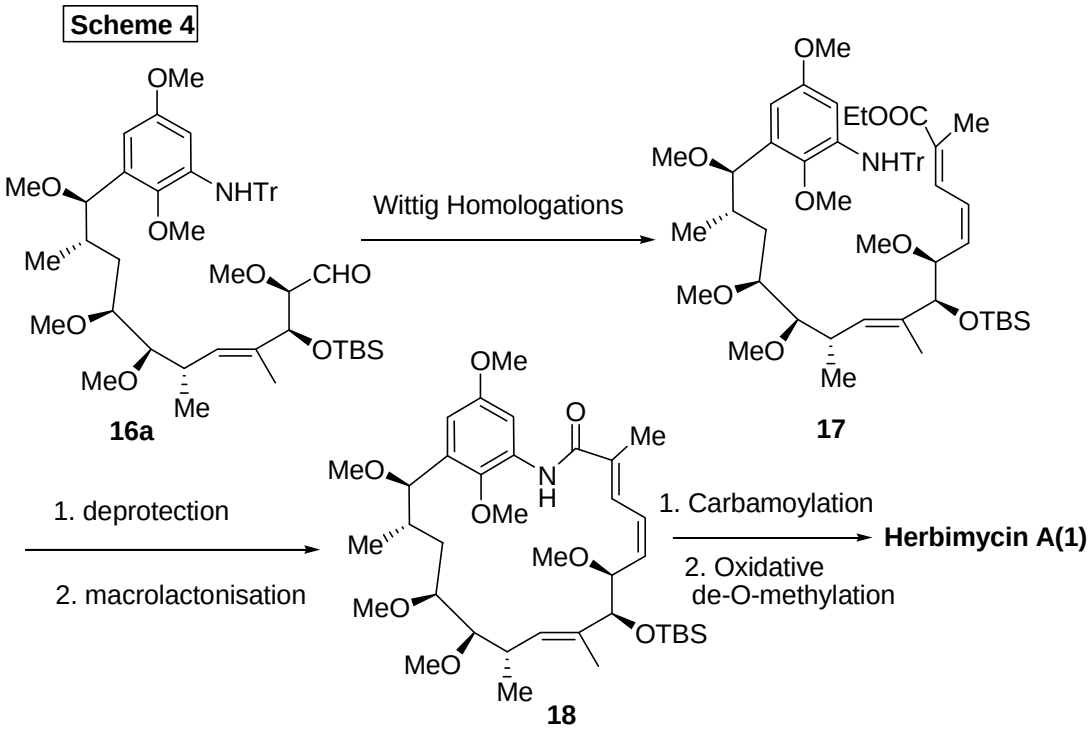


The compound having the correct C6/C7 steoreocenter was envisioned to be available through the addition of γ-alkoxyallyl organometallic reagent to aldehyde **13** under Brown's conditions to give desired **14** in 76% yield along with the separable diastereomeric syn-diol (13%). The synthesis of the required ansa-chain aldehyde **2** was completed by protection deprotection and subsequent oxidation (Scheme 2).

Scheme 3



The coupling of the above aldehyde **2** and the aromatic chromophore **3** was achieved by addition of **2** to the lithiated reagent prepared from **3** and *n*-BuLi to produce the desired coupling product-**16** (70%) along with the undesired C15-epimer (17) (Scheme 3).

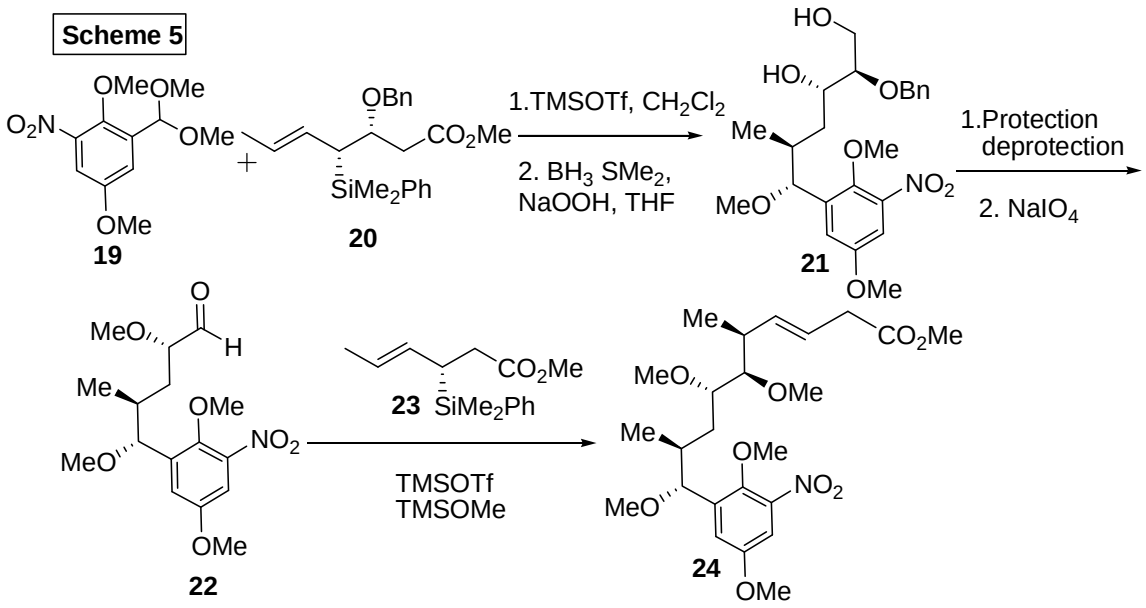


O-Methylation of desired couplied product-**16** followed by selective oxidative cleavage of olefin to afford the C5-aldehyde **16a** which was transfored to the target Herbimycin A by Still's olefination and a subsequent three step sequence 1. DIBAL reduction 2) PDC oxidation. 3) three carbon wittig olefination to afford **17**. Exposure of **17** to acidic and basic conditions to furnish the amino acid, which was on cyclized in a mixed anhydride way to produce 19-membered macrolactum **18**. Finally, deprotection protection subsequent oxidative de-o-methylation gave the target molecule (Herbimycin A) (Scheme 4).

James S. Panek. *et.al.* approach for the total synthesis of Herbimycin A:

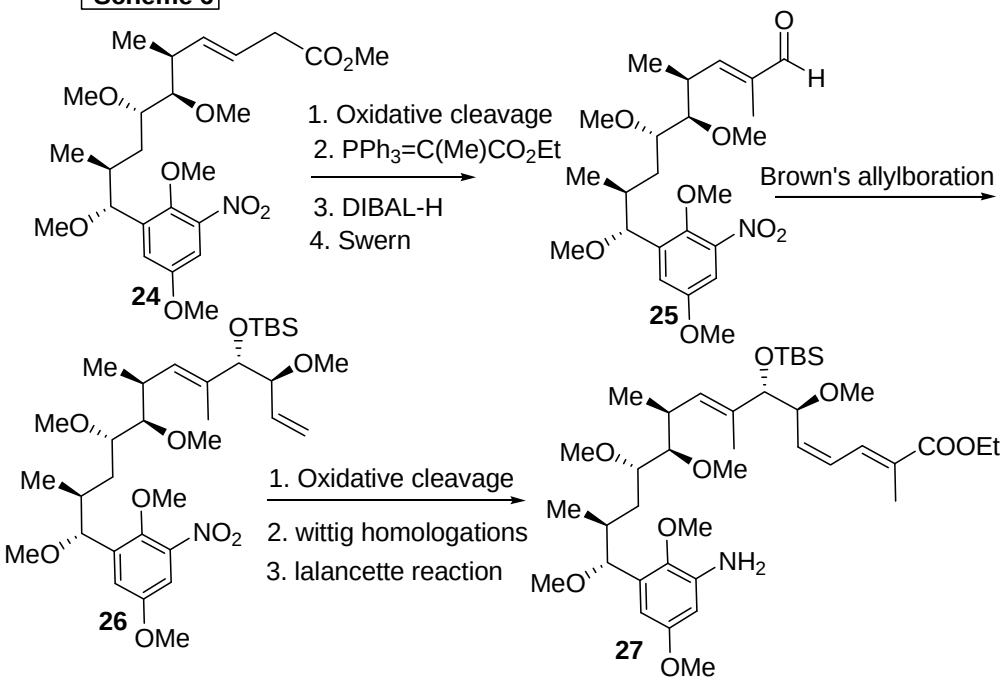
James S.Panek *et.al* in 2004[97] reported the second total synthesis of Herbimycin A.

Scheme 5



The Panek's group started the synthesis of Herbimycin A with TBS protection of the known primary alcohol in **21**. Followed by methylation of secondaryalcohol using Meerwein's reagent to give protected derivative. Removal of the silicon protecting group at C10 was followed by debenzylation of the C11 hydroxy group gave diol. The 1,2- diol was subjected to an oxidative cleavage reaction to yield aldehydes **22**, which was subjected to a second crotylation to afford the syn-homoallylic ether **24** (Scheme 5).

Scheme 6

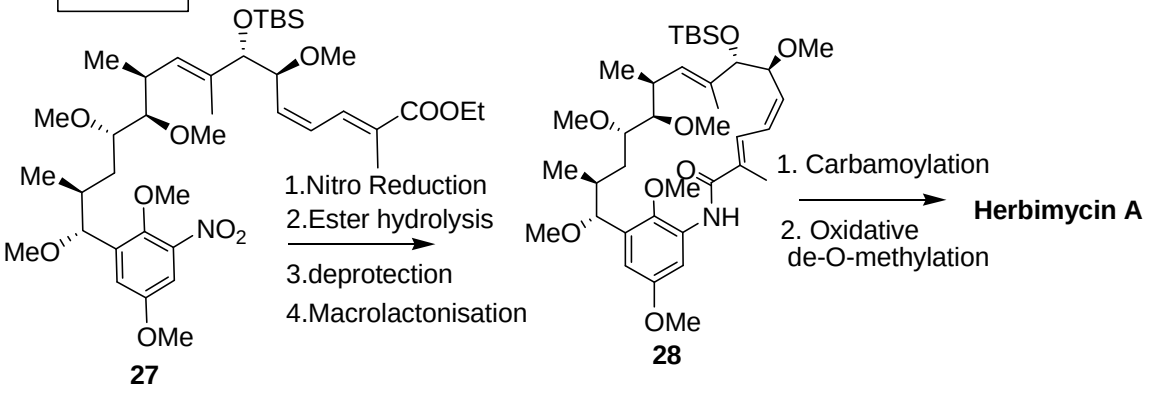


Compound-**24** was subjected to dihydroxylation , followed by cleavage of diol to afford an aldehyde which on wittig olefination with the stabilized ylide $Ph_3P=C(Me)CO_2Et$ in toluene gave the (E)-Olefin. The ester was reduced with DIBAL-H to the alcohol, which on Swern oxidation afforded aldehyde **25**. Using Brown's asymmetric allylboration technology, they constructed the C6-C7 syn-stereocenters from **25** with the γ-methoxyallyl organoborane reagent derived from (-)-α-pinene.

Protection of the C7 hydroxyl group as a TBS ether allowed incorporation of the carbomate toward the end of the synthesis. The installation of the C2-C5 (E,Z)- dienoate began with trans-formation of the terminal olefin in **26** to the aldehydes. In a two reaction sequence, the aldehyde was obtained with dihydroxylation followed by oxidative cleavage. The C4-C5 (Z)-olefin was then established by a Horner-Emmons olefination reaction using the Still-Gennari phosphonate to afford the (Z)-α,β-unsatured ethyl ester as a single isomer.

Reduction of the ester with DIBAL-H followed by Swern oxidation provided the α,β-unsatured aldehyde. the synthesis of the (E,Z)-dienoate was completed by installation of the C2-C3 trisubstituted (E)-olefin employing similar conditions used earlier to install the C8-C9 trisubstitued (E)-Olefin **27** (Scheme 6).

Scheme 7



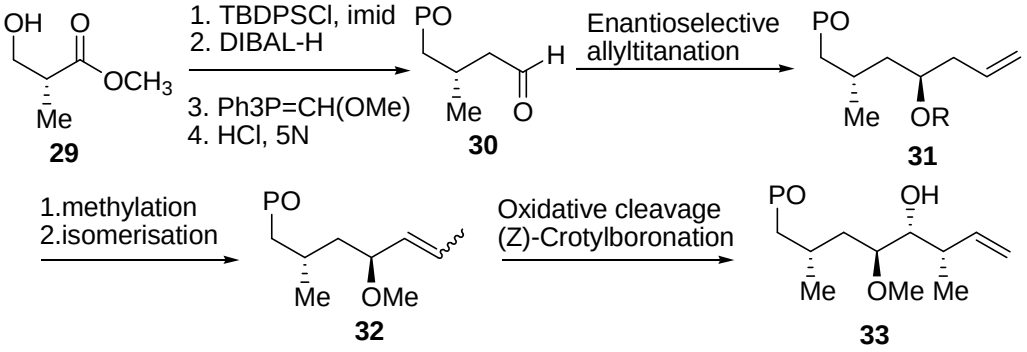
The aryl nitro group of **27** was reduced under the mild conditions developed by Lalancette which was followed by saponification of the ester to give the advanced intermediate. Macrolactonisation by using BOPCl and DIPEA as a base afforded **28**. Completion of the synthesis of Herbimycin A was accomplished by deprotection of the C7-silyl ether with TBAF in THF to provide secondary alcohol which on carbamate

formation, followed by oxidation of the dimethoxy aromatic core to the quinine with CAN, afforded synthetic Herbimycin A (Scheme 7).

Janine Cossy *et.al*. approach for the total synthesis of Herbimycin A:

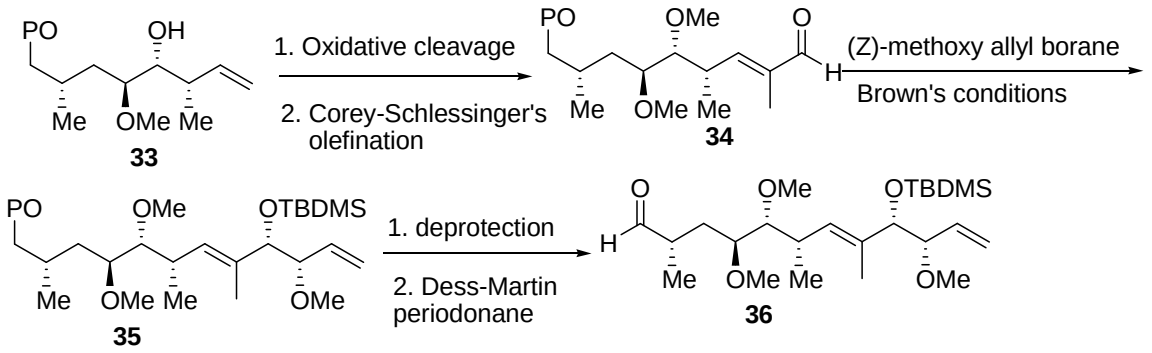
Janine Cossy et.al. in 2007[98] reproted the third total synthesis of Herbimycin A, by keeping allyl titanation reaction as a important step to assemble ansachain with the aryl group.

Scheme 8



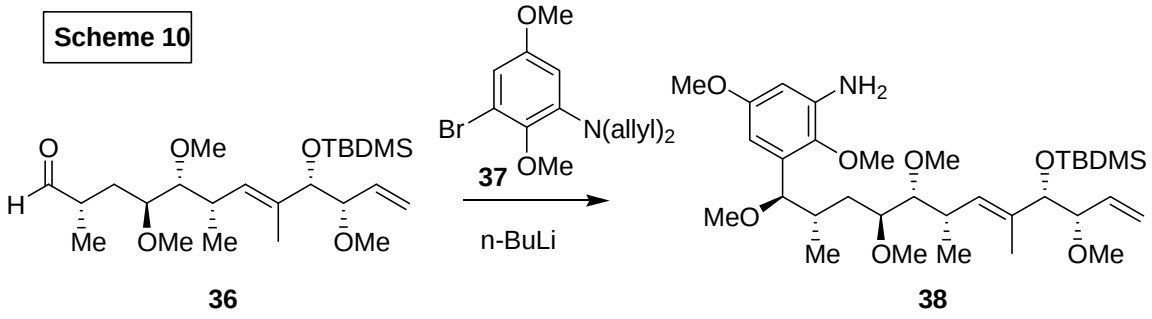
Hydroxyester **29** was transformed to aldehyde **30** in four steps which includes protection of the primary alcohol as a TBDPS ether, reduction of ester function by DIBAL-H to yield the corresponding aldehyde, homologation of the aldehyde to **30** in two steps using the methoxymethylphosphonium ylide followed by an acidic hydrolysis of the enol ether intermediate. Aldehyde **30** was then subjected to enantioselective allyltitanation with the highly face-selective (S,S)-I complex to afford the homoallylic alcohol **31**. After methylation of the secondary alcohol in **31**, the terminal double bond was isomerized by treatment with the second-generation Grubbs' catalyst GII in the presence of the N-allyl-N-tritylamine and diisopropylethylamine resulting in the formation of allylic ether **32** (Scheme 8).

Scheme 9



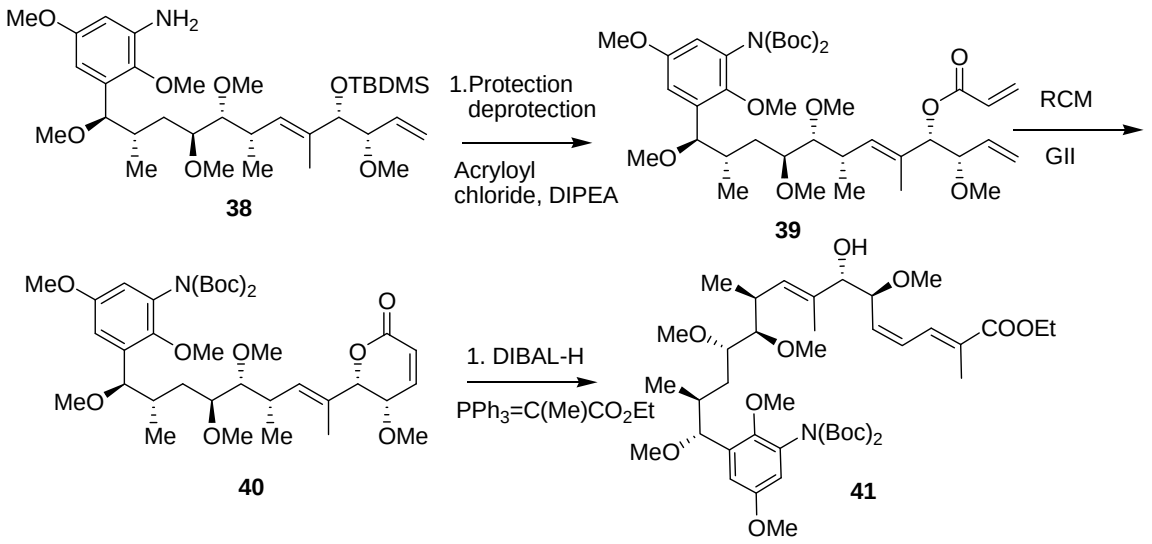
After oxidative cleavage of olefin **32** and treatment of the resulted aldehyde with the (Z)-crotylboronate allowed the control of the C10 and C11 stereocenters. Alcohol **33** on mehtylation and oxidative cleavage afforded an aldehydes, which under Corey-Schlessinger olefination conditions afforded the α,β-unsatured aldehyde **34**. At this stage, the control of the C6-C7 stereocenters was examined by addition of the (Z)-γ-methoxy allylborane, derived from (-)-α-pinene and developed by Brown; aldehyde **34** led to the desired syn-product, which was directly protected to produce the TBDMS ether. The selective deprotection of the primary alcohol, without affecting the secondary TBDMS ether at C7, was achieved by using NH_4F in methanol and the resulted primary alcohol was then oxidized to the corresponding aldehyde **36** by using Dess-Martin periodinane (Scheme 9).

Scheme 10



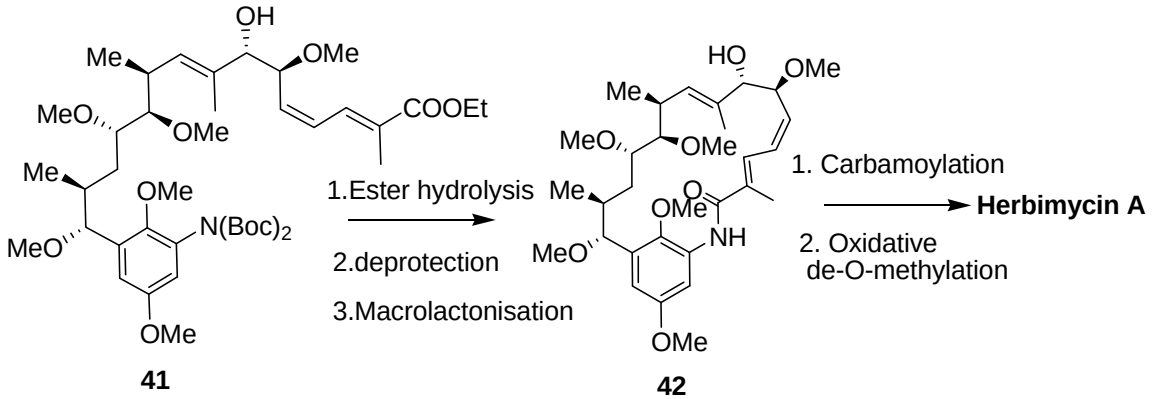
The organolithium reagent issued from **37** which was obtained by halogen-metal exchange using n-BuLi, followed by reacted with aldehyde **36** to provide the two epimers at C15, **38** and **38'**, in a 1.6/1 ratio (Scheme 10).

Scheme 11



After separation, the major epimer was methylated at C15 and N-deprotected to give aniline **38**. The compound **38** was transformed to the desired unsaturated lactone **40** in four steps. In order to perform the RCM, the aniline was protected with a deactivating group like N,N-biscarbamate. After deprotection of the hydroxyl group at C7 followed by esterification using acryloyl chloride, the obtained dienic ester-**39** was subjected to RCM using Grubb's catalyst from where unsatured lactone **40** was isolated. The transformation of **40** to the (E,Z)-conjugateddiene **41** was achieved in two steps. At first, the lactone **40** was reduced to the corresoponding lactol using DIBAL-H and resulting lactol was treated with the stabilized wittig reagent PPh_3=C(Me)CO_2Et in toluene to afford the (E,Z)-diene **41** (Scheme 11).

Scheme 12



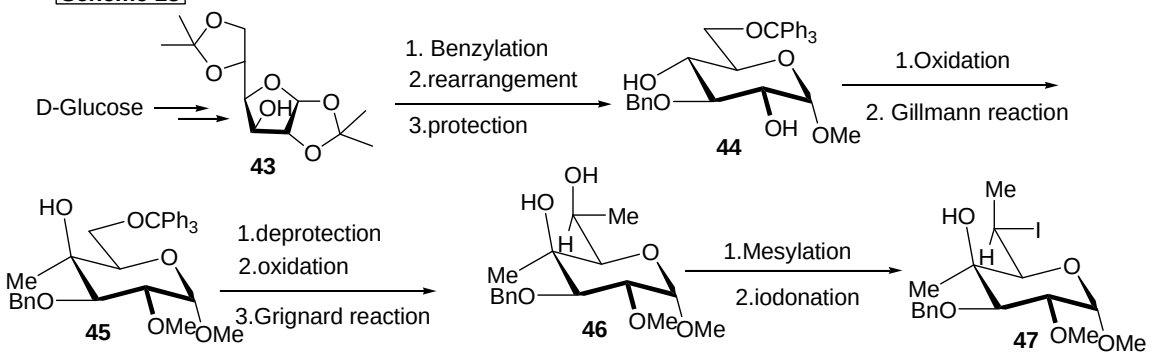
After deprotection of the aniline, and saponification of the ester, the treatment of the nonpurified seco acid with (BOPCl) and DIPEA afforded the macrocycle **42**. Completion of Herbimycin A synthesis was accomplished by formation of the carbamate at C7 with trichloroacetylisocyanate and K_2CO_3/MeOH followed by oxidation of the dimethoxy aromatic core to the quinine ring system with CAN (Scheme 12).

Synthesis of Advanced Fragments of Herbimycin A

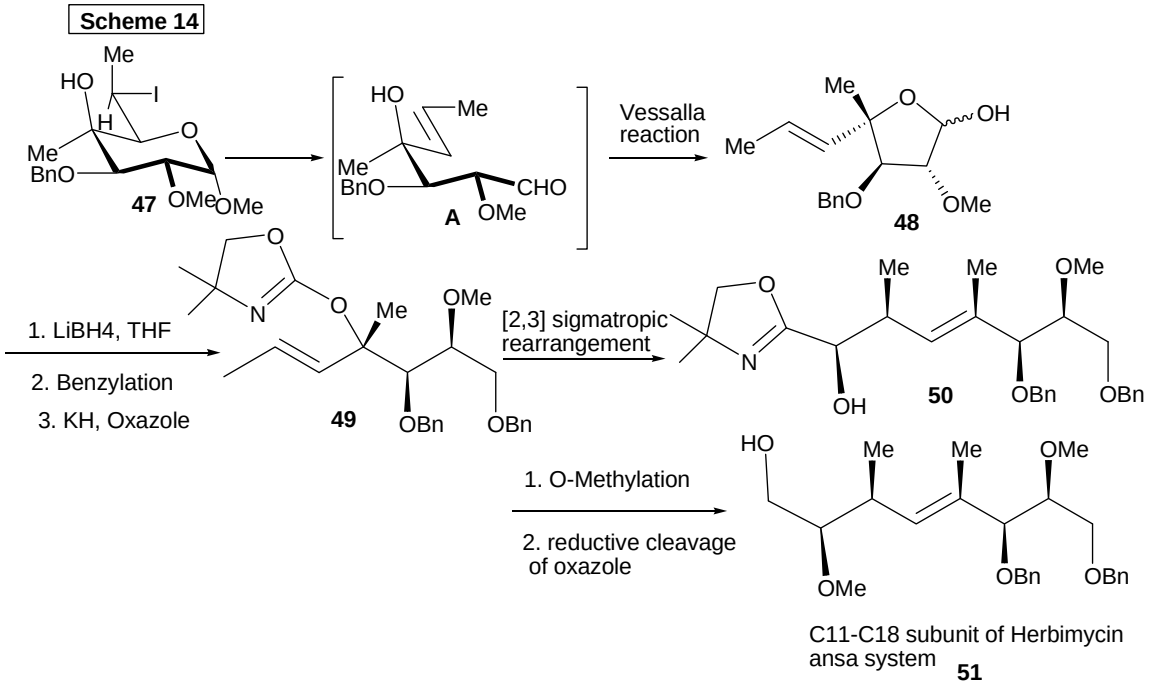
James Kallmerten ***et. al***.approach for synthesis of C11-C18 Fragment:

James Kallmerten *et.al* in 1993 [99] synthesized the C11-C18 fragment, in which the [2.3] Wittig rearrangement of a glucose derived tertiary aIlylic ether **49** establishes the key structural and stereochemical elements of an advanced Herbimycin A intermediate.

Scheme 13



Preparation of iodopyranose **47** initiated with glucopyranose **44**, prepared in three steps from commercially available 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **43**. Regioselective O-methylation of **44** and oxidation of the resulting C4 alcohol with SO_3-pyridine complex afforded ketone. Treatment of ketone with MeLi-Me_2CuLi Complex in Et_2O was accompanied by the expected equatorial addition, yielding the desired axial tertiary alcohol **45**. Deprotection of **45** and oxidation of the resulting diol furnished the sensitive aldehyde; subsequent treatment with methyl Grignard reagent afforded diol **46**. Finally, diol **46** was transformed to iodoalcohol **47** by mesylation and treatment of the resulting sulfonate with tetrabutylammonium iodide in benzene. Iodide **47** was obtained as a single diasteremer (Scheme 13).

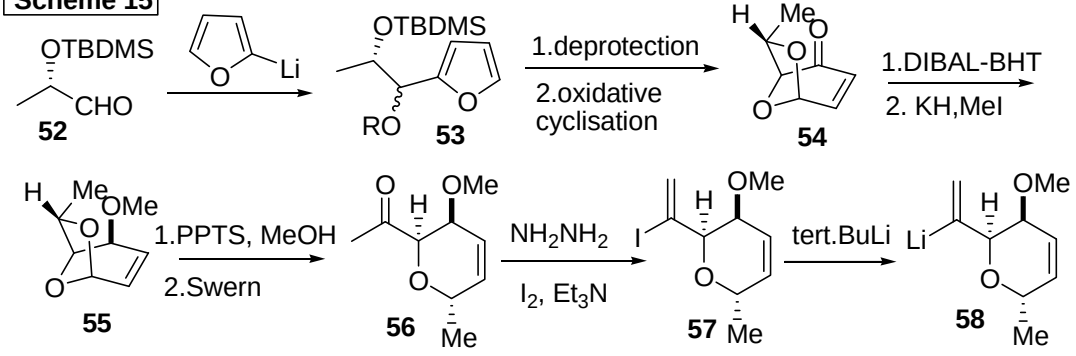


Iodide **47** was rapidly consumed upon treatment with Zn dust in ethanol; interestingly. the anticipated product of reduction, aldehyde (A), was not isolated. underwent cyclization to yield lactol **48** as a 3:l mixtuxe of anomers. Finally, reduction of **48** and mono-benzylation of the resulting diol afforded tertiary allylic alcohol. alkylation of the potassium alkoxide of tertiary allylic alcohol with chloromethyl oxazoline, followed by treatment of the resulting ether **49** with lithium diisopropylamide and subsequent [2,3] sigmatropic rearrangement afforded a single product **50**. O-Methylation of **50** followed by reductive cleavage of the oxazoline system afforded **51**, corresponding to the fully-functionalized C_{1l}-C_{18} subunit of the Herbimycin ansa system (Scheme 14).

Stephen F. Martin ***et. al.*** approach for synthesis of C3-C21 Fragment:

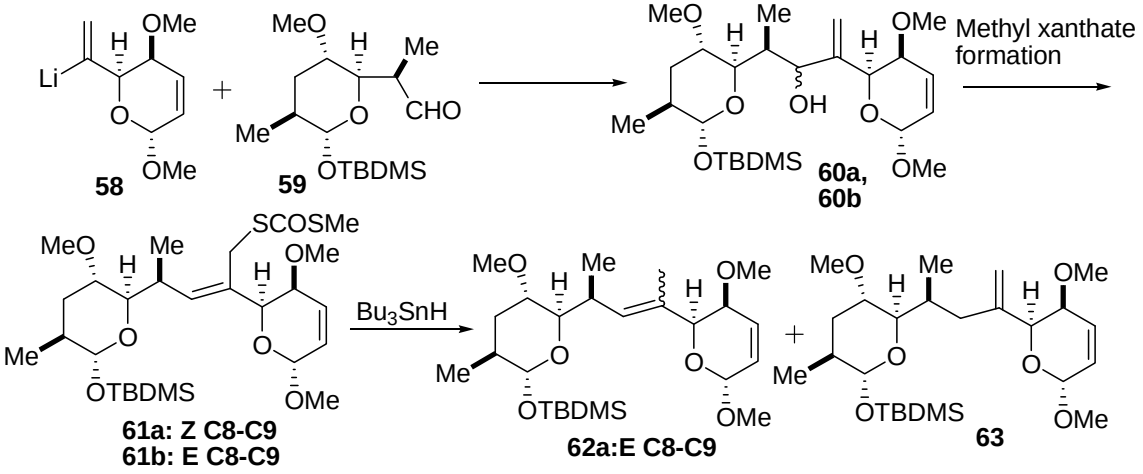
Stephen F. Martin [100] synthetic strategy was specifically designed to provide the opportunity to develop the stereoselective union of two complex fragments related to **58** and **59** to give trisubstituted alkenes. The hydropyrans **58** and **59** would then be accessible from the furans and **52**, respectively. the successful implementation of his strategy for the preparation of **67a**, which incorporates the C(3)-C(21) segment of herbimycin A

Scheme 15



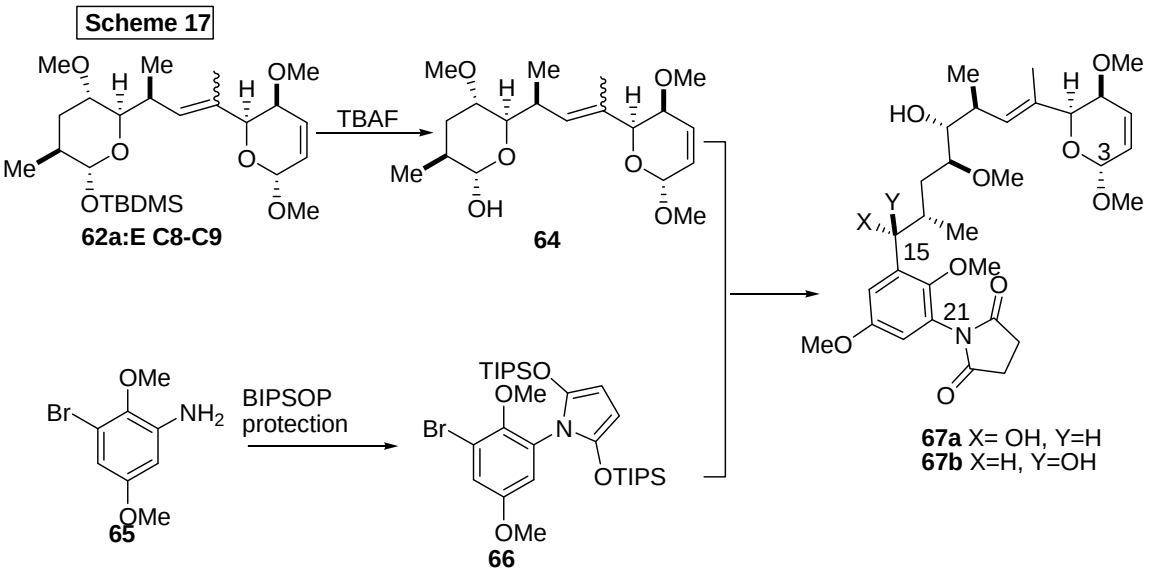
The synthesis commenced with the reaction of the known aldehyde **52**, which was prepared in two steps from S-ethyl lactate, with 2-furyllithium to furnish a separable mixture (11:1) of epimeric diols, from which **53** (R=β-OH) could be isolated. The addition of 2-furylmagnesium bromide to **52** proceeded with similar diastereoselection, The diol derived from **53** was oxidatively processed to give an intermediate hydropyranone that cyclized under dehydrating conditions to give **54**. Methylation of the intermediate allylic alcohol gave the methyl ether **55**. Acid-catalyzed rupture of the bicyclic ketal **55** in methanol gave a single methyl glycoside that was oxidized under Swern conditions to provide **56**. the ketone **56** was treated with excess hydrazine to give the corresponding hydrazone, which was allowed to react with iodine in the presence of a large excess of Et_3N to give **57** (Scheme 15)**.**

Scheme 16



The metal-halogen exchange of **57** leads to form **58** and the *initial* reaction of **58** with **59** were conducted at -95 °C to avoid possible β-elimination of **58** to produce an allene; an excess of **57** was required to ensure complete consumption of the aldehyde **59**. Although the reactants were combined at -95 °C, it was necessary to warm the reaction slowly to -50 °C to allow the addition to occur. In this fashion, a mixture (4:1) of epimeric alcohols **60a, 60b** was obtained. The allylic alcohols **60a, 60b** were converted to the corresponding xanthates, which were not isolated but were thermally isomerized via [3,3]-sigmatropic rearrangement **60** to give a mixture (1.6:1) of the allylic dithiocarbonates **61a, 61b .**Reduction of the mixture of **61a, 61b** under radical conditions with n-Bu_3SnH afforded a mixture (17:1) containing the desired E-alkene **62** as the major product together with the disubstitnted alkene **63** (Scheme 16).

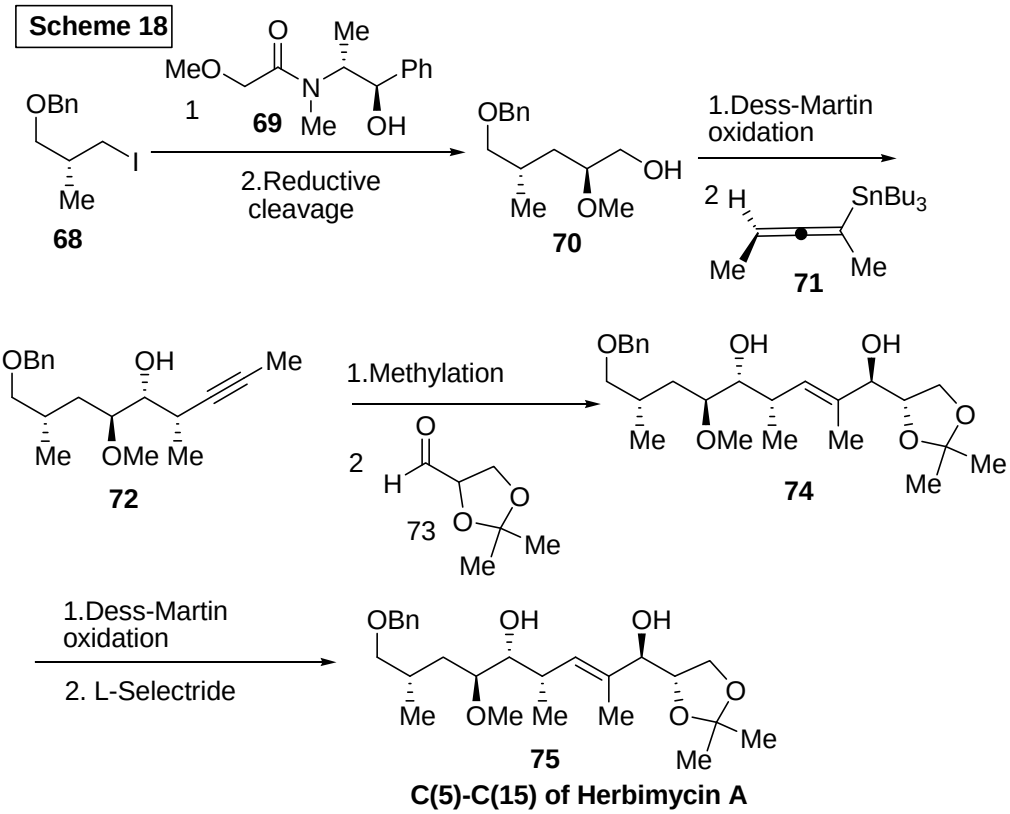
Scheme 17



Selective removal of the silyl protecting group from the hemiacetal moiety at C(15) of **62a** to give **64** was achieved using fluoride reagent n-Bu_4NF/HOAc. **65** was converted into the BIPSOP-protected aniline **66**. The anion generated from **66** by metal-halogen exchange added to the lactol **64** in the presence of TMEDA gave, after partial hydrolysis of the BIPSOP group, a mixture (5.5:1) of **67a** and **67b** (Scheme 17). One may envisage elaborating **67a** into Herbimycin A (1) via reactions closely related to those recently reported by Tatsuta.[96]

Glenn C. Micalizio *et. al*. approach for synthesis of C5-C15 Fragment:

Glenn C. Micalizio *et.al*.[101] studies revealed that a diastereoselective pentynylation (**68** to **72**), in conjunction with a titanium alkoxide-mediated regioselective reductive coupling (**72** to **74**) can provide general and flexible access to complex polyketides.



C(5)-C(15) of Herbimycin A

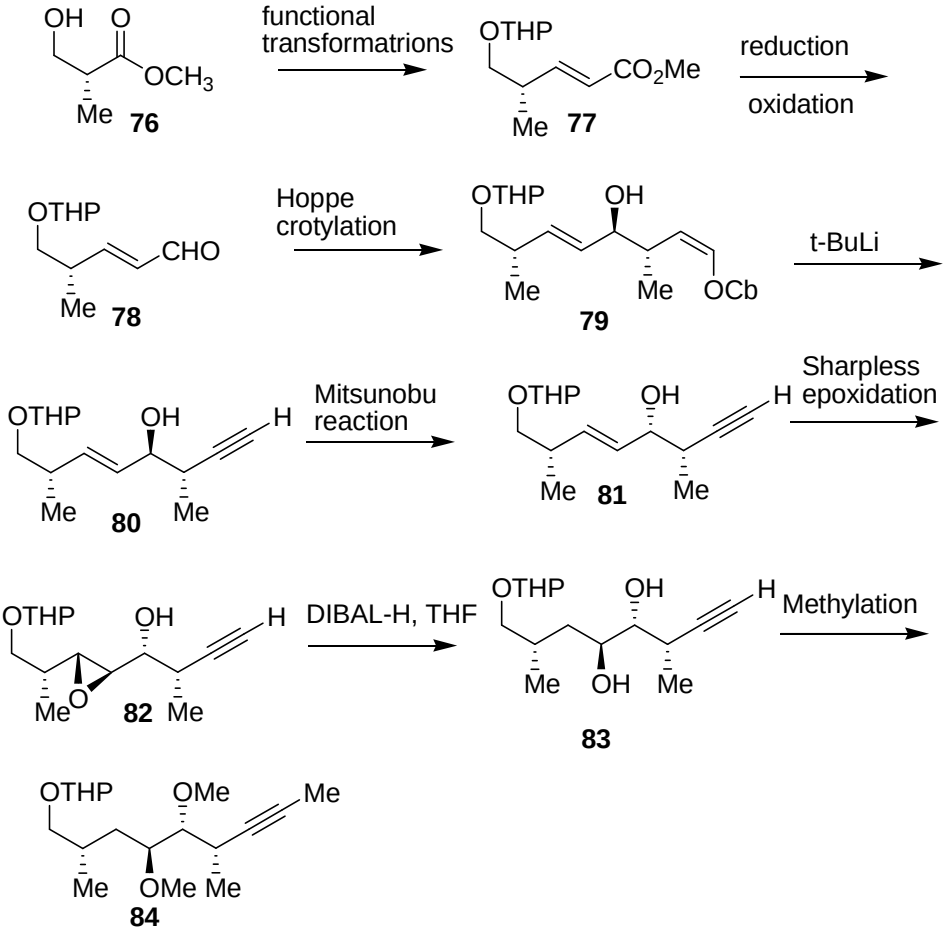
Myers' alkylation of the Roche iodide **68**, followed by LAB reduction (BH_3. NH_3, LDA, THF) of the amide provided the stereochemically defined primary alcohol **70** (dr 9:1). Oxidation to the aldehyde (Dess-Martin periodinane, CH_2Cl_2), followed by a double asymmetric pentynylation with the allenylstannane 7**1** ($BF3.OEt_2$, CH_2Cl_2, -78 °C) provided the homopropargylic alchol **72** which was converted to C5-C15 OF Herbimycin A as shown in (Scheme-18).

Janick Ardisson *et. al*. approach for synthesis of C1-C7, C8-C15, and C16-N22 Fragments of the Herbimycin:

Janick Ardisson *et.al*.[102] synthetic plan involved the convergent approach. His group prepared the C8-C15 fragment by using Hoppe Crotylation and sharpless epoxidation as key steps. The C1-C7 fragment was constructed by employing Shen's reaction conditions. Where as the C16-N22 fragment was prepared by regular functional group manipulations.

Synthesis of C8-C15 fragment of Herbimycin A

Scheme 19



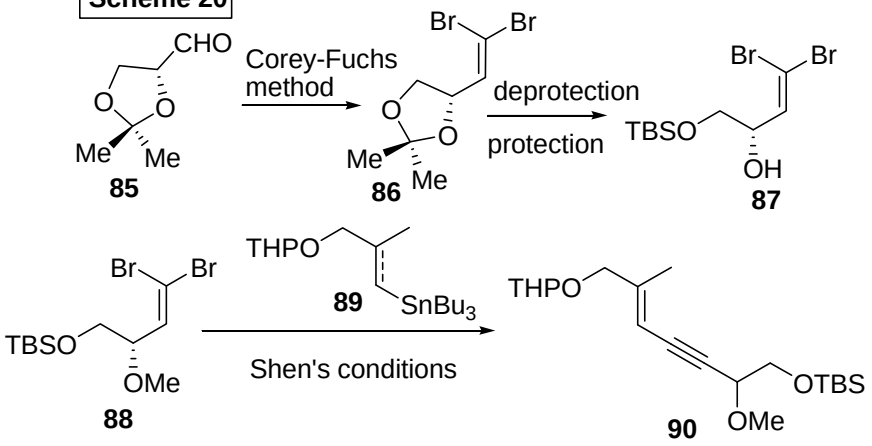
The elaboration of southern C8-C15 sub-unit started from the commercially available hydroxy-ester **76**; classical transformations gave ester **77** which was converted to the α,β-unsaturated aldehyde **78** in 6 steps. Elaboration of the C15-C8 skeleton was

initiated by an enantioselective Hoppe crotylation of aldehyde **78** to afford the pure vinyl carbamate **79**, followed by treatment with *t*-BuLi provided acetylenic derivative **80**.

Inversion of the C11 center of compound **80** was achieved under Mitsunobu conditions. Stereoselective Sharpless epoxidation of **81** using D-(-)-diethyltartarate gave epoxide **82**. followed by Reduction of **82** under DIBALH/THF conditions furnished the anti-1,3-diol **83**. Subsequent methylation of **83** was carried out using *n*-BuLi/MeI to furnish dimethoxyderivative **84** (Scheme 19).

Synthesis of C1-C7 Fragment of Herbimycin A

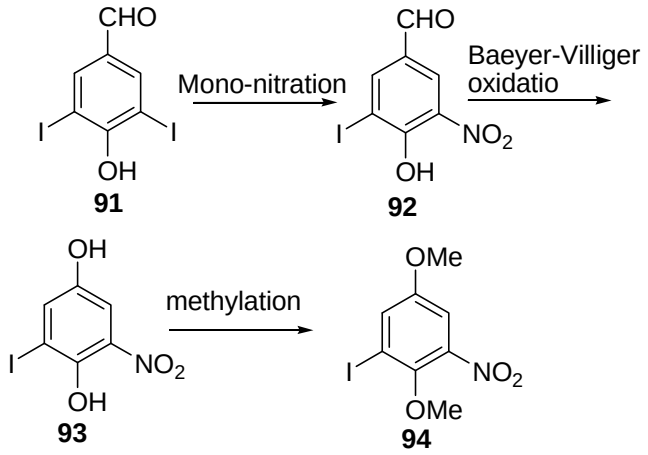
Scheme 20



Isopropylidene glyceraldehyde **85** was transformed into **86** by applying Corey-Fuchs method. Compound **86** was transformed to alcohol **87** which was converted into the corresponding 1,1-dibromo-alkene derivative **88**. The compound **88** and **89** under Shen's conditions [$Pd(PPh_3)_4$ or $Pd(CH_3CN)_2Cl_2$/CuI/diisopropylethylamine, in toluene or DMF at 80 ^oC] afforded excepted enyne **90** (Scheme 20).

Synthesis of C16-N22 Fragment of Herbimycin A

Scheme 21

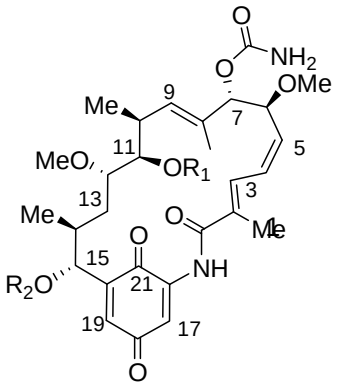


The Northern fragment **94** was prepared from commercially available diiodocompound **91** in three steps. Mono-nitration of **91** under classical conditions led to nitro-aldehyde **92**. Applying Baeyer-Villiger oxidation on **92** provided the excepted diphenol derivative **93**. The last step for the preparation of C16-N22 Northern fragment **94** (Scheme 21) was achieved by methylation of **93** by means of KOH/MeI in DMF at 20 ^{o}C for 4h.

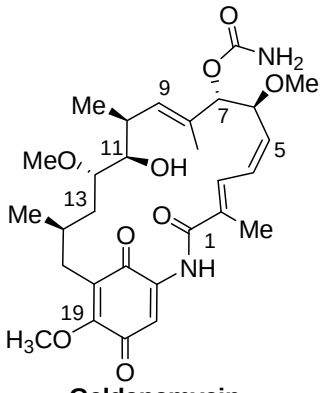
PRESENTWORK

Present work:

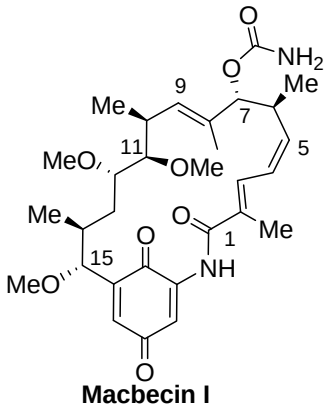
Herbimycin A, Geldanamycin, Macbecin I belong to ansamycin benzoquinone class of natural products, containing ansa-bridged macrocyclic lactam connected to *meta* position of the Benzoquinone. Herbimycin A, geldanamycin and its derivaties were isolated from fermentation broth of *streptomyces hygroscopicus* **AM-3672**.[1] Herbimycin A has a significant range of antitumor, antibacterial, antifungal, antiprotozoa activities, herbicidal, antiangiogenic, antiviral, antitabocco mosaic virus[2a] and antitumor activities[2]. Though it was isolated in 1979, only three total synthesis of Herbimycin A are reported in the literature[96-98]. Also one formal synthesis and few synthesis of advanced fragments have been reported[99-102]. The challenging structural complexity along with the significant biological properties of Herbimycin A and its derivaties motivated us to take up the synthesis of these molecules in our laboratory.



Herbimycin A (1) R_1 = Me, R_2 = OMe
Herbimycin B (1a) R_1 = H, R_2 = H
Herbimycin C (1b) R_1 = H, R_2 = OMe



Geldanamycin



Macbecin I

Figure 1. structure of novel natural products, Herbimycin (A-C), Geldanamycin, Macbecin I

The structure and absolute configuration of Herbimycin A was determined by its ^{1}H, ^{13}C NMR spectroscopic analysis and single crystal X-ray analysis.[2b,c] The absolute stereochemistry was determined by its first total synthesis by Tatsuta *et. al* in 1991.[96] Critical structural features of Herbimycin A are as follows: (I) Seven stereogenic centers (6*S*, 7*S*, 10*S*, 11*R*, 12*S*, 14*S*, 15*R*). (II) an aliphatic ansa-bridged chain bonded to *meta* position of suitably substituted benzoquinone. (III) Carbamate at C-7. (IV) an isolated trisubstituted (8*E*)-double bond. (V) 2*E*, 4*Z*-diene. (VI) 19- membered macrocyclic lactam along with a benzoquinone ring system

Retrosynthetic analysis:

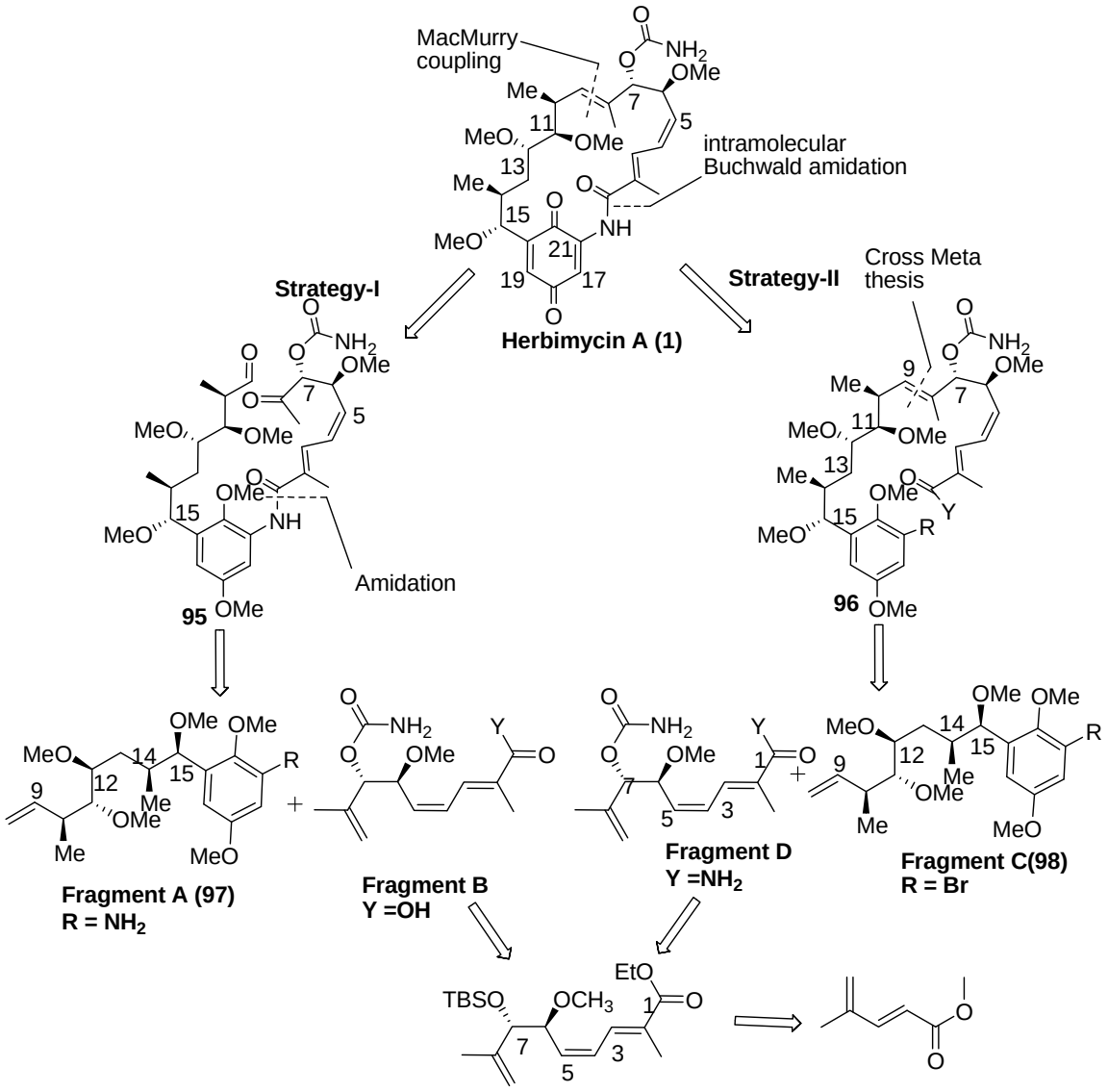


Figure 9. Retrosynthetic strategies for Herbimycin A

Our synthetic plan for Herbimycin A, as depicted in Figure-9, involves two strategies; first strategy involves a bond disconnection at C-**8** and C-**9** which leads to an opened dicarbonyl precursor **95** which can give the target molecule-**1** through MacMurry cyclization/ coupling. Int-**95** can be assembled from the two fragments A (**97**) and B by inter molecular amidation. Our 2nd strategy reveals that a cross metathesis of crucial fragments C(**98**) and D will leads to critical Int-**96** which would provide target-**1** through intramolecular Buchwald amidation. We decided to take advantage of the chirality present in sugar molecules to construct the critical Fragments [A (97) and C (98)] bearing

5 stereocenters. Thus we envisaged that Fragments (A and C) can be derived from suitably substituted Int-**99** or **100** by keeping zinc mediated reductive elimination (Vasselar-Bernet reaction).

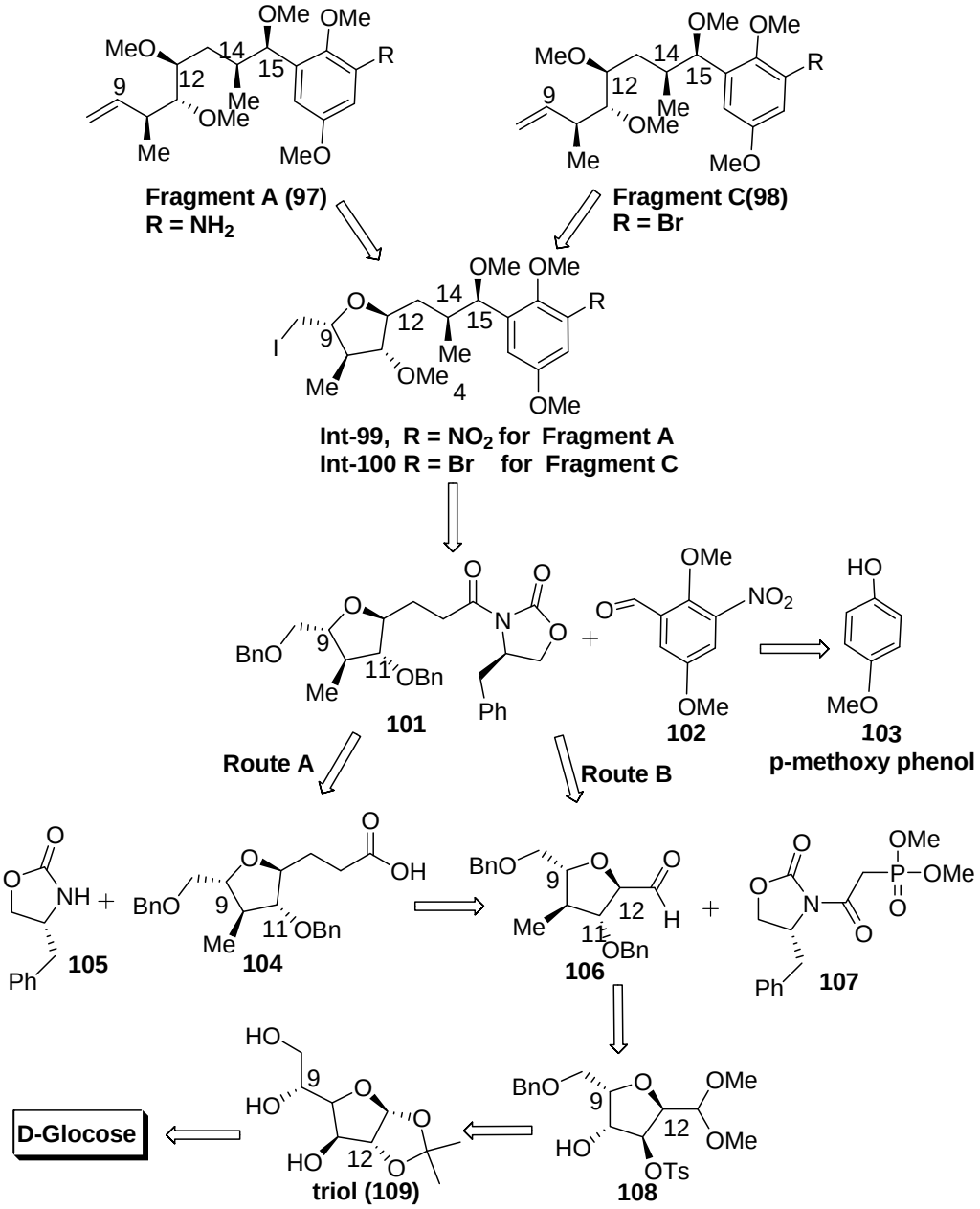


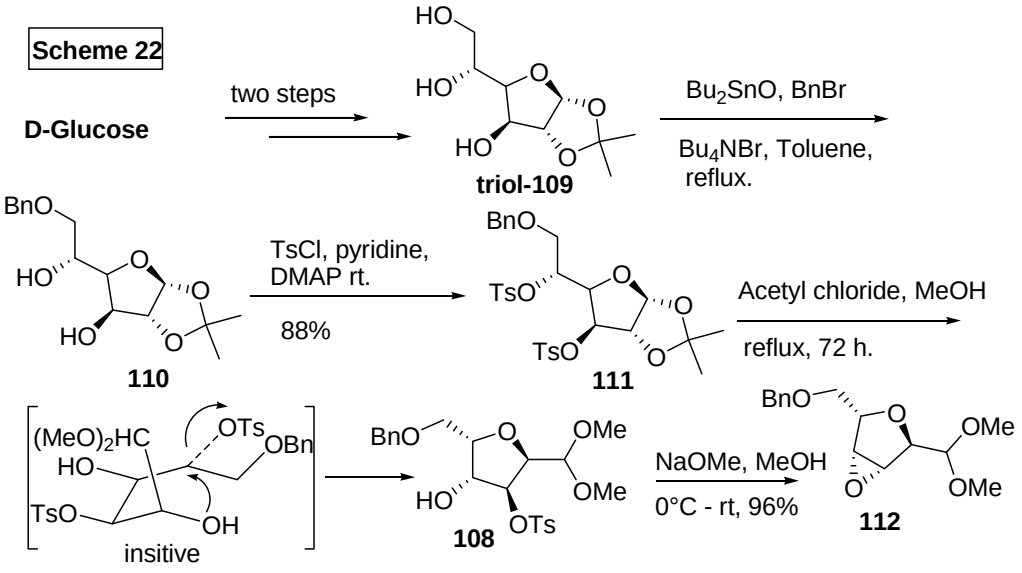
Figure 10. Retrosynthetic strategy for advanced right hand segment (99 and 100)

The key intermediates **(99** and **100)** can be obtained by chemical manipulation using Evan's *anti* aldol reaction as a key step (for construction of **C14** methyl and **C15** hydroxyl). We have visualised oxazolidinone derivative **101** as an important intermediate in our synthesis which could be obtained in two path ways. First *via* coupling of

oxazolidinone **105** and carbohydrate derived acid **104**, which could be prepared by homologation of aldehyde **106**. In the second path way, using Horner-Wardsworth-Emmons reaction for assembling the aldehyde **106** with the oxazolodinone phosphonate **107.** The aldehydes **106** can be obtained from D- Glucose by chemical manipulations as shown in **Figure 10**.

Synthesis of aldehyde-106 (Scheme 22):

Once we have zeroed on plan and the retrosynthesis, our synthesis started with the conversion of D-Glucose into epoxide-**16** as shown in Scheme-22.

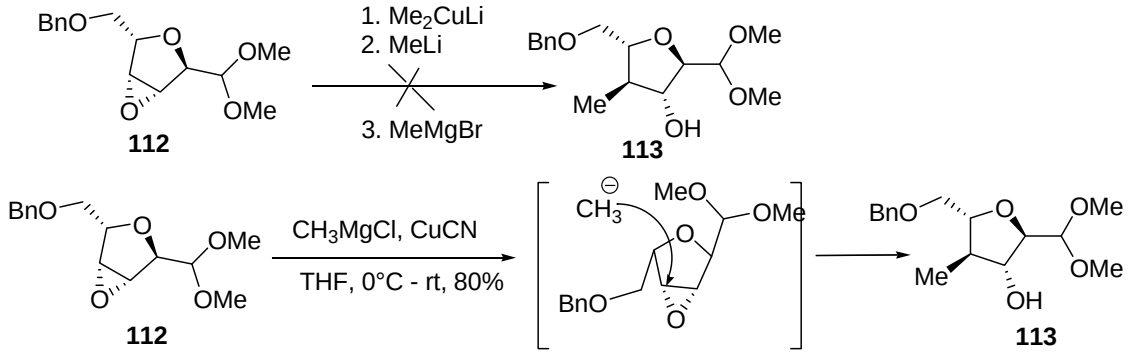


D-Glucose was converted into triol-**109** in good yield following two step sequence as reported in the literature.[103] The primary hydroxyl group of triol **109** was selectively protected as its benzyl ether by chelation controlled manner using dibutyltin oxide, BnBr, Bu_4NBr[104] in toluene to afford monobenzyl ether **110** in 88% yield (Scheme 22). The product was confirmed by its spectral and other analytical data. Di-tosylation of **110** by using tosyl chloride in pyridine, and catalytic DMAP gave **111** which was confirmed from its ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum showed two sharp singlets at δ 2.37 and 2.42 ppm each one integrating for three protons of the methyl groups attached to tosyl aromatic ring. The aromatic protons resonated at δ 7.09 to 7.86 ppm integrating for eight protons confirmed the formation of di-tosyl derivative **111**.

After having suitably protected di-tosyl derivative **111**, our first key step towards construction of basic skeleton of (C13-C8) Herbimycin A was the acid mediated ring isomerization (acid catalysed rearrangement) which would give rearranged product **108.**[105] This type of rearrangement was first observed by J. Defay in carbohydrate system.[105c] This methodology was further explored in the total synthesis of complex natural products like Jasmine B, central ring F of Halichondrin B.[105b] Mechanistically, during the rearrangement, C-2 Hydroxy of glucose attacks the O-Ts group on C-5 in a S_N2 fashion to afford the rearranged product **108,** which was characterized by the presence of only one tosyl methyl peak at δ 2.49 ppm in the ^1H NMR spectrum. The ^{13}C NMR spectrum further supported the assigned the structure **108**. Molecular ion peak at *m/z* 475.25 $[M+Na]^+$ was observed in ESI-MS spectrum, which corroborated the predicted structure.

This rearranged product **108** was then transferred into the desired epoxide **112** using sodium methoxide in methanol in 96% yield. The chemical shifts due to tosyl group were departed. Molecular ion peak at *m/z* 303.39 $[M+Na]^+$ was observed in the ESI-MS spectrum confirmed the structure **112**.

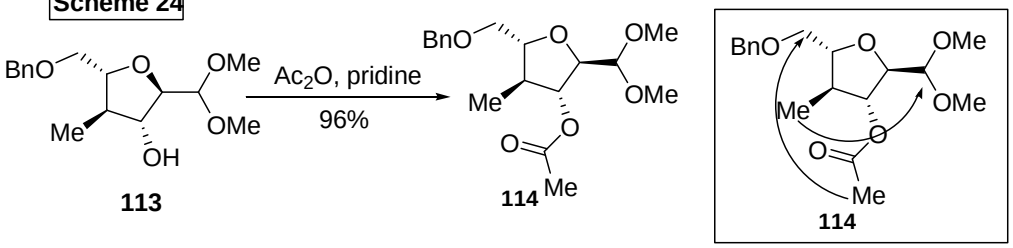
Scheme 23



Having Epoxide-**112** in hand, our next target was the stereoselective opening of the epoxide ring present in **112,** which would provide us the desired opened intermediate **113**. Our initial attempts for the stereoselective opening of the epoxide using the more common reagents Me_2CuLi, MeLi or MeMgBr failed to give us the desired product; all these cases gave mixture of epoxide opened isomers along with unreacted starting material. Fortunately this conversion was successfully achieved using modified Gillman reagent (methyl magnesium chloride and CuCN in THF) which afforded the critical

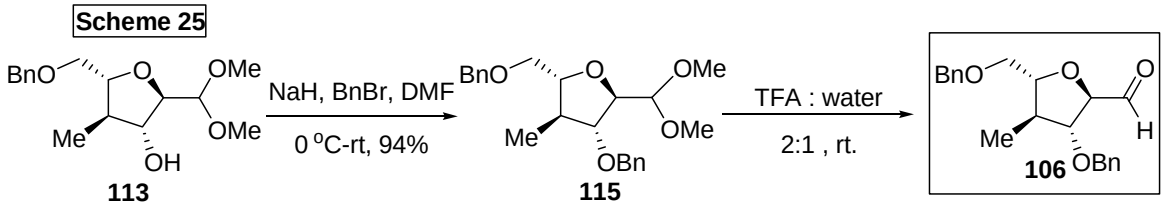
intermediate **113** in 80% yield[106]. The structure was confirmed by its ^{1}H and ^{13}C NMR spectral analysis. In ^{1}H NMR spectrum, the new methyl peak appeared in the upfield region of the spectrum at δ 1.1 ppm (J = 6.6) integrating for three protons. In the ^{13}C NMR spectrum the Methyl-carbon resonance at δ 15.12 ppm indicate the formation of the **113.** In the ESI-MS spectrum the presence of the molecular ion peak at *m/z* 319.47 $[M+Na]^{+}$ further confirmed that observation. The exclusive stereo and regioselectivity observed under modified Gilmann condition can be explained by the fact that the α-face of the epoxide was blocked at one side by the $–CH_2OBn$ group and hence allows the attack of the reactive nucleophile ($Me^{\ominus}$) only from *β* face of epoxide (Scheme 23).

Scheme 24



The regioselectivity of **113** was further confirmed by extensive ^{1}H NMR studies (NOESY) of the acetyl derivative **114** which was obtained by treating **113** with acetic anhydride in pyridine (Scheme 24). The NOESY analysis of **114** showed a strong NOE between C4-Me and acetals OMe group and also between acetyl-Me and benzylic methylene which clearly support the *cis* relationship.

Scheme 25



Having Intermediate-**113** in hand, our next target was to convert it into the desired aldehyde-**106,** which was achieved by two simple manipulations. Int-**113** was protected as its Bn-ether **115** by using BnBr/DMF at 0 °C condition, followed by deprotection of the acetal under acidic condition using TFA:Water to provid aldehyde **106**, which without any further purification was used in the next step (Scheme 25).

Synthesis of Oxazolidinone derivative 101 *via* Route-A:

After successfully achieving the synthesis of the critical aldehydes Int-**106**; we next focussed our efforts for synthesis of Int-**101**; which can be derived from aldehydes-**106** following **2** routes as described below.

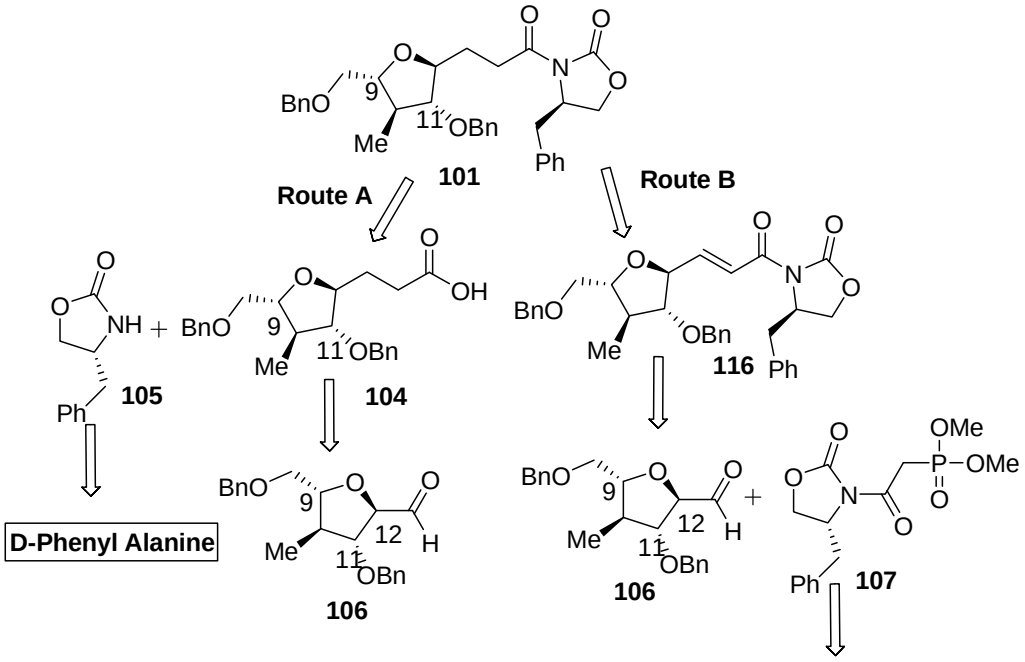
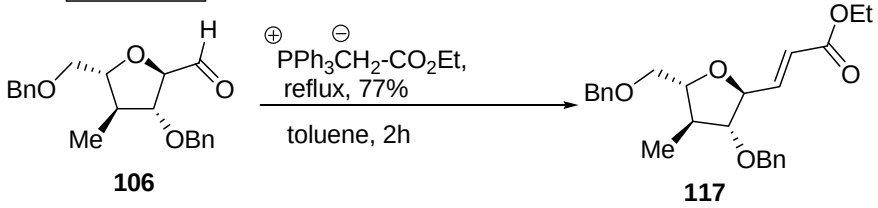


Figure 11. Retrosynthetic strategy for key Int-101

We first planned to try out Route **A** which involves the preparation of Int-**104** (acid-**104**); accordingly aldehyde-**106** was treated with 2-carbon stable Wittig ylide in toluene under reflux condition to afford olefin-**117** in 77% yield (Scheme26).

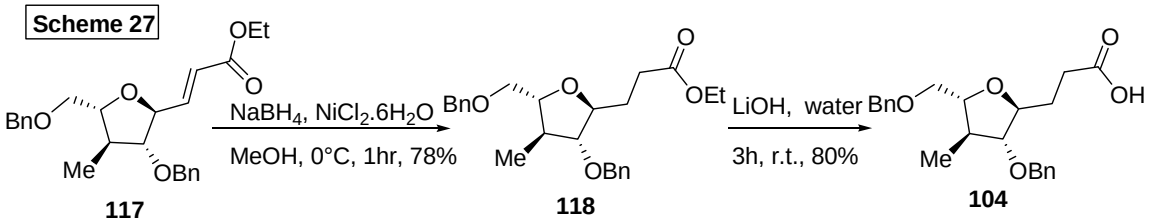
Scheme 26



The structure of Wittig product-**117** was elucidated by its ^{1}H NMR spectrum, in which new methyl signal resonances at δ 1.07 ppm integrating for three protons, methylene signal resonances at δ 4.20 ppm integrating for two protons and the characteristic olefinic protons appeared as doublet at δ 6.07, 6.92 ppm integrating for two protons and rest of protons appears at excepted chemical shift values. The structure

was further confirmed by its ^{13}C NMR spectrum, in which new methyl carbon appeared at δ 16.41 ppm, methylene carbon peak located at δ 60.47 ppm and characteristic olefinic carbon resonances at δ 121.2, 146.4 ppm was observed. Molecular ion peak at *m/z* 433.49 for $[M+Na]^+$ was observed in the ESI-MS spectrum was an additional support for unsaturated ethyl ester **117**.

Scheme 27



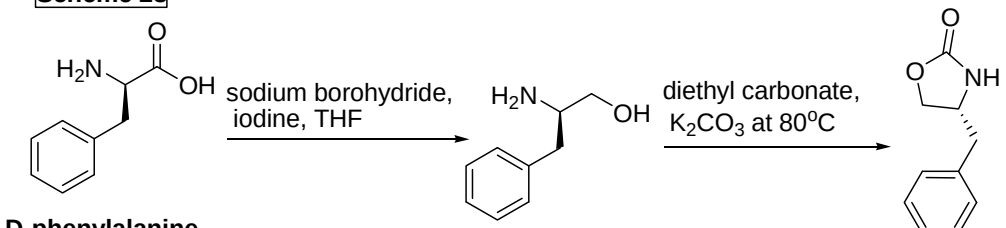
117 **118** **104**

The unsaturated ethyl ester **117** was reduced by treating with nickel borohydride in dry methanol to afford saturated ester **118.** The structure was confirmed by disappearance of olefinic proton peaks in ^1H NMR and the rest of the spectrum was in complete agreement with the assigned structure. Saturated ester **118** was saphonified by using LiOH in water:dioxane in 2:1 ratio to furnish acid **104** in 80% of yield (Scheme 27). The spectroscopic data were in good agreement with the assigned values along with the appearance of broad peak at 3390 cm^{-1} in IR spectrum which indicated acid functionality. Molecular ion peak at *m/z* 407.47 $[M+Na]^+$ was observed in the ESI-MS spectrum indicates it's formation.

Synthesis of Oxazolidinone derivative-101:

Oxazolidinone-**105** was prepared starting from D-Phenylalanine following literature procedure.[107]

Scheme 28

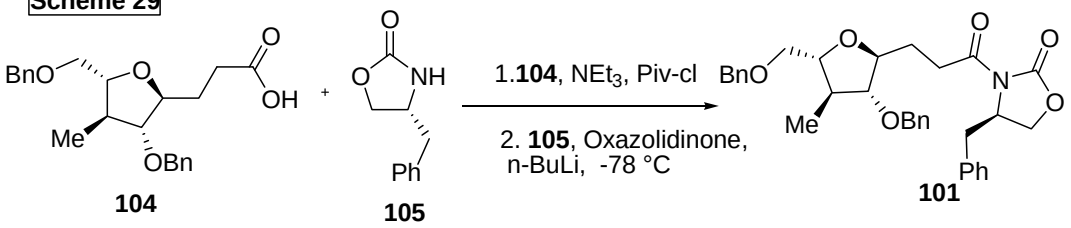


D-phenylalanine **D-phenylalanol** **105**

Accordingly, D-phenylalanine was reduced to D-phenylalanol with sodium borohydride and iodine in THF followed by treatment of the amino alcohol with diethyl

carbonate and K_2CO_3 at 80 ^oC to get oxazolidinone **105**. All the spectral and other analytical data were in good agreement with reported values (Scheme 28).[107]

Scheme 29

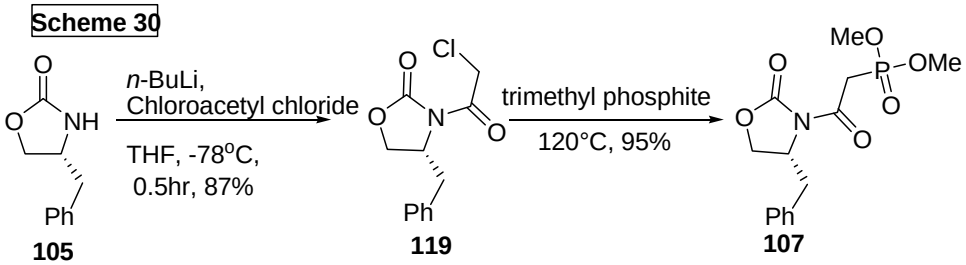


The next step was the coupling of Oxa-**105** and acid -**104** which would give us the critical Int-**101**. This was affected by converting the acid-**104** into its mixed anhydride using NEt_3, Piv-Cl followed by coupling with lithium salt of oxazolidinone which was prepared insitu using n-BuLi. Following this procedure we could get the desired coupled product-**101**, but unfortunately the yield was very low (Scheme 29).[108] The structure of oxazolidinone derivative **101** was confirmed by its ^1H NMR ,^{13}C NMR spectral study. In the ^1H NMR spectrum, in which peaks corresponding to benzylic protons of oxazolidinone resonating at δ 2.68, 3.26 ppm as a doublet of doublet integrating for two protons while all other protons of the oxazolidinone were appeared at assigned values. In the ^{13}C NMR spectrum showed benzylic methylene carbon resonating at δ 37.96 ppm, other oxazolidinone peaks appeared at their respective chemical shift values. Molecular ion peak at *m/z* 566.65 $[M+Na]^+$ was observed in the ESI-MS spectrum was an additional support for oxazolidinone derivative **101**.

Synthesis of Oxazolidinone derivative-101 *via* Route-B:

As the yield of Int-**101** following route-A was very low, we then attempted route-B for the preparation of Int-**101**. Accordingly Oxa-**105** was acylated using *n*-BuLi /chloroacetylchloride to afford chloroacetyl derivative-**119** in good yield.[109]

Scheme 30

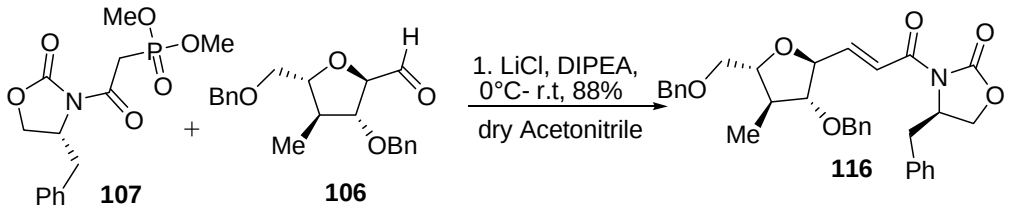


The Spectral data revealed that the methylene protons of chloroacetyl group resonated at δ 4.28 ppm as a singlet integrating for two protons in ^1H NMR spectrum.

The methylene carbon resonating at δ 66.8 ppm in ^{13}C NMR spectrum further supported the product **119**. In order to convert Int-**119** to our desired phosphonate ester-**107**, it was refluxed with trimethyl phosphite which provided the phosphonate ester-**107** in good yield[110] (Scheme 30). ^{1}H NMR of **107** showed signals at δ 3.81, 3.82 ppm integrating for six protons due to localized methoxy groups**.** The methoxy carbons were resonanced at δ 53.16 ppm in ^{13}C NMR spectra which further confirmed the structure of phosphonate **107**. Molecular ion peak at *m/z* 350.51 for $[M+Na]^{+}$ was observed in ESI-MS spectrum further support the formation of the phosphonate **107**.

After oxazolidinone phosphonate **107** was prepared successfully, our next task was to assemble phosphonate ester-**107** with aldehyde **106** under Horner Wadsworth Emmons reaction conditions which would afford us the conjugated oxazolidinone **116**.

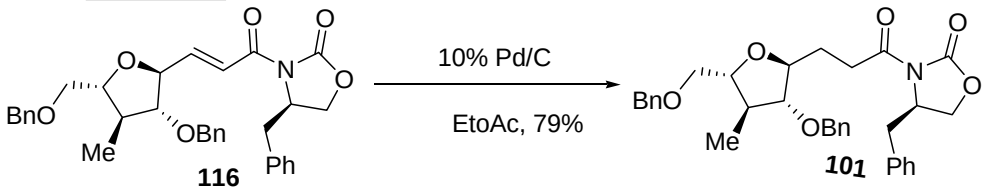
Scheme 31



To achieve this, oxazolidinone phosphonate **107** was treated with aldehyde **106** in presence of LiCl and DIPEA to provide conjugated oxazolidinone **116** in 88% of yield (Scheme 31). The structure of conjugated oxazolidinone **116** was confirmed from its ^{1}H NMR and ^{13}C NMR spectral study. The ^{1}H NMR spectrum showed that the characteristic oxazolidinone benzylic protons were resonated at δ 2.73, 3.35 ppm as doublet of doublet integrating for two protons, methylene group of oxazolidinone H-5,5' were located at δ 4.10 ppm as a triplet integrating for one proton and at δ 4.3 ppm as a doublet integrating for one proton, CH_2-**CH**-NH, H-4 of oxazolidinone appeared at δ 4.58-4.60 ppm as a multiplet integrating for one proton and significant olefinic protons resonances at δ 7.17, 7.35 ppm as a doublet of doublet integrating for two protons. All other protons were appeared at their expected chemical shifts. The ^{13}C NMR spectrum further supported the assigned structure of **116**. For instance, the characteristic olefinic carbons resonated at δ 120.43, 148.36 ppm corroborated the structure of **116**. Molecular

ion peak at *m/z* 564.48 $[M+Na]^+$ in ESI-MS spectrum was an additional support for the conjugated oxazolidinone **116**.

Scheme 32

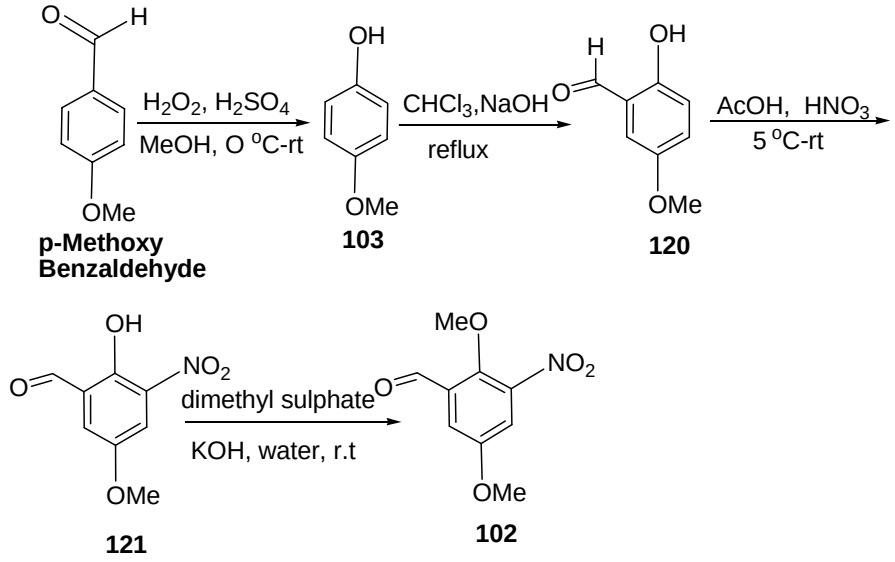


The conjugated oxazolidinone **116** was hydrogenated by using 10% Pd/C at 60 *psi* for 6 h to afford oxazolidinone derivative **101** (Scheme 32) in 79% of yield.[110b] All the spectroscopic and analytical data of this compound compared well with the product prepared by earlier route A. The present strategy, delivered us the required key intermediate-**101** in two steps with good yields starting with aldehydes-**106**.

Synthesis of Masked Quinine Aldehyde 102:

Having successfully arrived at the critical fragment A. our next objective was to synthesize the substitueted aldehyde **102** for the important Evan's *anti* Aldol reaction.

Scheme 33



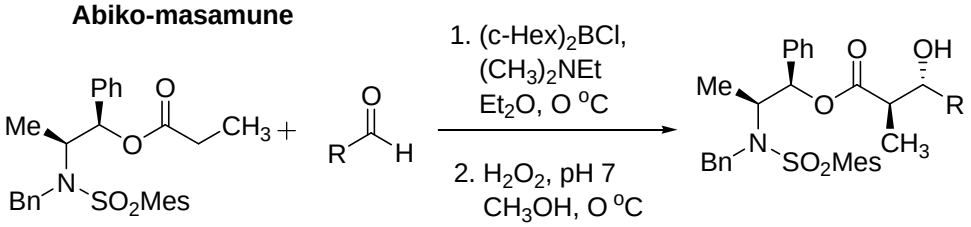
Accordingly, aldehyde **102** was prepared following literature procedure.[112] *p*-Methoxy benzaldehyde under acid catalysed Dakin rearrangement afforded *p*-methoxy phenol-**103**.[111] *ortho*-formylation of **103** under Reimer-Tiemen reaction conditions using $CHCl_3$ and NaOH as base provided **120**. Nitration of aldehyde **120** using HNO_3 : AcOH

in 1:1 ratio provided nitroaldehyde **121,** which on methylation using MeI and K_2CO_3 in DMF afforded masked quinine nitro aldehyde **102** (Scheme 33).[112] The structure of masked quinine nitro aldehyde **102** was determined by its spectroscopic and other analytical data (including M.P) which were in complete agreement with the reported values.[112]

With the two key intermediates required for aldol reaction in hand, the stage was set for the crucial Evan's asymmetric anti-aldol reaction to generate the two new stereogenic centers.

Evans anti aldol reaction : A brief overview

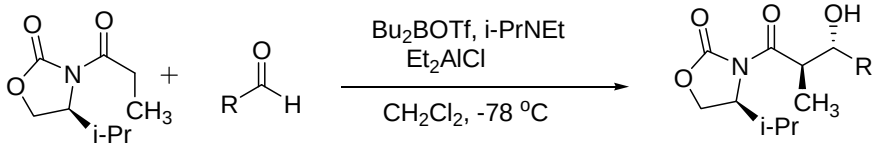
The aldol reaction is one the most powerful tool for formation of carbon-carbon bond reactions which lead to architecturing of complex intermediates with highly functionalized and stereoselective isomers. Even though good results are obtained from organocatalytic methods, the most generaliz methods are still in the area of research for construction of complex natural products. In that sense, auxillary based aldol reactions are the best known methods till today. This auxillary based aldol reactions will give high yields along with high stereoselectivity. A number of methods are available for syn-aldol adducts; amongst these reactions, Evans chiral auxillary based aldol reactions are the best known method. But a very few well known methods are reported in the literature for anti-aldol adducts, such as Abiko-Masamune norephedrine- based auxillary reactions which generally give fruitful results but not applicable to all systems.[114,115]



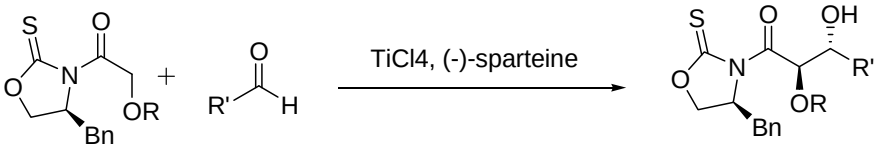
The first efficient stereoselestive anti aldol reactions are reported by Heathcock et. al., [116] *Crimmins et.al.* [117] *via boron-enolate and titanium-enolates by using stoichiometric amount of lewis acids. But in these reactions excess Lewis acid is required for complexation to the aldehydes. The explanation proposed for getting anti products that aldehyde is complexed to a lewis acid and these reactions go through an open*

transition state. Similar results were reported by our group [118] by keeping chirality in both partners for the aldolreaction. Other methods like Paterson method also give satisfactory selectivity with good yield, but it is only applicable to lactate derived ketones. Glycolate reactions provide another useful method but has limited applications. Other methods like Oxapyron boron enolates, selone auxillaries, chiral tin lewis acid catalysed reaction are little success in this regard.[119] A few methods for the formation of anti-aldol adducts are also reported by using stoichiometric addition of metals.

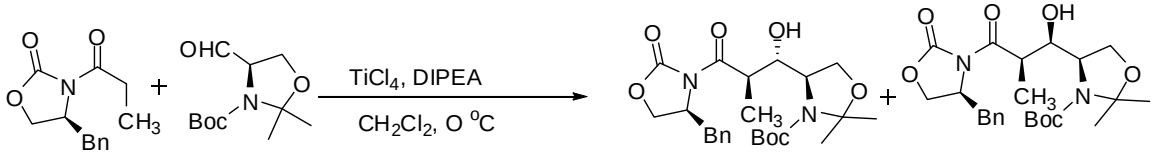
Heathcock



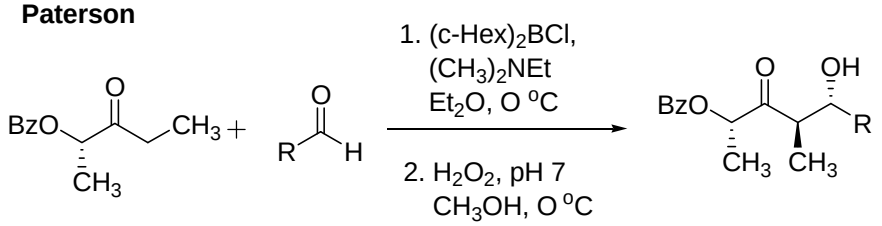
Crimmins



Gurjar. et.al

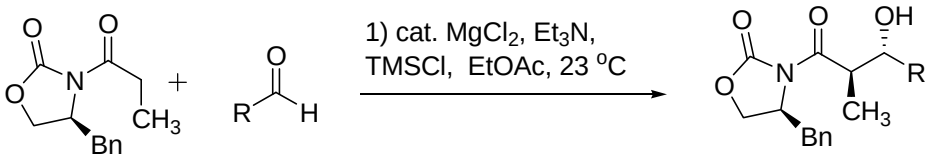


Paterson



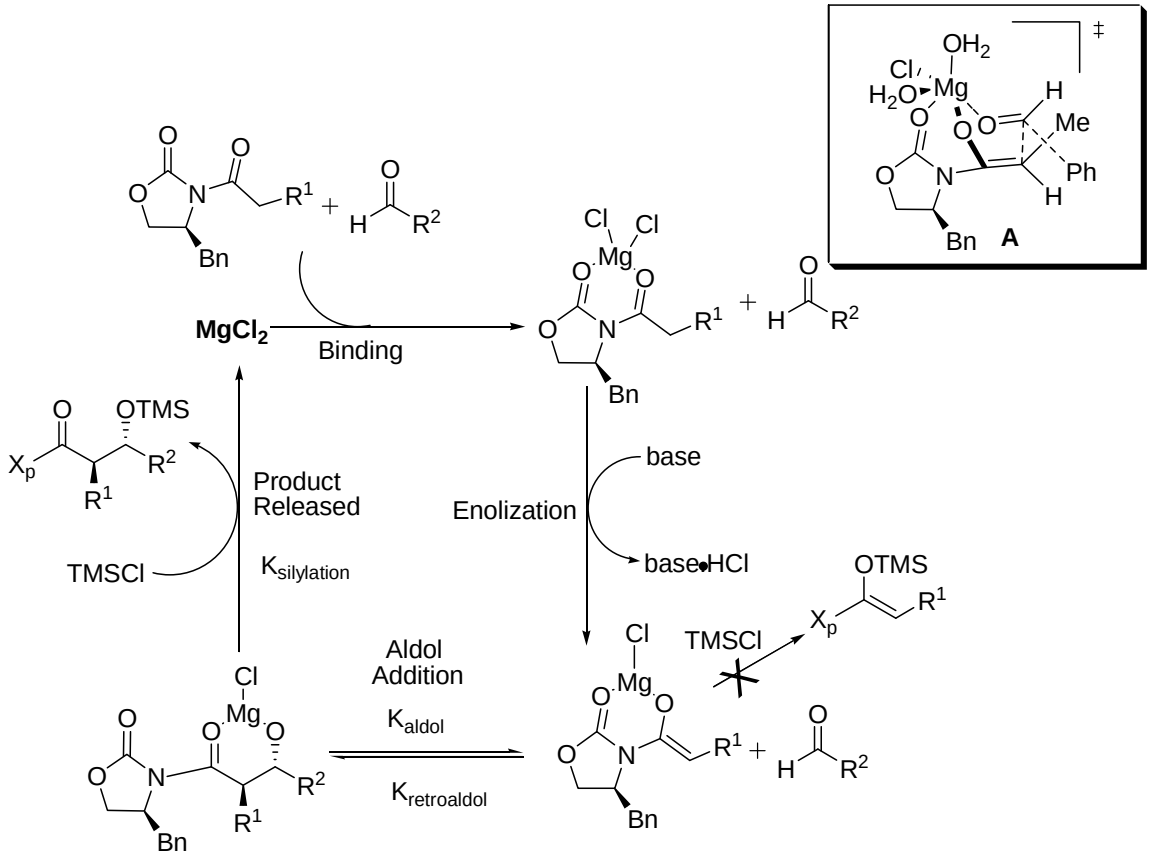
From all these, it is evident that currrently a good generalized method for the enantioselective formation of anti-aldol adducts is still not available. Evans and co-workers reported the first example of metal-catalysed aldol reactions by using both standard oxazolidinone[113a] and thiazolidine thione[113b] based auxiliaries. This is the most reliable method, in which magnesium halides catalyses the direct aldol reaction of chiral

N-acyloxazolidinones, N-acylthiazolidinethiones with aldehydes to give Evans anti aldol adducts with satisfactory yields and with high diastereoselectivity in the presence of an amine base and chlorotrimethylsilane. This methodology is applicable only to non-enolizable aldehydes, since self condensation of the aldehydes in those cases competes with the desired aldol reaction. It has been proven that this methodology is also applicable to sterically croweded, slow enolisable aldehydes.[113c] *The diastereoselectivity of this reaction depends considerably on both the structure of the aldehydes and the nature of the donor group on the part of the auxillary. When aliphatic imide reacts with aromatic aldehydes the product form in high yields and with high diastereoselectivies.*



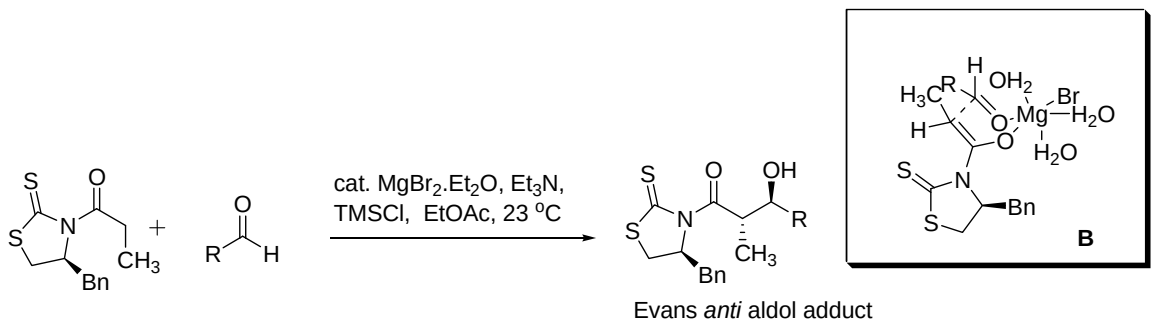
non-Evans *anti* aldol adduct

The control experiments indicate that the oxazolidinone-magnesium complex reacts with triethyl amine, yielding magnesium enolate, which adds reversibly to the aldehydes, forming the magnesium aldolate, this aldolate intermediate is silylated and thus the metal source ($MgCl_2$) is released and can proceed on to catalyse further reaction cycle. The mechanistic path way reveals mainly two points: enolate diastereoface selectivity and anti aldol diastereoselection. The enolate face selectivity observed for the N-acyloxazolidinone-derived magnesium enolate is fully consistent with a chelate-controlled process leading to the formation of non-Evans anti aldol adduct from the (Z)-metal enolate which will proceed by the boat-like transition state ***A***.[113a]



Proposed catalytic cycle for the magnesium halide-catalysed aldol reaction

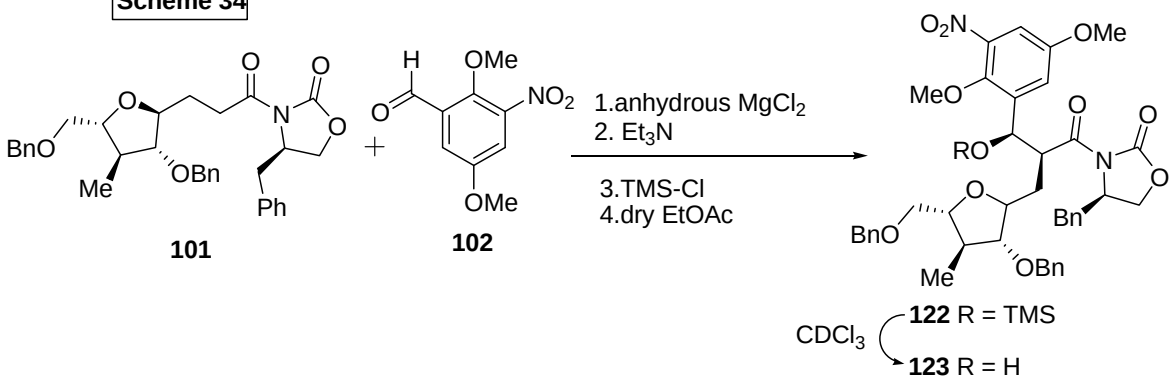
The thiazolidine thione auxillary based magnesium halide ($MgBr_2$)-catalysed aldol reactions affords opposite diastereomers of Evans anti aldol adduct compare to N-acyloxazolidinone. This anti aldol adducts are formed because of the N-acylthiazolidinethione-derived magnesium enolate exhibit the opposite face selection during these reactions proceeding through transition sate ***B*** *(non-chellated).*[113b]



Evans *anti* aldol adduct

Synthesis of Evans' *anti* aldol adduct 122:

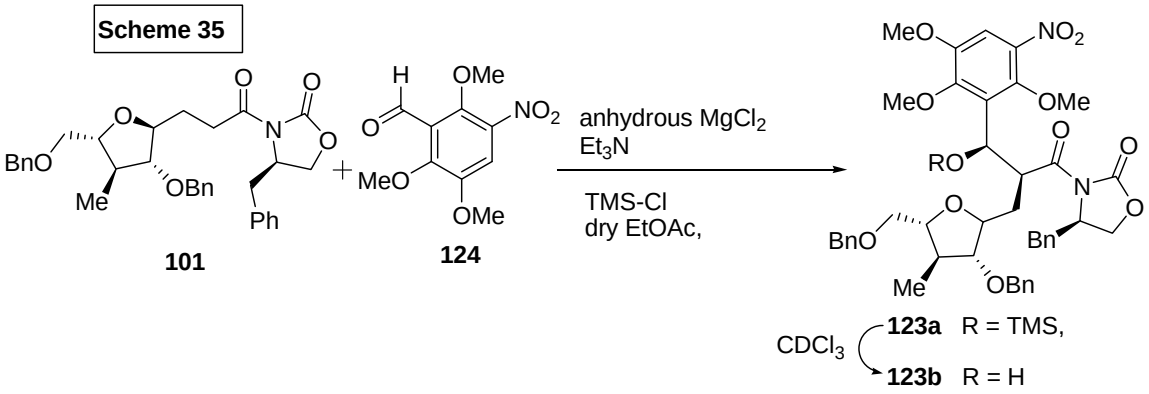
Scheme 34



Our first attempt was the Evan's *anti* aldol reaction between the carbohydrate derived oxazolidinone **101** with highly substituted arylaldehyde **102** by using standard Evan's *anti* aldol reaction condition[113a] to generate required chiral centers of the key fragment of Herbimycin A. This reaction condition using magnesium chloride as a chelating agent gives good distereoselectivity along with excellent yields. In the present case the oxazolidinone with chiral moiety would give the same results of the expected isomers in the course of the aldol reaction or will react in opposite way leading to other isomers. For instance, Oxazolidinone **101** was treated with anhydrous $MgCl_2$, triethylamine, benzaldehyde derivative **102** and chlorotrimethylsilane in dry ethylacetate as solvent at rt under nitrogen atmosphere for 20 h to give TMS ether derivative **122**, and free hydroxyl compound **123**, as a single isomer with excellent yield [light yellow color liquids and the aldol adducts **122** (OTMS) : **123** (OH) in 1:1 ratio] (Scheme 34). The reaction occurs by following non chelated transition state through Z- enolate to produce non-Evans *anti* aldoladduct. The structure of the Evans *anti* aldol adduct was confirmed by extensive spectroscopic studies and other analytical data. In the ^1H NMR spectrum of the OTMS aldol adduct showed characteristic OTMS protons resonances at δ 0.01 ppm as a siglet integrating nine protons, benzylic proton resonated at δ 5.44 ppm as a doublet of doublet of doublet integrating one proton and apprearence of new signal as doublet of doublet at δ 2.57 ppm integrating one proton. The rest of the protons appeared at the expected chemical shift values. In the ^{13}C NMR spectrum showed OTMS carbon

appeared at δ 0.08 ppm, benzylic carbon resonances at δ 79.54 ppm and new peak at δ 41.78 ppm was observed. In addition, the mass spectral analysis showed molecular adduct peak *m/z* at 849.34 $[M+Na]^+$ in ESI-MS spectrum. The elemental analysis data also confirmed the structure of **122**. The stereochemical assignment was done by similar reaction carried out in proceeding **section II** by using same oxazolidinone **101** with highly substituted arylaldehyde **124** under standard Evan's *anti* aldol reaction condition which afforded Evans' anti aldol adduct **123a,** in which the stereocentral ambiguity confirmed from its single X-ray crystal structure analysis along with spectroscopic and other analytical data (**Figure 9**).

Scheme 35



101 **124**

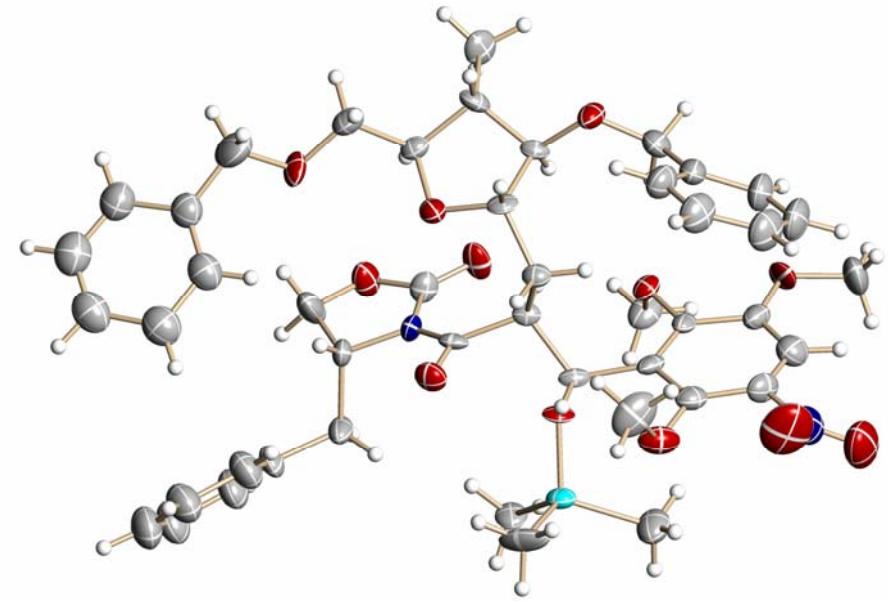
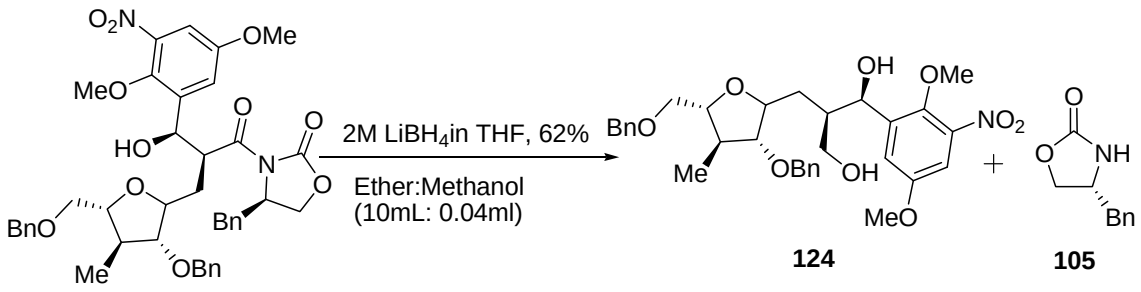


Figure 9: Crystal structure of 123a (Evans' anti aldol adduct)

The aldol adduct **123** (R = H) was confirmed by extensive NMR studies. The ^{1}H and ^{13}C NMR spectrum of **123** showed characteristic chemical shifts due to both fragments. The Benzylic proton appeared at δ 5.18 ppm as doublet integrating for one proton. Rest of the protons had expected chemical shifts. The ^{13}C NMR spectrum further established the assigned structure of **123** In addition, the mass spectral analysis showed the molecular ion peak at *m/z* 777.48 for $[M+Na]^{+}$. The OTMS derivative was very unstable in nature and immediately converts into hydroxy aldol adduct even in $CDCl_3$, or mild acidic conditions.

Scheme 36

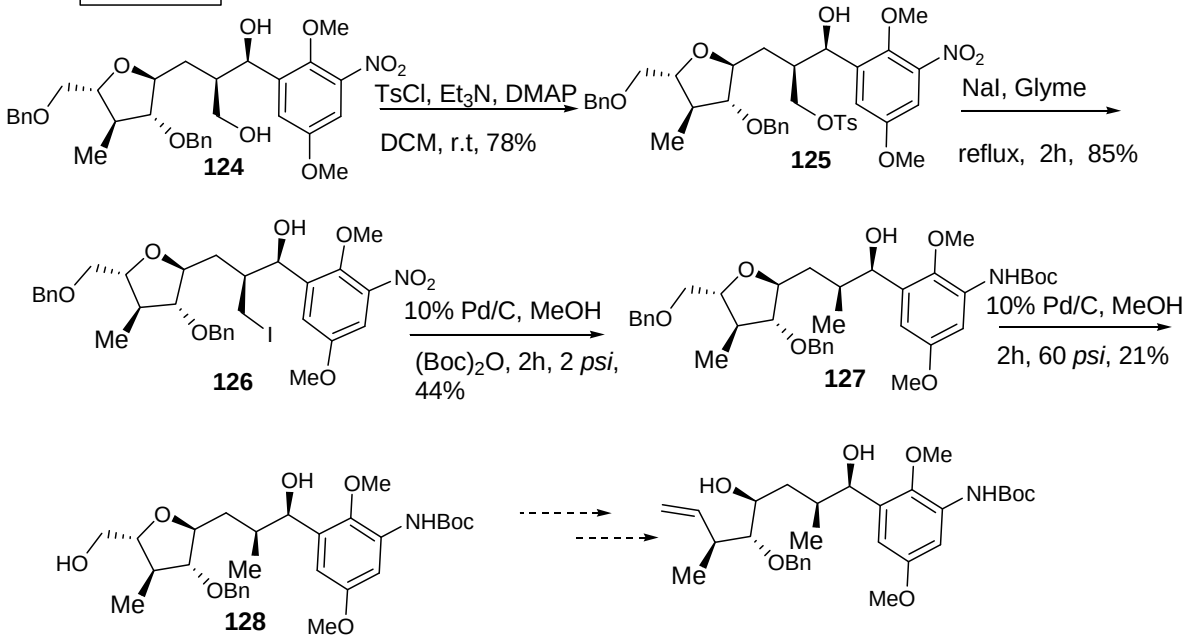


123 **124** **105**

Amongest the five stereocenters, in the aldol product- **122**, the 12-hydroxy with *S*-configuration is carried forward from the D-Glucose. The 10 *S*-Methyl and 11 *R*-OH created by the regioselective opening of epoxide and remaining two chiral centers (14 *S*-Methyl, 15 *R*-OH) generated by Evans' *anti* aldol reaction.

Our next target was to generate the required methyl group at C-14 position of key fragment of Herbimycin A. To achieve this, at first the oxazolidinone moiety was reductively removed by using 2M lithiumborohydride in THF and Evans' *anti* aldol adduct **123** was taken in a mixture of solvents (ether: methanol in a 10:0.4 ratio) to afford diol **124** as a sole product (Scheme 36).[120] The product was confirmed by its ^{1}H NMR in which appearance of new methylene protons at δ 3.55 ppm as a doublet integrating for two protons accounts for the $-CH_2OH$ group. The signal at at δ 71.25 ppm in ^{13}C NMR spectrum was further confirmed the structure of **124**.

Scheme 37

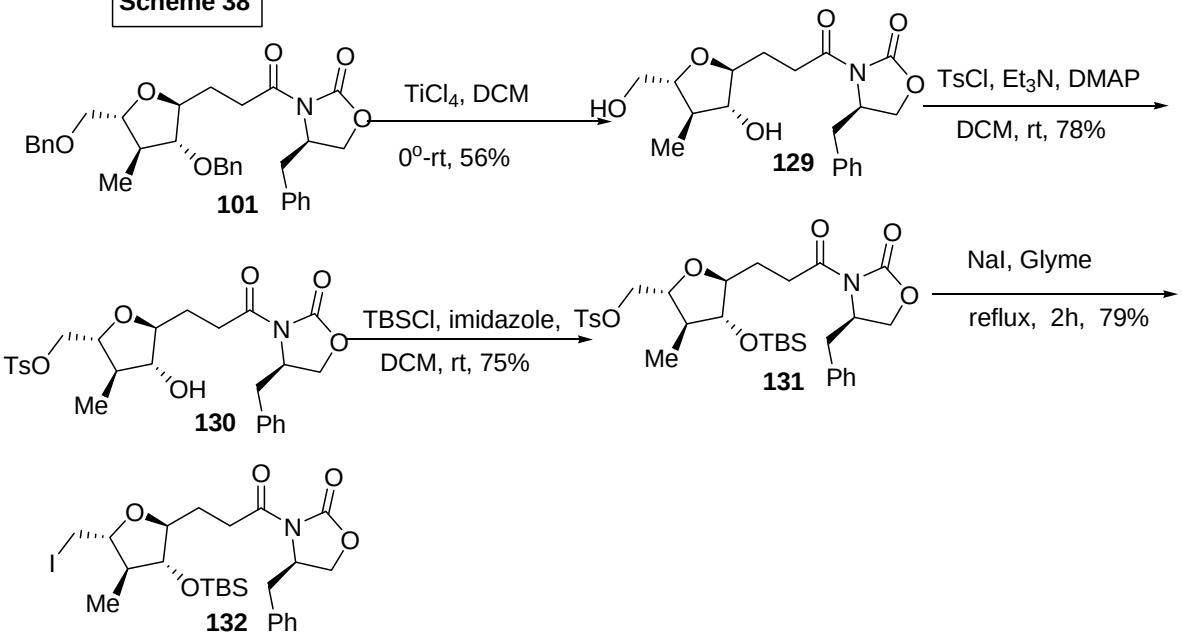


Once the reductive removal of Oxazolidinone afforded the primary alcohol **124**. next objective was the deoxygenation of this primary alcohol, which would provide us the required Me-group. To achieve this target, we protected the primary OH group of Diol **124** as its Tosyl ether using *p*-TsCl and Et_3N in CH_2Cl_2 at room temperature which furnished the tosylate **125** in 78% yield. **125** was characterirised by the ^1H NMR spectrum; a signal at δ 2.40 ppm due to -CH_3 group and two A_2B_2 doublets at δ 7.16 and 7.67 ppm confirmed the presence of p-toluene sulphonyl group. The tosylate **125** was refluxed with NaI in mono-glyme for 2h to afford the iodo derivative **126** which was confirmed with the help of ^1H and ^{13}C NMR spectra. For instance, the ^1H NMR spectrum showed the presence of up field peak at δ 1.99-2.13 ppm for methylene group. In the ^{13}C NMR spectrum showed new peak at δ 10.81 ppm indicates it's formation. The iodo derivative **126** was exposed to 10% Pd/C and Boc anhydride in MeOH at 2 *psi* of hydrogen gas to afford product **127** with the desired Me-group at C-14, and the reduction of the NO_2 group on phenyl ring to the amine followed by protection (Scheme 37). The ^1H NMR spectrum of **127** showed new doublet signal at up field region of the spectrum at δ 0.86 ppm due to the newly generated Me-group integrating for three protons, at δ 1.53 ppm integrating for nine protons represents Boc group, along with broad singlet at δ 6.89 ppm was attributed to N-H proton. In the ^{13}**C NMR** spectrum appearance of peak at δ

14.66 ppm for methyl carbon and a new peak due to Boc methyl carbon resonance at δ 28.32 ppm indicates it's formation. In addition, the mass spectral analysis showed molecular ion peak at *m/z* 658.64 $[M+Na]^+$ gave additional support for product **127**. The spectroscopic and elemental data confirmed the structure of **127**.[121]

Our next target was converting Int-**127** to Vassela-Bernet precursor. To achieve this, we tried the deprotection of primary benzyl group of **127** by using 10% Pd/C in MeOH at 60 *psi* which afforded primary alcohol **128** with very low yield. Several other unidentified side products formed during the reaction. Unfortunately to our destiny, Other debenzylation methods like Raney Ni mediated reaction were also unsuccessful leading to decomposition of starting material.

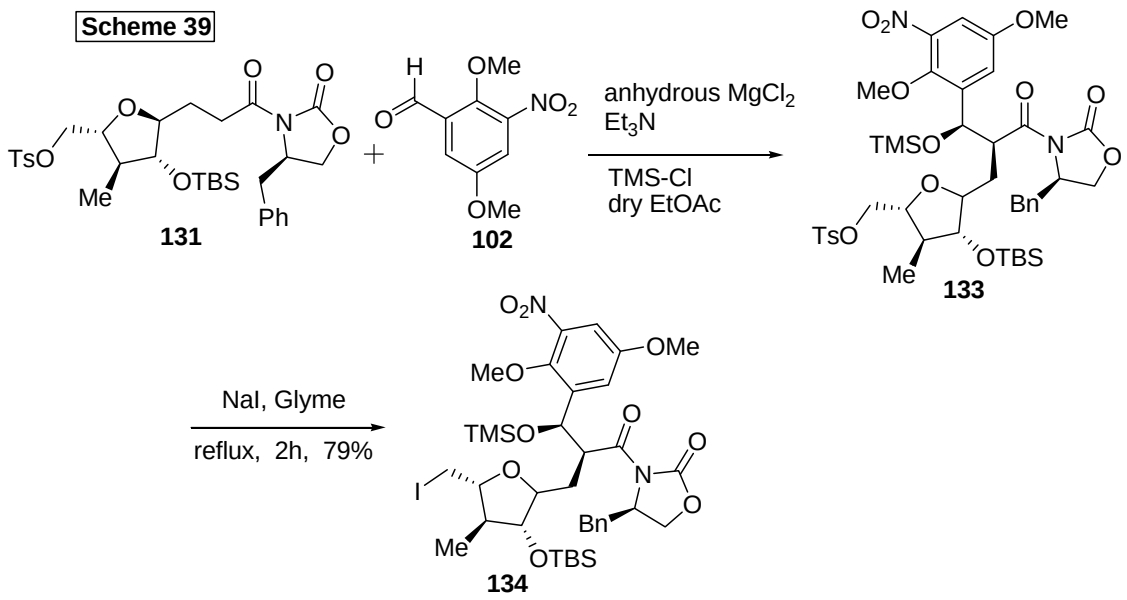
Scheme 38



To overcome this critical manipulation step at an advanced stage of the synthesis, we redesign our strategy by changing the protecting group from benzyl to other easily removable protecting groups like TBS in the early stage. The Bn-group of **101** were deprotected using strong Lewis acid like $TiCl_4$ in dichloromethane at 0 ^oC which afforded dioloxazolidinone derivative **129**.[122] The structure of **129** was confirmed by its ^1H and ^{13}C NMR spectra, in which appearance of only five protons in the aromatic region corresponding to oxazolidinone phenyl moiety. The primary OH group of **129** was selectively protected as its tosylate derivative **130** by using p-TsCl and Et_3N in CH_2Cl_2

at room temperature, **130** was confirmed from its ^{1}H and ^{13}C NMR spectral anlysis. The free hydroxyl group present in monotosyl derivative **130** was then converted into the corressponding TBS ether with TBS-Cl and Imidazole in CH_2Cl_2 at 0 ^{o}C to furnish **131**. The ^{1}H NMR spectrum of **131** showed the characteristic peaks of TBS group with the expected values. Refluxing tosyl derivative **131** with NaI in glyme for 2 h afforded iodoproduct **132** which was confirmed from ^{1}H and ^{13}C NMR spectra **(**Scheme 38**).** The ^{1}H NMR spectrum showed peaks in up field region of the spectrum at δ 2.76 ppm and 3.02 ppm as a doublet of doublet integrating for two protons attributed to methylene group and all other protons signals appeared at their respective chemical shift values. In the ^{13}C NMR spectrum appearance of peak at δ 9.82 ppm further confirmed the structure of **132**.

Scheme 39



We attempted the preparation of **134** following 2 routes. First, OTs derivative-**131** was coupled with aldehydes **102** under Evan's *Anti* aldol conditions in the presence of anhydrous $MgCl_2$, Et_3N and TMSCl in dry EtoAc to afford the aldol adduct **133** as its TMS ether **133**, as a single isomer with excellent yield (Scheme 39). The OTMS aldol adduct **133** was confirmed by extensive ^{1}H and ^{13}C NMR spectral analysis. The aldol adduct showed presence of characteristic benzylic hydroxyl group protected as TMS ether, which were appeared as a singlet at δ 0.01 ppm integrating for nine protons. Other significant peak due to benzylic proton resonated at δ 5.62 ppm integrating one proton and appearance of new peak at δ 2.26 ppm as a doublet of doublet integrating one proton

was confirmed the structure of **133**. In the ^{13}C NMR spectrum, the benzylic carbon resonances at δ 80.69 ppm and appearance of new peak at δ 42.88 ppm gave strong support for aldol adduct and other spectroscopic data were in good agreement with the assigned values. In addition, the mass spectral analysis showed a molecular ion peak at *m/z* 938.82 $[M+Na]^+$ further support for that observation. The tosyl group of **133** converted to its iododerivative by refluxing with NaI in glyme for 2h to afford iodoproduct **134**. The structure of the iodoproduct **134** confirmed by it's ^1H NMR spectrum, in which a signal due to methylene appeared at δ 2.59 and 3.13 ppm and all other proton signals appeared at their respective chemical shift values. The alternative approach was coupling of iododerivative-**132** with aldehydes-**102** under the same-anti Evan's aldol condition also afforded us the product-**134**. It's spectroscopic and elemental analysis data exactly matched with the data of **134** which was prepared by the earlier method (Scheme 39).

Our next aim was the reductive cleavage of iodoproduct **134** under Vassela-Bernet reaction conditions[123] to reach our target of getting Key fragment (C8-N22) of Herbimycin A.

A BRIEF INTRODUTION TO VASELLAR REACTION:

The area of complex natural products synthesis demands for new synthetic methods with economical and high yield. Vassela-Bernet reaction was one of the good method for preparing olefinic carbonyl compounds by using very cheaper and less toxic zinc metal on the haloderivative of carbohydrate moieties.[123] The reaction proceeds through the reductive cleavage of carbohydrate based haloderivatives which was first observed by Vassela. These olefinic carbonyl intermediates were very useful for construction of carbasugars,[124] fused heterocyclised products by cycloaddition,[123] barbier reaction on carbonyl group leading to olefins useful for RCM, enyne metathesis[125] and synthesis of other compounds[126].

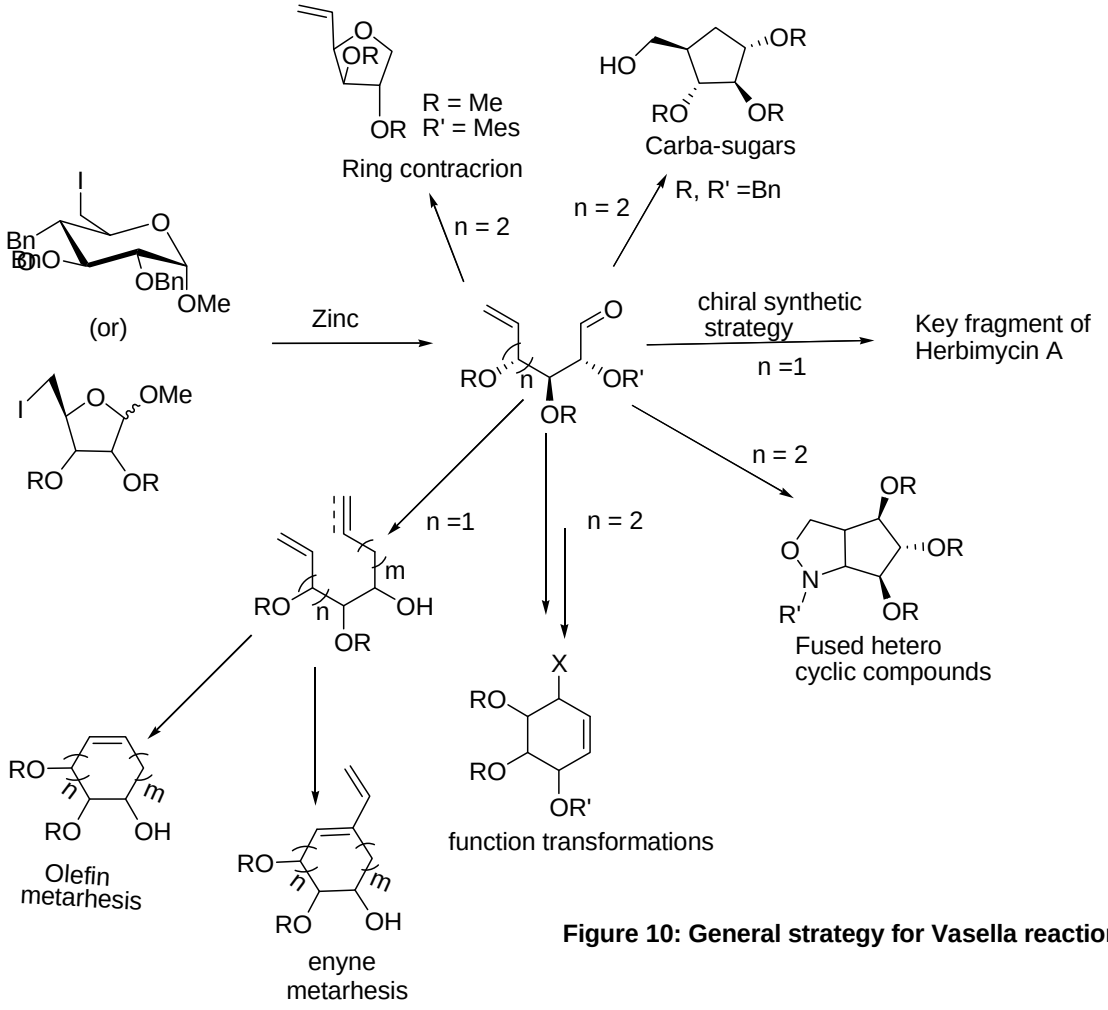


Figure 10: General strategy for Vasella reaction

Even though the Vassela-Bernet reactions usually results in olefinic carbonyl compounds, In our present strategy we planned to utilize this reaction for arriving at the chiral hydroxy olefinic intermediate which can be transformed into Key fragment of the Herbimycin A. it successful, this would be the first case for this type of transformation using the vassela-Bernet reaction.

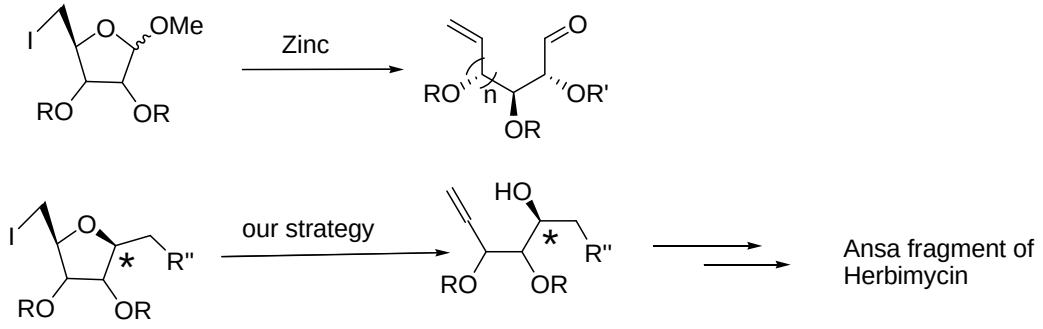
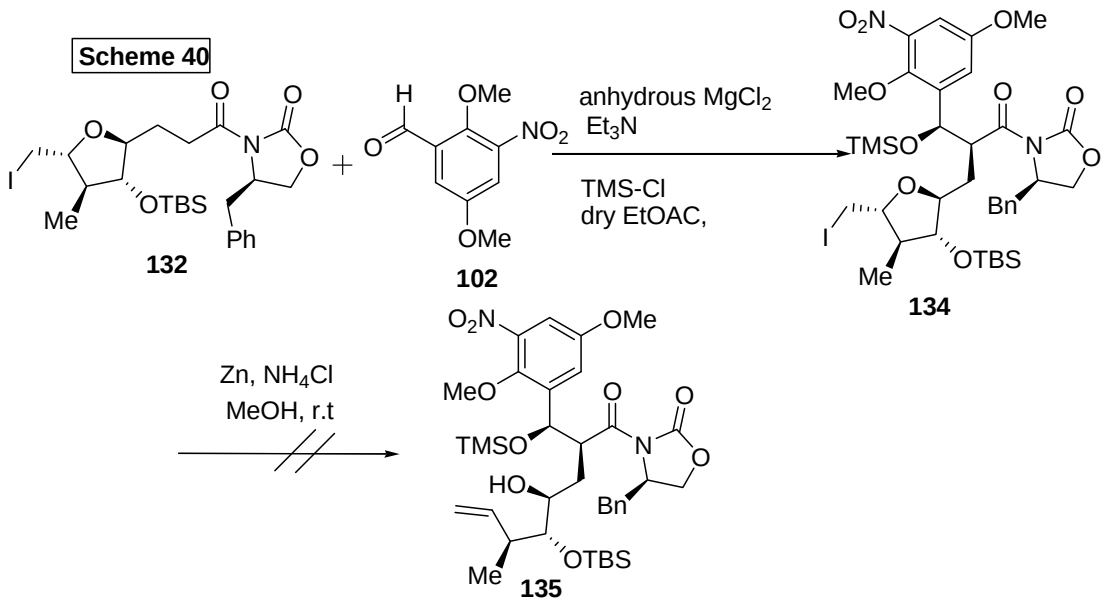


Figure 11: Our modification for Vasella reaction



Subjecting, our advanced iodo-intermediate **134** to vasellar reaction by treating with Zn/NH_4Cl in MeOH, unfortunately resulted in complete decomposition of the starting material (Scheme 40). This results drawn our attention towards finding out the factors responsible for the decomposition of Evan's anti aldol adduct **134** under vassela-Bernet reaction condition.

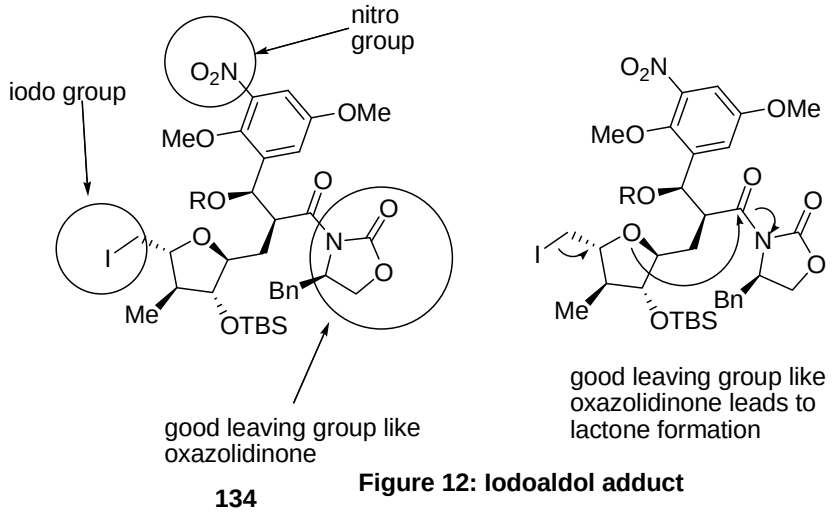


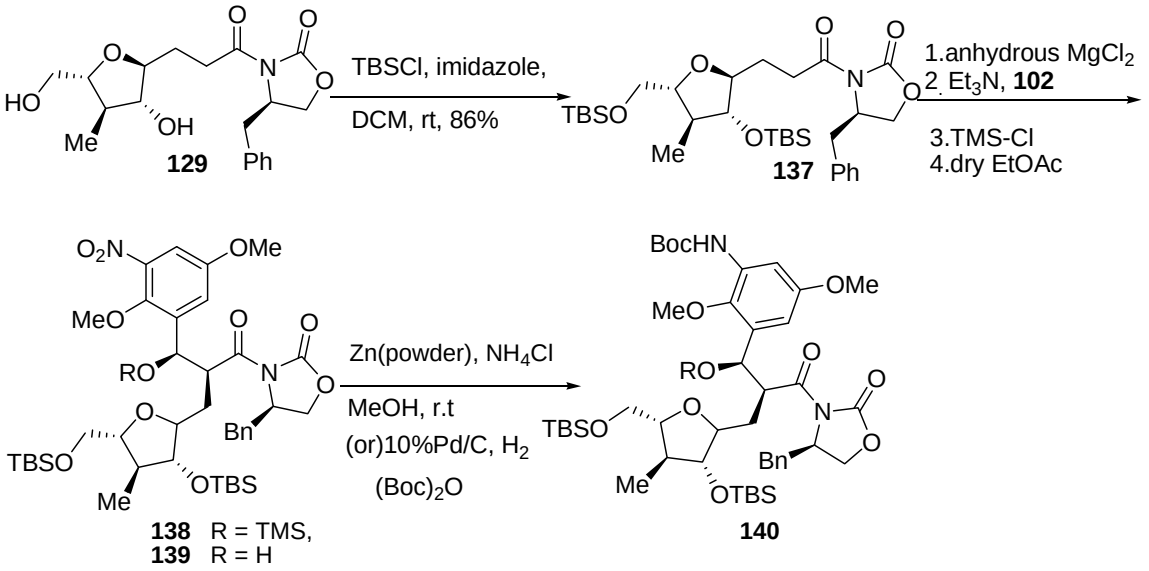
Figure 12: Iodoaldol adduct

Careful analysis of aldol adduct **134** reveals that three groups namely the iodo group on the carbohydrate moiety, the nitro group on the aromatic ring and the oxazolidinone moiety are in antiperiplanar position to each other. These 3 groups in the

same molecule could be responsible for decomposition. Also, the nitro group on the aryl moiety underwent reduction leading to amino group and further decomposition.

Accordingly, we planned to do controlled experiments to test the compatibility of int-**134**; following our new strategy we planned to reduce the nitro group prior to the Vassela-Bernet reaction.

Scheme 41

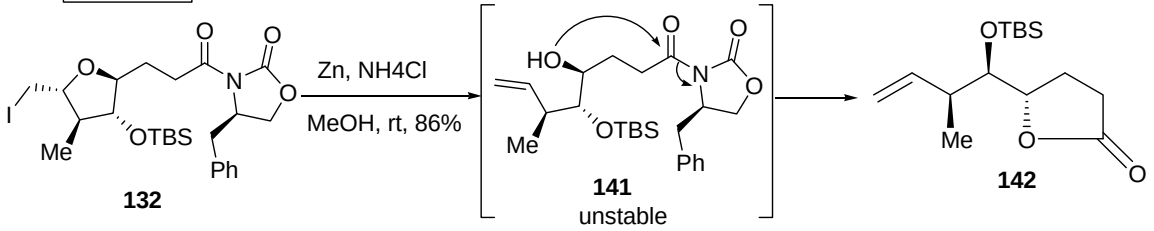


According to our new strategy, we prepared the di-TBS protected oxazolidinone **137** from diol **129** using TBS-Cl and Imidazole in CH_2Cl_2 at 0 ^oC. The ^1H NMR spectrum of **137** showed the characteristic peaks for two TBS groups and rest of the spectral data were in good agreement with excepted values. Under standard Evans *anti* aldol reaction conditions these two synthons **137** and aryl aldehyde **102** were coupled which afforded Evan's *anti* aldoladducts, **138** (TMS ether) and free hydroxyl compound **139** as single isomer [OTMS: OH in a 1:1 ratio] (Scheme 41). The structures of Evans' antialdol adducts were confirmed by extensive study of spectral data and other analytical analysis. For instance, the characteristic benzylic proton appeared as doublet at δ 5.40 ppm integrating for one proton, observation of new peak at δ 2.31 ppm as a doublet of doublet integrating for one proton. Rest of the proton signals appeared at their respective chemical shift values. The di-TBS Evans adduct **138** was exposed to activated zinc, catalytic NH_4Cl in dry MeOH to afford a very low percentage of **140** along with unidentified materials. Similar results were observed by treating **138** with 10% Pd/C in

methanol at 2 *psi* hydrogen atm. These results indicated that the nitro group present in the aromatic moiety may be responsible for the decomposition of aldol adducts.

When iodo derivative **132** was treated with activated Zn and catalytic NH_4Cl in MeOH, with in 0.5 hr the starting material was disappeared and a new compound was formed which converted into another product under prolonged reaction condition. The unstable intermediate was isolated and characterized and all the spectral data supported structure of the intermediate **141**.

Scheme 42

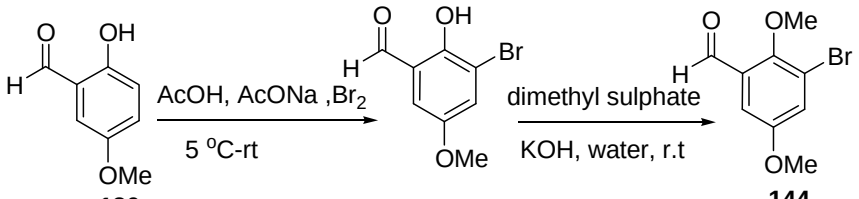


For instance, the ^{1}H NMR spectrum showed characteristic olefinic protons deshielded and appeared at δ 5.02-5.06, 5.72-5.79 ppm as multiplets integrating for three protons. all other proton signals appeared at their respective chemical shift values. The characteristic resonances at δ 115.12, 139.89 ppm were due to olefinic carbons observed in the ^{13}C NMR spectrum. In the mass spectral analysis showed a molecular ion peak at *m/z* 484.64 $[M+Na]^+$ and other analytical data was supporting the structure of hydroxyl olefine **141.** This hydroxy olefinic intermediate **141** readily undergoes transformation into a stable product which was characterized to be **142**. All the spectral data supported the assigned structure. In the ^{1}H NMR spectrum of **142,** the peaks due to oxazolidinone were departed and significant olefinic protons were appeared at δ 4.91-4.98 and 5.63 ppm in the down field region of spectrum. The peaks at δ 115.17 and 139.93 ppm were due to olefinic carbons in the ^{13}C NMR spectrum was observed. The IR absorption at 1640, 1776 cm^{-1} were attributed to lactone carbonyl functionality of **142.** Mass spectral analysis showed a molecular ion peak at *m/z* 307.64 for $[M+Na]^+$ gave additional support for lactone **142** formation.

All these results from the controlled experiments indicated that under Vassela-Bernet condition, in the presence of the oxazolidinone moiety the substrate under goes reductive cleavage leading to lactone formation.

To confirm the role of the NO_2 group (on the phenyl ring) in this kind of decomposition, we planned to keep a Bromo group instead of the NO_2 group and then try the vassela reaction. Accordingly, bromo-aldehyde **144** was prepared as shown in (scheme 43) following literature procedure. [13]

Scheme 43



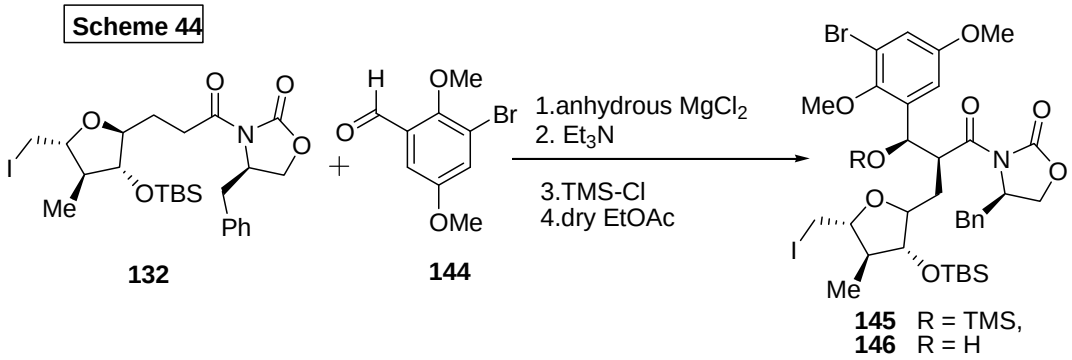
120
2-hydroxy-5-methoxy benzaldehyde

143

144

2-hydroxy-5-methoxy benzaldehyde **120** was converted its bromo derivative using Br_2/AcOH to afford **143** which was methylated using DMS/KOH to furnish **144** (Scheme 43). The structure of 3-bromo-2, 5-dimethoxybenzaldehyde was confirmed by comparing its spectral and other analytical data with reported one. [13]

Scheme 44



132

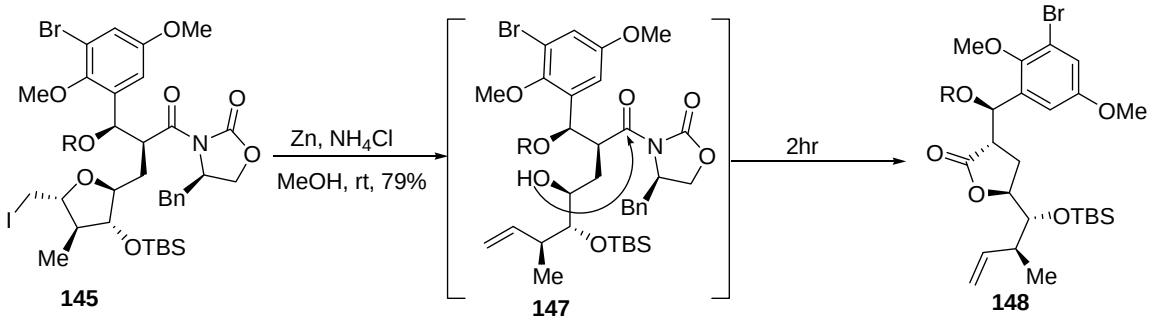
144

145 R = TMS,
146 R = H

Coupling of **132** and aldehydes **144** under Evan's anti aldol condition proceeded satisfactorily to afford the coupled adduct **145, 146** (Scheme 44). The structures of Evans' *anti* aldol adducts were confirmed by extensive study of speactral data and other analytical data.

When Iodo-adduct **146** was subjected to Vassela-Bernet reaction by treating with Zn/NH_4Cl in MeOH again similar results are observed and we could isolate the unstable hydroxyl olefinic intermediate **147** along with the more stable reductive cleavage bi-product lactone-**148**.

Scheme 45



The ^{1}H and ^{13}C NMR, IR and elemental analysis supported the structure of **147.** For instance, the ^{1}H NMR spectrum showed characteristic olefinic protons deshielded and appeared at δ 4.9-5.07, 5.61-5.68 ppm as a multiplets integrating for three protons. all other proton signals appeared at their respective chemical shift values. The characteristic resonance at δ 115.83, 142.51 ppm were due to olefinic carbons was observed in the ^{13}C NMR spectrum. The IR absorption at 1599 cm^{-1} was attributed to olefin functionality of **147.** In the mass spectral analysis showed a molecular ion peak at *m/z* 801.72 for $[M+Na]^{+}$ and other analytical data was supporting the Olefinic product **147** (Scheme 45).

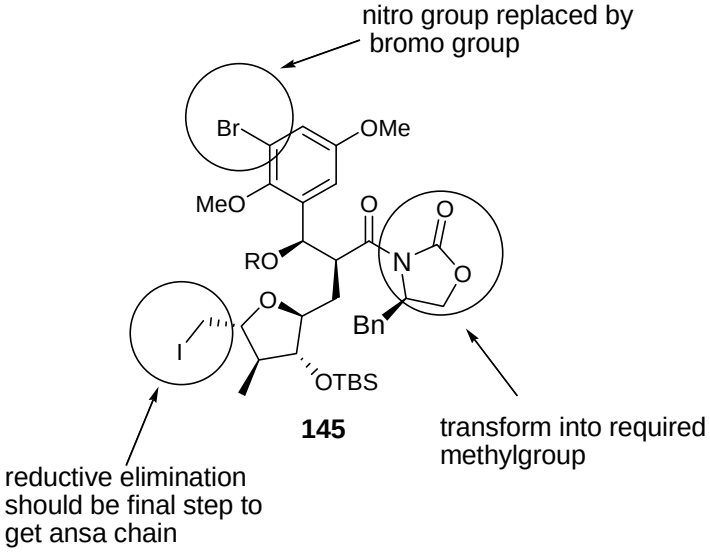
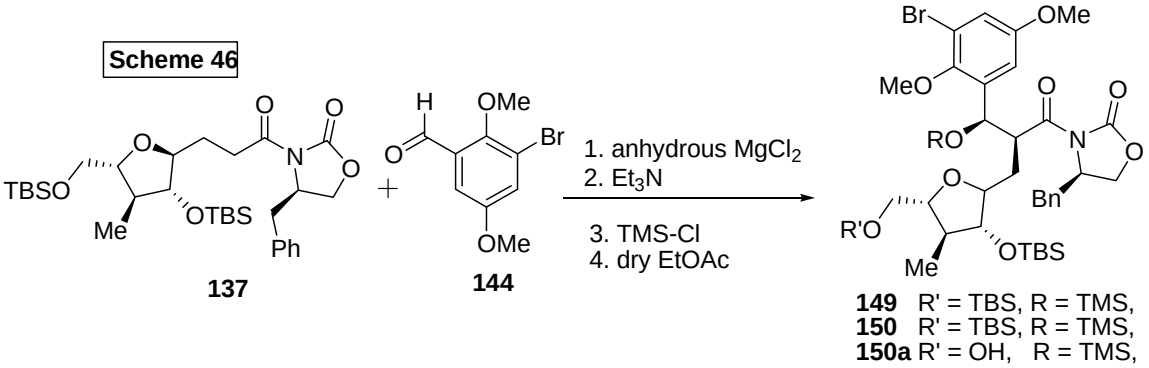


Figure 13: Revised Iodoaldol adduct

From the above controlled experiments we concluded that: the oxazolidinone moiety has to be removed and the C14 methyl group has to be created prior to the Vassela-Bernet reaction which should be carried out at the end of the synthetic sequence.

We replaced the NO_2 group of aryl moiety to the Bromo group due to its sustainability in the above controlled experiments.

Scheme 46



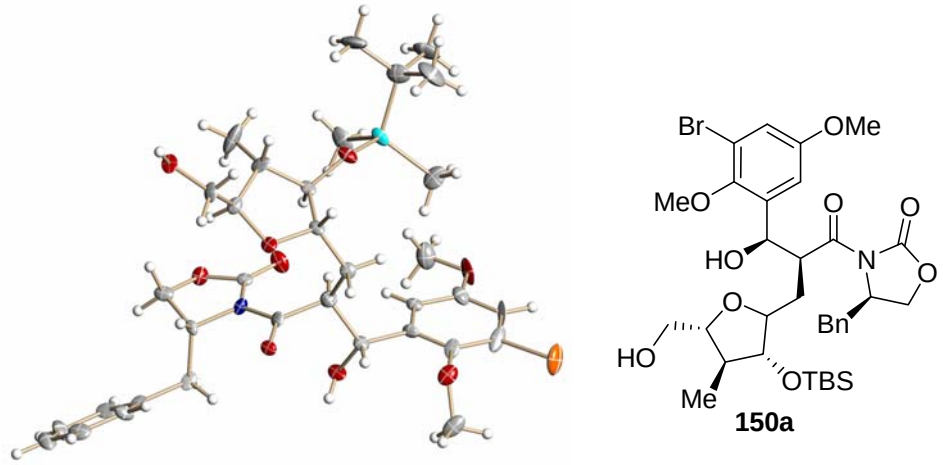
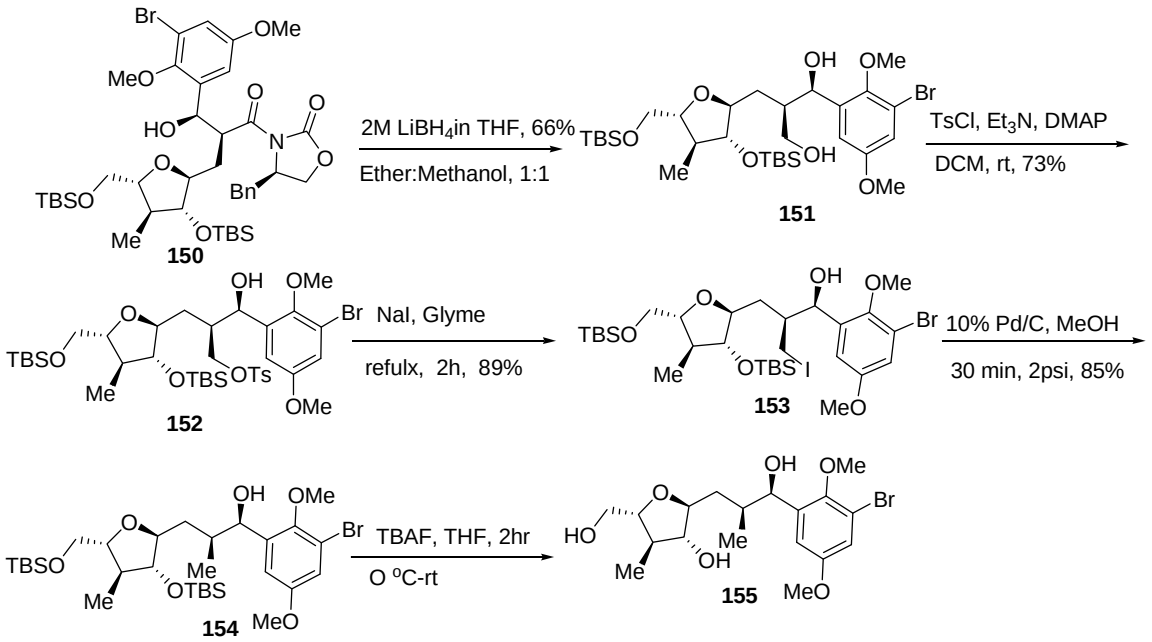


Figure13a: Crystal structure of Evan's anti aldol adduct 150a

Accordingly, oxazolidinone **137** was coupled with aldehyde **144** under standard Evan's anti aldol condition to provide the adducts **149** (TMS ether) and **150** (OH). The Evan's anti aldol adducts OTMS ether derivative **149,** and free hydroxyl compound **150** was obtained as a single isomer [(light yellow color liquid), **149 (**OTMS) : **150** (OH) : **150a** in a 1:1: 0.1 ratio)] (Scheme 46). The spectroscopic data were in good agreement with the assigned values.

Scheme 47



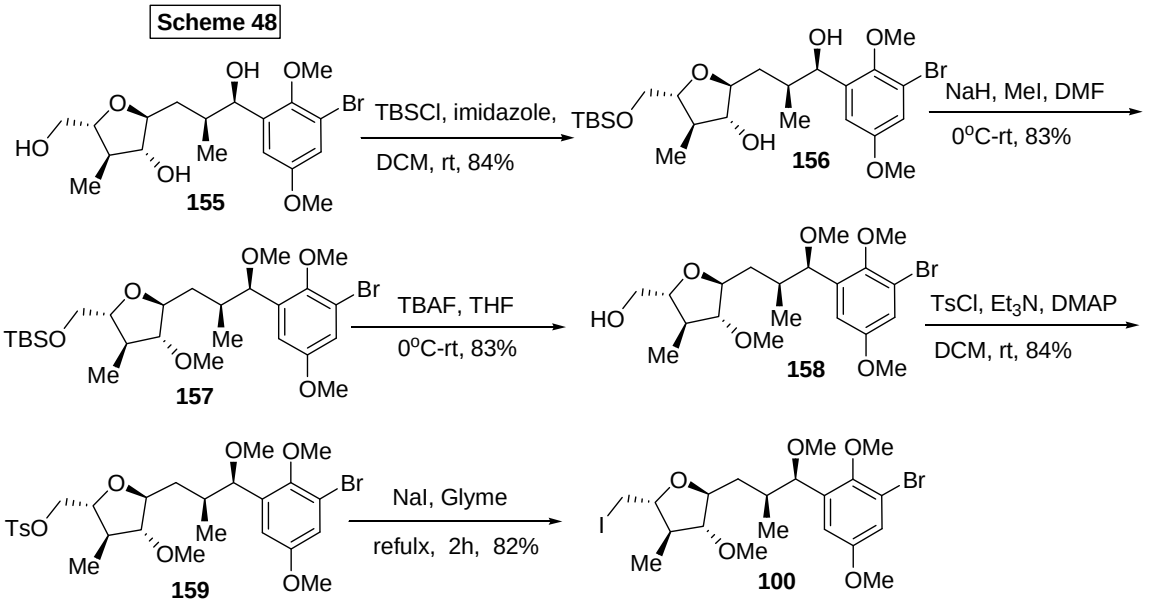
The oxazolidinone was reductively removed by using lithiumborohydride to afford primary alcohol **151**. The spectroscopic data of **151** were in good agreement with the assigned structure (Scheme 47). The primary OH of diol **151** was then selectively protected as its Tosyl ether using p-TsCl and Et_3N in CH_2Cl_2 at room temperature which furnished the tosylate derivative **152**. The tosyl derivative **152** was refluxed with NaI in glyme for 2h to afford iododerivative **153** which was confirmed from ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum showed the methylene proton was in shielded and appeared in the up field region of the spectrum at δ 3.38 ppm integrating two protons and all other proton signals appeared at their respective chemical shift values. In the ^{13}C NMR spectrum a methylene carbon resonances at δ 11.42 ppm was further confirmed the structure of **153**.

Our next target was the reduction of iodo group of **153** which would afford the Me-derivative **154**. this transformation was successfully accomplished using 10% Pd/C in MeOH at 2 *psi* H_2 atm with in 30 mins which afforded **154** with out disturbing the Bromo group on the phenyl ring. It's ^1H, ^{13}C NMR and other analytical data supported the structure of **154**. In the ^1H NMR spectrum of **154**, the new methyl group protons were shielded and appeared as doublet at δ 0.71 ppm integrating for three protons and all other proton signals appeared at their expected chemical shifts. The TBS groups of **154**

was removed by treating with TBAF in THF at rt to afford **155** (Scheme 47). The structure of the **155** was confirmed by it's ^{1}H NMR spectrum in which the peaks due to TBS groups were departed.

After having advanced key intermediate **155** with all the stereocenters with appropriate substituents, we went ahead and converted alcohol 155 into the desired iodosubstrate **100** as described below (Scheme-48) to try the critical Vassela-Bernet reaction which would provide us the Key Fragment (C8-C21) of Herbimycin A.

Scheme 48

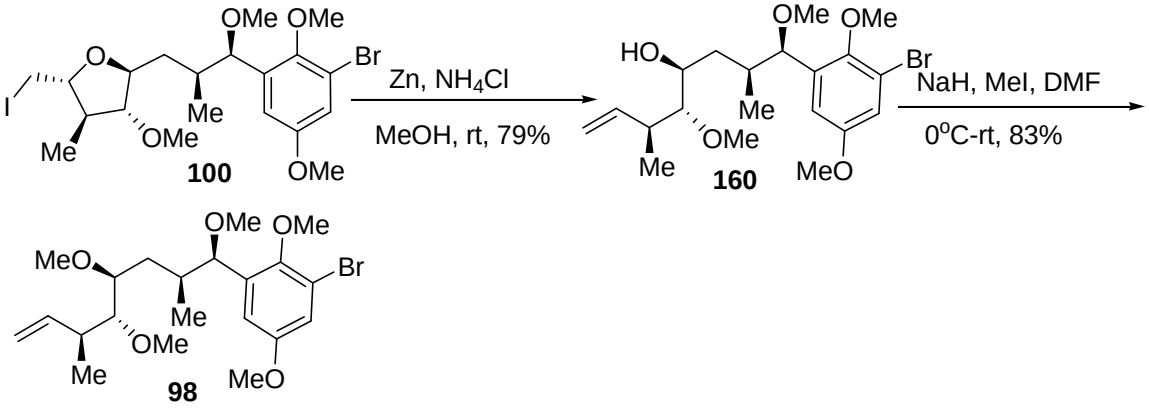


The primary hydroxyl group of triol **155** was selectively protected as its TBS ether **156** using TBSCl followed by protection of the two hydroxyl groups as their methyl ether derivatives **157**, which showed the appearence of characteristic TBS group peaks, two methoxy protons resonanced at δ 3.24, 3.36 ppm as singlets integrating for six protons in the ^{1}H NMR spectrum confirming the structure of **157**. Deprotection of TBS group of **157** was achieved by using TBAF in THF resulted in clean convertion to primary hydroxyl product **158**, which was converted into tosylate **159** whose structure was confirmed from the ^{1}H NMR, ^{13}C NMR and Mass spectral analysis**.** The tosyl derivative **159** was converted into iodo derivative **100** by refluxing with NaI in glyme for 2h; the structure of **100** was confirmed by ^{1}H and ^{13}C NMR spectral studies. For instance, the ^{1}H NMR spectrum showed the appearene of a doublet in the up field region

of specturm at δ 1.99-2.12 ppm for methylene group. In the ^{13}**C NMR** spectrum showed resonances at δ 9.42 ppm due to methelene carbon further confirmed the product **100**.

Having **100** in hand, the stage was set for Vassela-Bernet reaction, which would complete our synthetic campaign and would give us the Key fragment of Herbimycin-A.

Scheme 49

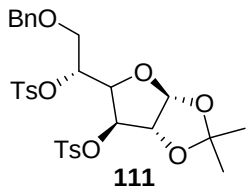


To our ought most satisfication, **100** under standard Vassela condition using Zn/NH_4Cl in MeOH afforded us the expected and desired hydroxyl olefin-**160** with excellent yield. (Scheme 49). The ^{1}H and ^{13}C NMR**,** IR and other analytical data supported the structure of **160.** The ^{1}H NMR spectrum showed the characteristic olefinic protons in a deshielded region and appeared as multiplets at δ 4.99 and 5.75 ppm. The rest of the protons were identified at their appropriate positions. In the ^{13}C NMR spectrum characteristic olefinic carbons resonance at δ 114.3, 141.41 ppm further supported the assigned the structure of **160**. In the IR, absorption at 1599 cm^{-1} was attributed to olefinic functionality of **160.** The mass spectral analysis showed a molecular ion peak at *m/z* 455.26 for $[M+Na]^{+}$ and other analytical data was supporting the structure of key fragment **160.** The free hydroxyl group present in **160** was then converted into as the corresponding methyl ether **98** by using NaH and MeI in DMF. The ^{1}H NMR spectrum, in which singlet at 3.32 ppm due to methoxy group were localized and rest of the protons had expected chemical shifts. The ^{13}C NMR spectrum further established the assigned structure of **98**.

In conclusion, we have successfully synthesized the C8 to N22 of Herbimycin A includes Evan's anti aldol reaction for construction of C14-Methyl, C-15 Hydroxy group and utilizing Vassela-Bernet reaction for constration of key fragment of Herbimycin A.

EXPERIMENTAL

(1*R*)-2-(Benzyloxy)-1-((6*S*,6a*R*)-2,2-dimethyl-6-(tosyloxy)tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethyl 4-methylbenzenesulfonate(111)



111

To a solution of the monobenzyl compound **110** (10 g, 32.2 mmol) in anhydrous pyridine (25 mL) at 0-5^{o}C, *p*-TSCl (11.77 g, 80.6 mmol) was slowly added over 2-h slowly. The mixture was stored for 3 days at room temperature. excess pyridine was removed by distillation to give thick residue, washed with water, and the solution partitioned between dichloromethane and water. The organic layer was washed with brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:6) to give as a colourless liquid **111** (17.5g, 88%). R_f 0.5(35% ethyl acetate/hexane).

Mol. Formula : $C_{30}H_{34}O_{10}S_2$

$[\alpha]_D^{25}$: -9.15 (*c* = 1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1020. 1215, 1719, 3020, 3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.23 (s, 3H), 1.26 (s, 3H), 2.37 (s , 3H), 2.42 (s, 3H), 3.58 (s, 2H), 4.21 (q, *J* = 12.2 Hz , 2H), 4.51 (dd, *J* = 2.5, 5.9, Hz, 1H), 4.79 (q, *J* = 5.9 Hz, 2H), 5.07 (d, *J* = 2.5 Hz, 1H), 5.80 (d, *J* = 3.5 Hz, 1H), 7.09-7.27 (m, 7H), 7.34 (d, *J* = 8.03 Hz, 2H), 7.71 (d, *J* = 8.03 Hz, 2H), 7.86 (d, *J* = 8.03 Hz, 2H) ppm.

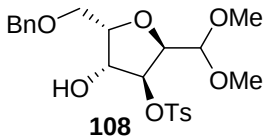
^{13}C NMR (125 MHz, $CDCl_3$) : δ 21.42 (q, Ts-CH_3), 26.13 (q, Ts-CH_3), 26.38 (q, CH_3), 67.81 (t, Bn- CH_2), 72.55 (t, CH_2), 76.68 (d, CH), 77.19 (d, CH), 80.68 (d, CH), 82.06 (d, CH), 104.13 (d, CH), 112.47 (s, C), 127.04 (d, CH), 127.71 (d, CH), 127.97 (d, CH), 129.28 (d, CH), 129.89 (d, CH), 132.37 (s, C), 134.16 (s, C), 137.56 (s, C), 144.28 (s, C), 145.34 (s, C) ppm.

ESI-MS (*m/z*) : 641.60 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 58.24; H, 5.54; S, 10.37 %

Found: C, 58.25; H, 5.56; S, 10.39 %

(2*R*, 3*S*, 4*R*, 5*S*)-5-((Benzyloxy)methyl)-tetrahydro-4-hydroxy-2-(dimethoxymethyl)furan-3-yl4-methylbenzenesulfonate (108).

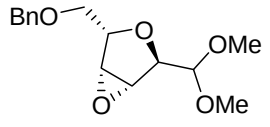


108

To a solution of the ditosylcompound **111** (17 g) in anhydrous methanol at 0-5^{o}, 5 mL acetyl chloride was slowly added over a 30 min period. The mixture was refluxed for 3 days. Methanol was removed under reduced pressure to give thick residue (**108**), which was proceed for next step with out purification. R_f 0.33(25% ethyl acetate/hexane).

Mol. Formula	: $C_{22}H_{28}O_8S$
$[\alpha]_D^{25}$	: +10.18 (*c* = 2.9, $CHCl_3$)
IR ($CHCl_3$) υ	: 667, 1020. 1216, 1633, 3390 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 2.49 (s, 3H), 3.18 (s, 3H), 3.42 (s , 3H), 3.88 (t, *J* = 4.3 Hz, 2H), 4.29-4.38 (m, 3H), 4.47 (d, *J* = 7.2, 2H), 4.58 (d, *J* = 4.33, 2H), 4.88 (d, *J* = 3.2 Hz, 1H), 7.30-7.41 (m, 7H), 7.85 (d, *J* = 8.3 Hz, 2H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 20.86 (q, Ts-CH_3), 51.94 (q, CH_3), 53.88 (q, CH_3), 67.79 (t, CH_2), 73.08 (t, CH_2), 76.36 (d, CH), 77.07 (d, CH), 77.90 (d, CH), 84.48 (d, CH), 100.51 (d, CH), 127.01 (s, C), 127.15 (d, CH), 127.73 (d, CH), 129.12 (d, CH), 132.53 (s, C), 136.43 (s, C), 144.38 (s, C) ppm.
ESI-MS (*m/z*)	: 475.25 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 58.39; H, 6.24; S, 7.09 %
	Found: C, 58.40; H, 6.26; S, 7.08 %

1*R*, 2*S*, 4*R*, 5*R*)-2-((Benzyloxy)methyl)-4-(dimethoxymethyl)-3,6-dioxa-bicyclo[3.1.0]hexane (112).



112

To a freshly prepared solution of sodium methoxide (0.62 g, 26.1 mmol) in methanol (to a anhydrous solution of methanol at 0^{o}C add pinchs of sodium were added carefully and maintained same temperature until it dissolve), at 0-5^{o}C

compound **108** (12 g, 26.5 mmol) in methanol solution was added slowly over an 45 min. after completion of reaction ice was added slowly and remove methanol under reduced pressure to afford residue which was partitioned between EtOAc and water. The organic layer was washed with brine, dried, and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:7) to give epoxide (**112**) (7.1 g, 96 %) as a syrup. R_f 0.5 (25% ethyl acetate/hexane).

Mol. Formula : $C_{15}H_{20}O_5$

$[\alpha]_D^{25}$: +54.83 (*c* = 2.8, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1089. 1216, 1719, 3018, 3436 cm^{-1}

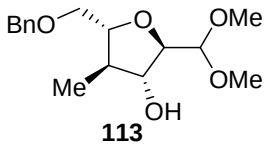
^{1}H NMR (500 MHz, $CDCl_3$) : δ 3.37 (s, 3H), 3.39 (s, 3H), 3.54 (d, *J* = 6.4 Hz, 2H), 3.74 (q, *J* = 5.4,3.0 Hz, 2H), 4.05 (d, *J* = 4.2 Hz, 1H), 4.15 (t, *J* = 6.4 Hz, 1H), 4.24 (d, *J* = 4.2 Hz, 1H), 4.51 (t, *J* = 2.3 Hz, 2H), 7.16-7.26 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 55.44(d, CH), 56.74 (q, CH_3), 56.94 (q, CH_3), 68.62 (t, CH_2), 73.52 (t, CH_2), 76.65 (d, CH), 78.05 (d, CH), 104.97 (d, CH), 127.73 (d, C), 128.33 (d, CH), 137.88 (s, C) ppm.

ESI-MS (*m/z*) : 303.39 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 64.27; H, 7.19 %
Found: C, 64.30; H, 7.22 %

(2*R*, 3*R*, 4*R*, 5*R*)-5-((Benzyloxy)methyl)-tetrahydro-2-(dimethoxymethyl)-4-methylfuran-3-ol (113).



113

A solution of 3M CH_3MgCl in THF (121mL, 364 mmol) was added to a stirred suspension of CuCN (1.1g, m.mol) in a 45 mL of dry THF under argon at 0°C. After calu. 10 min a clear yellow solution was obtained. This was stirred and a solution of epoxide **112** (8.5 g , 30.35 mmol) in 7 mL of dry THF was slowly added, and the evolution of gas was noted during this addition. The solution was warmed to 20°C and stirred for 3h, and then 10 mL of 5% water in THF was slowly added at 0°C, followed by 10 mL of saturated aqueous NH_4Cl. The mixture was partitioned between 50 mL of water and 70 mL of CH_2Cl_2 , and the CH_2Cl_2 was washed with 5% aqeous $NaHCO_3$, dried and concentrated. The residue was purified by filtered through

silica gel EtOAc-hexane (1:5) to give **113** (7.2 g, 80%), R_f 0.33 (30% ethyl acetate/hexane).

Mol. Formula : $C_{16}H_{24}O_5$

$[\alpha]_D^{25}$: +12.64 (*c* = 3.4, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1027. 1216,1275,1475, 1721, 3016, 3417cm^{-1}

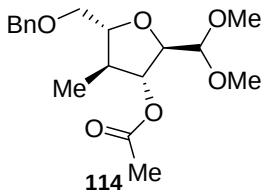
^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.09 (d, *J* = 6.6 Hz, 3H), 2.10 (q, *J* = 6.6 Hz , 1H), 2.80 (brs , OH), 3.43 (s, 3H), 3.46 (s, 3H), 3.56 (qd, *J* = 3.16,10.5 Hz, 2H), 3.76-3.83 (m, 3H), 4.34 (d, *J* = 5.3 Hz, 1H), 4.58 (q, *J* = 12.0 Hz, 2H), 7.20-7.32 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 15.07 (q, CH_3), 42.98 (d, CH), 53.92 (q, CH_3), 55.70 (q, CH_3), 71.60 (t, CH_2), 73.41 (t, CH_2), 77.63 (d, CH), 82.94 (d, CH), 83.70 (d, CH), 105.62 (d, CH), 127.57 (s, C), 128.30 (s, C), 137.99 (d, CH) ppm.

ESI-MS (*m/z*) : 319.47 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 64.84; H, 8.16%
Found: C, 64.86; H, 8.17%

(2*R*, 3*R*, 4*S*)-5-((Benzyloxy)methyl)-tetrahydro-2-(dimethoxymethyl)-4-methylfuran-3-yl acetate (114).



114

The epoxide opened product **113** (100 mg, 0.3 mmol) was dissolved in acetic anhydride (5 mL) and pyridine (2 mL). This solution was stirred for overnight at room temperature. The excess pyridine was removed under reduced pressure , washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:6) to give acetate derivative **114** (98 mg, 86%) as a syrup. R_f 0.5 (25% ethyl acetate/hexane).

Mol. Formula : $C_{18}H_{26}O_6$

$[\alpha]_D^{25}$: -20.75 (*c* = 1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 712, 1071,1275, 1724, 2401,3020, 3439 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.1 (d, *J* = 7.2 Hz, 3H), 2.05 (s , 3H), 2.22 (q, *J* = 7.2 Hz, 1H), 3.43 (s, 6H), 3.56 (dd, *J* = 4.5, 9.2 Hz, 2H), 3.86 (q, *J* =

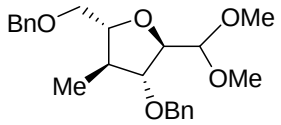
4.5, 9.2 Hz, 1H), 3.99 (t, *J* = 5.4 Hz, 1H), 4.38 (d, *J* = 4.5 Hz, 1H), 4.58 (qt, *J* = 12.5 Hz, 2H), 5.05 (qt, *J* = 5.41 Hz, 1H), 7.28-7.32 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.97 (q, CH_3), 21.08 (d,CH), 42.53 (q, acetlyCH_3), 54.72 (q, CH_3), 55.79 (q, CH_3),70.77 (t, CH_2), 73.46 (t, CH_2), 80.74 (d, CH), 81.91 (d, CH), 84.44 (d, CH), 104.94 (d, CH), 127.62 (d, CH), 128.35 (d, CH), 138.29 (s, CH), 170.43 (s, C=O) ppm.

ESI-MS (*m/z*) : 361.16 $[M]^+$.

Elemental Analysis Calcd.: C, 63.89; H, 7.74 %
Found: C, 63.91; H, 7.76 %

2*R*, 3*R*, 4*S*, 5*R*)-3-(Benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-2-(dimethoxymethyl)-4-methylfuran (115).



115

The epoxide opened product **113** (8.2 g, 27.7 mmol) in dry DMF (30 mL) was cooled to 0°C and NaH (60% dispersion in oil, 1.59 g, 69.1 mmol) was added portion-wise at 0°C. After 25 min, benzyl bromide 5.6 g (32.7 mmol) was added. After 3 h, the reaction mixture was worked up to give the residue, which was purified on silica gel by eluting with EtOAc-hexane (1:14) to give **115** (9.8 g, 91%)as a syrup. R_f 0.6(5% ethyl acetate/hexane).

Mol. Formula : $C_{23}H_{30}O_5$

$[\alpha]_D^{25}$: +15.54 (*c* = 2.0, $CHCl_3$)

IR ($CHCl_3$) υ : 698, 713, 1075,1273, 1719, 2933 3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.05 (d, *J* = 6.7 Hz, 3H), 2.18 (q, *J* = 6.7, 13.7 Hz, 1H), 3.44 (s, 3H), 3.46 (s, 3H), 3.55 (d, *J* = 4.92 Hz, 2H), 3.80 (dd, *J* = 5.8, 8.2 Hz, 1H), 3.78 (m, 1H), 4.05 (t, *J* = 4.3 Hz, 1H), 4.32 (d, *J* = 4.4 Hz, 1H), 4.51 (q, *J* = 6.7, 13.5 Hz, 2H), 4.57(s, 2H), 7.28-7.31 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 15.50 (q, CH_3), 43.08 (q, CH_3), 54.76 (q, CH_3), 56.23 (q, OCH_3),71.33 (t, CH_2), 71.98 (t, Bn-CH_2), 73.36 (t, Bn-CH_2), 83.43 (d, CH), 84.10 (d, CH), 86.71 (d, CH), 105.3 (d, CH), 127.41 (d, Bn-CH), 127.48 (d, Bn-CH), 127.75 (d, Bn-CH),

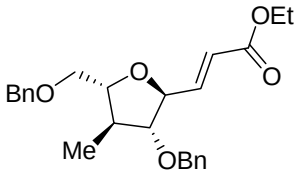
128.29 (d, Bn-CH), 138.34 (s, CH), 138.61 (s,)ppm.

ESI-MS (*m/z*) : 409.45 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.48; H, 7.82 %

Found: C, 71.51; H, 7.84 %

(*E*)-Ethyl3-((2*S*,3*R*,4*S*,5*R*)-3-(benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)acrylate (117).



117

A mixture of aldehydes **106** (0.56 g, 1.64 mmol) and two carbon stable wittig yielide were taken in toluene (10 mL) and refluxe for 3h. The reaction mixture was concentrated to remove toluene to give yellow residue. Purification was done by using silica gel EtOAc-hexane (1:3) to give **117** (0.52 g, 77%) as a liquid. R_f 0.63 (10% ethyl acetate/hexane).

Mol. Formula : $C_{25}H_{30}O_5$

$[\alpha]_D^{25}$: +10.52 (*c* = 2.08, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1026,1215, 1719, 2400, 3020, 3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.30 (t, *J* = 7.26,7.02 Hz, 3H), 2.25 (dq, *J* = 6.9,13.5 Hz, 1H), 3.55 (d, *J* = 5.7 Hz, 1H), 3.57 (d, *J* = 4.9 Hz, 2H), 3.82 (dt, *J* = 3.6, 8.26 Hz, 1H), 4.20 (q, *J* = 7.1, 14.2 Hz, 2H), 4.51 (dd, *J* = 3.8, 5.3 Hz, 1H), 4.56 (d, *J*=1.8 Hz, 2H), 4.59 (s, 2H), 6.07 (dd, *J* = 1.5, 15.45 Hz, 1H), 6.92 (dd, *J*=5.2, 15.2 Hz, 1H), 7.27-7.34 (m, 10H) ppm.

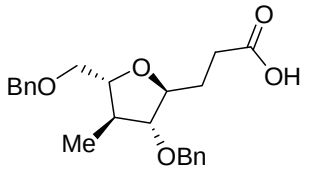
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.05, 60.47 , 61.44, 63.15, 72.11, 72.65, 73.41, 78.69, 83.73, 89.92, 121.20, 128.33, 128.43, 130.12, 133.64, 135.06, 146.37, 158.70, 170.91 ppm.

ESI-MS (*m/z*) : 433.49 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.15; H, 7.37 %

Found: C, 73.17; H, 7.38 %

3-((2*S*, 3*R*, 4*S*, 5*R*)-3-(Benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)propanoic acid (104).



104

Ester **118** (0.3 g, 0.73 mmol) was taken in a mixture of dioxane and water 1:1 (5mL:5mL) ratio anhydrous lithium hydroxide was added at 0^{o}C. After 1h, completion of reaction, volatiles were removed by rotary evaporation. The water layer was extrated with 10 mL portions of ethylacetate (three times). The combined organic phase was dried over sodiumsulfate and concentrate. The resultant crude residue was filtered through silica gel EtOAc-hexane (2:1) to get **104** (0.25 g, 89%) as a syrup. R_f 0.8 (75% ethyl acetate/hexane).

Mol. Formula : $C_{23}H_{28}O_5$

$[\alpha]_D^{25}$: -3.65 (*c* = 1.3, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1070, 1274, 1634, 1712, 3019, 3390 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.1 (d, *J* = 6.7 Hz, 3H), 1.87 (dt, *J* = 6.7, 14.7 Hz, 2H), 2.18 (dq, *J* = 6.7, 13.2 Hz, 1H,), 2.51 (dt, *J* = 8.3, 15.2 Hz, 2H), 3.41 (t, *J* = 6.08 Hz, 1H), 3.54 (d, *J* = 5.04 Hz, 2H), 3.72 (dq, *J* = 3.5, 8.2 Hz, 1H), 3.95 (qn, *J* = 3.5, 8.8 Hz, 1H), 4.56 (s, 2H), 4.58 (s, 2H), 7.28-7.31 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 16.63 (q, CH_3) , 28.94 (t, CH_2), 30.61 (t, CH_2), 42.5 (d, CH), 71.28(t, CH_2), 72.26 (t, CH_2), 73.35 (t, CH_2), 81.53 (d, CH), 83.06 (d, CH), 90.1(d, CH), 127.65(d, CH), 128.34(d, CH), 138.2(s, C), 138.1(s), 178.6 (s,) ppm.

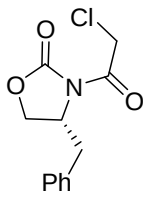
ESI-MS (*m/z*) : 407.47 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.85; H, 7.34 %

Found: C, 71.86; H, 7.37 %

(*R*)-4-Benzyl-3-(2-chloroacetyl)oxazolidin-2-one (119).

.

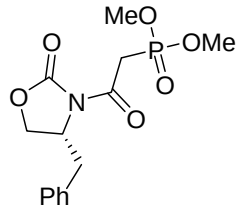


119

To a solution of Oxazolidinone **105** (8.5g, 48.02mmol) in 40 mL of tetrahydrofuran at a -78^{o} C was added (31mL, 48.02mmol, 1equiv, 1.6M in hexane) n-butyllithium, followed by 6.5g (4.6mL, 57.5m.mol, 1.2equiv) of chloroccetyl chloride. The resulting bright yellow solution was stirred at -78^{o}C for 10 min, and then the cooling bath was removed. After 20 min, the reaction was quenched by the addition of 100 mL of saturated aqueous ammonium chloride solution and volatiles were removed by rotary evaporation. The residue was extrated with 20 mL portions of methylene chloride (three times). The combined organic phase was dried over sodiumsulfate and concentrate. The resulting dark yellow oil was filtered through silica gel EtOAc-hexane (1:14) to give **119** (10.6 g, 87%) as a syrup, which crystallized. R_f 0.33 (25% ethyl acetate/hexane); mp 41-44 ^{o}C .

Mol. Formula	: $C_{12}H_{12}ClNO_3$
$[\alpha]_D^{25}$	: -44.61 (*c* = 1.45, $CHCl_3$)
IR ($CHCl_3$) υ	: 755, 1020,1216, 1719,1781, 3025, 3401 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 2.82 (dd, *J* = 9.48, 13.39 Hz, 1H), 3.34 (dd, *J* = 3.28, 13.39 Hz, 1H), 4.28 (dd, *J* = 3.92, 7.07 Hz, 2H), 4.72 (dt, *J* = 3.67, 6.95 Hz, 1H), 4.76(s, 2H), 7.19-7.35 (m, 5H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 37.03 (t, CH_2), 43.58 (t, CH_2), 54.95 (d, CH), 66.80 (t, CH_2Cl), 127.08 (d, CH), 128.6 (d, CH), 129.05 (d, CH), 134.5 (s), 153.01 (s, CH), 165.7 (s,) ppm.
ESI-MS (*m/z*)	: 276.21 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 56.81; H, 4.77; N, 5.52 % Found: C, 56.80; H, 4.79; N, 5.53 %

Dimethyl2-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethylphosphonate (107).



107

The compound **119** (10.2g, 40.31mmol) was taken in a 12mL of trimethoxyphosphite and refluxed for 3h and after consumption of the starting material most of the trimethoxyphosphite was remove by distillation under reduced pressure to give residue. The resultant dark yellow residue was filtered through silica gel MeOH-DCM (1:12) to give **107** (12.5g, 95%) as a syrup liquid. R_f 0.33 (2% Methnaol/dichloromethane) .

Mol. Formula : $C_{14}H_{18}NO_6P$

$[\alpha]_D^{25}$: -29.95 (*c* = 2.1, $CHCl_3$)

IR ($CHCl_3$) υ : 756, 1036,1216, 1703,1782,2401, 3018, 3444 cm^{-1}

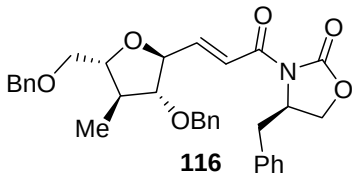
^{1}H NMR (500 MHz, $CDCl_3$) : δ 2.82 (dd, *J* = 9.48, 13.39 Hz, 1H), 3.34 (dd, *J* = 3.28, 13.39 Hz, 1H), 3.79 (app sext, *J* = 13.8 Hz, 2H) 3.81 (s, 3H), 3.82 (s, 3H), 4.28 (dd, *J* = 3.9,9.3 Hz, 1H), 4.71 (t, *J* = 8.7 Hz, 1H), 5.47 (dd, *J* = 3.9, 8.7Hz, 1H), 7.40-7.30 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 32.16 (t, CH_2), 34.81 (t, CH_2), 37.59 (t, CH_2), 53.16 (q, $2CH_3$), 55.43 (d, CH), 66.04 (t, CH_2), 127.37 (d, CH), 128.96 (d, CH), 134.99 (s), 153.32 (s,C==O), 164.73 (s, C=O) ppm.

ESI-MS (*m/z*) : 350.51 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 51.38; H, 5.54; N, 4.28 %
Found: C, 51.39; H, 5.56; N, 4.26 %

(*S*)-4-Benzyl-3-((*E*)-3-((2*R*, 3*R*, 4*S*, 5*R*)-3-(benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)acryloyl)oxazolidin-2-one (116).



116

The oxazolidinonephosphate **107** (7.5 g, 22.93 mmol) was added to a stirred solution of anhydrous lithium chloride (0.998 g, 23.54 mmol) in dry acetonitrile in a flame dried two neck RBF. To this ethyldiisopropylamine (2.5 g, 3.44 mL, 19.35

mmol) was added dropwise at 0°C. After 30min, aldehyde **106** (6.6 g, 19.35 mmol) in dry CH_3CN was added slowly at 0°C. After 1h, ice water was added to the reaction mixture, extracted with ethylacetate (with 20mL, three times), dried over sodiumsulfate and concentrate to get a crude residue, which on purification over silica gel column chromatography using EtOAc-hexane (1:5) to afford **116** (9.2 g, 88 %) as a syrup. R_f 0.4 (25% ethyl acetate/hexane).

Mol. Formula : $C_{33}H_{35}NO_6$

$[\alpha]_D^{25}$: -26.61 (*c* = 1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1072, 1274, 1684, 1780, 2400, 3020, 3390 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.02 (d, *J* = 6.89 Hz, 3H), 2.22 (dq, *J* = 6.8, 13.5 Hz, 1H), 2.73 (dd, *J* = 9.5,13.3 Hz, 1H), 3.35 (dd, *J* = 3.5, 13.5 Hz, 1H), 3.54 (d, *J* = 4.3 Hz, 2H), 3.58 (d, *J* = 6.2 Hz, 1H), 3.8 (qn, *J* = 4.2, 8.4 Hz, 1H), 4.10 (t, *J* = 5.2 Hz, 1H,), 4.3 (d, *J* = 4.31 Hz, 1H,), 4.45 (dd, *J* = 6.36, 11.15 Hz, 2H), 4.53 (s, 2H), 4.6 (m, 2H), 7.12 (d, *J* = 5.7 Hz, 2H), 7.17 (d, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 4.3 Hz, 2H),7.23-7.29 (m, 11H), 7.35 (dd, *J*=1.6, 15.4 Hz, 1H) ppm.

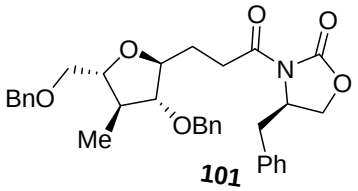
^{13}C NMR (125 MHz, $CDCl_3$) : δ 15.82 (q, CH_3) , 37.77 (t, CH_2), 42.41 (d, CH), 55.29 (d, CH), 66.11 (t, CH_2), 71.04 (t, CH_2), 72.7 (t, CH_2), 73.37 (t, CH_2), 82.09 (d, CH), 83.72 (d, CH), 90.05 (d, CH), 120.43 (d, CH olefinic), 127.31(d, CH), 127.82(d, CH), 128.93(d, CH), 129.41(d, CH), 135.25 (s, C), 137.7 (s, C), 138.22 (s, C), 148.36 (d, CH olefinic), 153.13 (s, C), 164.7 (s, C) ppm.

ESI-MS (*m/z*) : 564.45 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.18; H, 6.51; N, 2.59 %

Found: C, 73.19; H, 6.54; N, 2.57 %

(*S*)-3-(3-((2*R*, 3*R*, 4*S*, 5*R*)-3-(Benzyloxy)-5((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)propanoyl)-4-benzyloxazolidin-2-one (101).



101

The conjugated oxazolidinone **116** (9.1 g, 40.31 mmol) taken in dry ethylacetate (500 mL) in hydrogenation flask was treated with 10% Pd/C under 60*psi*

of hydrogen for 6h. After completion of reaction the mixture was filtered through celite, concentrate to get residue which on purification over silica gel column chromatography using EtOAc-hexane (1:5) to afforded **101** (7.2 g, 79%)as a liquid. R_f 0.4(25% ethyl acetate/hexane).

Mol. Formula : $C_{33}H_{37}NO_6$

$[\alpha]_D^{25}$: -23.71 (*c* = 0.9, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1070, 1273, 1603, 1713, 1779, 3019, 3436 cm^{-1}

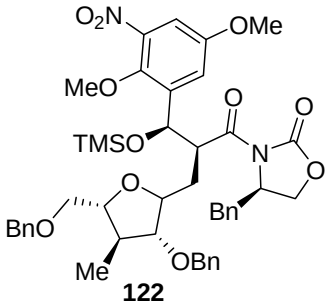
^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.12 (d, *J* = 6.9 Hz, 3H),1.9-2.02 (m, 2H,), 2.15 (hept, *J* = 7.05,14.11 Hz, 1H), 2.68 (dd, *J* = 9.5, 13.1 Hz, 1H), 2.98 (dt, *J* = 7.72,17.4 Hz, 1H), 3.14 (dt, *J* = 7.72, 17.4 Hz, 1H), 3.26 (dd, *J* = 3.2, 13.2 Hz, 1H), 3.47 (t, *J* = 5.86 Hz, 1H,), 3.53 (dt, *J* = 5.86, 19.76 Hz, 1H), 3.53 (s, 1H), 3.74 (dq, *J* = 4.02, 9.6 Hz, 1H), 4.01 (ddd, *J* = 4.5, 9.96 Hz, 1H), 4.04 (d, *J* = 4.5 Hz, 2H), 4.55-4.57 (m, 4H), 4.60 (dt, *J* = 4.02, 9.6 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.25-7.35 (m, 13H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 16.71 (q, CH_3), 28.62 (t, CH_2), 32.02 (t, CH_2), 37.96 (t, CH_2), 42.73 (d, CH), 55.23 (d, CH), 66.04 (t, CH_2), 71.69 (t, CH_2), 72.19 (t, CH_2), 73.37 (t, CH_2), 81.58 (d, CH), 82.95 (d, CH), 90.11 (d, CH), 127.66 (d, CH), 128.33 (d, CH), 128.93 (d, CH), 129.43 (d, CH), 135.49 (s), 138.21 (s), 153.35 (s), 172.91 (s) ppm.

ESI-MS (*m/z*) : 567.65 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 72.91; H, 6.86; N, 2.58 %
Found: C, 72.93; H, 6.88; N, 2.59 %

(4*R*)-4-Benzyl-3-((2*S*,3*R*)-2-(((3*R*,4*S*,5*R*)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (122).



122

Aldol adduct :

The oxazolidinone derivative **101** (285 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **102** (132 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel (230-400) by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **122** (38 mg), and free hydroxyl compound **123** (36 mg), as a single isomers with excellent yeild (light yellowcolor liquid).OTMS:OH in a 1:1 ratio R_f 0.2: 0.5 (10% ethyl acetate/hexane).

Mol. Formula : $C_{45}H_{54}N_2O_{11}Si$

$[\alpha]_D^{25}$: -2.45 (*c* = 1.34, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1053, 1215, 1620, 1701, 1774, 2401, 3019, 3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.01 (s, 9H), 1.03 (d, *J* = 6.75 Hz, 3H), 1.25 (brs, 1H), 1.55 (dd, *J* = 3.3, 13.8 Hz, 1H), 1.94 (hex, *J* = 6.7 Hz, 1H), 2.25 (ddd, *J* = 4.5, 11.2, 14.7 Hz, 1H), 2.57 (dd, *J* = 11.1, 13.1 Hz, 1H), 3.35 (t, *J* = 7.2 Hz, 1H), 3.41-3.47 (m, 3H), 3.52 (dt, *J* = 3.1, 6.1, 9.1 Hz, 1H), 3.75 (s, 3H), 3.81 (d, *J* = 4.1 Hz, 2H), 3.83-3.86 (m, 1H), 3.89 (s, 3H), 4.23 (q, *J* = 11.1 Hz, 2H), 4.43 (q, *J* = 11.1 Hz, 2H), 4.51-4.55 (m, 1H), 5.44 (appd, 1H), 7.10-7.35 (m, 17H) ppm.

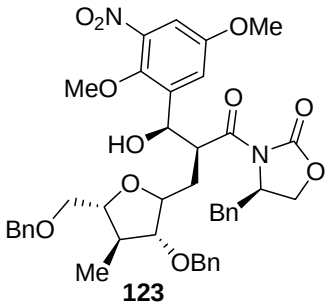
^{13}C NMR (125 MHz, $CDCl_3$) : δ 0.07 (q, CH_3), 15.75 (q, CH_3), 29.63 (t, CH_2), 38.13 (t, CH_2), 41.80 (d, CH), 55.92 (q, CH_3), 56.05 (q, CH_3), 60.34 (d, CH), 65.70 (t, CH_2), 72.20 (t, CH_2), 72.76 (t, CH_2), 73.34 (t, CH_2), 79.55 (d, CH), 83.23 (d, CH), 87.97 (d, CH), 109.69 (d, CH), 119.76 (d, CH), 127.04 (d, CH), 127.25 (d, CH), 127.61 (d, CH), 128.31 (d, CH), 128.84 (d, CH), 129.35 (d, CH), 136.08 (s, C), 137.99 (s, C), 140.14 (s, C), 153.72 (s, C), 155.23 (s, C), 174.29 (s, C) ppm.

ESI-MS (*m/z*) : 849.34 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 65.35; H, 6.58; N, 3.39 %

Found: C, 65.38; H, 6.59; N, 3.43 %

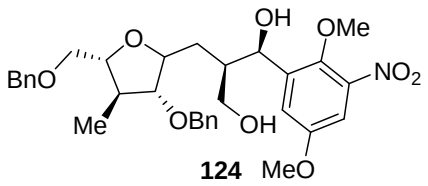
(4*R*)-4-Benzyl-3-((2*S*,3*R*)-2-(((3*R*,4*S*,5*R*)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxypropanoyl)oxazolidin-2-one (123).



123

Mol. Formula	: $C_{42}H_{46}N_2O_{11}$
$[\alpha]_D^{25}$	: +2.62 (*c* = 2.3, $CHCl_3$)
IR ($CHCl_3$) υ	: 668, 1052, 1216, 1620, 1700, 1774, 2926, 3449 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 0.97 (d, *J* = 6.75 Hz, 3H), 1.19-1.21 (m, 1H), 1.50 (dq, *J* = 3.01, 5.7, 14.2 Hz, 1H), 1.60 (s, 1H) 1.92 (hex, *J* = 6.7 Hz, 1H), 2.24 (ddd, *J* = 4.2, 9.7, 14.2 Hz, 1H), 2.63 (dd, *J* = 9.3, 13.5 Hz, 1H), 3.12(dd, *J* = 3.01, 13.5 Hz, 1H), 3.27 (t, *J* = 7.01 Hz, 1H), 3.39-3.46 (m, 3H), 3.68 (s, 3H), 3.72-3.80 (m, 2H), 3.76 (dd, *J* = 6.7, 9.1 Hz, 1H), 3.83 (s, 3H), 4.31 (q, *J* = 11.4, 19.5 Hz, 2H), 4.39 (q, *J* = 11.1, 19.5 Hz, 2H), 4.46 (d, *J* = 8.4 Hz, 1H), 5.18 (d, *J* = 8.4 Hz, 1H), 7.07-7.28 (m, 17H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 15.79 (q, CH_3), 32.36 (t, CH_2), 37.67 (t, CH_2), 41.96 (d, CH), 45.28 (d, CH), 55.92 (q, CH_3), 55.99 (q, CH_3), 63.31 (d, CH), 66.13 (t, CH_2), 70.67 (d, CH), 72.15 (t, CH_2), 72.70 (t, CH_2), 73.43 (t, CH_2), 79.58 (d, CH), 83.27 (d, CH), 88.57 (d, CH), 109.38 (d, CH), 118.79 (d, CH), 125.24 (d, CH), 127.17 (d, CH), 127.32 (d, CH), 127.63 (d, CH), 127.75 (d, CH), 128.17 (d, CH), 128.26 (d, CH), 128.36 (d, CH), 128.80 (d, CH), 128.98 (d, CH), 129.43 (d, CH), 135.36 (s, C), 137.88 (s, C), 139.33 (s, C), 143.64 (c, C), 144.96 (c, C), 154.41 (s, C), 155.31 (s, C), 174.93 (s, C) ppm.
ESI-MS (*m/z*)	: 777.48$[M+Na]^+$.
Elemental Analysis	Calcd.: C, 66.83; H, 6.14; N, 3.71 % Found: C, 66.85; H, 6.16; N, 3.72 %

(1*R*,2*R*)-2-(((2*S*,3*R*,4*S*,5*R*)-3-(Benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)methyl)-1-(2,5-dimethoxy-3-nitrophenyl)propane-1,3-diol (124).



124

A mixture of the aldol adduct **123** (220 mg, 0.29 mmol), 10 mL of drydiethylether and anhydrous methanol (0.04 mL) were cooled to 0°C. Lithium borohydrate (2.0M in THF, 0.51 mL, 1 m.mol) was added dropwise, and the mixture was stirred for 2h at 0°C . The reaction was quenched with 15% NaOH and then concentrated *in vacuo*. The aqueous layer was extracted with ether and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography gave **124** (105 mg, 62%) of diol. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{32}H_{39}NO_9$

$[\alpha]_D^{25}$: +1.95 (*c* = 3.8, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1051, 1216, 1619, 1752, 2402, 3019, 3434 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.08 (d, *J* = 6.8 Hz, 3H), 1.74 (dd, *J* = 6.7, 10.1 Hz, 1H), 1.81 (ddd, *J* = 1.8, 6.8, 14.4 Hz, 1H), 2.15 (hex, *J* = 6.8 Hz, 1H), 2.86 (ddd, *J* = 5.75, 9.5, 23.1 Hz, 1H), 3.06 (brs, 1H), 3.37 (t, *J* = 6.4 Hz, 1H), 3.51 (s, 1H), 3.53 (d, *J* = 4.5 Hz, 2H), 3.75 (dd, *J* = 4.5, 6.8 Hz, 1H), 3.80 (s, 3H), 3.82(s, 3H), 4.11 (dd, *J* = 5.5, 15.3 Hz, 1H), 4.13 (ddd, *J* = 2.5, 5.5, 12.5 Hz, 1H), 4.45-4.47 (m, 1H), 4.55 (q, *J* = 11.2 Hz, 2H), 4.54-4.60 (m, 2H), 5.21 (dd, *J* = 4.7, 9.1 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.24-7.38 (m, 10H), 7.38 (d, *J* = 3.3 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 16.38 (q, CH_3), 32.65 (t, CH_2), 42.00 (d, CH), 42.39 (d, CH), 55.77 (q, CH_3), 62.63 (q, CH_3), 62.70 (t, CH_2), 71.16 (d, CH), 71.25 (t, CH_2), 72.25 (t, CH_2), 73.18 (t, CH_2), 80.44 (d, CH), 82.71 (d, CH), 90.39 (d, CH), 108.46 (d, CH), 118.83 (d, CH), 127.47 (d, CH), 127.52 (d, CH), 127.59 (d, CH), 127.67 (d, CH), 127.81 (d, CH), 128.23 (d, CH), 128.29 (d, CH), 128.80 (d, CH), 128.83 (d, CH), 128.90 (d, CH), 137.86 (s, C),

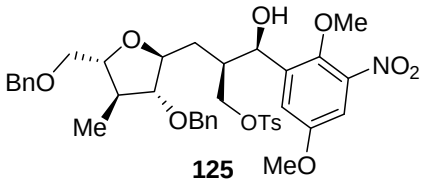
140.67 (s, C), 143.43 (s, C), 144.01 (s, C), 155.10 (s, C) ppm.

ESI-MS (*m/z*) : 604.53 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 66.08; H, 6.76; N, 2.41 %

Found: C, 66.10; H, 6.79; N, 2.44%

(2*R*,3*R*)-2-(((3*R*,4*S*,5*R*)-3-(Benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxypropyl 4-methylbenzenesulfonate (125)



125

To a stirred solution of **124** (0.35 mg, 0.6 mmol), Et_3N (0.1 mL,0.66 mmol) and DMAP (10 mg),in dichloromethane (30 mL) was added *p*-toluenesulfonyl chloride (97 mg, 0.66 mmol), at 0^oC. The reaction mixture was stirred for 6h at room temperature, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (2:1) to afford monotosyl compound **125** (0.345mg, 78%)as a syrup. R_f 0.8 (75 % ethyl acetate/hexane).

Mol. Formula : $C_{39}H_{45}NO_{11}S$

$[\alpha]_D^{25}$: +7.2 (*c* = 0.87, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 755, 1051, 1216, 1603, 1746, 3065, 3376 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.05 (d, *J* = 6.7 Hz, 3H), 1.41 (ddd, *J* = 7.3, 14.4, 21.5 Hz, 1H), 1.80 (dd, *J* = 7.3, 14.3 Hz, 1H), 2.00 (hex, *J* = 6.7 Hz, 1H), 2.20-2.24 (m, 1H), 2.40 (s, 3H), 2.86 (d, *J* = 6.1 Hz, 1H), 3.34 (q, *J* = 6.1 Hz, 1H), 3.49 (d, *J* = 5.3 Hz, 2H), 3.60-3.67 (m, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 3.95 (dd, *J* = 3.5, 9.8 Hz, 1H), 4.15 (dt, *J* = 5.5, 10.7 Hz, 1H), 4.51 (s, 2H), 4.53 (q, *J* = 11.2 Hz, 2H), 5.16 (t, *J* = 5.3 Hz, 1H), 5.32 (brs, 1H), 7.16-7.38 (m, 14H), 7.67 (d, *J* = 8.3 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 16.28 (q, CH_3), 21.51 (q, CH_3), 31.84 (t, CH_2), 41.32 (d, CH), 42.00 (d, CH), 53.68 (q, CH_3), 55.89 (q, CH_3), 62.53 (d, CH), 67.57 (t, CH_2), 69.55 (t, CH_2), 72.40 (t, CH_2), 73.24 (t, CH_2), 80.53 (d, CH), 82.85 (d, CH), 90.46 (d, CH), 109.05 (d, CH), 118.40 (d, CH), 127.16 (d, CH), 127.48 (d, CH), 127.68

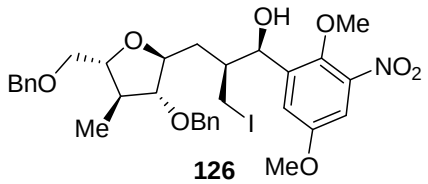
(d, CH), 128.29 (d, CH), 128.92 (d, CH), 129.74 (d, CH), 132.59 (s, C), 135.91 (s, C), 137.98 (s, C), 139.43 (s, C), 143.40 (s, C), 144.12 (s, C), 144.78 (s, C), 155.12 (s, C), 159.19 (s, C) ppm.

ESI-MS (*m/z*) : 758.66 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 63.66; H, 6.16; N, 1.90 %

Found: C, 63.68; H, 6.19; N, 1.91 %

(1*R*,2*S*)-3-((3*R*,4*S*,5*R*)-3-(Benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)-2-(iodomethyl)-1-(2,5-dimethoxy-3-nitrophenyl)propan-1-ol (126).



126

A mixture of **125** (0.325 g, 0.44 mmol) and NaI (790 mg, 5.3 mmol) taken in a glyme was reflux for 2h, after complition of reaction, glyme was removed under reduced pressure to get residue which was purified on silica gel by eluting with EtOAC-hexane (1:3) to give iododerivative **126** (0.26 mg, 85%) as a colorless liquid. R_f 0.4(25 % ethyl acetate/hexane).

Mol. Formula : $C_{32}H_{38}INO_8$

$[\alpha]_D^{25}$: -12.81 (*c* = 1.7, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1051, 1216, 1533, 1620, 1728, 3018, 3435 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.06 (d, *J* = 6.7 Hz, 3H), 1.34 (ddd, *J* = 7.1, 10.7, 18.7 Hz, 1H), 1.92 (dd, *J* = 6.7, 13.3 Hz, 1H), 1.99-2.05 (m, 1H), 2.13 (hex, *J* = 6.7 Hz, 1H), 3.11 (m, 1H), 3.27 (dd, *J* = 2.5, 7.8 Hz, 1H), 3.37 (dd, *J* = 6.1, 10.7 Hz, 2H), 3.53 (d, *J* = 4.3 Hz, 2H), 3.66 (dt, *J* = 4.4, 13.3 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.01 (dt, *J* = 5.5, 13.1, 17.6 Hz, 1H), 4.54 (t, *J* = 13.1 Hz, 2H), 4.60 (q, *J* = 11.2 Hz, 2H), 5.12 (t, *J* = 5.1 Hz, 1H), 7.26-7.34 (m, 12H) ppm.

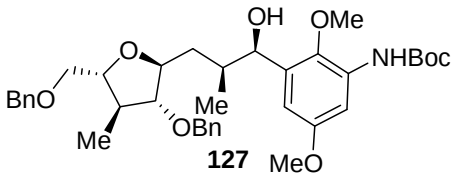
^{13}C NMR (125 MHz, $CDCl_3$) : δ 10.81 (t, CH_2), 16.22 (q, CH_3), 35.50 (t, CH_2), 42.07 (d, CH), 42.79 (d, CH), 55.99 (q, CH_3), 62.77 (q, CH_3), 69.61 (d, CH), 71.30(t, CH_2), 72.50 (t, CH_2), 73.32 (t, CH_2), 80.58 (d, CH), 82.92 (d, CH), 90.23 (d, CH), 109.11 (d, CH), 119.17 (d,

CH), 127.55 (d, CH), 127.63 (d, CH), 127.78 (d, CH), 127.86 (d, CH), 128.36 (d, CH), 128.49 (d, CH), 137.87 (s, C), 138.05 (s, C), 139.38 (s, C), 143.61 (s, C), 144.41 (s, C), 155.29 (s, C) ppm.

ESI-MS (*m/z*) : 714.39 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 55.58; H, 5.54; N, 2.03 %
Found: C, 55.61; H, 5.53; N, 2.06 %

tert-Butyl 3-((1*R*, 2*S*)-3-((3*R*, 4*S*, 5*R*)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)-1-hydroxy-2-methylpropyl)-2,5-dimethoxyphenylcarbamate (127).



127

A mixture of the iodocompound **126** (0.21g, .303 mmol) and $(BOC)_2O$ in dry methanol (10mL) was treated with Pd/c (10%) under hydrogen atmosphere (2psi) at r.t for 6h. After completion of reaction, the mixture was filtered through celite, concentrated to get residue which on purification over silica gel column chromatography using EtOAc-hexane (1:6) to afforded **127** (90 mg, 47%) as a liquid. R_f 0.6 (20% ethyl acetate/hexane).

Mol. Formula : $C_{37}H_{49}NO_8$

$[\alpha]_D^{25}$: -41.32 (*c* = 0.3, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 756, 1056, 1216, 1604, 1717, 2401, 3017, 3429 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.86 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.22-1.29 (m, 2H), 1.53 (s, 9H), 2.07-2.22 (m, 2H), 3.15 (brs, 1H), 3.35 (dt, *J* = 5.6, 9.7 Hz, 1H), 3.55 (d, *J* = 5.01 Hz, 2H), 3.65 (s, 3H), 3.71 (dt, *J* = 5.01 Hz, 1H), 3.77 (s, 3H), 4.00-4.10 (m, 1H), 4.52-4.56 (m, 4H) 4.93 (d, *J* = 5.1 Hz, 1H), 6.65 (d, *J* = 3.1 Hz, 1H), 6.89 (s, 1H), 7.26-7.35 (m, 10H), 7.63 (d, *J* = 2.7 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.66 (q, CH_3), 16.52 (q, CH_3), 28.32 (q, CH_3), 36.93 (d, CH), 37.84 (t, CH_2), 42.15 (d, CH), 55.55 (q, CH_3), 61.18 (q, CH_3), 71.37 (t, CH_2), 71.54 (d, CH), 72.43 (t, CH_2), 73.28 (t,

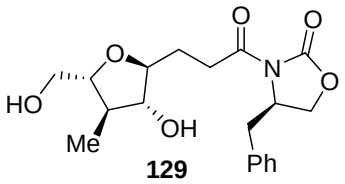
CH_2), 81.13 (d, CH), 82.80 (d, CH), 91.08 (d, CH), 103.05 (d, CH), 106.59 (d, CH), 127.52 (d, CH), 128.29 (d, CH), 132.24 (s, C), 136.38 (s, C), 138.14 (s, C), 139.20 (s, C), 152.64 (s, C), 156.25 (s, C) ppm.

ESI-MS (*m/z*) : 658.64$[M+Na]^+$.

Elemental Analysis Calcd.: C, 69.90; H, 7.77; N, 2.20 %

Found: C, 69.92; H, 7.79; N, 2.24 %

(*R*)-3-(3-((2*R*, 3*R*, 4*R*, 5*R*)-Tetrahydro-3-hydroxy-5-(hydroxymethyl)-4-methylfuran-2-yl)propanoyl)-4-benzyloxazolidin-2-one (129).



129

To a solution of dibenzylcarboxazolidinone **101** (9.6g, 17.67mmol) in dichloromethane $TiCl_4$ (2.1 mL, 176.7mmol) was added dropwise at 0^o C. After complition of reaction (3h), the reaction mixture was poured into icewater, extracted with dichloromethane, washed with saturated sodium bicarbonate solution, dried over sodiumsulfate and concentrate to get crude residue **129** (3.6g, 56%), which was proceed for next step with out further purification. R_f 0.8(70% ethyl acetate/hexane).

Mol. Formula : $C_{19}H_{25}NO_6$

$[\alpha]_D^{25}$: +33.30 (*c* = 5.3, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 756,1049, 1290, 1698, 1778, 3417 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.12 (d, *J* = 6.7 Hz, 3H), 1.95(q, *J* = 7.23, 13.8 Hz, 1H), 2.05 (brs, 1H), 2.06 (q, *J* = 6.93, 13.5 Hz, 2H), 2.76 (dd, *J* = 9.7, 13.3 Hz, 1H), 3.04 (dt, *J* = 7.2,17.4 Hz, 1H), 3.14 (dt, *J* = 7.2, 17.4 Hz, 1H), 3.28 (dt, *J* = 4.5, 13.1 Hz, 1H), 3.59 (qn, *J* = 7.2 Hz, 2H), 3.66 (dt, *J* = 4.7, 11.9 Hz, 1H), 3.76 (dd, *J* = 5.1, 8.9 Hz, 1H), 3.81 (m, 2H), 4.19 (dd, *J* = 6.7, 15.6 Hz, 1H), 4.20 (dd, *J* = 8.7, 16.1 Hz, 1H,), 4.67 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.23 Hz, 2H), 7.33 (m, 3H) ppm.

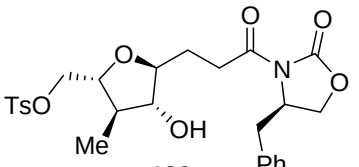
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.87 (q, CH_3), 27.92 (t, CH_2), 31.97 (t, CH_2), 37.30 (t, CH_2), 42.34 (d, CH), 55.12 (d, CH), 63.13 (t, CH_2), 66.22 (t, CH_2), 82.34 (d, CH), 82.72 (d, CH), 83.94 (d, CH), 125.20 (d,

CH), 127.24(d, CH), 128.86 (d, CH), 129.32 (d, CH), 135.19 (s), 153.55 (s), 173.19 (s) ppm.

ESI-MS (*m/z*) : 386.75 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 62.80; H, 6.93; N, 3.85 %
Found: C, 62.79; H, 6.95; N, 3.88 %

((2*R*,3*R*,4*R*,5*S*)-5-(3-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-3-oxopropyl)-4-hydroxy-3-methyltetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (130).



130

To a stirred solution of **129** (3.5 g, 9.64 mmol), Et_3N (1.47 mL, 10.6 mmol), and DMAP (50 mg), in dichloromethane (30 mL) was added *p*-toluenesulfonyl chloride (1.54 g, 10.6 mmol), at 0°C. The reaction mixture was stirred for 6h at room temperature, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (2:1) to afford **130** (3.9g, 78%)as a liquid. R_f 0.8 (75 % ethyl acetate/hexane).

Mol. Formula : $C_{26}H_{31}NO_8S$

$[\alpha]_D^{25}$: -29.55 (*c* = 0.75, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 758, 1097, 1290, 1703, 1780, 3400 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 1.09 (d, *J* = 6.7 Hz, 3H), 1.93 (q, *J* = 7.2, 13.8 Hz, 1H), 2.03 (q, *J* = 6.9,13.5 Hz, 2H), 2.45 (s, 3H), 2.76 (dd, *J* = 9.7, 13.3 Hz, 1H), 3.01 (dt, *J* = 7.2,17.4 Hz, 1H), 3.09 (dt, *J* = 7.2, 17.4 Hz, 1H), 3.27 (dt, *J* = 4.5, 13.1 Hz, 1H), 3.51 (brs, 1H), 3.53 (t, *J* = 7.2 Hz, 1H), 3.66 (dt, *J* = 4.7, 11.9 Hz, 1H), 3.46 (dd, *J* = 5.1, 8.9, 1H), 3.79 (m, 1H), 4.11 (dd, *J* = 6.9, 15.6 Hz, 1H), 4.18 (dd, *J* = 8.7, 16.1 Hz, 1H), 4.20-4.23 (m, 1H), 4.67 (t, *J* = 7.5 Hz,, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.74 (q, CH_3), 21.58 (q, CH_3), 27.42 (t, CH_2), 31.57 (t, CH_2), 37.71 (t, CH_2), 43.2 (d, CH), 55.16 (d, CH), 66.21 (t, CH_2), 70.45 (t, CH_2), 80.34 (d, CH), 81.58 (d, CH), 82.16 (d,

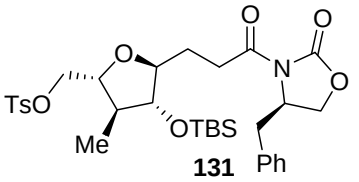
CH), 127.25 (d, CH), 127.9 (d, CH), 128.88 (d, CH), 129.35 (d, CH), 129.82 (d, CH), 135.23 (s, C), 144.84 (s, C),153.45 (s, C), 173.13 (s, C), ppm.

ESI-MS (*m/z*) : 540.58 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 60.33; H, 6.04; N, 2.71 %

Found: C, 60.35; H, 6.06; N, 2.74 %

((2*R*,3*S*,4*R*,5*S*)-5-(3-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-3-oxopropyl)-4-(tert-butyldimethylsilyloxy)-3-methyltetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (131).



131

A mixture of **130** (3.5 g, 6.76 mmol), imidazole (0.515 g, 8.46 mmol), TBDMSCl (1.27 g, 8.46 mmol) and DMAP (54 mg) in CH_2Cl_2 (50 mL) was stirred for 6 h at room temperature. After completion of the reaction, the mixture was diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:4) to give TBS ether derivative **131** (3.1g, 74%), as a colorless liquid. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{32}H_{45}NO_8SSi$

$[\alpha]_D^{25}$: -42.07 (*c* = 2.0, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1076, 1253, 1703, 1781, 2400, 3023 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.01 (s, 6H), 0.80 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 1.72 (dq, *J* = 6.7, 8.7, 14.7 Hz, 1H), 1.84 (hex, *J* = 6.7 Hz, 1H), 1.91-1.99 (m, 1H), 2.37 (s, 3H), 2.70 (dd, *J* = 9.7, 13.4 Hz, 1H), 2.89 (dt, *J* = 6.7, 14.7, 16.9 Hz, 1H), 3.01 (dq, *J* = 6.1, 8.7, 17.3 Hz, 1H), 3.23 (dd, *J* = 3.1, 13.4 Hz, 1H), 3.45 (t, *J* = 6.7 Hz, 1H), 3.52-3.57 (m, 1H), 3.65-3.69 (m, 1H), 3.96-3.97(m, 2H), 4.11 (q, *J* = 9.1 Hz, 1H), 4.10-4.12 (m, 1H), 4.57-4.63 (m, 1H), 7.15-7.29 (m, 7H), 7.73 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.33 (q, CH_3), -4.19 (q, CH_3), 15.45 (q, CH_3), 17.81 (s, C), 21.59 (q, CH_3), 25.68 (q, CH_3), 27.74 (t, CH_2), 32.13 (t,

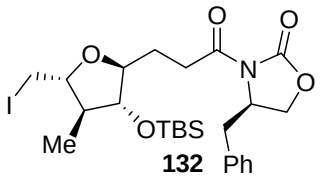
CH_2), 37.75 (t, CH_2), 43.93 (d, CH), 55.24 (d, CH), 66.17 (t, CH_2), 70.60 (t, CH_2), 80.68 (d, CH), 82.54 (d, CH), 83.02 (d, CH), 127.25 (d, CH), 127.99 (d, CH), 128.91 (d, CH), 129.41 (d, CH), 129.84 (d, CH), 132.86 (s, C), 135.45 (s, C), 144.73 (s, C), 153.45 (s, C), 172.91 (s, C) ppm.

ESI-MS (*m/z*) : 654.66 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 60.83; H, 7.18; N, 2.22 %

Found: C, 60.85; H, 7.20; N, 2.20 %

(*R*)-4-Benzyl-3-(3-((2*S*,3*R*,4*S*,5*R*)-3-(tert-butyldimethylsilyloxy)-5-(iodomethyl)-4-methyltetrahydrofuran-2-yl)propanoyl)oxazolidin-2-one (132).



132

A mixture of **131** (3 g, 4.75mmol) and NaI (8.5 g, 57.05 mmol) was taken in a glyme (12 mL). After Refluxing the reaction mixture for 2h, the volaties removed under reduced pressure to get residue which was purified on silica gel by eluting with EtOAC-hexane (1:3) to give iododerivative **132** (2.2 g,79%), as a colorless liquid. R_f 0.4 (25 % ethyl acetate/hexane).

Mol. Formula : $C_{25}H_{38}INO_5Si$

$[\alpha]_D^{25}$: -32.11 (*c* = 1.55, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1052, 1258, 1703, 1782, 3025 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.09 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.8 (hex, *J* = 7.2, 21 Hz, 1H), 2.05 (q, *J* = 5.1, 11.3 Hz, 1H), 2.06 (m, 1H), 2.76 (dd, *J* = 8.9, 12.9 Hz, 1H), 2.97 (q, *J* = 5.8, 12.5 Hz, 1H), 3.02 (dd, *J* = 5.8, 15.2 Hz, 1H), 3.16 (dd, *J* = 5.8, 15.2 Hz, 1H), 3.39 (dd, *J* = 5.8, 12 Hz, 1H), 3.64 (m 2H), 3.85 (qn, *J* = 3.5, 8.5 Hz, 1H), 4.17 (dd, *J* = 9.4, 14 Hz, 2H), 4.18-4.20 (m, 1H,), 4.69 (dq, *J* = 3.2, 12.9 Hz, 1H), 7.22 (d, *J*= Hz, 1H), 7.26 (d, *J*= Hz, 1H), 7.35 (t, *J*= Hz, 3H) ppm.

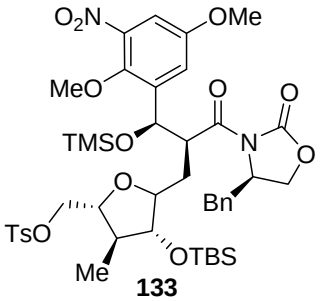
^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.33 (q, CH_3), -4.17 (q, CH_3), 9.82 (t, CH_2), 16.35 (q, CH_3), 17.87 (s, C), 25.73 (q, CH_3), 27.76 (t, CH_2), 32.11 (t, CH_2), 37.89 (t, CH_2), 47.80 (d, CH), 55.21 (d, CH), 66.17 (t,

CH_2), 82.23 (d, CH), 83.01 (d, CH), 83.24 (d, CH), 127.31 (d, CH), 128.94 (d, CH), 129.41 (d, CH), 135.38 (d, CH), 153.43 (s, C), 172.88 (s, C) ppm.

ESI-MS (*m/z*) : 610.39 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 51.10; H, 6.52; N, 2.38 %
Found: C, 51.12; H, 6.51; N, 2.36 %

((2*R* ,3*S*, 4*R*)-5-((*S*)-3-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-((*R*)-(2,5-dimethoxy-3-nitrophenyl)(trimethylsilyloxy)methyl)-3-oxopropyl)-4-(tert-butyldimethylsilyloxy)-3-methyltetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (133)



133

Oxazolidinone **131** (332 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **102** (133 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **133** (398 mg) as single isomer with 83% yeild (light yellowcolor liquid). R_f values shows 0.2 (10 % ethyl acetate/hexane).

Mol. Formula : $C_{44}H_{62}N_2O_{13}SSi_2$

$[\alpha]_D^{25}$: -100.5 (*c* = 0.25, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 760, 1051, 1252, 1598, 1701, 1780, 3064, 3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.24 (s, 3H), -0.05 (s, 3H), 0.01 (s, 9H), 0.77 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.27 (s, 1H), 1.35 (dd, *J* = 2.8, 8.1 Hz, 1H), 1.73 (q, *J* = 7.5 Hz, 1H), 2.26 (dt, *J* = 4.6, 14.1, 26.1 Hz, 1H), 2.44 (s, 3H), 2.60 (dd, *J* = 11.1, 13.5 Hz, 1H), 3.39 (t, *J* = 7.79 Hz, 1H), 3.48-3.60 (m, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 3.98 (dd, *J* = 2.9, 10.4 Hz, 1H), 4.10 (dd, *J* = 2.9, 9.1 Hz, 1H), 4.25

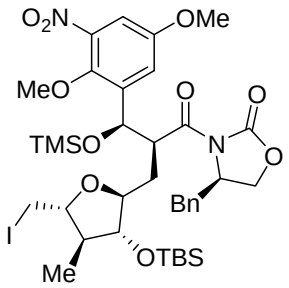
(t, *J* = 8.5 Hz, 1H), 4.58 (t, *J* = 10.1 Hz, 1H), 4.73 (td, *J* = 2.7, 10.1, 18.9 Hz, 1H), 5.37 (d, *J* = 8.8 Hz, 1H), 7.28-7.34 (m, 8H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.77 (q, CH_3), -4.36 (q, CH_3), 0.07 (q, CH_3), 14.70 (q, CH_3), 17.67 (s, C), 21.59 (q, CH_3), 25.52 (q, CH_3), 30.11 (t, CH_2), 38.33 (t, CH_2), 42.88 (d, CH), 55.77 (q, CH_3), 55.91 (q, CH_3), 62.71 (d, CH), 65.89 (t, CH_2), 70.88 (t, CH_2), 80.56 (d, CH), 80.69 (d, CH), 110.05 (d, CH), 119.46 (d, CH), 127.09 (d, CH), 127.85 (d, CH), 128.87 (d, CH), 129.32 (d, CH), 129.82 (d, CH), 132.51 (s, C), 135.97 (s, C), 140.10 (s, C), 143.24 (s, C), 144.85 (s, C), 153.74 (s, C), 155.29 (s, C), 174.09 (s, C) ppm.

ESI-MS (*m/z*) : 938.82 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 57.74; H, 6.83; N, 3.06 %
Found: C, 57.76; H, 6.84; N, 3.07 %

(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-(iodomethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (134).



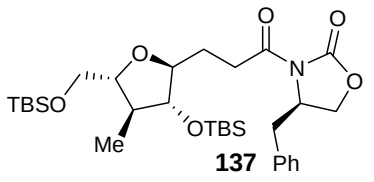
134

Oxazolidinone **132** (308 mg, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **102** (132 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23°C for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **134** (406 mg, 89%), as single isomer with excellent yeild (light yellowcolor liquid). R_f 0.2 (10% ethyl acetate/hexane).

Mol. Formula : $C_{37}H_{55}IN_2O_{10}Si_2$

$[\alpha]_D^{25}$	: -0.82 (*c* = 2.9, $CHCl_3$)
IR ($CHCl_3$) υ	: 667, 758, 1053, 1252, 1605, 1698, 1776, 2401, 3088 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ -0.17 (s, 3H), 0.01 (s, 12H), 0.80 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.32 (dq, *J* = 3.3, 13.7 Hz, 1H), 1.81 (q, *J* = 7.6, 14.5 Hz, 1H), 2.28 (td, *J* = 3.7, 13.7, 25.1 Hz, 1H), 2.59 (dd, *J* = 10.8, 12.9 Hz, 1H), 3.15 (dd, *J* = 6.25, 13.3 Hz, 1H), 3.29 (dd, *J* = 4.2, 10.3 Hz, 1H), 3.34-3.39 (m, 1H), 3.51 (t, *J* = 7.7 Hz, 1H), 3.57 (dd, *J* = 2.5, 13.1 Hz, 1H), 3.64-3.69 (m, 1H), 3.86 (s, 3H), 3.91(s, 3H), 4.12 (dd, *J* = 2.3, 11.3 Hz, 1H), 4.28 (dd, *J* = 8.27 Hz, 1H), 4.62 (s, 1H), 4.77 (dd, *J* = 7.9, 10.5 Hz, 1H), 5.38 (d, *J* = 7.27 Hz, 1H), 7.28-7.34 (m, 7H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ -4.69 (q, CH_3),-4.27 (q, CH_3), 0.08 (q, CH_3), 10.87 (t, CH_2), 15.39 (q, CH_3), 17.73 (s, C), 25.60 (q, CH_3), 30.34 (t, CH_2), 38.31 (t, CH_2), 46.10 (d, CH), 47.60 (d, CH), 55.93 (q, CH_3), 62.69 (d, CH), 65.89 (t, CH_2), 80.39 (d, CH), 81.63 (d, CH), 82.61 (d, CH), 110.06 (d, CH), 119.50 (d, CH), 127.13 (d, CH), 128.92 (d, CH), 129.36 (d, CH), 136.02 (s, C), 140.07 ((s, C), 143.23 (s, C), 144.39 (s, C), 153.47 (s, C), 155.27 (s, C), 173.95 (s, C) ppm.
ESI-MS (*m/z*)	: 893.66 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 51.03; H, 6.37; N, 3.22 % Found: C, 51.05; H, 6.39; N, 3.25 %

(*R*)-4-Benzyl-3-(3-((2*S*,3*R*,4*S*,5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)propanoyl)oxazolidin-2-one (137).



137

A mixture of diol **129** (3.2 g, 8.81 mmol), imidazole (1.79 g, 26.44 mmol), TBDMSCl (3.98 g, 26.44 mmol) and DMAP (54 mg) in CH_2Cl_2 (50 mL) was stirred for 6 h at roomtemperature. After completion of the reaction, the mixture was diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by eluting with EtOAC-hexane (1:4) to give TBS

ether derivative **137** (4.5 g, 86%), as a colorless liquid. R_f 0.5(20 % ethyl acetate/hexane).

Mol. Formula : $C_{31}H_{53}NO_6Si_2$

$[\alpha]_D^{25}$: -41.24 (*c* = 0.65, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 756, 1077, 1254, 1604, 1701, 1782, 2400, 3020 cm^{-1}

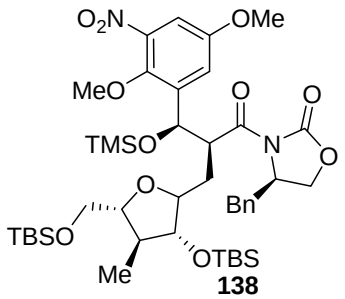
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.06 (s, 6H), 0.10 (s, 6H), 0.89 (s, 9H), 0.91 (s, 9H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.78 (dq, *J* = 5.4, 9.2, 14.3 Hz, 1H), 2.01 (q, *J* = 7.2, 14.3 Hz, 1H), 2.04-2.10 (m, 1H), 2.74 (dd, *J* = 9.7, 13.3 Hz, 1H), 3.02 (dq, *J* = 6.3, 8.9, 15.3 Hz, 1H), 3.14 (dq, *J* = 5.6, 9.2, 14.7 Hz, 1H), 3.31 (dd, *J* = 3.1, 13.3 Hz, 1H), 3.53 (t, *J* = 7.1 Hz, 1H), 3.59 (dt, *J* = 5.6, 9.2 Hz, 1H), 3.63-3.71 (m, 3H), 4.16 (q, *J* = 9.1 Hz, 2H), 4.14-4.16 (m, 1H), 7.21 (d, *J* = 7.1 Hz, 2H), 7.26-7.29 (m, 1H), 7.33 (d, *J* = 7.1 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.40 (q, CH_3), -5.36 (q, CH_3), -4.27 (q, CH_3), -4.11 (q, CH_3), -3.65 (q, CH_3), 15.83 (q, CH_3), 17.80 (s, C), 18.29 (s, C), 25.58 (q, CH_3), 25.68 (q, CH_3), 25.86 (q, CH_3), 27.45 (t, CH_2), 32.27 (t, CH_2), 37.76 (t, CH_2), 43.81 (d, CH), 55.07 (d, CH), 65.06 (t, CH_2), 66.02 (t, CH_2), 82.21 (d, CH), 82.97 (d, CH), 83.76 (d, CH), 127.18 (d, CH), 128.83 (d, CH), 129.33 (d, CH), 135.31 (s, C), 153.29 (s, C), 172.95 (s, C) ppm.

ESI-MS (*m/z*) : 614.48 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 62.90; H, 9.02; N, 2.37 %
Found: C, 62.91; H, 9.03; N, 2.39 %

(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (138).



138

Oxazolidinone **137** (311 mg, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **102** (133 mg,

0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^{o}C for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **138** (263 mg), and free hydroxyl compound **139** (58 mg), as single isomer with excellent yeild (light yellowcolor liquid). The aldol adducts **138** (OTMS) : **139** (OH) were gave in a 5:1 ratio of yield and show R_f 0.2: 0.5(10 % ethyl acetate/hexane) on the TLC plate.

Mol. Formula : $C_{43}H_{70}N_2O_{11}Si_3$

$[\alpha]_D^{25}$: -5.95 (*c* = 5.7, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 760, 1078, 1251, 1604, 1694, 1737, 1783, 3019 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.28 (s, 3H), -0.03 (s, 3H), -0.02 (s, 6H), 0.01 (s, 9H), 0.76 (s, 9H), 0.84 (s, 9H) 1.03 (d, *J* = 6.7 Hz, 3H), 1.35-1.43 (m, 1H), 1.74-1.82 (m, 1H), 2.31 (ddd, *J* = 3.9, 13.2, 16.1 Hz, 1H), 2.61 (dd, *J* = 11.1, 12.8 Hz, 1H), 3.33 (qn, *J* = 5.4 Hz, 1H), 3.47 (t, *J* = 7.5 Hz, 1H), 3.52-3.60 (m, 4H), 3.87 (s, 3H), 3.92 (s, 3H), 4.10 (dd, *J* = 2.2, 8.8 Hz, 1H), 4.16 (t, *J* = 7.5 Hz, 1H), 4.58 (s, 1H), 4.67 (ddd, *J* = 3.1, 8.5, 11.2 Hz, 1H), 5.40 (d, *J* = 7.3 Hz, 1H), 7.28-7.38 (m, 6H), 7.53-7.55 (m, 1H). ppm.

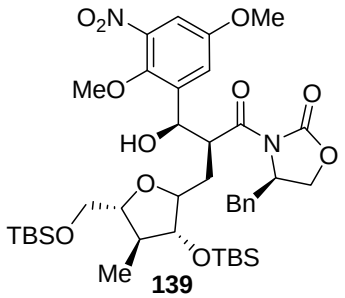
^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.53 (q, CH_3), -5.37 (q, CH_3), -4.85 (q, CH_3), -4.25 (q, CH_3), 0.02 (q, CH_3), 15.59 (q, CH_3), 17.66 (s, C), 18.30 (s, C), 25.53 (q, CH_3), 25.84 (q, CH_3), 30.02 (t, CH_2), 38.39 (t, CH_2), 43.23 (d, CH), 45.73 (d, CH), 55.87 (q, CH_3), 55.98 (q, CH_3), 62.72 (d, CH), 65.55 (t, CH_2), 65.76 (t, CH_2), 69.92 (d, CH), 80.44 (d, CH), 84.42 (d, CH), 110.20 (d, CH), 119.41 (d, CH), 127.09 (d, CH), 128.85 (d, CH), 129.35 (d, CH), 136.04 (s, C), 140.21 (s, C), 143.26 (s, C), 144.46 (s, C), 153.66 (s, C), 155.29 (s, C), 174.23 (s, C) ppm.

ESI-MS (*m/z*) : 897.82 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 59.01; H, 8.06; N, 3.20 %

Found: C, 59.04; H, 8.08; N, 3.22 %

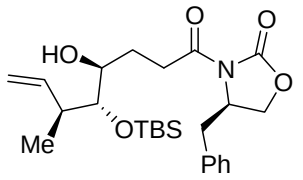
(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxypropanoyl)oxazolidin-2-one (139).



139

Mol. Formula	: $C_{40}H_{62}N_2O_{11}Si_2$
$[\alpha]_D^{25}$	: +2.49 (*c* = 2.0, $CHCl_3$)
IR ($CHCl_3$) υ	: 668, 837, 1053, 1252, 1620, 1702, 1778, 2401, 3020, 3453 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ -0.08 (s, 3H), 0.01 (s, 6H), 0.03 (s, 3H), 0.83 (s, 9H), 0.84 (s, 9H), 1.01 (d, *J* = 6.7 Hz, 3H), 1.53 (dq, *J* = 3.2, 14.1 Hz, 1H), 1.64 (brs, 1H), 1.82-1.84 (m, 1H), 2.41 (ddd, *J* = 3.9, 10.8, 14.4 Hz, 1H), 2.64 (dd, *J* = 9.7, 13.5 Hz, 1H), 3.26 (dd, *J* = 3.3, 13.5 Hz, 1H), 3.33 (qn, *J* = 4.34, 8.8 Hz, 1H), 3.46 (t, *J* = 7.5 Hz, 1H), 3.54 (d, *J* = 4.3 Hz, 2H), 3.63 (ddd, *J* = 5.5, 9.8, 11.7 Hz, 1H), 3.81 (s, 3H), 3.92 (s, 3H), 4.10 (dd, *J* = 2.1, 8.9 Hz, 1H), 4.18 (t, *J* = 8.5 Hz, 1H), 4.54 (ddd, *J* = 3.3, 7.5, 10.5, 1H), 4.64 (ddd, *J* = 3.3, 7.5, 10.5 Hz, 1H), 5.24 (t, *J* = 7.5 Hz, 1H), 7.17-7.19 (m, 2H) 7.28-7.32 (m, 5H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ -5.53 (q, CH_3), -5.45 (q, CH_3), -4.57(q, CH_3), -4.22 (q, CH_3), 15.42 (q, CH_3), 17.68 (s, C), 18.25 (s, C), 25.55 (q, CH_3), 25.80 (q, CH_3), 31.67 (t, CH_2), 37.76 (t, CH_2), 43.18 (d, CH), 44.15 (d, CH), 55.80 (q, CH_3), 55.68(q, CH_3), 63.02 (d, CH), 65.37 (t, CH_2), 65.95 (t, CH_2), 70.72 (d, CH), 80.53 (d, CH), 80.95 (d, CH), 84.34 (d, CH), 109.40 (d, CH), 118.56 (d, CH), 127.15 (d, CH), 128.77 (d, CH), 129.30 (d, CH), 135.28 (s, C), 139.36 (s, C), 143.38 (s, C), 144.81 (s, C), 153.92 (s, C), 155.13 (s, C), 174.99 (s, C) ppm.
ESI-MS (*m/z*)	: 825.95 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 59.82; H, 7.78; N, 3.49 % Found: C, 59.85; H, 7.79; N, 3.50 %

(*R*)-4-Benzyl-3-((4*S*,5*R*,6*S*)-5-(tert-butyldimethylsilyloxy)-4-hydroxy-6-methyloct-7-enoyl)oxazolidin-2-one (141).



141

A mixture of iodocompound **132** (0.2 g, 0.34 mmol) and NH_4Cl (10 mg, catalytic) in a dry methanol, activated zinc (0.22 g, 3.4 mmol), was added at 0^oC. After complition of reaction, the mixture was filtered through celite, concentrate the oganic layer to get residue. The residue was purified on silica gel by eluting with EtOAC-hexane (1:5) to give hydroxyl fragment **141** (0.11 g, 67%), as a colorless liquid. R_f 0.5 (40%ethyl acetate/hexane).

Mol. Formula : $C_{25}H_{39}NO_5Si$

$[\alpha]_D^{25}$: -8.64 (*c* = 4.0, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 756, 1089, 1215, 1626, 1763, 2400, 2928, 3454 cm^{-1}

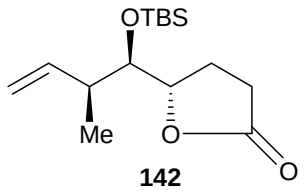
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.09 (s, 6H), 0.90 (s, 9H), 1.08 (d, *J* = 6.7 Hz, 3H), 2.00-2.07 (m, 1H), 2.23-2.36 (m, 1H), 2.46-2.51 (m, 1H), 2.86 (dd, *J* = 3.1, 8.5 Hz, 1H), 3.28 (dd, *J* = 3.2, 13.1 Hz, 1H), 3.58-3.64 (m, 1H), 3.84 (dd, *J* = 2.3, 7.6 Hz, 1H), 4.11 (qn, *J* = 6.7, 1H), 4.15-4.22 (m, 2H), 4.47 (t, *J* = 8.27 Hz, 1H), 4.57 (dt, *J* = 2.2, 7.38 Hz, 1H), 5.02-5.06 (m, 2H), 5.38 (brs, 1H), 5.72-5.79 (m, 1H), 7.18-7.36 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.44 (q, CH_3), -4.20 (q, CH_3), 16.82 (q, CH_3), 18.13 (s, C), 20.65 (t, CH_2), 25.89 (q, CH_3), 28.72 (t, CH_2), 41.28 (t, CH_2), 41.82 (d, CH), 53.74 (d, CH), 69.58 (t, CH_2), 75.27 (d, CH), 81.46 (d, CH), 115.12 (t, CH_2), 127.14 (d, CH), 128.90 (d, CH), 128.96 (d, CH), 129.34 (d, CH), 135.86 (s, C), 139.89 (d, CH), 159.51 (s, C), 177.23 (s, C) ppm.

ESI-MS (*m/z*) : 484.64 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 65.04; H, 8.51; N, 3.03 %
Found: C, 65.06; H, 8.52; N, 3.04 %

(*S*)-5-((1*R*,2*S*)-1-(Tert-butyldimethylsilyloxy)-2-methylbut-3-enyl)dihydrofuran-2(3H)-one (142).



142

A mixture of iodocompound **132** (150 mg, 0.25 mmol), and NH_4Cl (10 mg)in a dry methanol, activated zinc (0.167 g, 2.57 mmol), was added at 0°C. after complition of reaction, the mixture was filtered through celite concentrate the oganic layer to get residue. The residue was purified on silica gel by eluting with EtOAC-hexane (1:6) to give lactone **142** (62 mg, 87 %), as a colorless liquid. R_f 0.5 (20 % ethyl acetate/hexane).

Mol. Formula : $C_{15}H_{28}O_3Si$

$[\alpha]_D^{25}$: -21.88 (*c* = 2, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 838, 1077, 1254, 1640, 1701, 1776, 1782, 2448, 3081 cm^{-1}

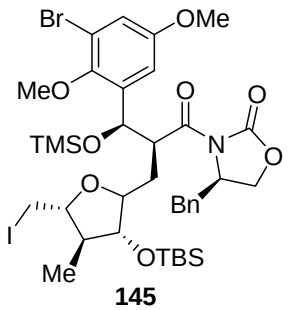
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.01 (s, 6H), 0.81 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.97 (dd, *J* = 7.3, 14.4 Hz, 1H), 2.14-2.26 (m, 2H), 2.38 (dd, *J* = 5.9, 17.4 Hz, 1H), 2.43 (dd, *J* = 5.9, 17.4 Hz, 1H), 3.75 (dd, *J* = 2.3, 7.6 Hz, 1H), 4.48 (td, *J* = 2.3, 7.6, 15 Hz,1H), 4.91 (s, 1H), 4.98 (dd, *J* = 2.7, 7.6 Hz, 1H), 5.63 (dq, *J* = 8.3, 18.8 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.41 (q, CH_3), -4.16 (q, CH_3), 16.94 (q, CH_3), 18.17 (s, C), 20.62 (t, CH_2), 25.92 (q, CH_3), 28.76 (t, CH_2), 41.89 (d, CH), 75.24 (d, CH), 81.46 (d, CH), 115.17 (t, CH_2), 139.93 (d, CH), 177.24 (s, C) ppm.

ESI-MS (*m/z*) : 307.64 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 63.33; H, 9.92 %
Found: C, 63.38; H, 9.93 %

(4*R*)-4-benzyl-3-((2*S*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-(iodomethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (145).



145

Oxazolidinone **132** (308 mg, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **144** (154 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 m.mol) in 6 mL of ethylacetate at 23^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **145** (256 mg) and free hydroxyl compound **146** (52 mg), as single isomers with excellent yeild (light yellowcolor liquids and **145** (OTMS) : **146** (OH) in a 5:1 product ratio, their R_f values are in the 0.2: 0.5(10 % ethyl acetate/hexane).

Mol. Formula : $C_{37}H_{55}BrINO_8Si_2$

$[\alpha]_D^{25}$: +9.34 (*c* = 2.9, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 758, 1049, 1252, 1600, 1699, 1775, 2401, 3019, 3088 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.22 (s, 3H) 0.04 (s, 12H), 0.78 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.32 (dq, *J* = 2.5, 13.2 Hz, 1H), 1.78 (m, 1H), 2.3 (dt, *J* = 3.5, 13.5 Hz, 1H), 2.59 (dd, *J* = 11.3, 12.6 Hz, 1H), 3.13 (dd, *J* = 6.7, 10.2 Hz, 1H), 3.28 (dd, *J* = 4.3, 10.3 Hz, 1H), 3.35-3.38 (m, 1H), 3.52 (t, *J* = 7.5 Hz, 1H), 3.57 (dd, *J* = 2.7, 13.2 Hz, 1H), 3.65-3.71 (m, 1H), 3.79 (s, 3H), 3.87 (s, 3H), 4.11 (dd, *J* = 2.2, 8.7 Hz, 1H), 4.27 (t, *J* = 8.3 Hz, 1H), 4.61 (s, 1H), 4.78 (dt, *J* = 3.1, 8.3 Hz, 1H), 5.27 (appeareddoublet, *J* = 6.3 Hz, 1H), 7.02-7.03 (m, 1H), 7.13-7.18 (m, 1H), 7.26-7.39 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.76 (q, CH_3), -4.33 (q, CH_3), 0.12 (q, CH_3), 10.81 (t, CH_2), 15.42 (q, CH_3), 17.73 (s, C), 25.63 (q, CH_3), 30.26 (t,

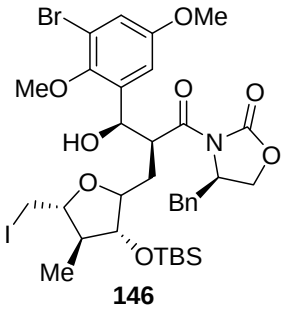
CH_2), 38.44 (t, CH_2), 46.04 (d, CH), 47.72 (d, CH), 55.66 (q, CH_3), 55.91 (q, CH_3), 56.62 (d, CH), 61.24 (d, CH), 65.85 (t, CH_2), 80.60 (d, CH), 81.25 (d, CH), 82.89 (d, CH), 112.79 (d, CH), 118.64 (s, C), 118.83 (d, CH), 127.08 (d, CH), 128.90 (d, CH), 129.37 (d, CH), 136.17 (s, C), 138.02 (s, C), 148.05 (s, C),153.52 (s, C), 156.39 (s, C), 174.62 (s, C) ppm.

ESI-MS (*m/z*) : 927.72 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 49.11; H, 6.13; N, 1.55 %

Found: C, 49.11; H, 6.13; N, 1.55 %

(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-(iodomethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-hydroxypropanoyl)oxazolidin-2-one (146).



146

Mol. Formula : $C_{34}H_{47}BrINO_8Si$

$[\alpha]_D^{25}$: -8.85 (*c* = 3.3, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 771, 1048, 1218, 1603, 1776, 3139cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.15 (s, 3H), 0.06 (s, 3H), 0.77 (s, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 1.33 (dq, *J* = 3.4, 14.1 Hz, 1H), 1.58 (brs, 1H), 1.73-1.78 (m, 1H), 2.30 (ddd, *J* = 4.2, 11.5, 14.5 Hz, 1H), 2.62 (dd, *J* = 9.2, 13.6 Hz, 1H), 3.08 (dd, *J* = 6.7, 10.2 Hz, 1H), 3.24 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.28 (dd, *J* = 3.8, 14.1 Hz, 1H), 3.31-3.34 (m, 1H), 3.44 (dd, *J* = 7.26, 9.8 Hz, 1H), 3.63-3.67 (m, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 4.04 (dd, *J* = 2.1, 8.7 Hz, 1H), 4.23 (t, *J* = 8.5 Hz, 1H), 4.52 (ddd, *J* = 3.1, 8.5, 11.2, 1H), 4.71 (dd, *J* = 4.5, 9.45 Hz, 1H), 5.05 (t, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 2.7, 1H), 6.97 (d, *J* = 2.7, 1H) 7.14-7.27 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.54 (q, CH_3), -4.28 (q, CH_3), 10.73 (t, CH_2), 15.28 (q, CH_3), 17.77 (s, C), 25.64 (q, CH_3), 31.70 (t, CH_2), 37.74 (t, CH_2), 44.72 (d, CH), 47.62 (d, CH), 55.68 (q, CH_3), 55.77

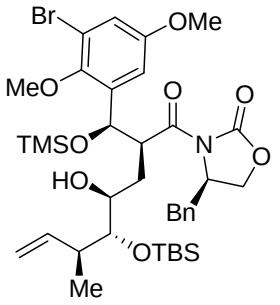
(q, CH_3), 61.74 (d, CH), 66.11 (t, CH_2), 72.38 (d, CH), 80.60 (d, CH), 81.73 (d, CH), 82.77 (d, CH), 112.05 (d, CH), 117.50 (s, C), 118.44 (d, CH), 127.15 (d, CH), 128.85 (d, CH), 129.44 (d, CH), 135.48 (s, C), 137.37 (s, C), 148.47 (s, C), 154.13 (s, C), 156.36 (s, C), 175.12 (s, C) ppm.

ESI-MS (*m/z*) : 855.48 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 49.04; H, 5.69; N, 1.68%

Found: C, 49.05; H, 5.70; N, 1.69 %

(4*R*)-4-Benzyl-3-((2*S*, 5*R*, 6*S*)-2-((*R*)-(3-bromo-2,5-dimethoxyphenyl)(trimethylsilyloxy)methyl)-5-(tert-butyldimethylsilyloxy)-4-hydroxy-6-methyloct-7-enoyl)oxazolidin-2-one (147).



147

A mixture of iodocompound **145** (0.10 g, 0.11 mmol), and NH_4Cl (catalytic) in a dry methanol treated with activated zinc (0.082 g, 2.51 mmol) at 0^oC for 30min. after complition of reaction, the mixture was filtered through celite, concentrated the oganic layer to get residue which was purified on silica gel by eluting with EtOAC-hexane (1:4) to give hydroxyl olefinic compound **147** (0.08 g, 93%), as a colorless liquid. R_f 0.4 (20 % ethyl acetate/hexane).

Mol. Formula : $C_{37}H_{56}BrNO_8Si_2$

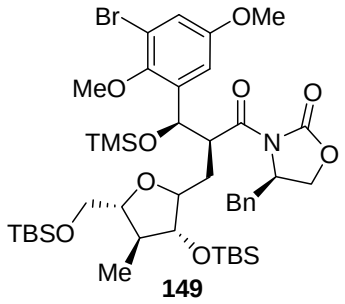
$[\alpha]_D^{25}$: -18.96 (*c* = 0.6, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1049, 1252, 1600, 1699, 1775, 3019,3088 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.22 (s, 3H), 0.04 (s, 12H), 0.87 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.77-1.86 (m, 1H), 2.02-2.11 (m, 1H), 2.34-2.39 (m, 1H), 2.68 (dd, *J* = 9.5, 13.4 Hz, 1H), 2.87 (dd, *J* = 5.3, 8.5 Hz, 1H), 2.98 (m, 1H), 3.16 (dd, *J* = 6.7, 10.6 Hz, 1H), 3.30 (dd, *J* = 4.07, 10.3 Hz, 1H), 3.35-3.41 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.06-4.13 (m, 1H), 4.16 (dd, *J* = 5.8, 8.9 Hz, 1H), 4.49 (t,

	J = 8.5 Hz, 1H), 4.59 (m, 1H), 4.9-5.07 (m, 2H), 5.61-5.68 (m, 1H), 7.04 (d, *J* = 3.01 Hz, 1H), 7.08 (d, *J* = 3.01 Hz, 1H) 7.17 (m, 5H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ -4.47 (q, CH_3), -4.17 (q, CH_3), 0.15 (q, CH_3), 15.38 (q, CH_3), 17.82 (s, C), 23.88 (t, CH_2), 26.02 (q, CH_3), 41.58 (d, CH), 41.85 (t, CH_2), 46.70 (d, CH), 47.72 (d, CH), 53.80 (q, CH_3), 55.75 (q, CH_3), 61.80 (d, CH), 66.19 (t, CH_2), 72.50 (d, CH), 76.17 (d, CH), 111.63 (d, CH), 115.83 (t, CH_2 olefinic), 118.56 (d, CH), 127.22 (d, CH), 128.91 (d, CH), 129.50 (d, CH), 139.34 (d, CH), 142.51 (d, CH olefinic),148.59 (s, C), 156.44 (s, C), 175.16 (s, C) ppm.
ESI-MS (*m/z*)	: 801.72 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 57.05; H, 7.25; N, 1.80 % Found: C, 57.07; H, 7.28; N, 1.82 %

(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (149).



149

Oxazolidinone **137** (311 mg, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **144** (154 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23^{o}C for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **149** (258mg), and free hydroxyl compound **150** (51mg), as single isomer with excellent yeild (light yellowcolor liquid). The aldol adducts **149** (OTMS) : **150** (OH) were gave in a 5:1 ratio of yield and show R_f 0.2: 0.5(10 % ethyl acetate/hexane).

Mol. Formula : $C_{43}H_{70}BrNO_9Si_3$

$[\alpha]_D^{25}$: +3.35 (*c* = 1.8, $CHCl_3$)

IR ($CHCl_3$) υ : 668,760, 1078, 1251, 1604, 1694, 1737, 1783, 3019 cm^{-1}

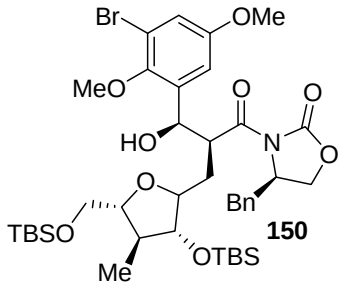
^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.29 (s, 3H), -0.02 (s, 3H), -0.01 (s, 6H), 0.01 (s, 9H), 0.78 (s, 9H), 0.86 (s, 9H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.30-1.46 (m, 1H), 1.71-1.86 (m, 1H), 2.37 (ddd, *J* = 4.8, 12.3, 16.8 Hz, 1H), 2.65 (dd, *J* = 11.1, 13.1 Hz, 1H), 3.30 (qn, *J* = 5.4 Hz, 1H), 3.47-3.60 (m, 5H), 3.84 (s, 3H), 3.92 (s, 3H), 4.09-4.23 (m, 2H), 4.65 (s, 1H), 4.72 (ddd, *J* = 3.1, 10.1, 13.2 Hz, 1H), 5.32 (d, *J* = 8.9 Hz, 1H), 7.06(d, *J* = 3.1 Hz, 1H), 7.21(d, *J* = 3.1 Hz, 1H), 7.31-7.43 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.53 (q, CH_3), -5.35 (q, CH_3), -4.92(q, CH_3), -4.33 (q, CH_3), 0.07 (q, CH_3), 15.60 (q, CH_3), 17.68 (s, C), 18.31 (s, C), 25.60 (q, CH_3), 25.86 (q, CH_3), 30.02 (t, CH_2), 38.50 (t, CH_2), 43.30 (d, CH), 45.60 (d, CH), 55.60 (q, CH_3), 55.96 (q, CH_3), 61.29 (d, CH), 65.67 (t, CH_2), 80.09 (d, CH), 80.58 (d, CH), 84.46 (d, CH), 112.65 (d, CH), 117.09 (s, C), 118.92 (d, CH), 127.04 (d, CH), 128.83 (d, CH), 129.36 (d, CH), 136.18 (s, C), 138.16(s, C), 148.05(s, C), 153.68 (s, C), 156.41(s, C), 174.91 (s, C) ppm.

ESI-MS (*m/z*) : 932.21 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 56.81; H, 7.76; N, 1.54 %
Found: C, 56.82; H, 7.77; N, 1.56 %

(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-hydroxypropanoyl)oxazolidin-2-one (150).



150

Mol. Formula : $C_{40}H_{62}BrNO_9Si_2$

$[\alpha]_D^{25}$: -10.31 (*c* = 0.8, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 837, 1072, 1252, 1601, 1701, 1776, 2401, 3064, 3475 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.10 (s, 3H), -0.02 (s, 6H), -0.01 (s, 3H), 0.83 (s, 9H), 0.85 (s, 9H) 1.06 (d, *J* = 6.7 Hz, 3H),1.49 (dq, *J* = 3.25, 14.1 Hz, 1H), 1.60 (brs, 1H), 1.75-1.92 (m, 1H), 2.43 (ddd, *J* = 4.4, 11.1, 15.4 Hz, 1H), 2.69 (dd, *J* = 9.8, 13.5 Hz, 1H), 3.28-3.38 (m, 2H), 3.48 (t, *J* = 7.8 Hz, 1H), 3.56 (d, *J* = 5.54 Hz, 2H), 3.60-3.68 (m, 1H), 3.77 (s, 3H), 3.89 (s, 3H), 4.10 (dd, *J* = 2.8, 9.1 Hz, 1H), 4.18 (t, *J* = 8.5 Hz, 1H), 4.54 (ddd, *J* = 2.8, 8.1, 10.9 Hz, 1H), 4.67 (ddd, *J* = 2.8, 7.5, 10.9 Hz, 1H), 5.15 (d, *J* = 8.5 Hz, 1H), 7.01(d, *J* = 2.8 Hz, 1H), 7.21(d, *J* = 2.8 Hz, 1H), 7.31-7.43 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.48 (q, CH_3), -5.38 (q, CH_3), -4.58 (q, CH_3), -4.23 (q, CH_3), 15.51 (q, CH_3), 17.75 (s, C), 18.33 (s, C), 25.63 (q, CH_3), 25.87 (q, CH_3), 31.60 (t, CH_2), 37.84 (t, CH_2), 43.40 (d, CH), 44.39 (d, CH), 55.63 (q, CH_3), 55.79 (q, CH_3), 61.69 (d, CH), 65.54 (t, CH_2), 65.99 (t, CH_2), 72.12 (d, CH), 80.68 (d, CH), 80.87 (d, CH), 84.41 (d, CH), 111.99 (d, CH), 117.48 (s, C), 118.45 (d, CH), 127.13 (d, CH), 128.81 (d, CH), 129.43 (d, CH), 135.49 (s, C), 137.44 (s, C), 148.45 (s, C), 154.12(s, C), 156.36 (s, C), 175.39 (s, C) ppm.

ESI-MS (*m/z*) : 861.38 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 57.40; H, 7.47; N, 1.67 %

Found: C, 57.42; H, 7.49; N, 1.68 %

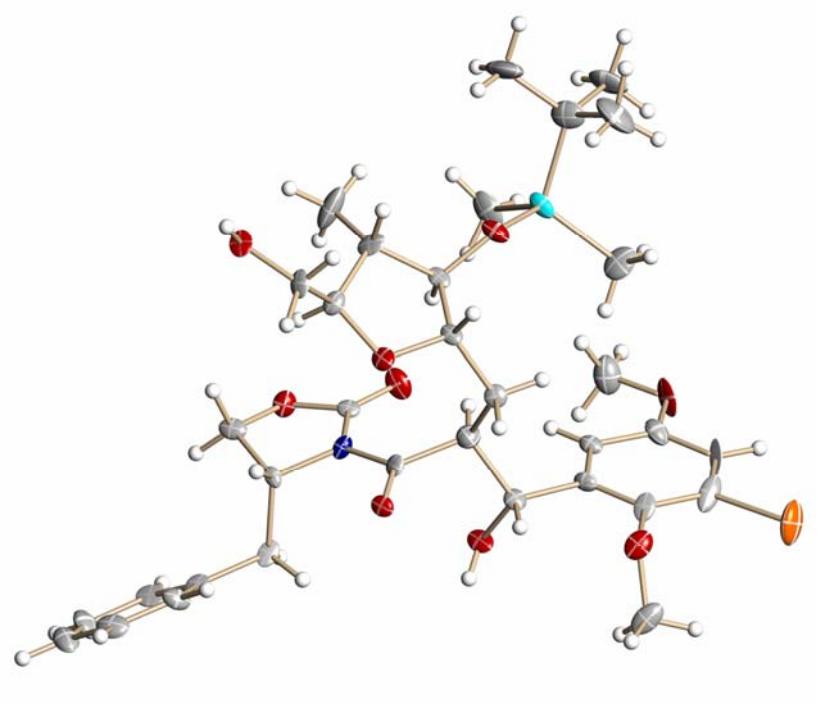
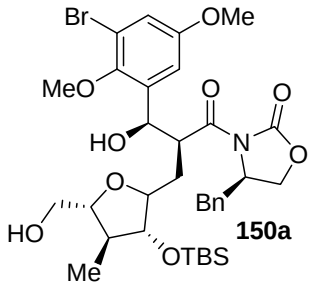


Table 1. Crystal data and structure refinement for 150a.

Identification code	**150a**
Empirical formula	C_{37} H_{51} Br N O_9 Si .0.5 (C6H6)
Formula weight	761.79
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2
Unit cell dimensions	a = 18.302(5) A alpha = 90 deg. b = 11.886(5) A beta = 101.492(7) deg. c = 18.350(5) A gamma = 90 deg.
Volume	3912(2) A^3
Z, Calculated density	4, 1.294 Mg/m^3
Absorption coefficient	1.133 mm^-1
F(000)	1604
Crystal size	0.29 x 0.05 x 0.02 mm

Theta range for data collection	2.06 to 25.00 deg.
Limiting indices	-21<=h<=21, -14<=k<=14, -21<=l<=21
Reflections collected / unique	13875 / 6803 [R(int) = 0.0733]
Completeness to theta = 25.00	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9777 and 0.7347
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6803 / 133 / 437
Goodness-of-fit on F^2	1.165
Final R indices [I>2sigma(I)]	R1 = 0.0911, wR2 = 0.1839
R indices (all data)	R1 = 0.1075, wR2 = 0.1924
Absolute structure parameter	0.052(16)
Largest diff. peak and hole	0.780 and -1.044 e.A^-3

(4*R*)-4-Benzyl-3-((2*S*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-2-(((3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-4-methyltetrahydrofuran-2-yl)methyl)-3-hydroxypropanoyl)oxazolidin-2-one (150a).



150a

Mol. Formula : $C_{34}H_{48}BrNO_9Si$

$[\alpha]_D^{25}$: -9.72 (*c* = 1.1, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 837, 1072, 1252, 1601, 1701, 1776, 2401, 3064, 3475 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.12 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H),1.56 (dq, *J* = 3.25, 14.1 Hz, 1H), 1.79-1.83 (m, 2H), 2.43 (ddd, *J* = 4.4, 11.1, 15.4 Hz, 1H), 2.25 (s, 1H), 2.69 (dd, *J* = 9.8, 13.5 Hz, 1H), 3.31-3.38 (m, 2H), 3.48 (t, *J* = 7.8 Hz, 1H), 3.56 (d, *J* = 5.54 Hz, 2H), 3.60-3.68 (m, 1H), 3.79 (s, 3H), 3.92

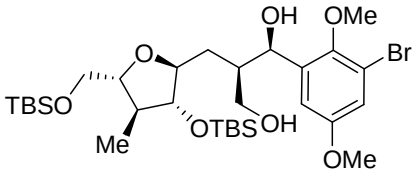
(s, 3H), 4.14 (dd, *J* = 2.8, 9.1 Hz, 1H), 4.20 (t, *J* = 8.5 Hz, 1H), 4.58 (ddd, *J* = 2.8, 8.1, 10.9 Hz, 1H), 4.71 (ddd, *J* = 2.8, 7.5, 10.9 Hz, 1H), 5.18 (d, *J* = 8.5 Hz, 1H), 7.07(d, *J* = 2.8 Hz, 1H), 7.24 (d, *J* = 2.8 Hz, 1H), 7.31-7.43 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.66 (q, CH_3), -4.31 (q, CH_3), 14.81 (q, CH_3), 17.73 (s, C), 25.60 (q, CH_3), 31.62 (t, CH_2), 37.75 (t, CH_2), 42.63 (d, CH), 44.55 (d, CH), 55.65 (q, CH_3), 55.72 (q, CH_3), 61.37 (d, CH), 64.25 (t, CH_2), 65.66 (t, CH_2), 72.08 (d, CH), 80.77 (d, CH), 84.25 (d, CH), 112.09 (d, CH), 117.57 (s, C), 118.52 (d, CH), 127.17 (d, CH), 128.85 (d, CH), 129.41 (d, CH), 135.41 (s, C), 137.33 (s, C), 148.48 (s, C), 154.17 (s, C), 156.41 (s, C), 175.71 (s, C) ppm

ESI-MS (*m/z*) : 744.58 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 56.50; H, 6.69; N, 1.94 %
Found: C, 56.52; H, 6.70; N, 1.92 %

(1*R*, 2*R*)-1-(3-Bromo-2,5-dimethoxyphenyl)-2-(((2*S*, 3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)propane-1,3-diol (151).

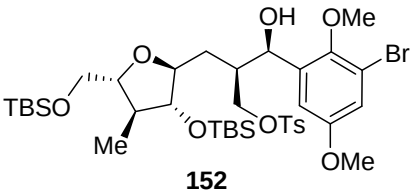


151

A mixture of the aldol adduct **150** (2.5 g, 2.98 mmol), 10 mL of drydiethylether and anhydrous methanol (0.04 mL) were cooled to 0 ^oC. Lithium borohydrate (2.0M in THF , 0.51 mL mmol) was added dropwise, and the mixture was stirred for 2h at 0^oC . The reaction was quenched with 15% NaOH and then concentrated *in vacuo*. The aqueous layer was extracted with ether , and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave diol **151** (1.32 g, 66%). R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula	: $C_{30}H_{55}BrO_7Si_2$
$[\alpha]_D^{25}$	: -8.87 (*c* = 1.6, $CHCl_3$)
IR ($CHCl_3$) υ	: 668, 758, 1048, 1254, 1600, 2400, 3064, 3400 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 0.03 (s, 3H), 0.02 (s, 6H), 0.01 (s, 3H), 0.84(s, 9H), 0.86 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.55 (ddd, *J* = 6.2, 10.3, 16.2 Hz, 1H), 1.81 (dd, *J* = 7.5, 14.4 Hz, 1H), 1.93-2.01 (m, 1H), 2.13 (s, 1H), 3.38 (t, *J* = 7.5 Hz, 1H), 3.59 (m, 2H), 3.59-3.62 (m, 1H,), 3.63-3.64 (m, 2H), 3.69 (brs, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 3.84 (t, *J* = 7.5 Hz, 1H), 4.28 (d, *J* = 5.2 Hz, 1H), 5.14 (t, *J* = 5.2 Hz, 1H), 6.96 (d, *J* = 3.01 Hz, 1H), 7.03(d, *J* = 3.01 Hz, 1H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ -5.44 (q, CH_3), -4.20 (q, CH_3), -4.03 (q, CH_3), 15.56 (q, CH_3), 17.84 (s, C), 18.25 (s, C), 25.69 (q, CH_3), 25.84 (q, CH_3), 32.79 (t, CH_2), 43.09 (d, CH), 43.24 (d, CH), 55.69 (q, CH_3), 61.13(q, CH_3), 63.39 (t, CH_2), 64.87 (t, CH_2), 71.87 (d, CH), 81.42 (d, CH), 83.45 (d, CH), 83.87 (d, CH), 112.58 (d, CH), 117.03 (s, C), 117.34 (d, CH), 138.56 (s, C), 147.57 (s, C), 156.26 (s, C) ppm.
ESI-MS (*m/z*)	: 685.43 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 54.28; H, 8.35 % Found: C, 54.30; H, 8.34 %

(2*R*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-2-(((2*S*,3*R*,4*S*,5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-hydroxypropyl-4-methylbenzenesulfonate (152).



152

To a stirred solution of **151** (1.25 g, 1.88 mmol), Et_3N (0.315 mL, 2.26 mmol), and DMAP (25 mg) in dichloromethane (25 mL) added *p*-toluenesulfonyl chloride (0.33 g, 2.26 mmol) at 0°C. The mixture was stirred for 6h at room temperature, followed by wash with water, brine, dried (over Na_2SO_4) and

concentrated and the residue was purified on silica gel by using EtOAc-hexane (2:1) to afford **152** (1.12 g, 73%)as a syrup. R_f 0.8(75 % ethyl acetate/hexane).

Mol. Formula : $C_{37}H_{61}BrO_9SSi_2$

$[\alpha]_D^{25}$: -14.73 (*c* = 0.51, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 759, 1035, 1219, 1601,1738, 2934,3419 cm^{-1}

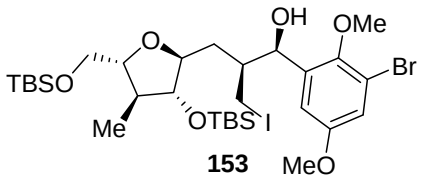
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.03 (s, 3H), 0.02 (s, 6H), 0.01 (s, 3H), 0.85 (s, 9H), 0.86 (s, 9H) 0.92-0.93 (m, 3H), 1.17 (brs, 1H), 1.72-1.78 (m, 2H), 2.07 (brs, 1H), 2.33 (s, 3H), 3.27-3.29 (m, 2H), 3.48-3.59 (m, 5H), 3.65(s, 3H), 3.68(s, 3H), 4.95 (m, 2H), 6.98 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -2.57 (q, CH_3), 15.31 (q, CH_3), 19.07 (q, CH_3), 21.41 (s, C), 26.29 (q, CH_3), 33.08 (t, CH_2), 49.10 (d, CH), 49.74 (d, CH), 56.37 (q, CH_3), 61.99 (q, CH_3), 64.46 (t, CH_2), 71.00 (t, CH_2), 71.54 (d, CH), 82.23 (d, CH), 84.11 (d, CH), 85.16 (d, CH), 113.84 (d, CH), 118.15 (s, C), 118.55 (d, CH), 127.04 (d, CH), 129.93 (d, CH), 140.92 (s, C), 141.88 (s, C), 143.50 (s, C), 149.46 (s, C), 157.93 (s, C) ppm.

ESI-MS (*m/z*) : 857.30 $[M+k]^+$.

Elemental Analysis Calcd.: C, 54.33; H, 7.52 %
Found: C, 54.35; H, 7.53 %

(1*R*, 2*S*)-1-(3-bromo-2,5-dimethoxyphenyl)-3-((2*S*, 3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)-2-(iodomethyl)propan-1-ol (153).



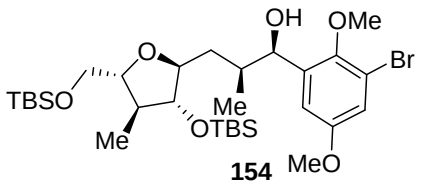
153

A mixture of **152** (1 g, 1.22 mmol) and NaI (1.49 g, 14.6mmol) taken in a glyme was Reflux for 2h. after complition of reaction, glyme was removed under reduced pressure to get residue which was purified on silica gel by eluting with EtOAC-hexane (1:3) to give iododerivative **153** (0.842 g, 89%), as a colorless liquid. R_f 0.4(25 % ethyl acetate/hexane).

Mol. Formula : $C_{30}H_{54}BrIO_6Si_2$

$[\alpha]_D^{25}$	: -17.52 (*c* = 1.4, $CHCl_3$)
IR ($CHCl_3$) υ	: 668, 758, 838, 1048, 1254, 1599, 2400, 3018, 3435 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 0.04 (s, 6H), 0.08 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H) 1.04 (d, *J* = 6.7 Hz, 3H),1.20 (ddd, *J* = 6.7, 10.5, 17.2 Hz, 1H), 1.6 (brs, 1H), 1.95-2.01 (m, 3H), 3.24 (dt, *J* = 5.6, 9.8, 14.7 Hz, 1H), 3.38 (dt, *J* = 6.7, 9.8, 14.7 Hz, 2H), 3.56 (q, *J* = 4.8 Hz, 1H), 3.64 (d, *J* = 4.8 Hz, 2H), 3.70 (dd, *J* = 6.7, 10.2 Hz, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 5.03 (t, *J* = 5.2 Hz, 1H), 6.97 (d, *J* = 3.01 Hz, 1H), 7.02 (d, *J* = 3.01 Hz, 1H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ -5.40 (q, CH_3), -5.37 (q, CH_3),-4.01 (q, CH_3),11.42 (t, CH_2), 15.41 (q, CH_3), 17.89 (s, C), 18.28 (s, C), 25.80 (q, CH_3), 25.84 (q, CH_3), 34.95 (t, CH_2), 42.98 (d, CH), 43.12 (d, CH), 55.72 (q, CH_3), 61.16 (q, CH_3),65.00 (t, CH_2), 70.47 (d, CH), 81.27 (d, CH), 83.52 (d, CH), 83.76 (d, CH), 112.62 (d, CH), 117.21 (d, CH), 117.72 (s, C), 137.43 (s, C), 147.83 (s, C), 156.23 (s, C) ppm.
ESI-MS (*m/z*)	: 797.39 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 46.57; H, 7.03 % Found: C, 46.58; H, 7.05 %

(1*R*, 2*S*)-1-(3-Bromo-2,5-dimethoxyphenyl)-3-((2*S*, 3*R*, 4*S*, 5*R*)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)-2-methylpropan-1-ol (154).

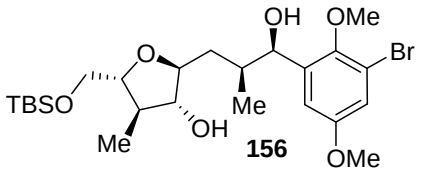


154

The iodocompound 1**53** (0.72 g, 0.93 mmol) in dry methnol (30 mL) was treated with 10% Pd/c under hydrogen atmosphere (2psi) at rt. for 1h. After completion of reaction, the mixture was filtered through celite, concentrated to get residue which on purification over silica gel column chromatography using EtOAc-hexane (1:6) afforded **154** (0.510 g, 85 %)as liquid. R_f 0.6(20% ethyl acetate/hexane).

Mol. Formula	: $C_{30}H_{55}BrO_6Si_2$
$[\alpha]_D^{25}$	: -18.43 (*c* = 0.4, $CHCl_3$)
IR ($CHCl_3$) υ	: 668, 756, 838, 1047, 1215, 1600, 2400, 3019, 3434 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 0.01 (s, 6H), 0.08 (s, 6H), 0.71 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 9H), 0.87 (s, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.55 (brs, 1H), 1.59-1.61 (m, 2H), 1.89-2.00 (m, 1H), 2.03-2.16 (m,1H), 3.21 (q, *J* = 7.3 Hz, 1H), 3.36 (t, *J* = 7.3 Hz, 1H), 3.56-3.59 (m, 1H), 3.60-3.63 (m, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 5.04 (d, *J* = 4.1 Hz, 1H), 6.93-6.97 (m, 2H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ -5.42 (q, CH_3), -4.09 (q, CH_3), -3.97 (q, CH_3), 14.74 (q, CH_3), 15.51 (q, CH_3), 17.89 (s, C), 18.27 (s, C), 25.73 (q, CH_3), 25.84 (q, CH_3), 37.17 (d, CH), 37.54 (t, CH_2), 43.22 (d, CH), 55.67 (q, CH_3), 61.02 (q, CH_3), 65.02 (t, CH_2), 71.14 (d, CH), 82.32 (d, CH), 83.67 (d, CH), 83.85 (d, CH), 112.57 (d, CH), 116.83 (s, C), 116.97 (d, CH), 138.80 (s, C), 147.54 (s, C), 156.01 (s, C) ppm.
ESI-MS (*m/z*)	: 670.53 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 55.62; H, 8.56 % Found: C, 55.63; H, 8.58 %

(3*R*, 4*R*, 5*R*)-2-((2*S*, 3*R*)-3-(3-bromo-2,5-dimethoxyphenyl)-3-hydroxy-2-methylpropyl)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-3-ol (156).



156

A mixture of **153** (0.45 g, 1.07 mmol), imidazole (0.87 g, 1.28 mmol), TBDMSCl (0.194 g, 1.28 mmol) and DMAP (5 mg) in CH_2Cl_2 (20 mL) was stirred for 6h at room temperature. After completion of the reaction, the mixture was diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4), and concentrated to get residue, which was purified on silica gel by eluting with EtOAC-hexane (1:4) to give TBS ether derivative **156** (0.48 g, 89 %), as a colorless liquid. R_f 0.5 (30 % ethyl acetate/hexane).

Mol. Formula : $C_{24}H_{41}BrO_6Si$

$[\alpha]_D^{25}$: -8.11 (*c* = 0.22, $CHCl_3$)

IR ($CHCl_3$) υ : 669, 755, 1047, 1253, 1600, 2400, 3019, 3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.07 (s, 6H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.61-1.63 (m, 2H), 2.05-2.17 (m, 2H), 2.58 (brs, 1H), 2.95 (brs, 1H), 3.47 (t, *J* = 6.7 Hz, 1H), 3.61-3.69 (m, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.90 (dq, *J*=2.7,5.7,9.1 Hz, 1H), 5.03 (t, *J* = 4.3 Hz, 1H), 6.96-7.00 (m, 2H) ppm.

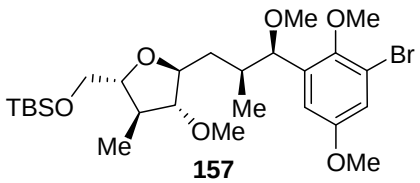
^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.48 (q, CH_3), -5.40 (q, CH_3), 14.52 (q, CH_3), 16.06 (q, CH_3), 18.32 (s, C), 25.87 (q, CH_3), 36.90 (d, CH), 37.99 (t, CH_2), 43.52 (d, CH), 55.70 (q, CH_3), 61.12 (q, CH_3), 65.21 (t, CH_2), 71.29 (d, CH), 83.28 (d, CH), 83.41 (d, CH), 84.26 (d, CH), 112.61 (d, CH), 116.87 (s, C), 117.07 (d, CH), 138.81 (s, C), 147.59 (s, C), 156.06 (s, C) ppm.

ESI-MS (*m/z*) : 557.40 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 54.02; H, 7.75 %

Found: C, 54.04; H, 7.76 %

(2*R*, 3*S*, 4*R*, 5*S*)-5-((2*S*, 3*R*)-3-(3-Bromo-2,5-dimethoxyphenyl)-3-methoxy-2-methylpropyl)-tetrahydro-4-methoxy-3-methylfuran-2-yl)methoxy)(tert-butyl)dimethylsilane (157).



157

The diol product **156** (0.45 g, 0.844 mmol) in dry DMF (8 mL) was cooled to 0°C and NaH (60% dispersion in oil, 0.84 g, 2.11 mmol) was added portion-wise at 0°C. After 25 min, iodo methane 0.3g (0.13 mL, 32.7 mmol) was added . After 3 h, the reaction mixture was worked up to give the residue, which was purified on silica gel by eluting with EtOAc-hexane (1:6) to give **157** (0.392 g, 82 %)as liquid. R_f 0.5(25 % ethyl acetate/hexane).

Mol. Formula : $C_{26}H_{45}BrO_6Si$

$[\alpha]_D^{25}$: +7.35 (*c* = 1.8, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 758, 837, 1049, 1254, 1599, 1730, 2401, 3010, 3472cm^{-1}

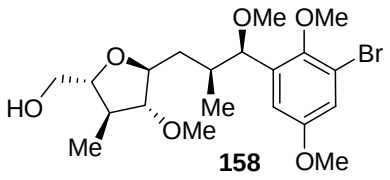
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.04 (s, 6H), 0.88 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H),1.42 (ddd, *J* = 3.3, 9.3, 12.6 Hz, 1H), 1.58 (ddd, *J* = 4.5, 10.1, 14.6 Hz, 1H), 1.99-2.08 (m, 2H), 3.13 (t, *J* = 5.2 Hz, 1H), 3.24 (s, 3H), 3.36 (s, 3H), 3.48 (dt, *J* = 5.2, 10.4 Hz, 1H), 3.60 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.66 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.87-3.93 (m, 1H), 4.43 (d, *J* = 5.3 Hz, 1H), 6.86 (d, *J* = 3.1 Hz, 1H), 7.00 (d, *J* = 3.1 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.36 (q, CH_3), 14.00 (q, CH_3), 17.34 (q, CH_3), 18.31 (s, C), 25.89 (q, CH_3), 36.34 (d, CH), 37.80 (t, CH_2), 42.07 (d, CH), 55.73 (q, CH_3), 57.29 (q, CH_3), 57.81 (q, CH_3), 61.24 (q, CH_3), 65.01 (t, CH_2), 80.45 (d, CH), 81.84 (d, CH), 84.07 (d, CH), 93.45 (d, CH), 112.28 (d, CH), 117.08 (s, C), 117.41 (d, CH), 136.95 (s, C), 149.18 (s, C), 156.19 (s, C) ppm.

ESI-MS (*m/z*) : 585.75 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 55.60; H, 8.08 %
Found: C, 55.61; H, 8.10 %

(2*R*, 3*S*, 4*R*, 5*S*)-5-((2*S*,3*R*)-3-(3-Bromo-2,5-dimethoxyphenyl)-3-methoxy-2-methylpropyl)-tetrahydro-4-methoxy-3-methylfuran-2-yl)methanol (158).



158

To a solution of TBSether **157** (0.35 g, 0.623 mmol) in THF (15 mL) was added tetrabutylammonium fluoride (1.0M in THF,1.56 mL,1.55 mmol) and stirred for 3h at room temperature. The reaction mixture was quenched with water, extracted with ethylacetate, dried (over $NaSO_4$) and concentrated to get a crude residue, which on purification over silica gel column chromatography using EtOAc-hexane (1:4) afforded **158** (0.232 g, 83 %) as a colorless liquid. R_f 0.7 (25 % ethyl acetate/hexane).

Mol. Formula : $C_{20}H_{31}BrO_6$

$[\alpha]_D^{25}$: +39.66 (*c* = 0.75, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 756, 1048, 1215, 1599, 1731, 2400, 3019, 3468 cm^{-1}

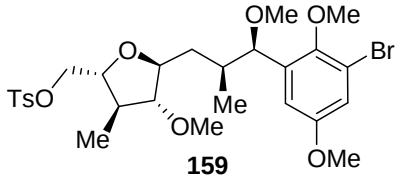
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.91 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H),1.37-1.45 (m, 2H), 1.96-2.06 (m, 2H), 2.01 (brs, 1H), 3.06-3.28 (m, 1H), 3.24 (s, 3H), 3.35 (s, 3H), 3.45-3.51 (m, 1H), 3.53-3.58 (m, 1H), 3.63-3.68 (m, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 3.94-3.98 (m, 1H), 4.42 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 3.02 Hz, 1H), 7.02(d, *J* = 3.02 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.09 (q, CH_3), 16.76 (q, CH_3), 36.36 (d, CH), 37.57 (t, CH_2), 40.84 (d, CH), 55.72 (q, CH_3), 57.29 (q, CH_3), 57.61 (q, CH_3), 61.18 (q, CH_3), 63.27 (t, CH_2), 80.91 (d, CH), 81.85 (d, CH), 84.03 (d, CH), 93.40 (d, CH), 112.26 (d, CH), 117.09 (s, C), 117.42 (d, CH), 136.79 (s, C), 149.08 (s, C), 156.20 (s, C) ppm.

ESI-MS (*m/z*) : 470.27 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 53.70; H, 6.98 %
Found: C, 53.71; H, 6.99 %

(2*R*, 3*S*, 4*R*, 5*S*)-5-((2*S*,3*R*)-3-(3-Bromo-2,5-dimethoxyphenyl)-3-methoxy-2-methylpropyl)-tetrahydro-4-methoxy-3-methylfuran-2-yl)methyl4-methylbenzenesulfonate (159).



159

To a stirred solution of **158** (0.2 g, 0.44 mmol), Et_3N (0.07 mL, 0.54 mmol) and DMAP (10 mg) in dichloromethane (10 mL) was added *p*-toluenesulfonyl chloride (0.78 g, 0.54 mmol) at 0^{o}C. The reaction mixture was stirred for 6h at room temperature, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:5) to afforded **159** (0.226 g, 85 %) as liquid. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{27}H_{37}BrO_8S$

$[\alpha]_D^{25}$: +2.63 (*c* = 1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 755, 1047, 1216, 1599, 2401, 3015 cm^{-1}

^{1}H NMR : δ 0.84 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.40

(500 MHz, $CDCl_3$) (ddd, *J* = 3.2, 8.9, 13.7 Hz, 1H), 1.55 (ddd, *J* = 4.8, 10.8, 14.8 Hz, 1H), 1.89-1.98 (m, 2H), 2.42 (s, 3H), 3.11 (t, *J* = 4.8 Hz, 1H), 3.22 (s, 3H), 3.30 (s, 3H), 3.65 (dt, *J* = 5.3, 10.8 Hz, 1H), 3.77 (s, 6H), 3.80-3.85 (m, 1H), 4.01 (d, *J* = 5.3, 2H), 4.40 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 3.1 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H) ppm.

^{13}C NMR : δ 13.79 (q, CH_3), 16.81 (q, CH_3), 21.51 (q, CH_3), 36.32 (d, CH), 37.86 (t, CH_2), 41.70 (d, CH), 55.70 (q, CH_3), 57.25 (q, CH_3), 57.71 (q, CH_3), 61.14 (q, CH_3), 70.40 (t, CH_2), 80.89 (d, CH), 81.22 (d, CH), 81.59 (d, CH), 92.71 (d, CH), 112.22 (d, CH), 117.04 (s, C), 117.28 (d, CH), 127.85 (d, CH), 129.71 (d, CH), 132.90 (s, C), 136.79 (s, C), 144.66 (s, C), 149.00 (s, C), 156.14 (s, C) ppm.

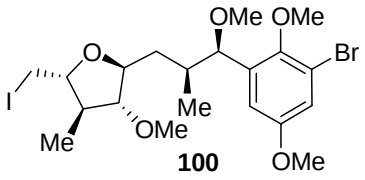
(125 MHz, $CDCl_3$)

ESI-MS (*m/z*) : 625.47 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 53.91; H, 6.20 %

Found: C, 53.93; H, 6.24 %

(2*S*, 3*R*, 4*R*, 5*R*)-2-((2*S*, 3*R*)-3-(3-Bromo-2,5-dimethoxyphenyl)-3-methoxy-2-methylpropyl)-tetrahydro-5-(iodomethyl)-3-methoxy-4-methylfuran (100).



100

A mixture of **159** (0.2 g, 0.33 mmol) and NaI (0.598 g, 3.9 mmol) taken in a glyme was Reflux for 2h, after complition of reaction, glyme was removed under reduced pressure to get residue which was purified on silica gel by eluting with EtOAC-hexane (1:5) to give iododerivative **100** (0.152 g, 82%) as a colorless liquid. R_f 0.6 (25 % ethyl acetate/hexane).

Mol. Formula : $C_{20}H_{30}BrIO_5$

$[\alpha]_D^{25}$: +8.26 (*c* = 0.5, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 756, 1048, 1215, 1599, 3016 cm^{-1}

^{1}H NMR : δ 0.92 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H),1.44 (ddd, *J* = 3.2, 8.9, 13.8 Hz, 1H), 1.55 -1.64 (m, 1H), 1.99-2.12

(500 MHz, $CDCl_3$)

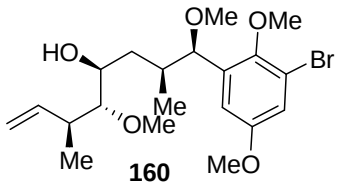
(m, 2H), 3.19-3.23 (m, 2H), 3.25 (s, 3H), 3.33 (t, *J*=6.2 Hz, 1H), 3.35 (s, 3H), 3.50 (q, *J* = 6.2 Hz, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 4.01 (dt, *J* = 3.5, 10.1, 1H), 4.44 (d, *J* = 5.1 Hz, 1H), 6.86 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 3.1 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 9.42 (t, CH_2), 14.05 (q, CH_3), 17.64 (q, CH_3), 36.51 (d, CH), 37.95 (t, CH_2), 45.20 (d, CH), 55.79 (q, CH_3), 57.37 (q, CH_3), 57.80 (q, CH_3), 61.37 (q, CH_3), 81.16 (d, CH), 81.63 (d, CH), 83.28 (d, CH), 93.46 (d, CH), 112.30 (d, CH), 117.13 (s, C), 117.37 (d, CH), 136.92 (s, C), 149.08 (s, C), 156.21 (s, C) ppm.

ESI-MS (*m/z*) : 579.43 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 43.11; H, 5.43 %
Found: C, 43.14; H, 5.45 %

(1*R*, 2*S*, 4*S*, 5*R*, 6*S*)-1-(3-Bromo-2,5-dimethoxyphenyl)-1,5-dimethoxy-2,6-dimethyloct-7-en-4-ol (160).



160

A mixture of iodocompound **100** (0.14 g, 0.25 mmol) and NH_4Cl (catalytic) in a dry methanol was treated with activated zinc (0.164 g, 2.51 mmol) at 0^{o}C for 30 min. after complition of reaction, the mixture was filtered through celite, concentrated the oganic layer to get residue which on purification over silica gel by eluting with EtOAC-hexane (1:4) to give hydroxyl olefinic compound **160** (0.86 g, 79 %) as a colorless liquid. R_f 0.4 (20 % ethyl acetate/hexane).

Mol. Formula : $C_{20}H_{31}BrO_5$

$[\alpha]_D^{25}$: +76.08 (*c* = 0.75, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 757, 1048, 1216, 1599,1639, 1734, 2401, 2933, 3468 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.86 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.26 (bs, 1H), 1.47-1.50 (m, 1H), 1.99 (dd, *J* = 6.8, 1H), 2.02-2.08 (m, 1H), 2.42 (qn, *J* = 4.7, 6.8 Hz, 1H), 3.00 (dd, J = 4.7, 6.7, 1H), 3.25 (s, 3H), 3.48 (s, 3H), 3.70-3.76 (m, 1H), 3.78 (s, 3H), 3.81 (m, 3H), 4.42 (d, *J* = 4.7, 1H), 4.99 (d, *J* = 10.2, 17.8 Hz, 2H),

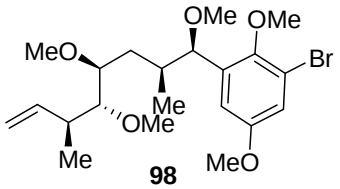
5.75 (ddd, *J* = 10.2, 17.8, 1H), 6.86 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 3.1 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.02 (q, CH_3), 16.05 (q, CH_3), 35.50 (t, CH_2), 35.88 (d, CH), 40.15 (d, CH), 55.74 (q, CH_3), 57.35 (q, CH_3), 60.95 (q, CH_3), 61.24 (q, CH_3), 70.81 (d, CH), 82.50 (d, CH), 88.59 (d, CH), 112.52 (d, CH), 114.34 (t, CH_2), 117.18 (s, C),117.39 (d, CH), 136.45 (s, C), 141.41 (d, CH), 149.09 (s, C), 156.14 (s, C) ppm.

ESI-MS (*m/z*) : 455.26 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 55.69; H, 7.24 %
Found: C, 55.72; H, 7.25 %

1-Bromo-2,5-dimethoxy-3-((1*R*, 2*S*, 4*S*, 5*R*, 6*S*)-1,4,5-trimethoxy-2,6-dimethyloct-7-enyl)benzene (98).



98

The alcohol product **160** (0.045 g, 0.104 mmol) in dry DMF (8 mL) was cooled to 0^{o}C and NaH (60% dispersion in oil, 0.084 g, 2.11 mmol) was added portion-wise at 0^{o}C. After 25 min, iodo methane 0.03g (0.013 mL, 32.7 mmol) was added . After 3 h, the reaction mixture was worked up to give the residue, which was purified on silica gel by eluting with EtOAc-hexane (1:6) to give **98** (0.038 g, 82 %) as a syrup. R_f 0.5(25 % ethyl acetate/hexane).

Mol. Formula : $C_{21}H_{33}BrO_5$

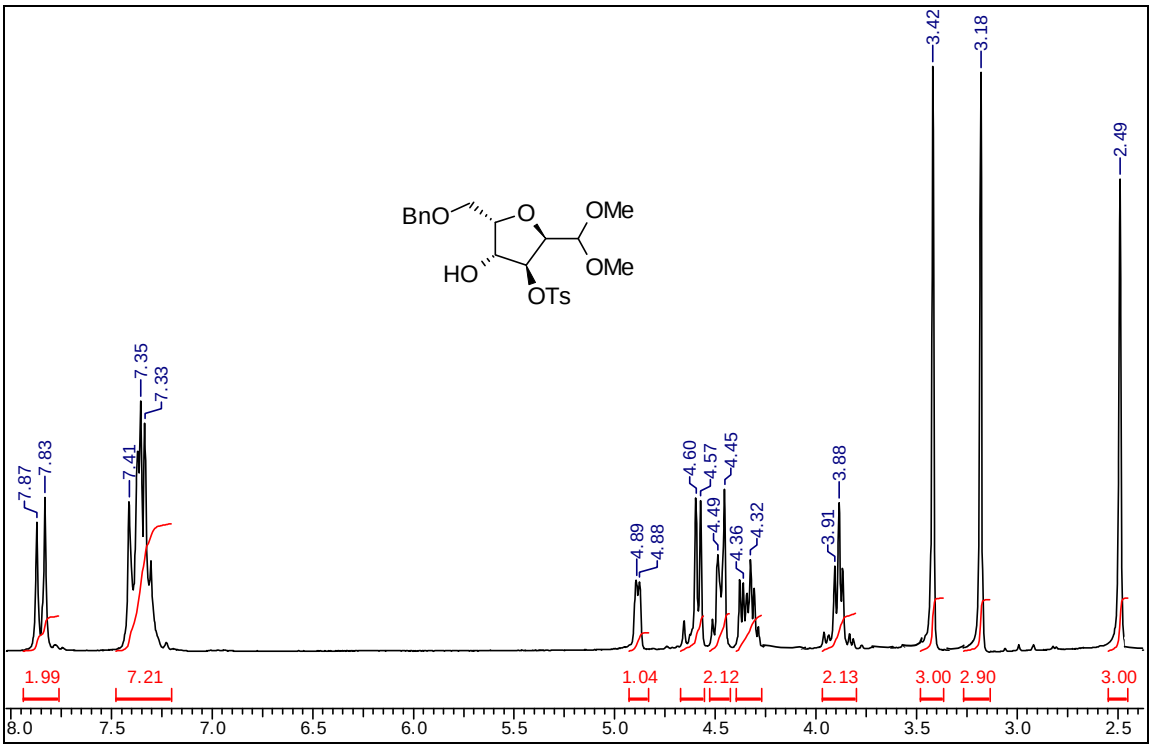
$[\alpha]_D^{25}$: +24.39 (*c* =0.25, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 757, 1048, 1216, 1599,1639, 1734, 2933, 3468 cm^{-1}

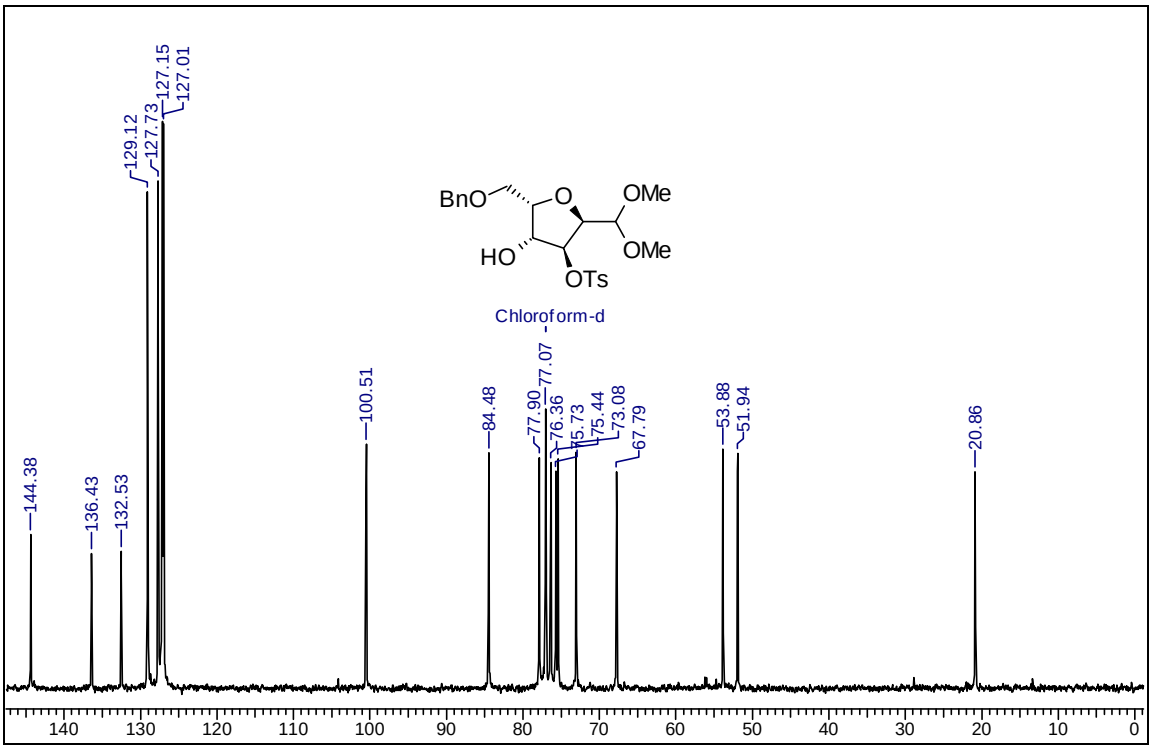
^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.82 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.44 (ddd, *J* = 2.2, 10.2, 14.3 Hz, 1H), 1.67 (ddd, *J* = 3.5, 10.2, 14.3 Hz, 1H), 1.97-2.05 (m,1H), 2.30 (dq, *J* = 6.7, 14.3, 21.5 Hz, 1H), 3.14 (dd, *J* = 3.03, 7.63 Hz, 1H), 3.22 (dd, *J* = 6.97, 10.2 Hz, 1H), 3.23 (s, 3H), 3.32 (s, 3H), 3.47 (s, 3H), 3.77(s, 3H), 3.81 (s, 3H), 4.40 (d, *J* = 4.3, 1H), 4.99 (d, *J* = 16.9, 23.2 Hz,

	2H), 5.75 (ddd, J = 10.2, 17.8, 1H), 6.86 (d, J = 3.1 Hz, 1H), 7.01 (d, J = 3.1 Hz,1H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 13.50 (q, CH_3), 16.66 (q, CH_3), 33.48 (t, CH_2), 35.46 (d, CH), 40.46 (d, CH), 55.70 (q, CH_3), 57.05 (q, CH_3), 57.40 (q, CH_3), 60.60 (q, CH_3), 61.21 (q, CH_3), 80.75 (d, CH), 82.53 (d, CH), 84.57 (d, CH), 112.38 (d, CH), 114.51 (t, CH_2), 117.06 (d, CH), 117.29 (s, C), 136.99 (s, C), 141.32 (d, CH), 149.08 (s, C), 156.07 (s, C) ppm.
ESI-MS (*m/z*)	: 468.41 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 56.63; H, 7.47 % Found: C, 56.66; H, 7.48 %

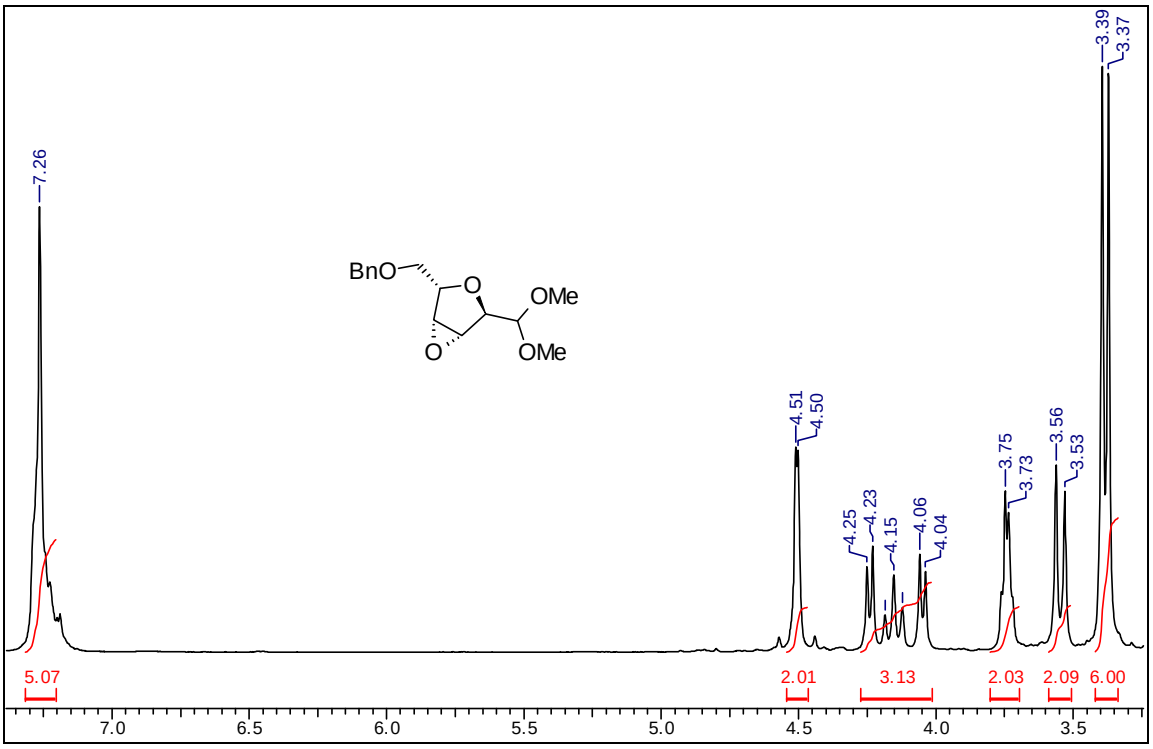
SPECTROSCOPIC DATA



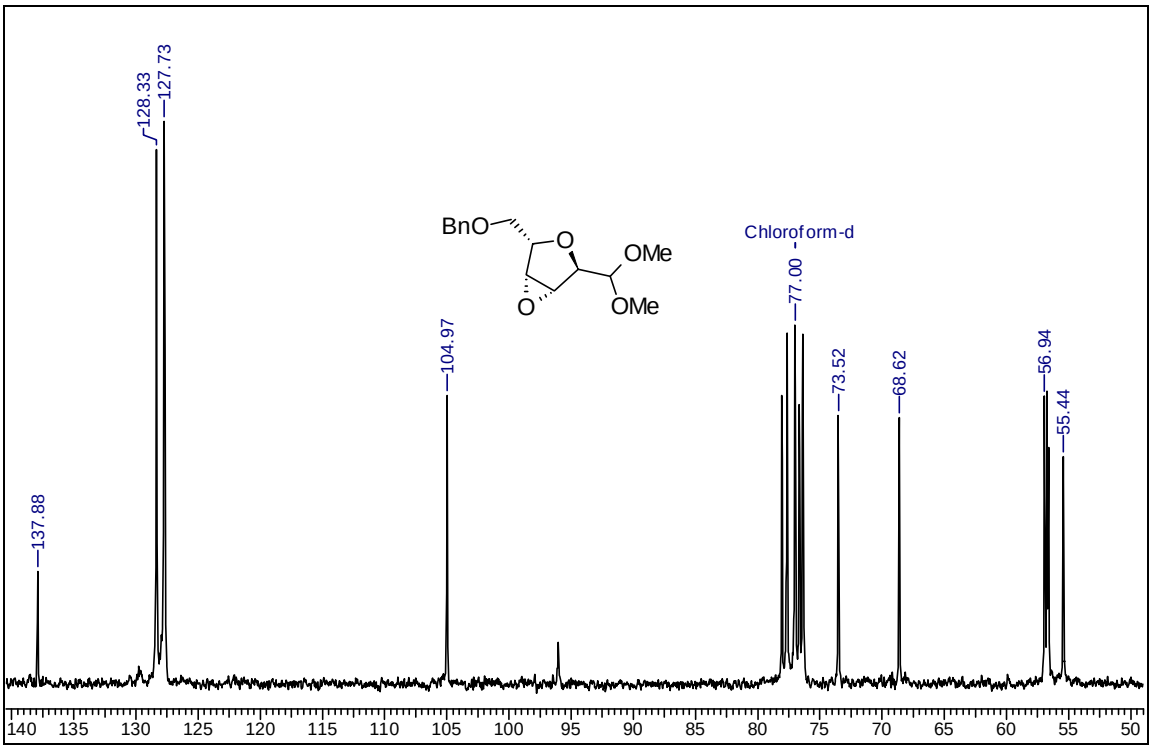
^{1}H NMR Spectrum of Rearranged product 108 in $CDCl_3$



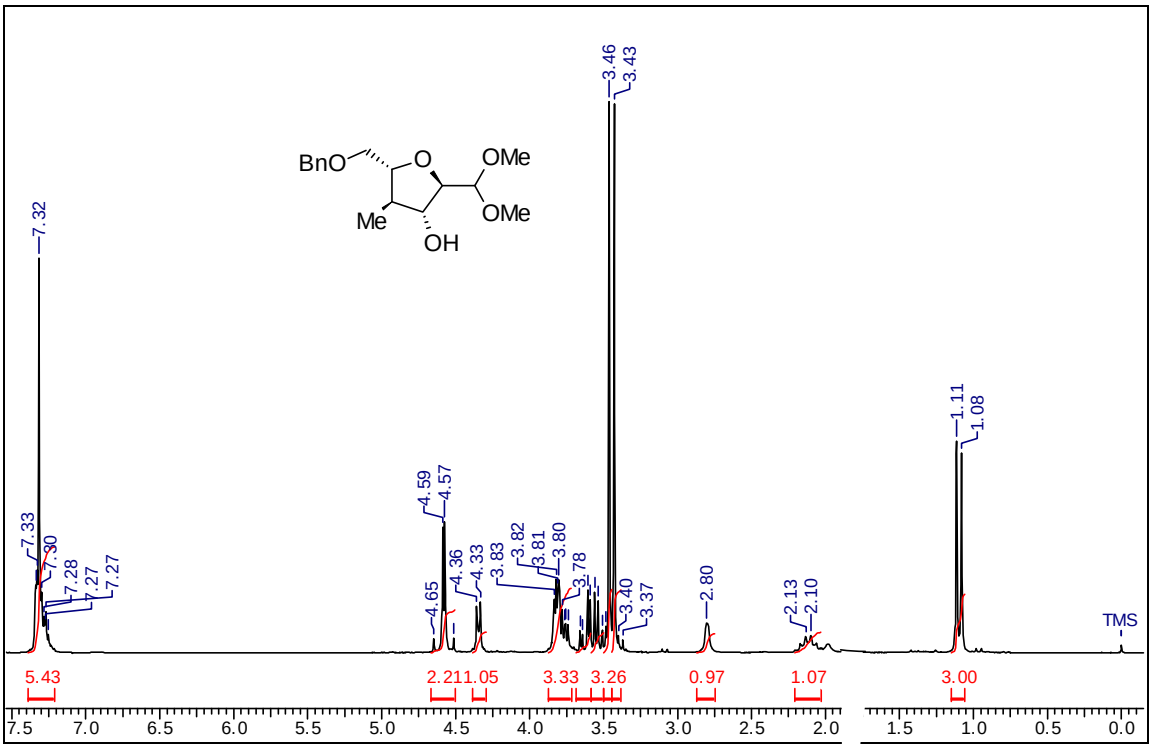
^{13}CNMR Spectrum of Rearranged product 108 in $CDCl_3$



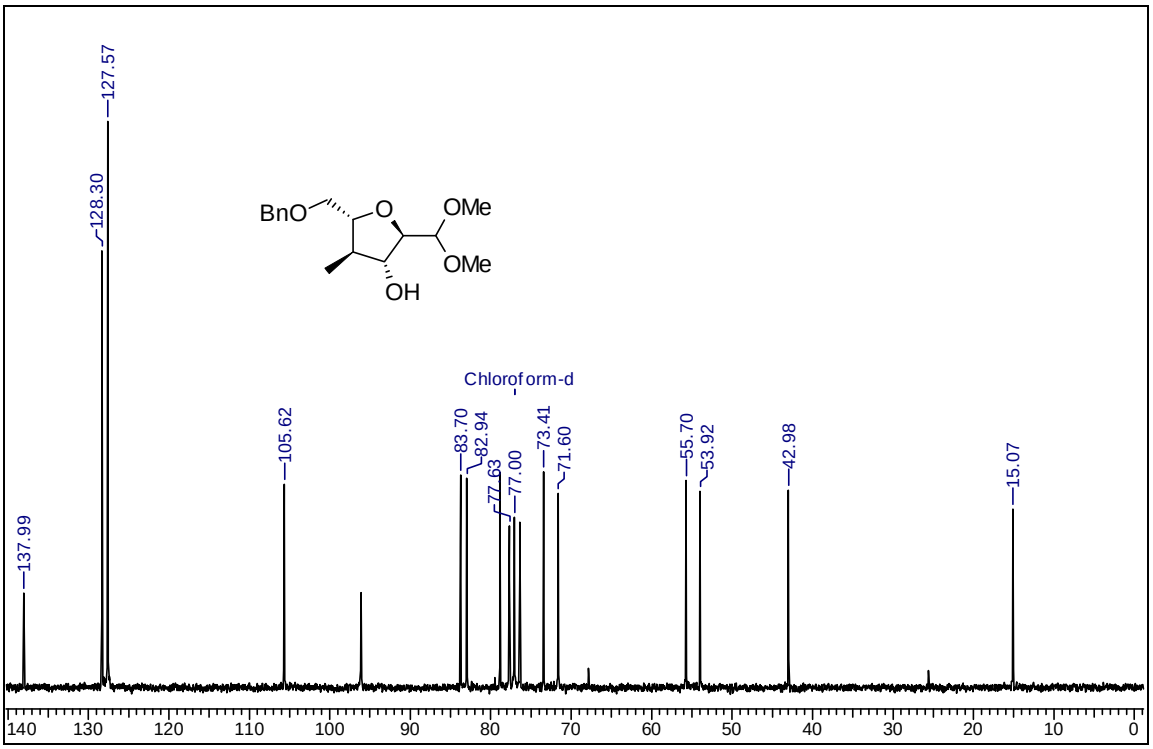
^{1}H NMR Spectrum of Epoxide-112 in $CDCl_3$



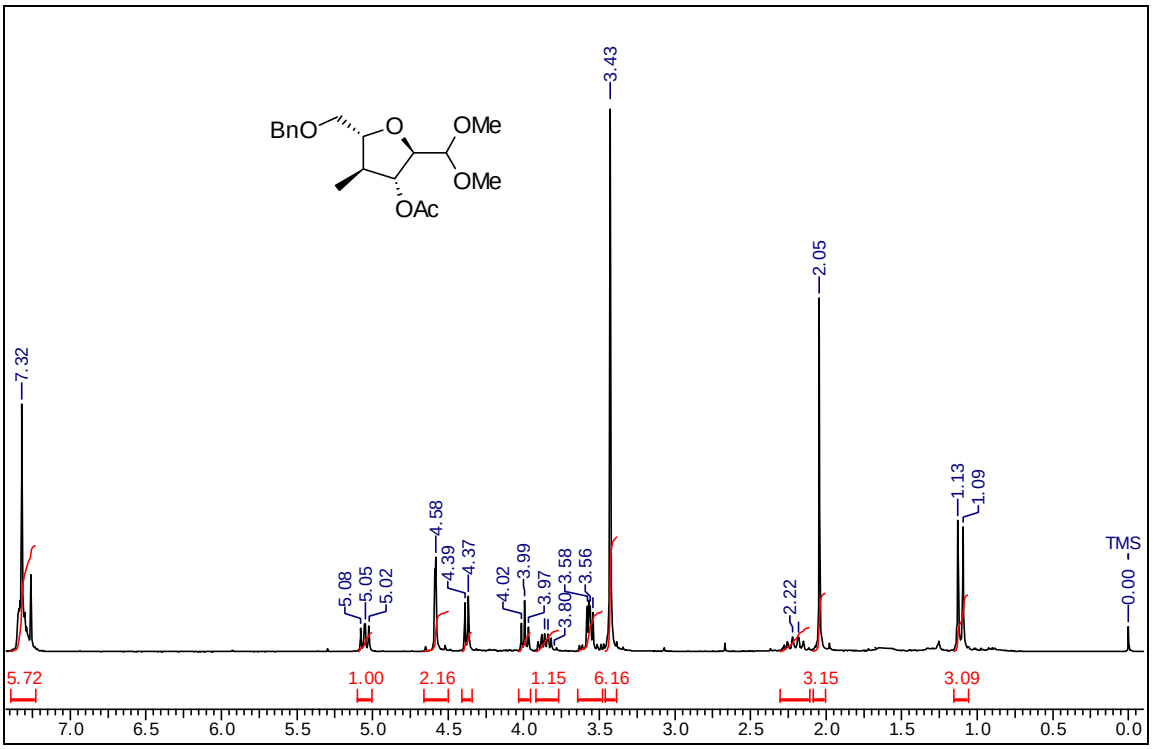
^{13}C NMR Spectrum of Epoxide-112 in $CDCl_3$/CCl_4



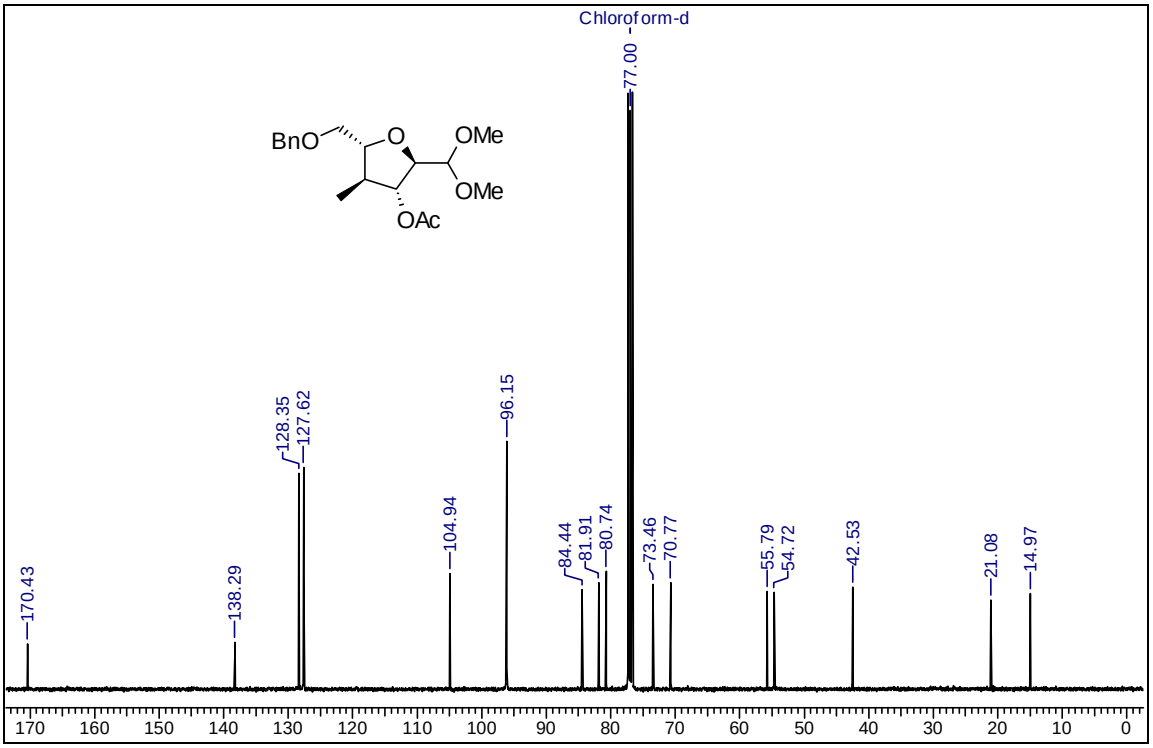
^{1}H NMR Spectrum of Epoxide Opened Product 113 in $CDCl_3$



^{13}C NMR Spectrum of Epoxide Opened Product 113 in $CDCl_3$/ CCl_4



^{1}H NMR Spectrum of Ac-Acetal 114 in $CDCl_3$



^{13}C NMR Spectrum of Ac-Acetal 114 in $CDCl_3$/ CCl_4

BRUKER
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PROCNO 1
F2 - Acquisition Parameters
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Time 21.21
INSTRUM spect
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PULPROG cosygpqf
TD 1024
SOLVENT CDCl3
NS 16
DS 2
SWH 3001.200 Hz
FIDRES 2.930860 Hz
AQ 0.1706484 sec
RG 256
DW 166.600 usec
DE 20.00 usec
TE 298.2 K
d0 0.00000300 sec
D1 2.50000000 sec
d13 0.00000400 sec
D16 0.00010000 sec
IN0 0.00033323 sec
======== CHANNEL f1 ========
NUC1 1H
P0 14.20 usec
P1 14.20 usec
PL1 1.00 dB
SFO1 400.1316700 MHz
====== GRADIENT CHANNEL =====
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GPNAM2 SINE.100
GPZ1 10.00 %
GPZ2 10.00 %
P16 1500.00 usec
F1 - Acquisition parameters
NDO 1
TD 256
SFO1 400.1317 MHz
FIDRES 11.722560 Hz
SW 7.500 ppm
FnMODE QF
F2 - Processing parameters
SI 1024
SF 400.1300000 MHz
WDW QSINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 QF
SF 400.1300000 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
D.Rambabu COSY
ppm
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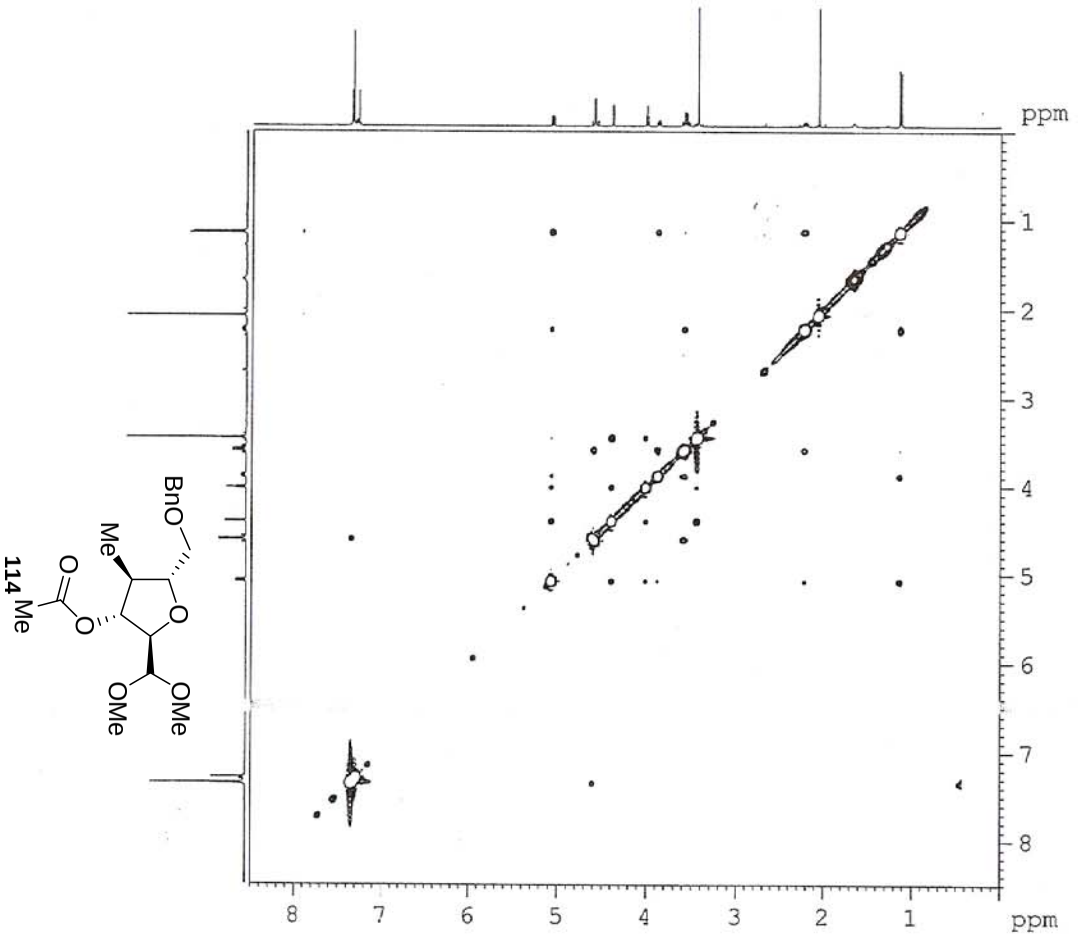
BnO
OMe
OMe
Me
O
O
Me
114

D.Rambabu Noesy



114 Me

BRUKER

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EXPNO                   3
PROCNO                  1

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PULPROG        noesygpph
TD                   1024
SOLVENT              CDCl3
NS                      16
DS                      16
SWH              3001.200 Hz
FIDRES           2.930860 Hz
AQ               0.1706484 sec
RG                     256
DW               166.600 usec
DE                20.00 usec
TE                299.7 K
d0             0.00014853 sec
D1             3.00000000 sec
D8             1.00000000 sec
D16            0.00010000 sec
IN0            0.00033323 sec
ST1CNT                128
TAU            0.49840000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 14.20 usec
P2                 28.40 usec
PL1                 1.00 dB
SFO1         400.1316700 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1               40.00 %
GPZ2              -40.00 %
P16              1500.00 usec

F1 - Acquisition parameters
ND0                     1
TD                    256
SFO1         400.1317 MHz
FIDRES       11.722560 Hz
SW                7.500 ppm
FnMODE       States-TPPI

F2 - Processing parameters
SI                   1024
SF           400.1300000 MHz
WDW                    GM
SSB                     0
LB                 -2.00 Hz
GB                  0.015
PC                   1.00

F1 - Processing parameters
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MC2          States-TPPI
SF           400.1300000 MHz
WDW                 QSINE
SSB                     2
LB                  0.00 Hz
GB                      0
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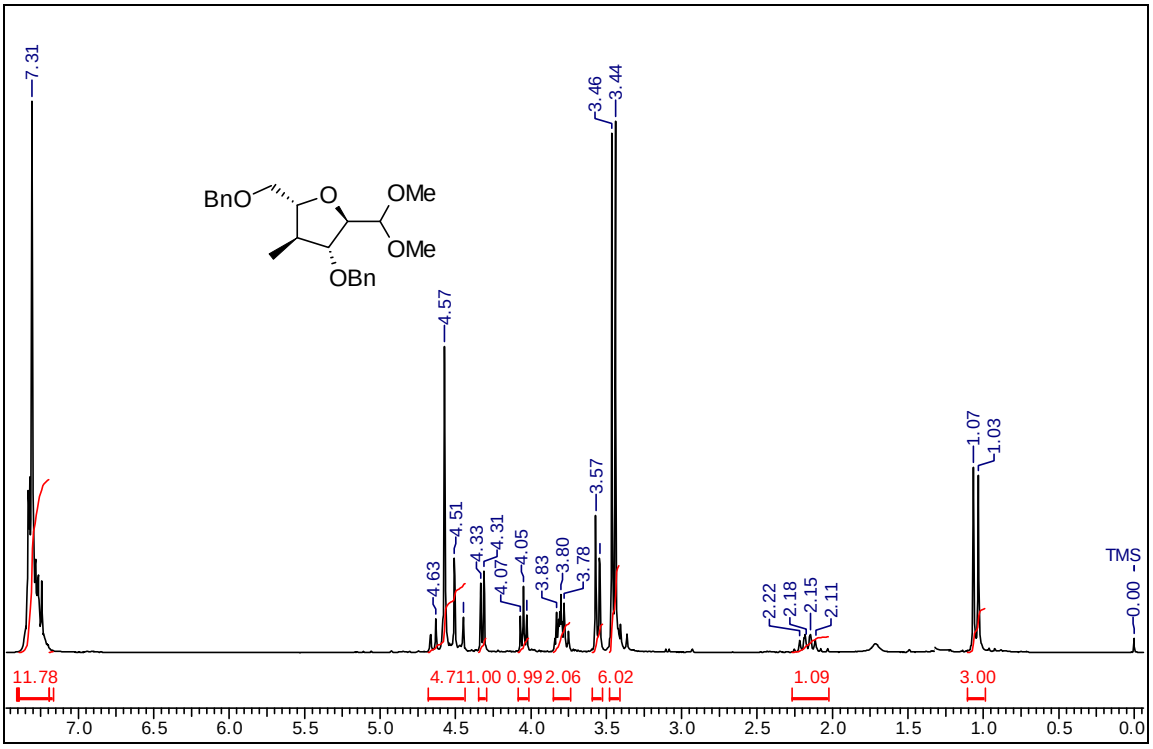
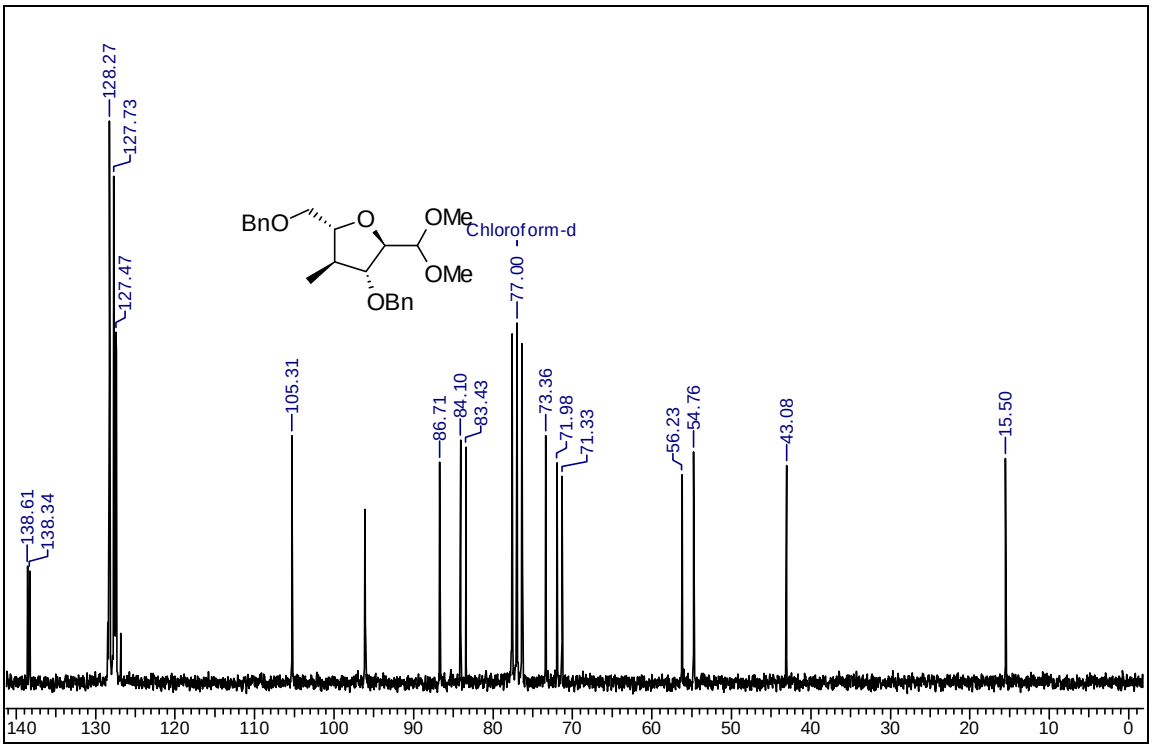
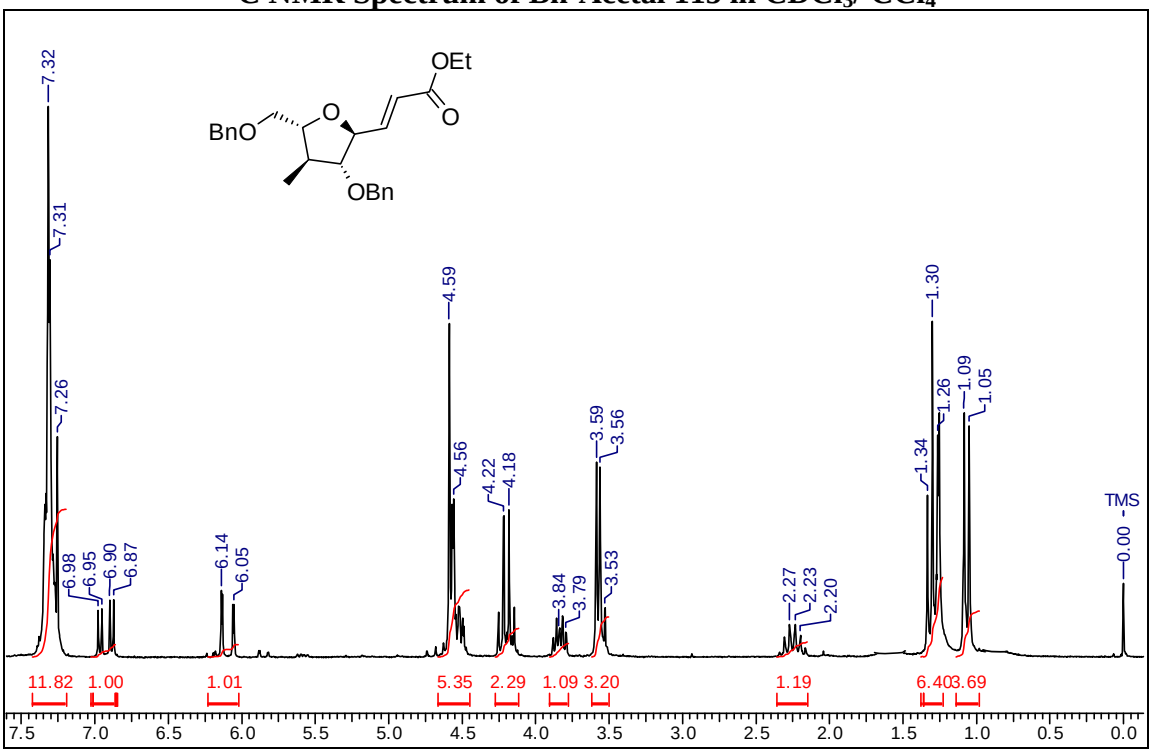


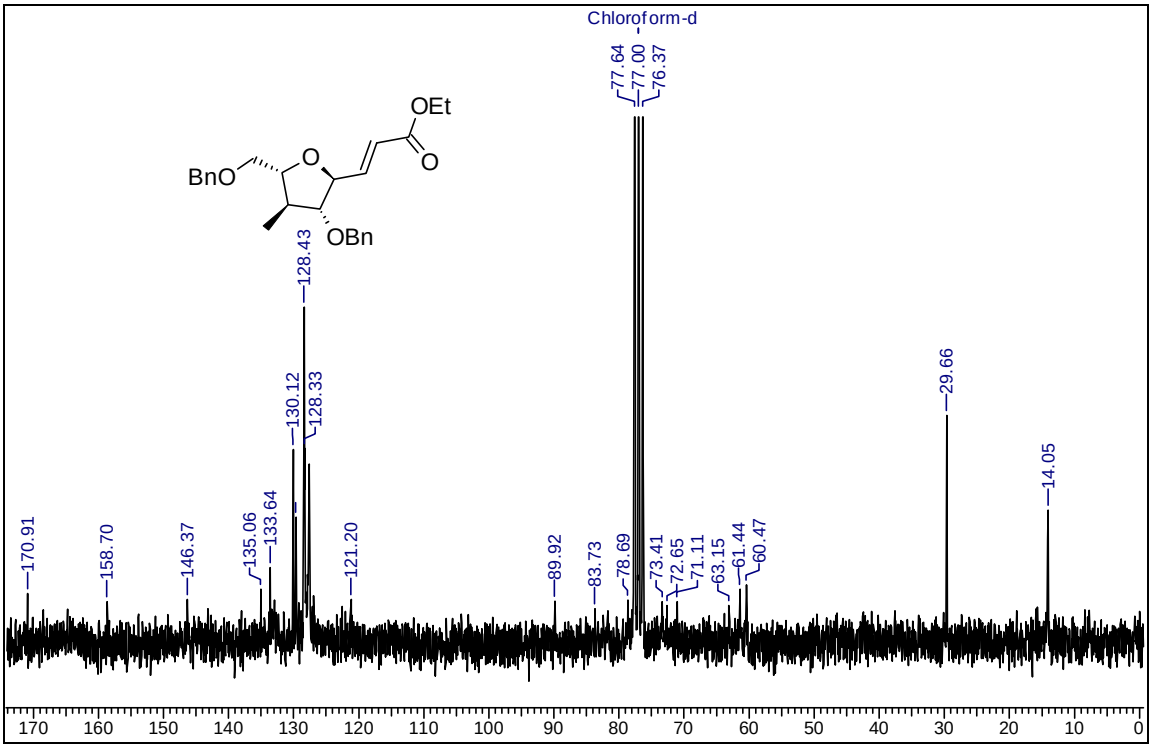
^{1}H NMR Spectrum of Bn-Acetal 115 in $CDCl_3$



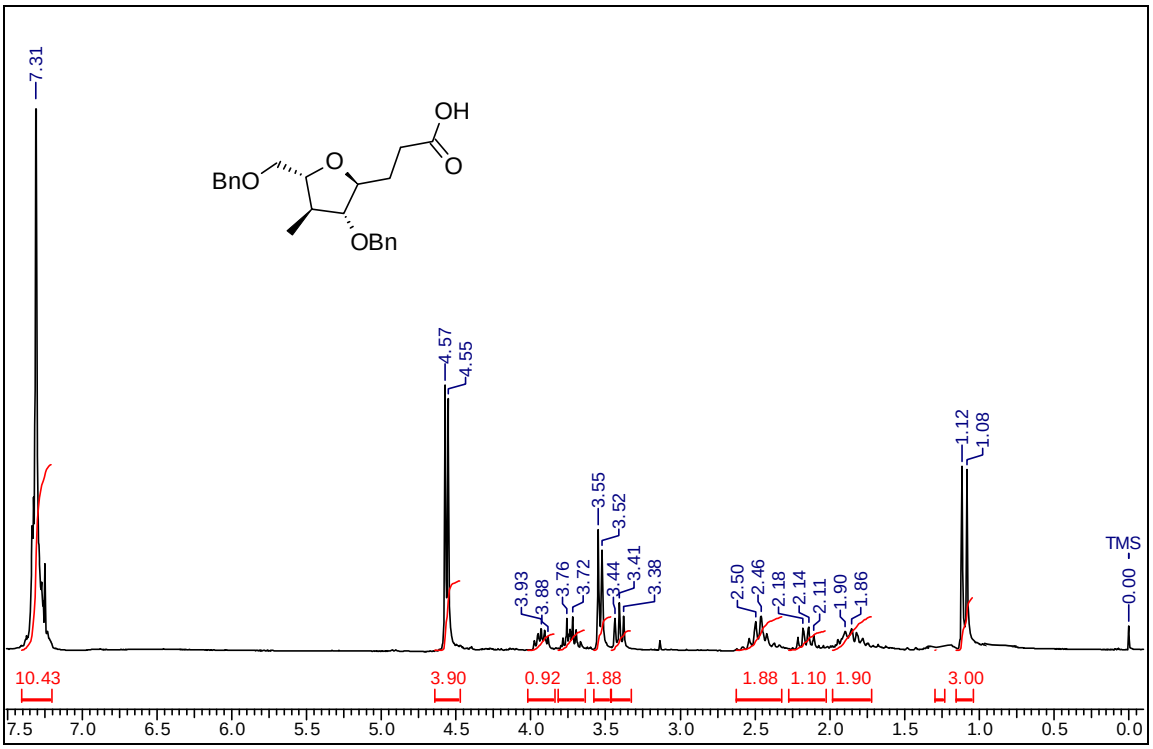
^{13}C NMR Spectrum of Bn-Acetal 115 in $CDCl_3$/ CCl_4



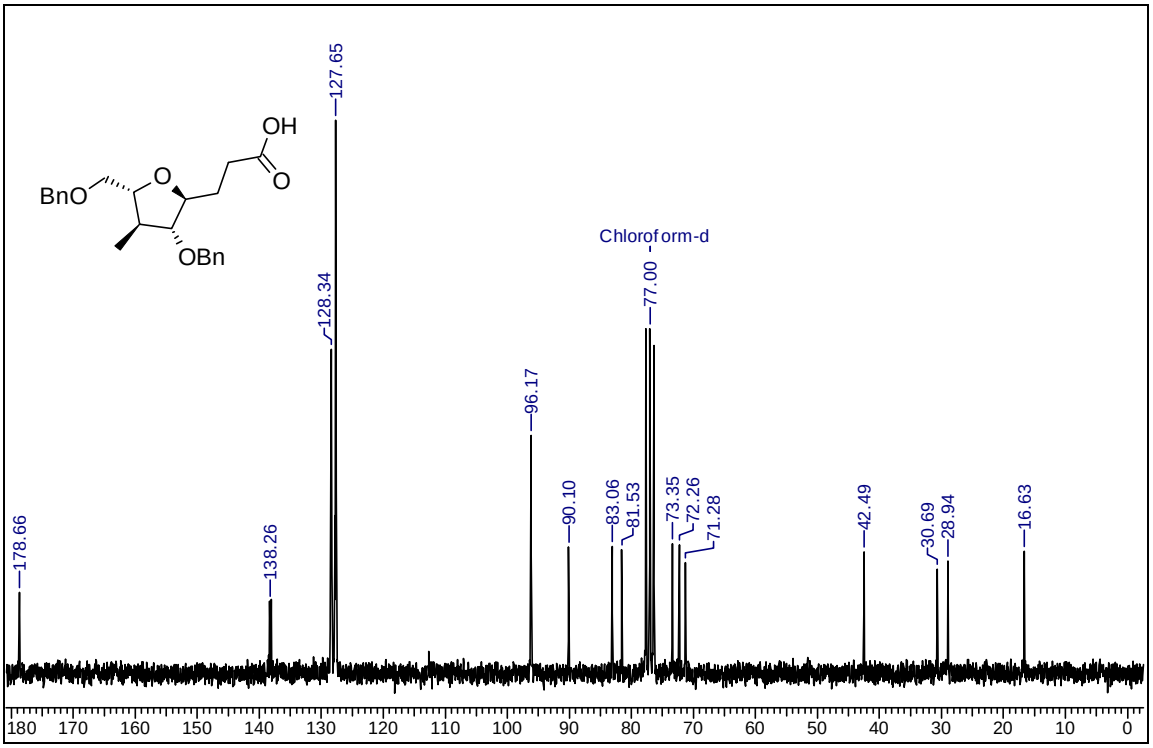
^{1}H NMR Spectrum of Conjugated ester 117 in $CDCl_3$



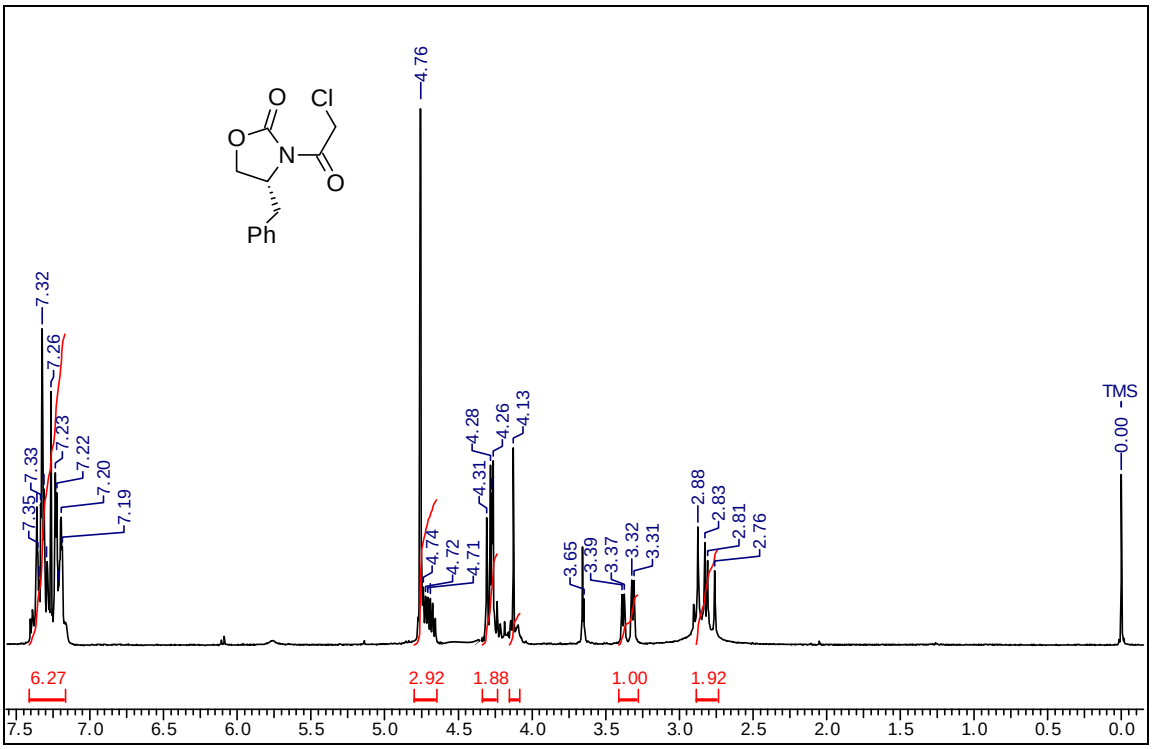
^{13}C NMR Spectrum of Conjugated ester 117 in $CDCl_3$



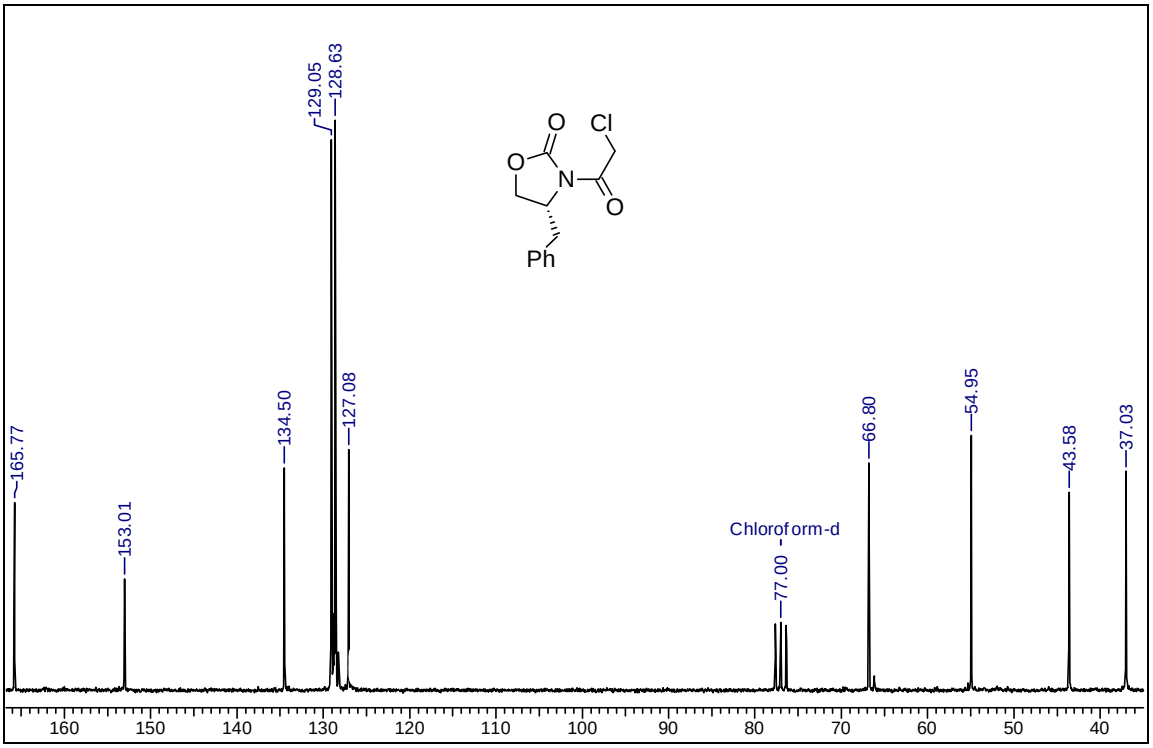
^{1}H NMR Spectrum of Acid 104 in $CDCl_3$



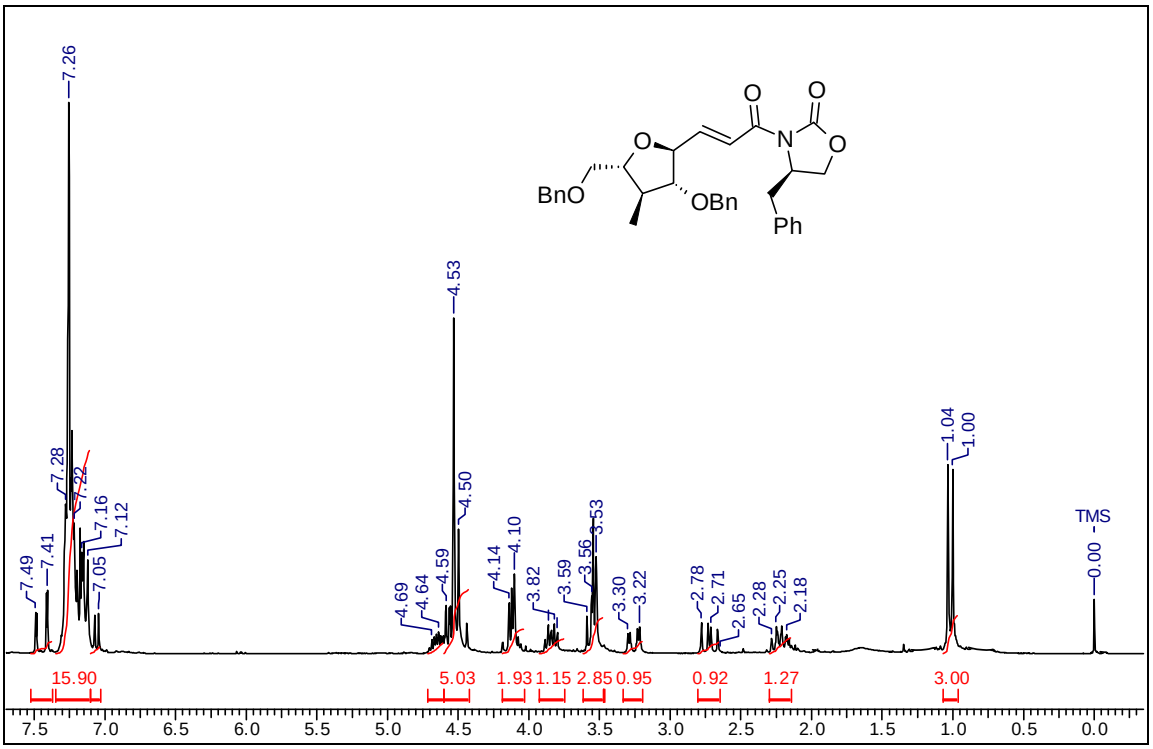
^{13}C NMR Spectrum of Acid-104 in $CDCl_3$/ CCl_4



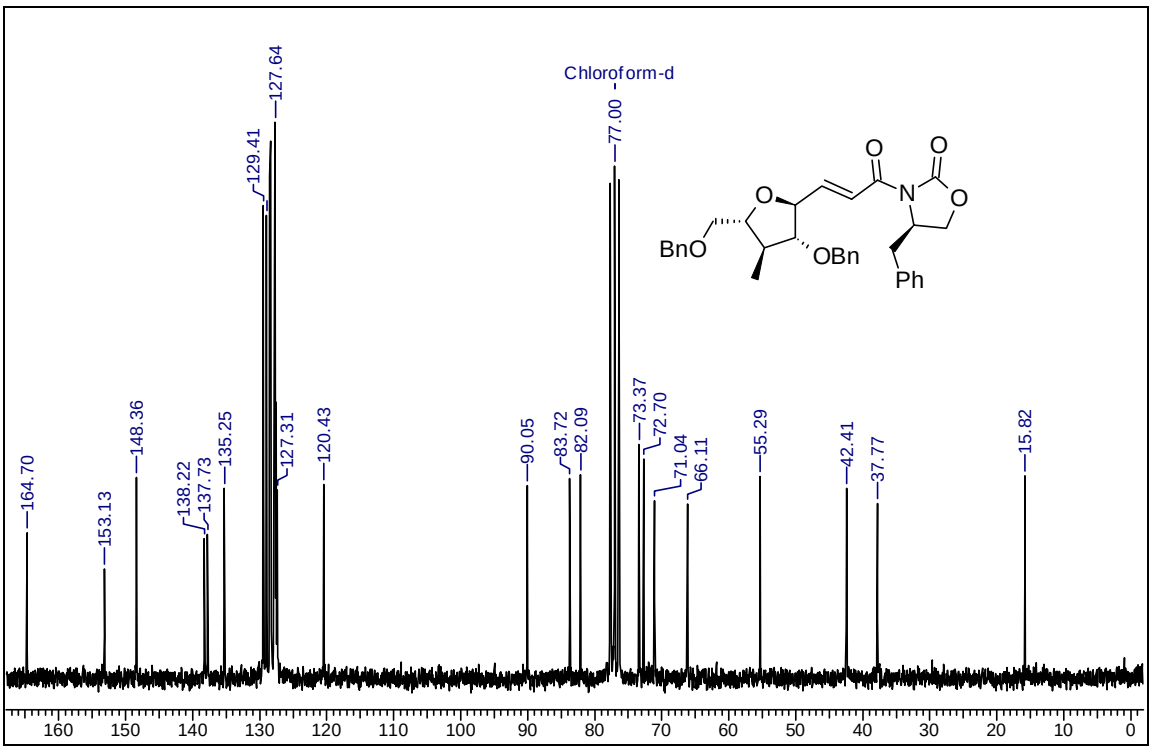
^{1}H NMR Spectrum of Chloro acetyl Oxazolidinone 119 in $CDCl_3$



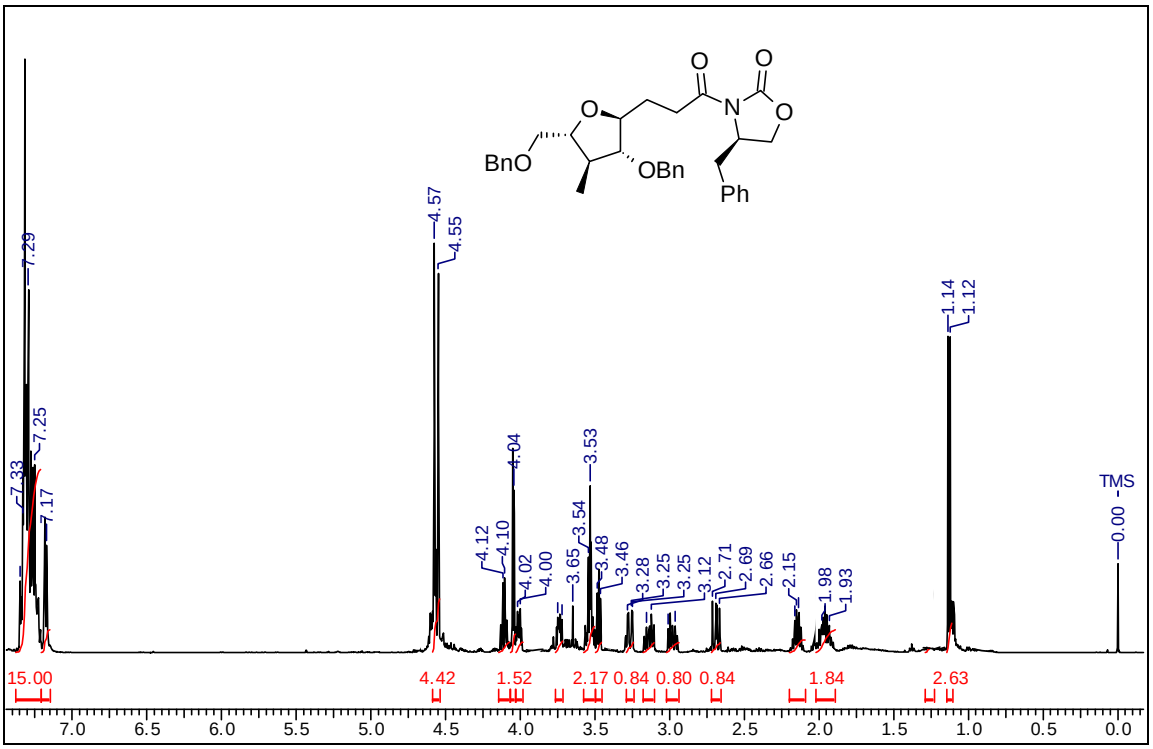
^{13}C NMR Spectrum of Chloro acetyl Oxazolidinone 119 in $CDCl_3$



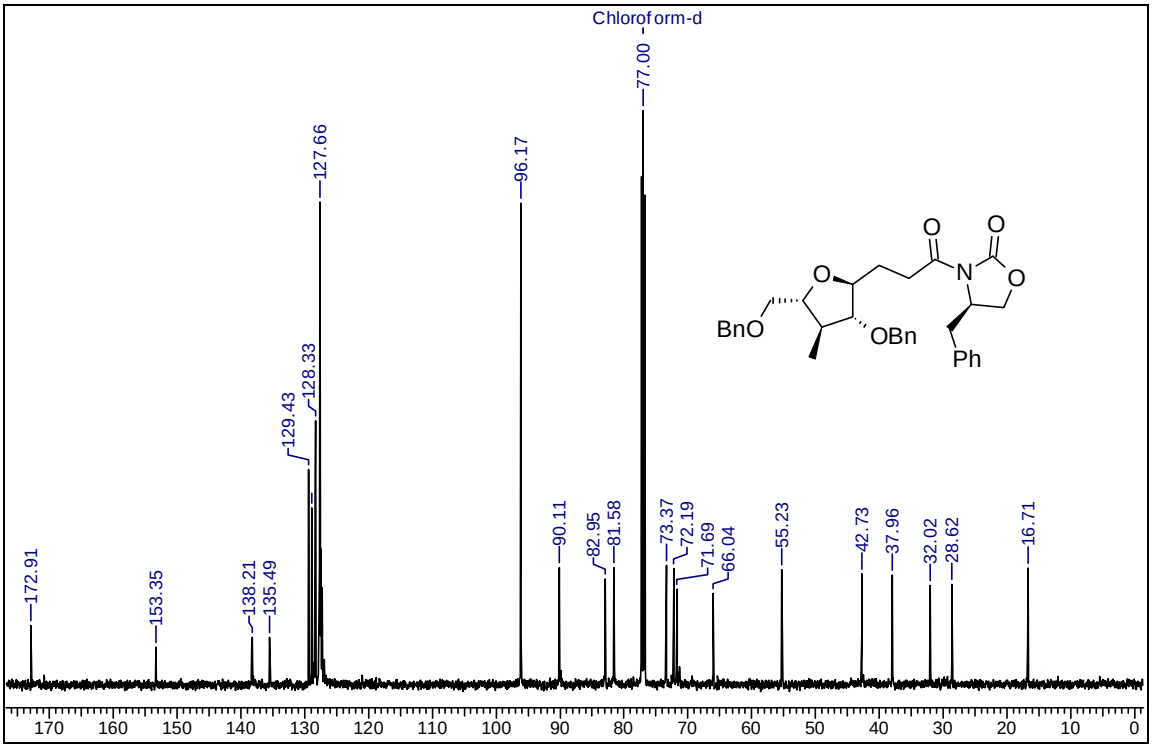
^{1}H NMR Spectrum of Conjugated Oxazolidinone 116 in $CDCl_3$



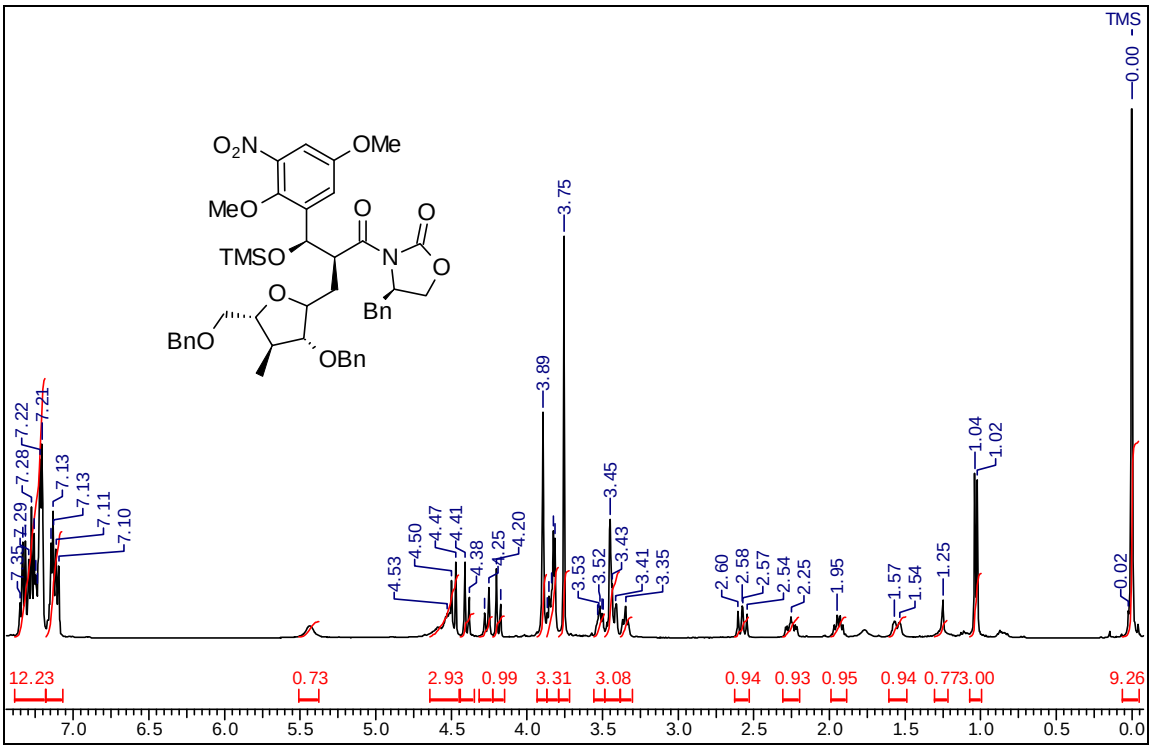
^{13}C NMR Spectrum of Conjugated Oxazolidinone 116 in $CDCl_3$



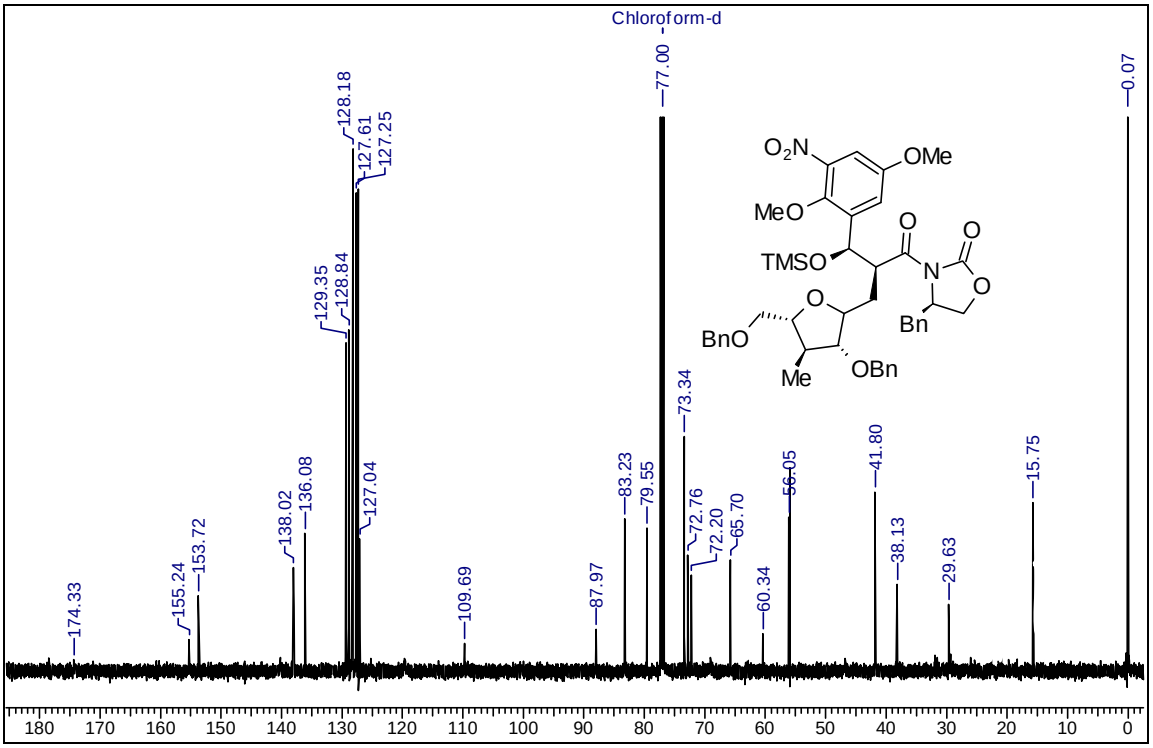
^{1}H NMR Spectrum of Di-Bn Oxazolidinone 101 in $CDCl_3$



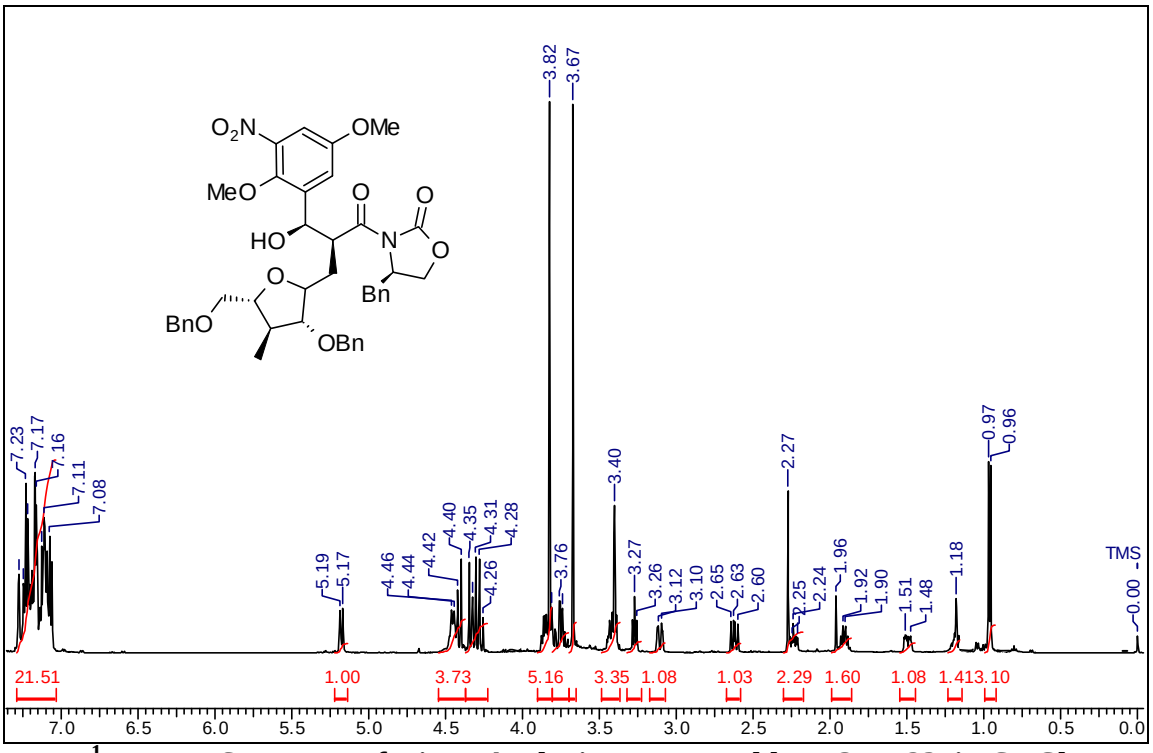
^{13}C NMR Spectrum of Di-Bn Oxazolidinone 101 in $CDCl_3$/ CCl_4



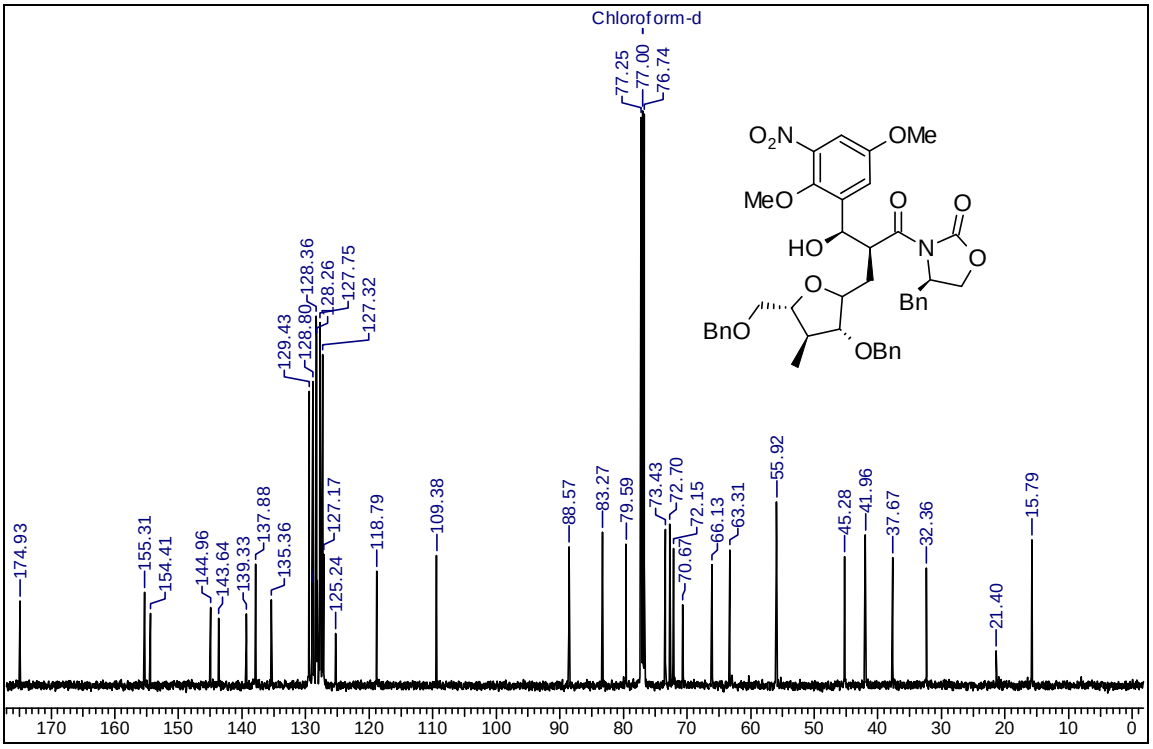
^{1}H NMR Spectrum of Di-Bn Aryl Nitro Evans adduct-OTMS 122 in $CDCl_3$



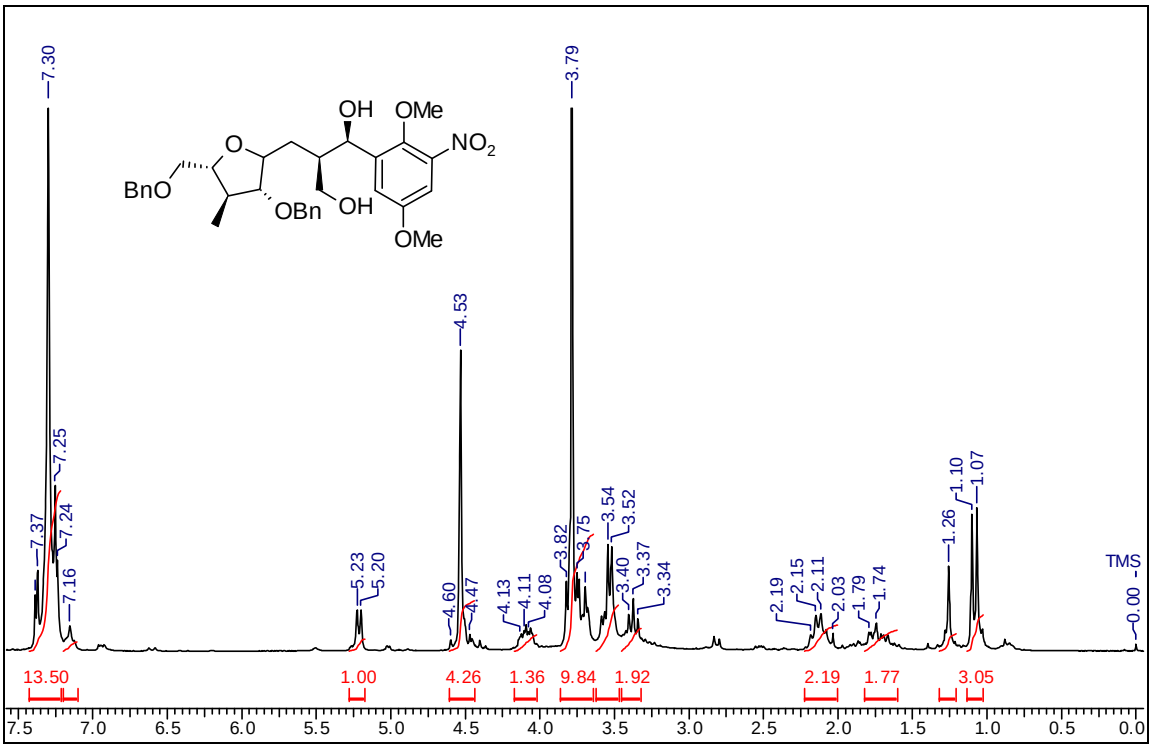
^{13}C NMR Spectrum of Di-Bn Aryl Nitro Evans adduct-OTMS 122 in $CDCl_3$



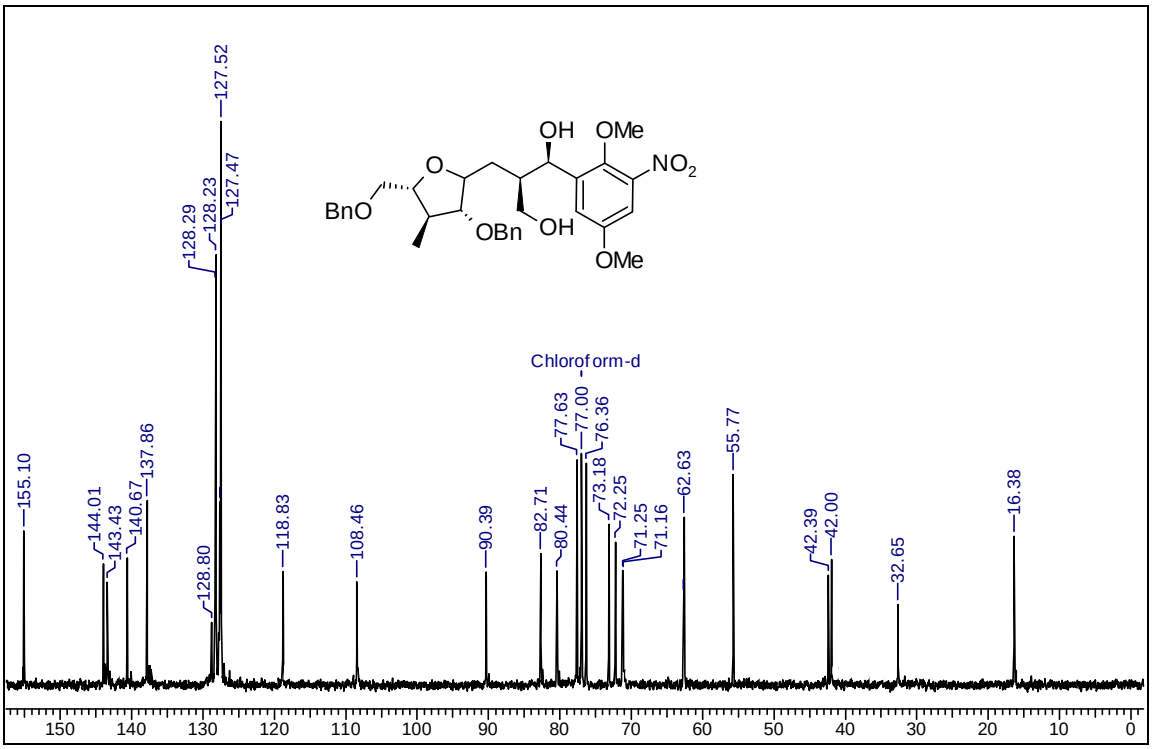
^{1}H NMR Spectrum of Di-Bn Aryl Nitro Evans adduct-OH 123 in $CDCl_3$



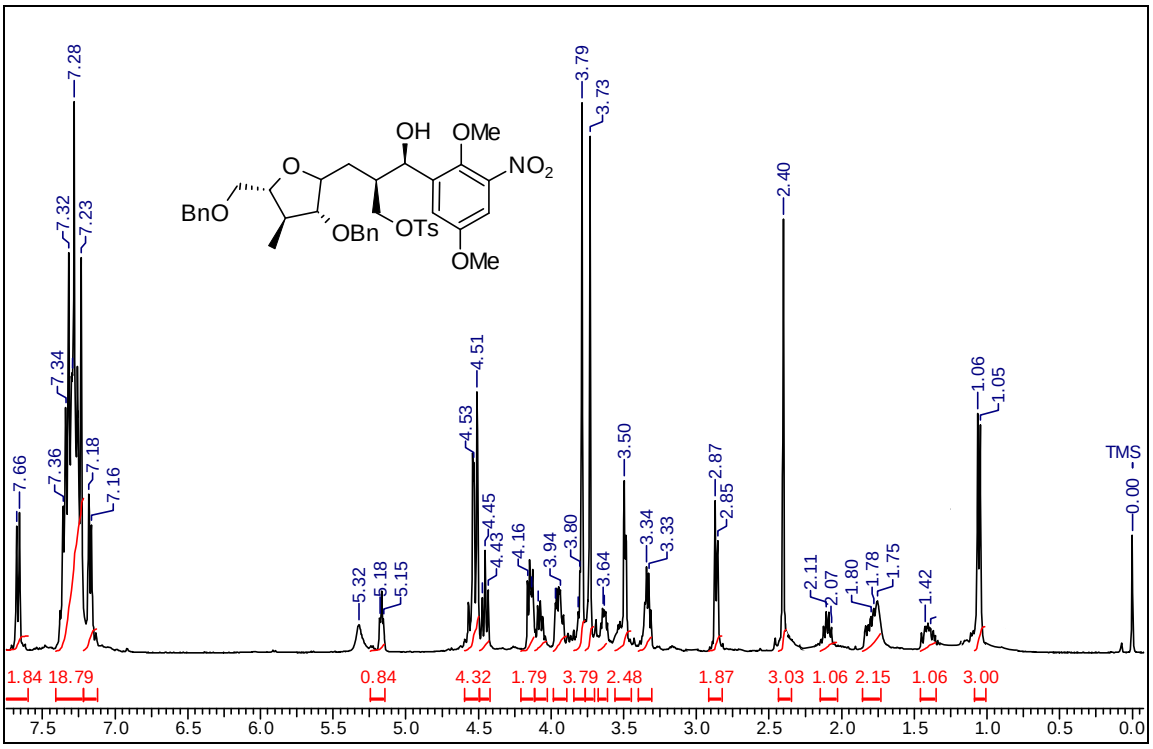
^{13}C NMR Spectrum of Di-Bn Aryl Nitro Evans adduct-OH 123 in $CDCl_3$



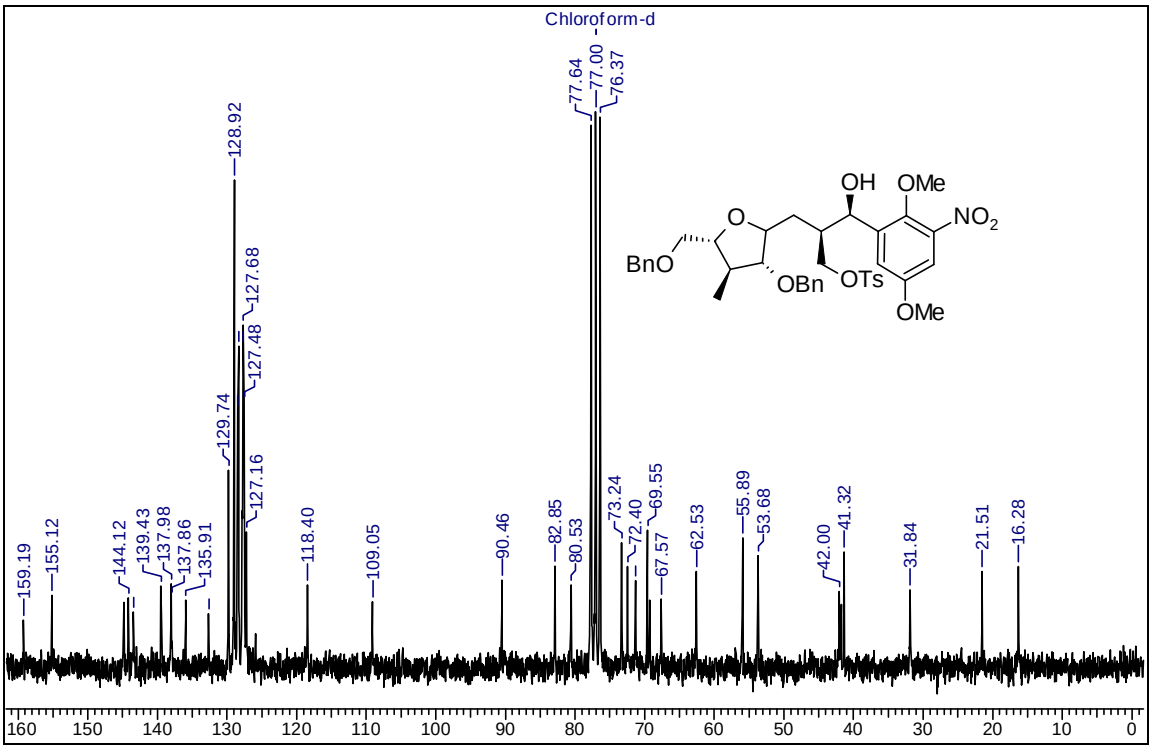
^{1}H NMR Spectrum of Diol-124 in $CDCl_3$



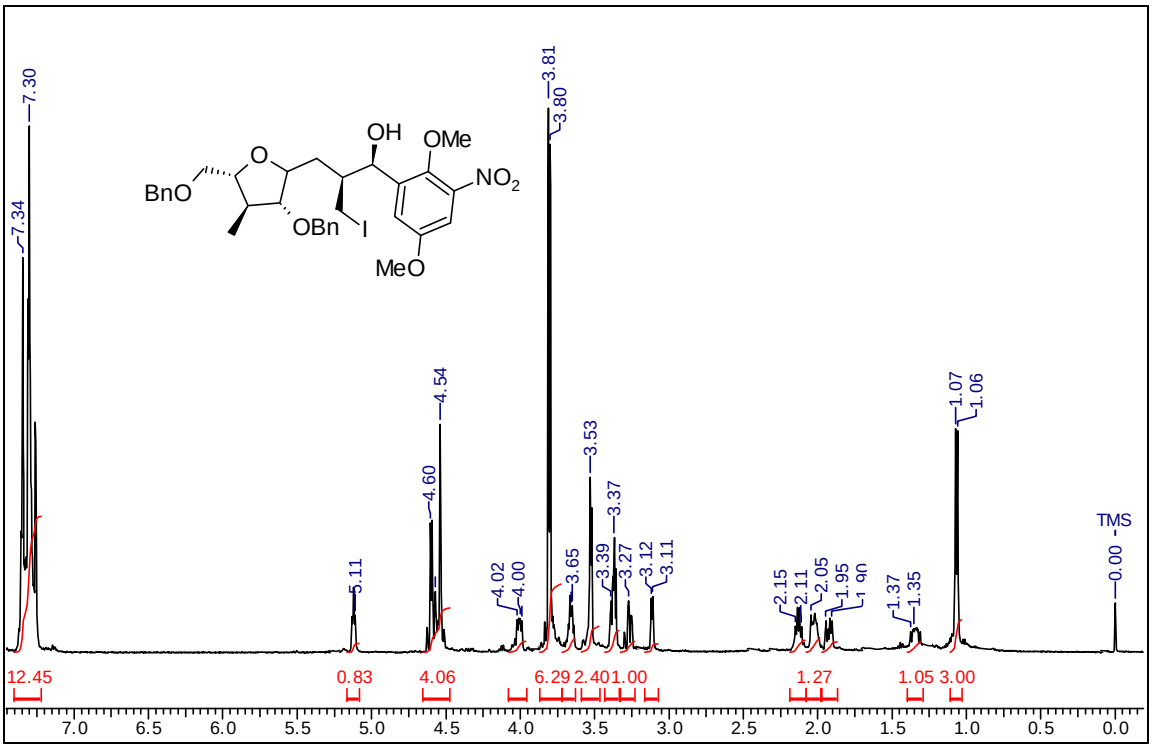
^{13}C NMR Spectrum of Diol-124 in $CDCl_3$



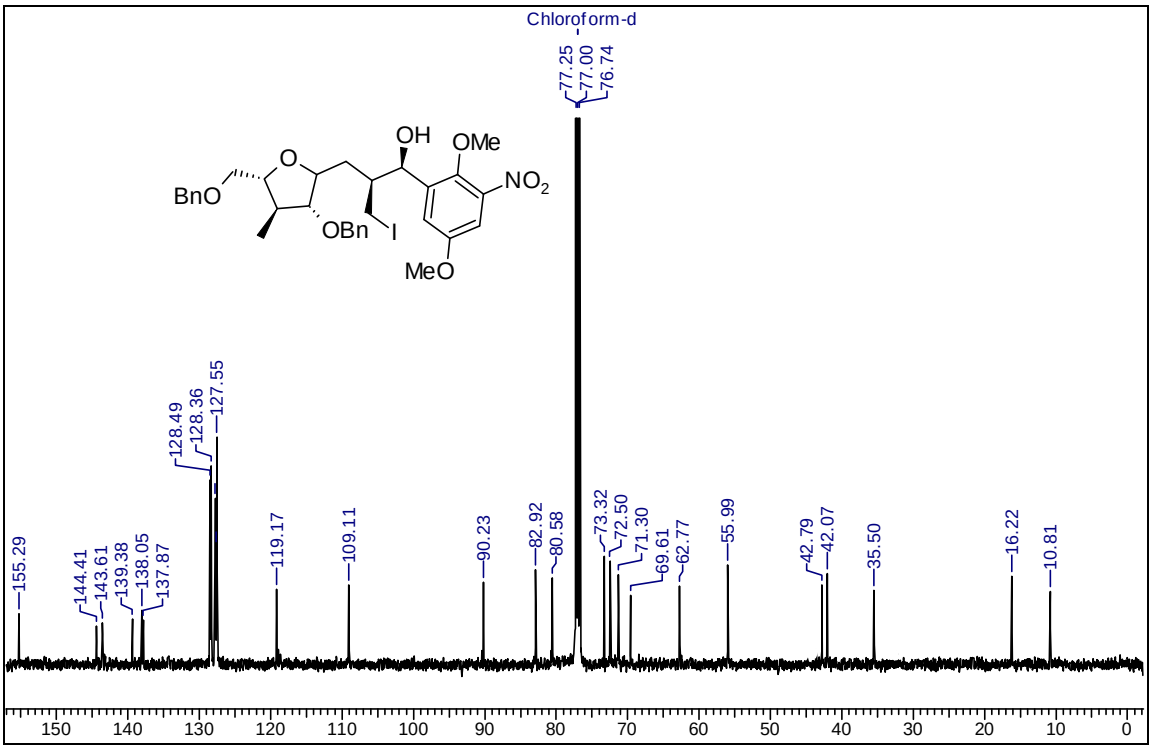
^{1}H NMR Spectrum of Tosylate-125 in $CDCl_3$



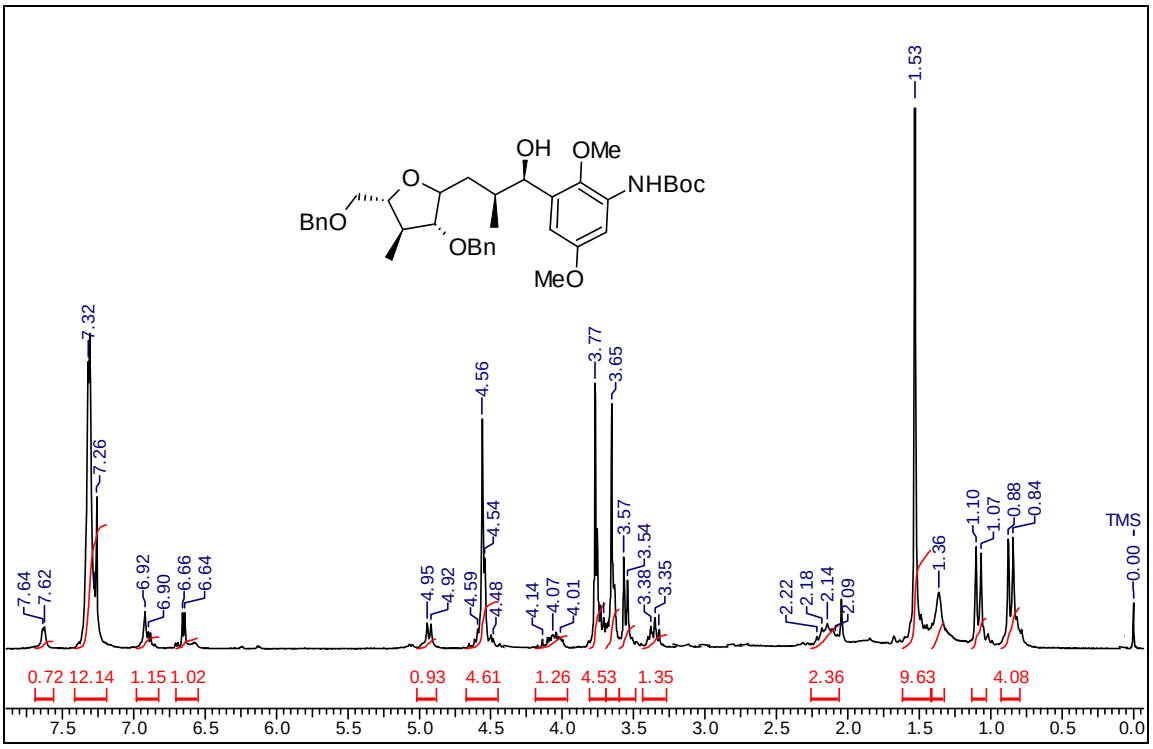
^{13}C NMR Spectrum of Tosylate-125 in $CDCl_3$



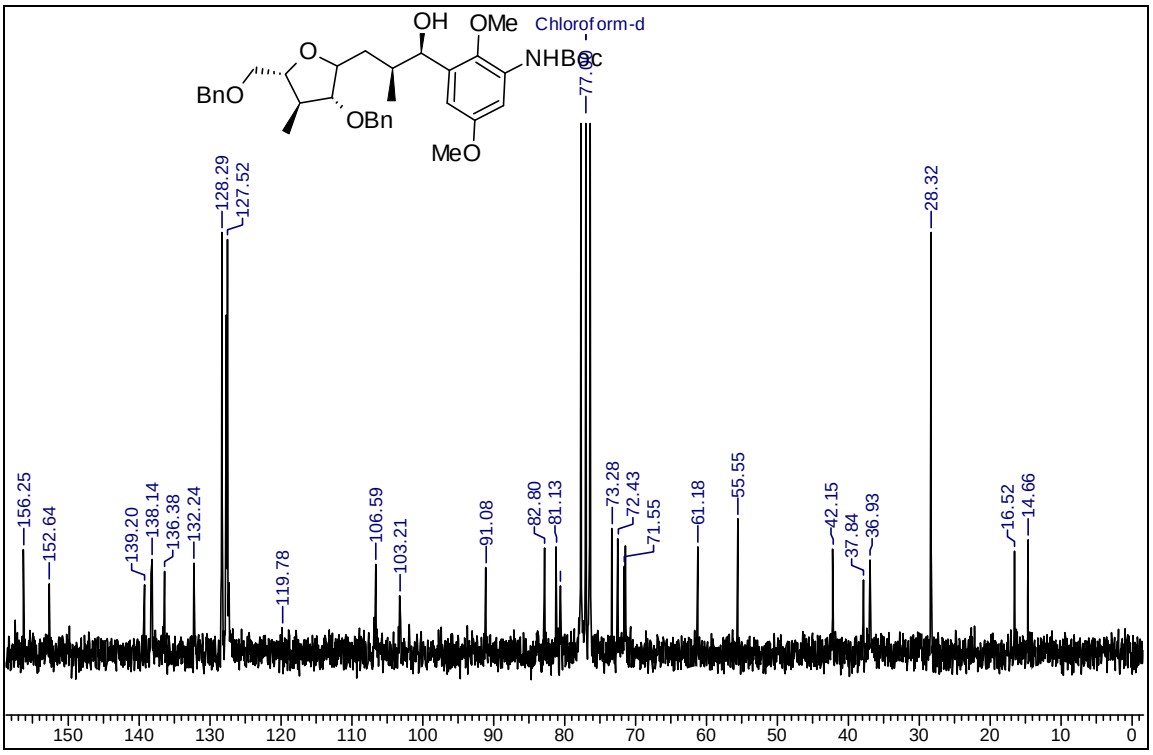
^{1}H NMR Spectrum of Iodo product-126 in $CDCl_3$



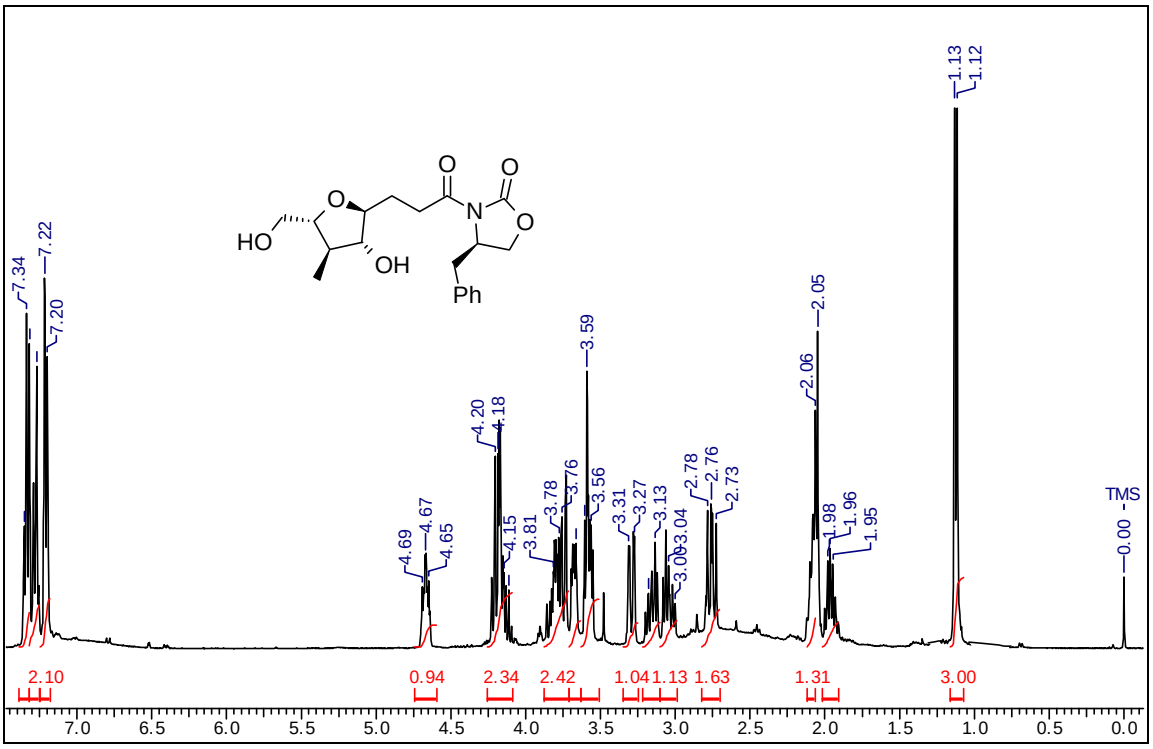
^{13}C NMR Spectrum of Iodo product-126 in $CDCl_3$



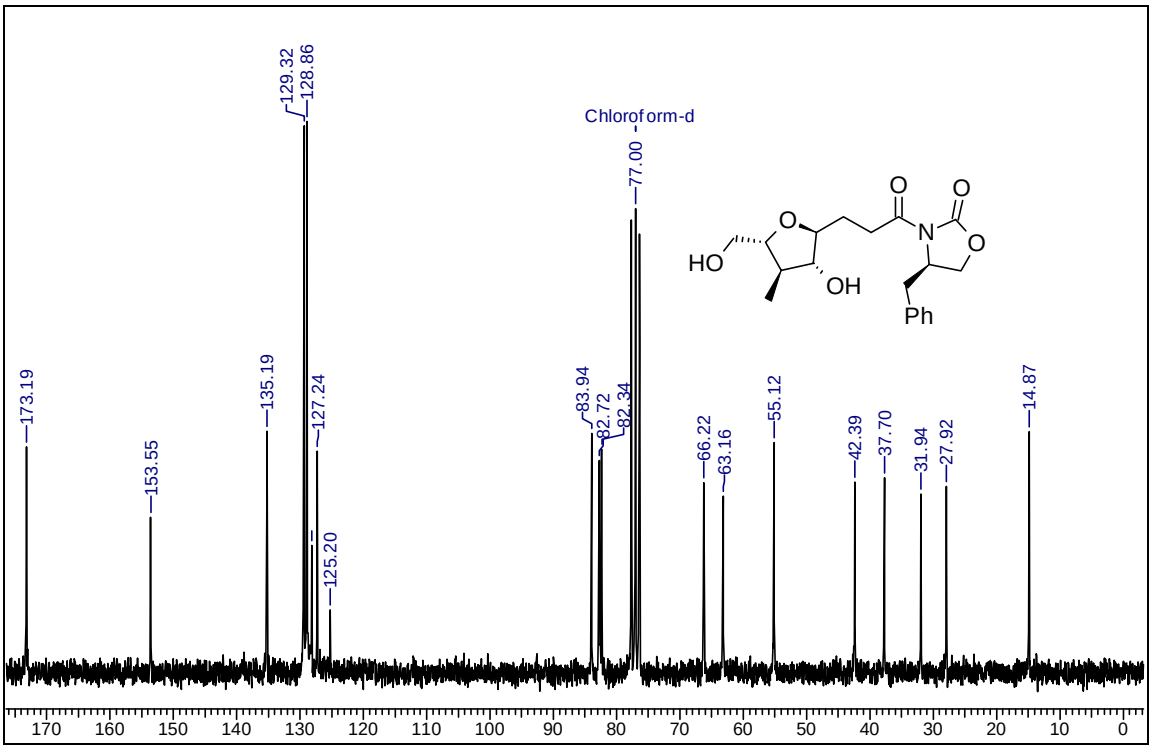
^{1}H NMR Spectrum of Deiodo-NH-Boc-127 in $CDCl_3$



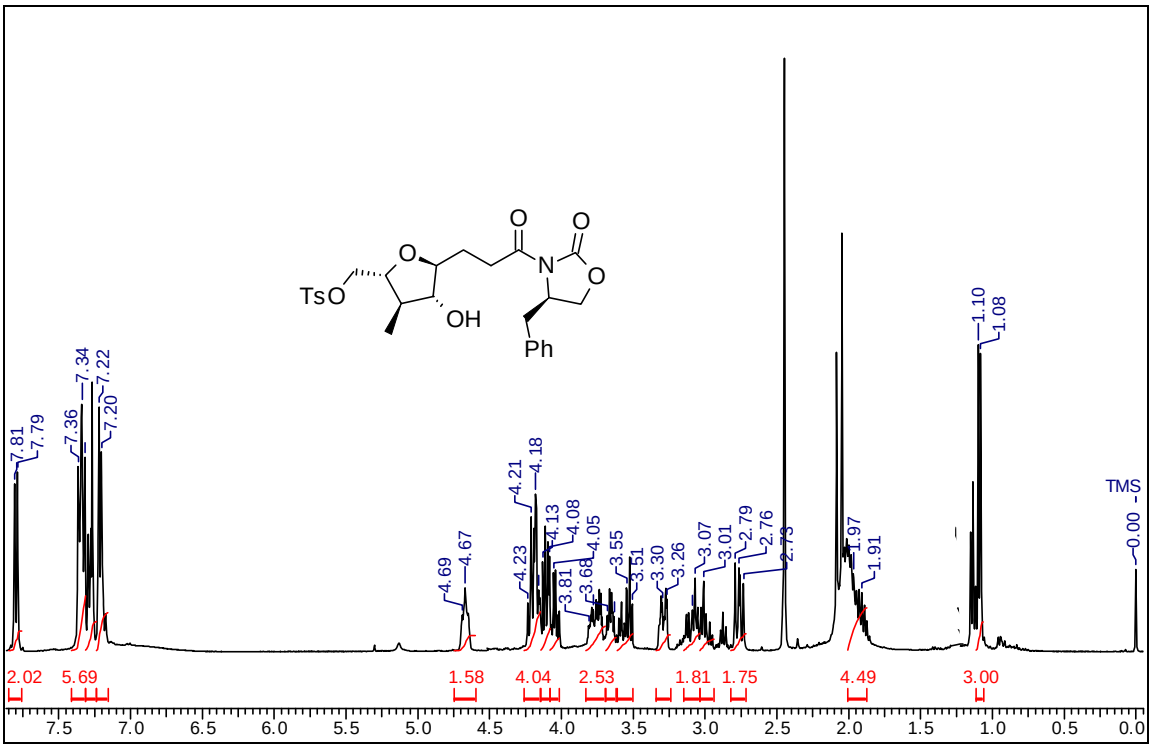
^{13}C NMR Spectrum of Deiodo-NH-Boc-127 in $CDCl_3$/ CCl_4



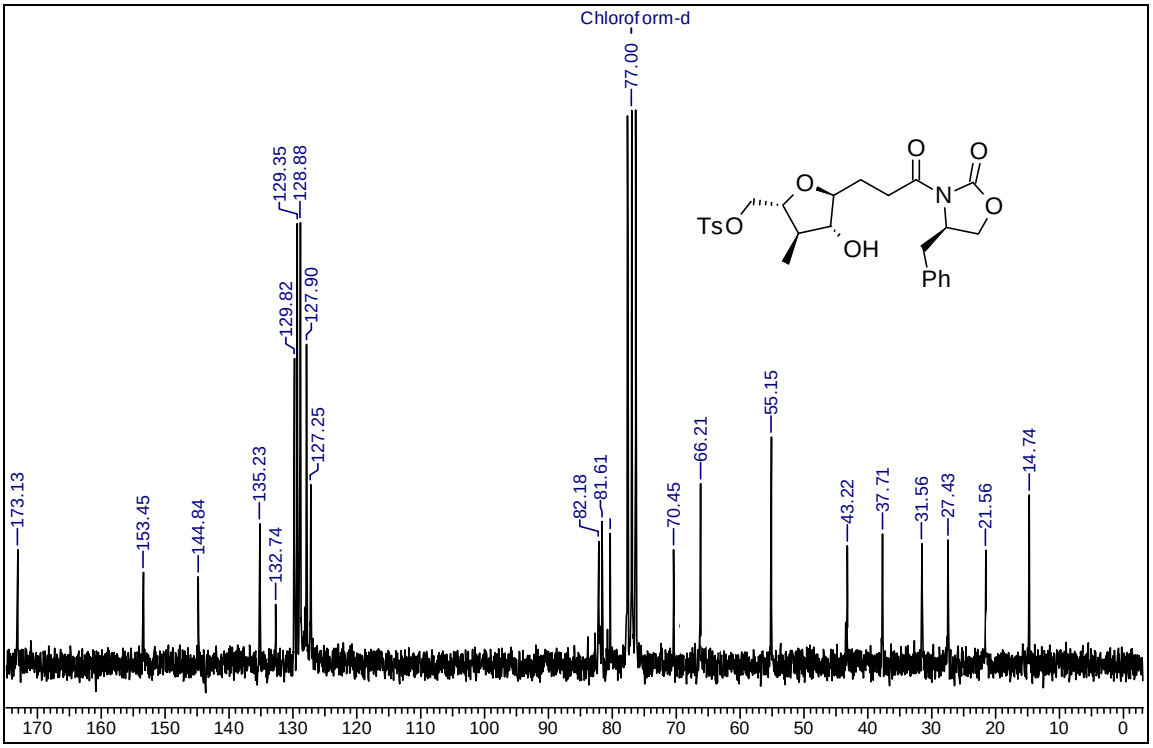
^{1}H NMR Spectrum of Diol Oxazolidinone-129 in $CDCl_3$



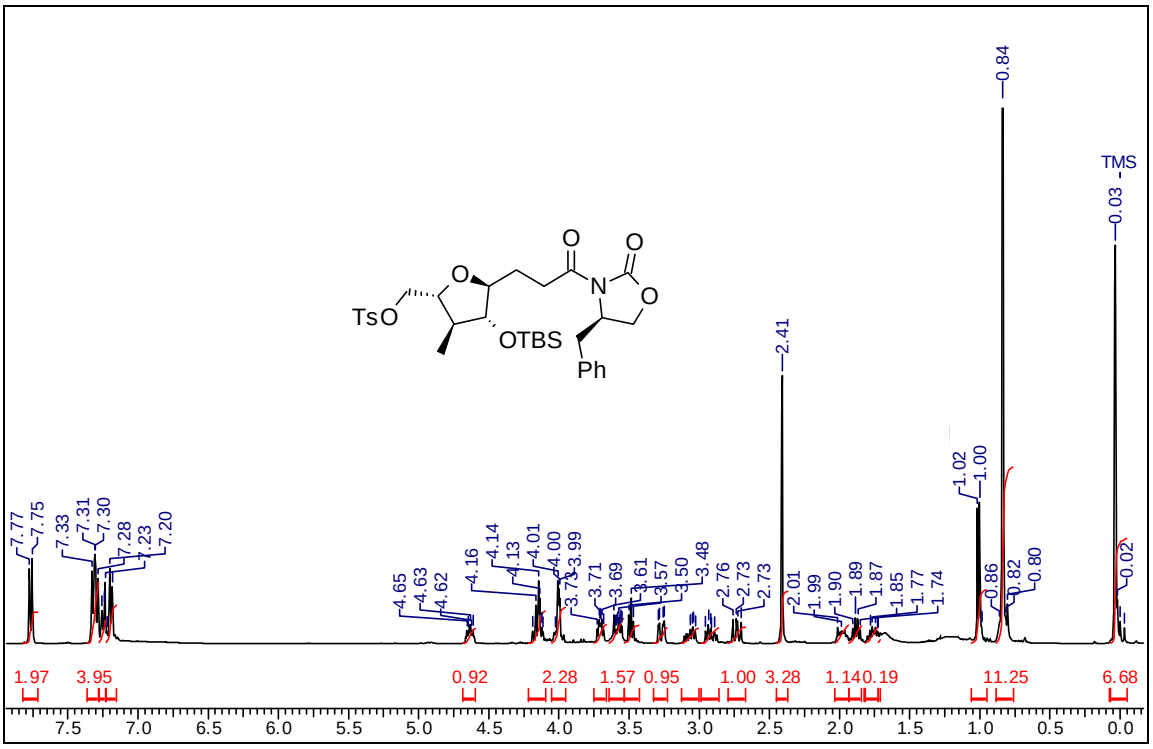
^{13}C NMR Spectrum of Diol Oxazolidinone-129 in $CDCl_3$



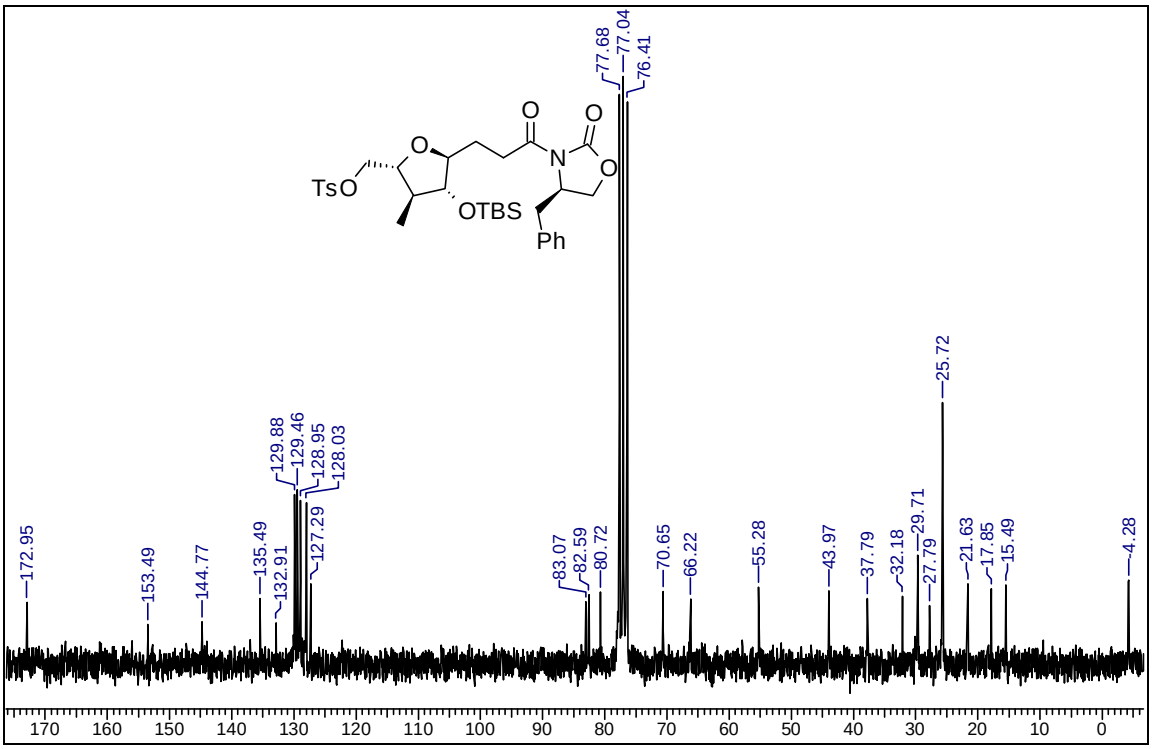
^{1}H NMR Spectrum of MonoTosyl Oxazolidinone-130 in $CDCl_3$



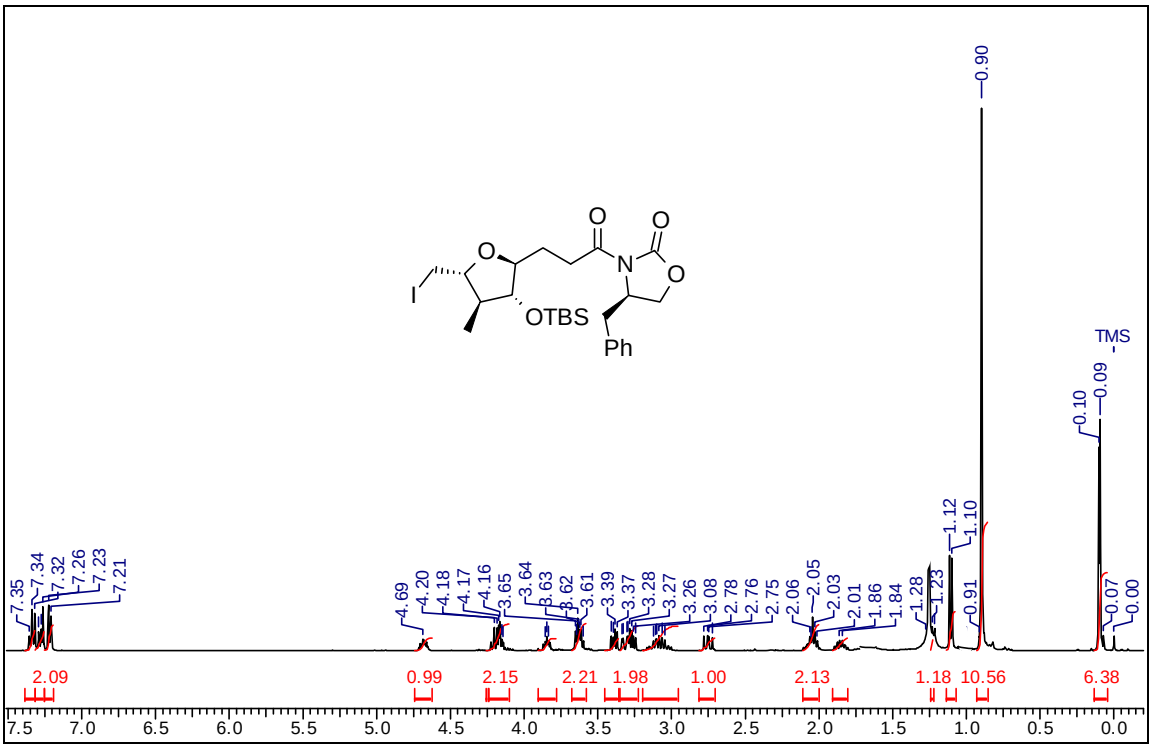
^{13}C NMR Spectrum of MonoTosyl Oxazolidinone-130 in $CDCl_3$



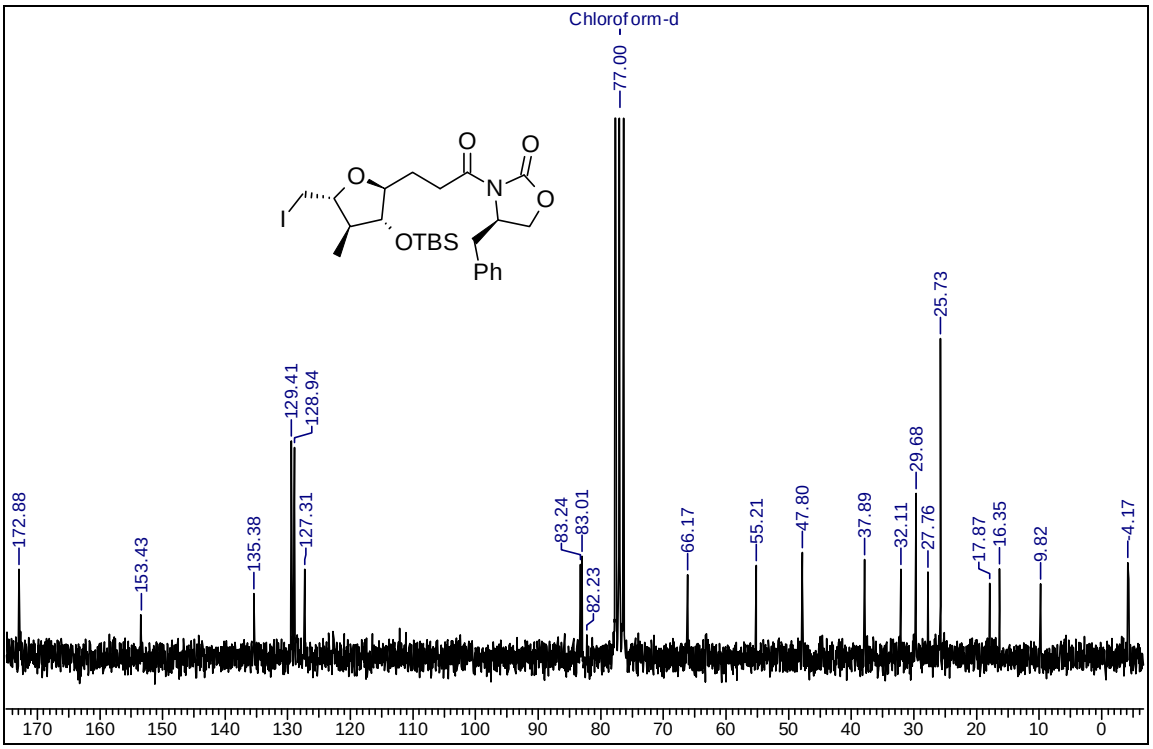
^{1}H NMR Spectrum of Tosyl-TBS Oxazolidinone-131 in $CDCl_3$



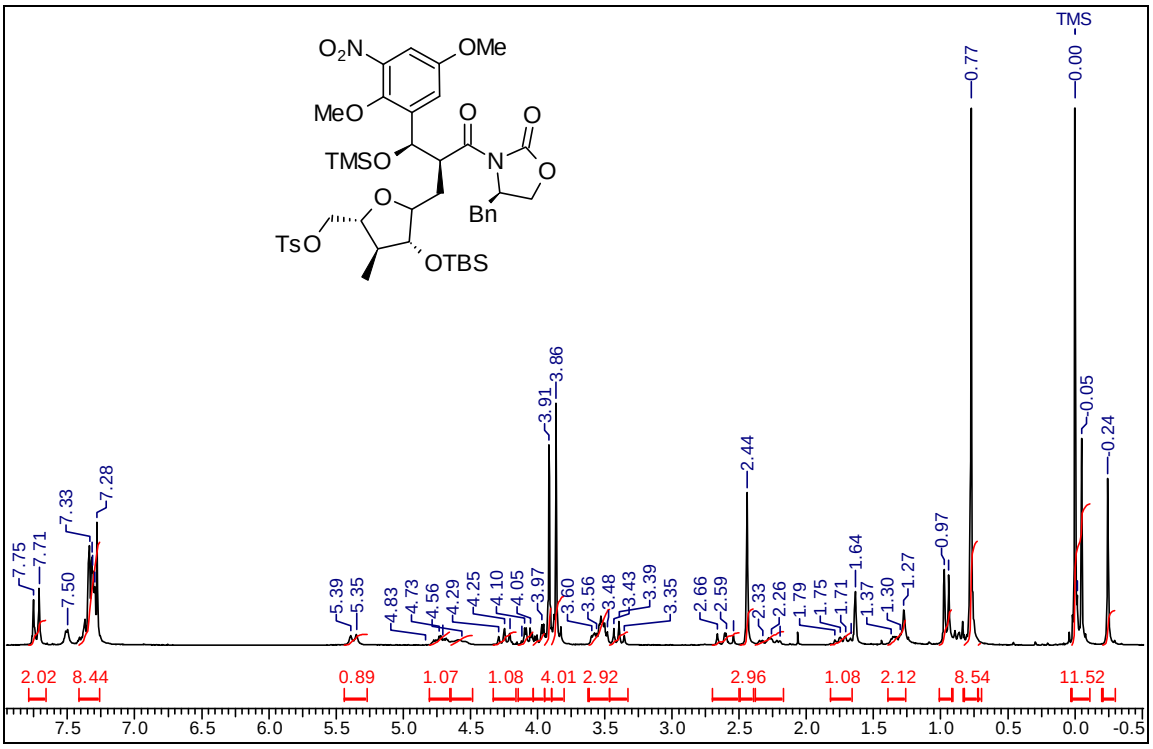
^{13}C NMR Spectrum of Tosyl-TBS Oxazolidinone-131 in $CDCl_3$



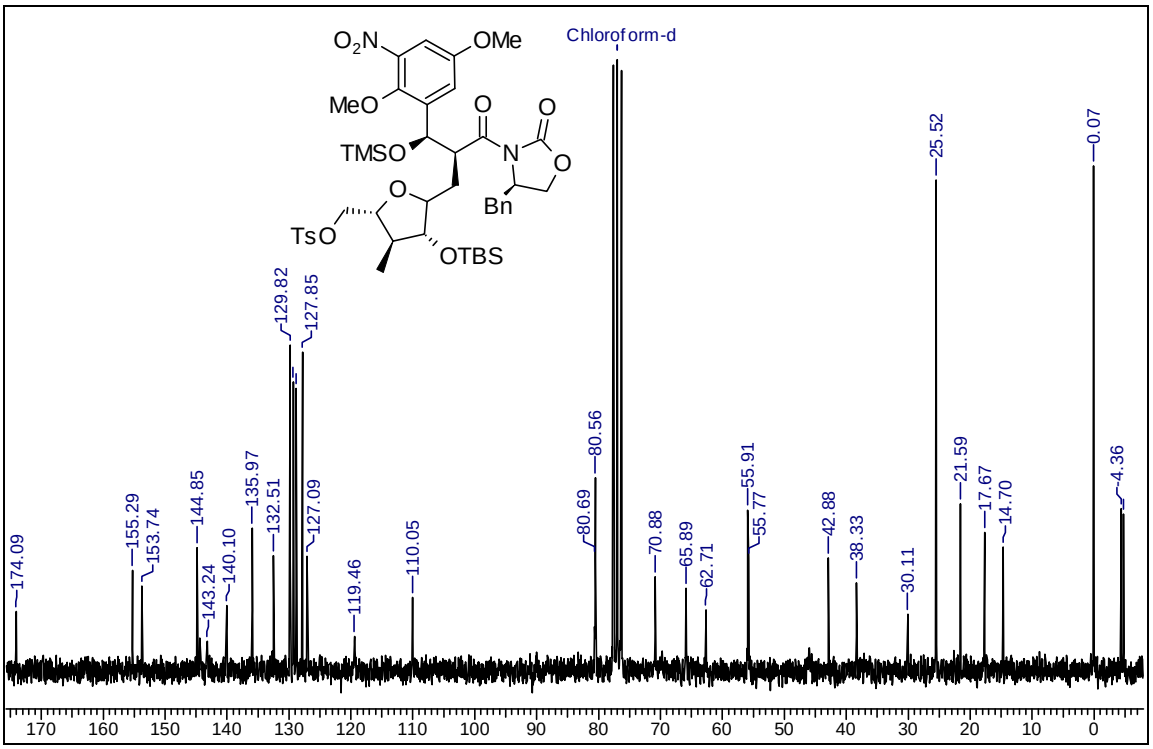
^{1}H NMR Spectrum of Iodo-TBS Oxazolidinone-132 in $CDCl_3$



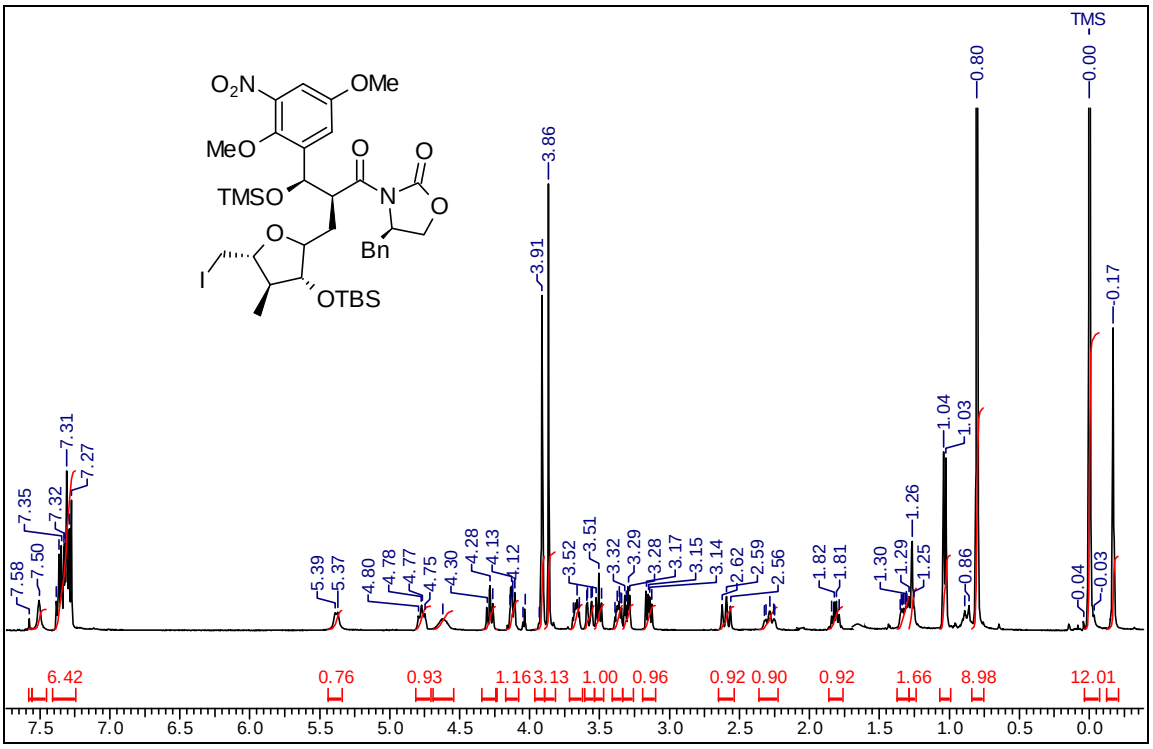
^{13}C NMR Spectrum of Iodo-TBS Oxazolidinone-132 in $CDCl_3$



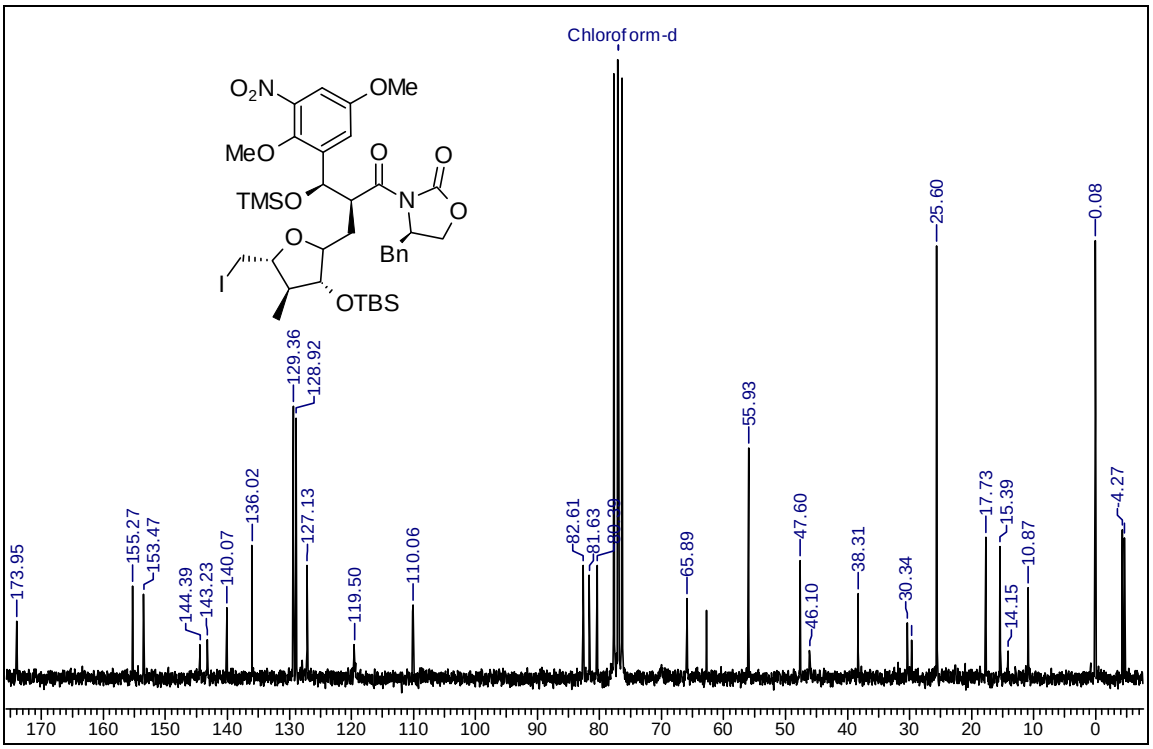
^{1}H NMR Spectrum of Tosyl-TBS Aryl Nitro Evans adduct-OTMS 133 in $CDCl_3$



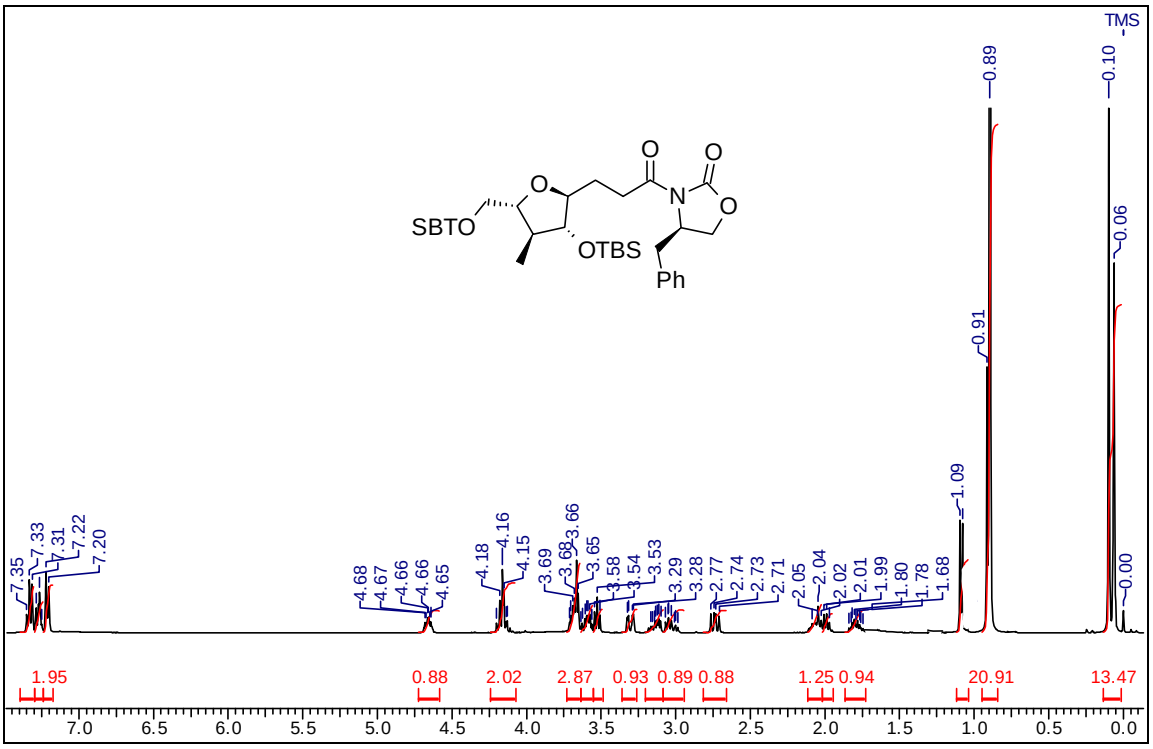
^{13}C NMR Spectrum of Tosyl-TBS Aryl Nitro Evans adduct-OTMS 133 in $CDCl_3$



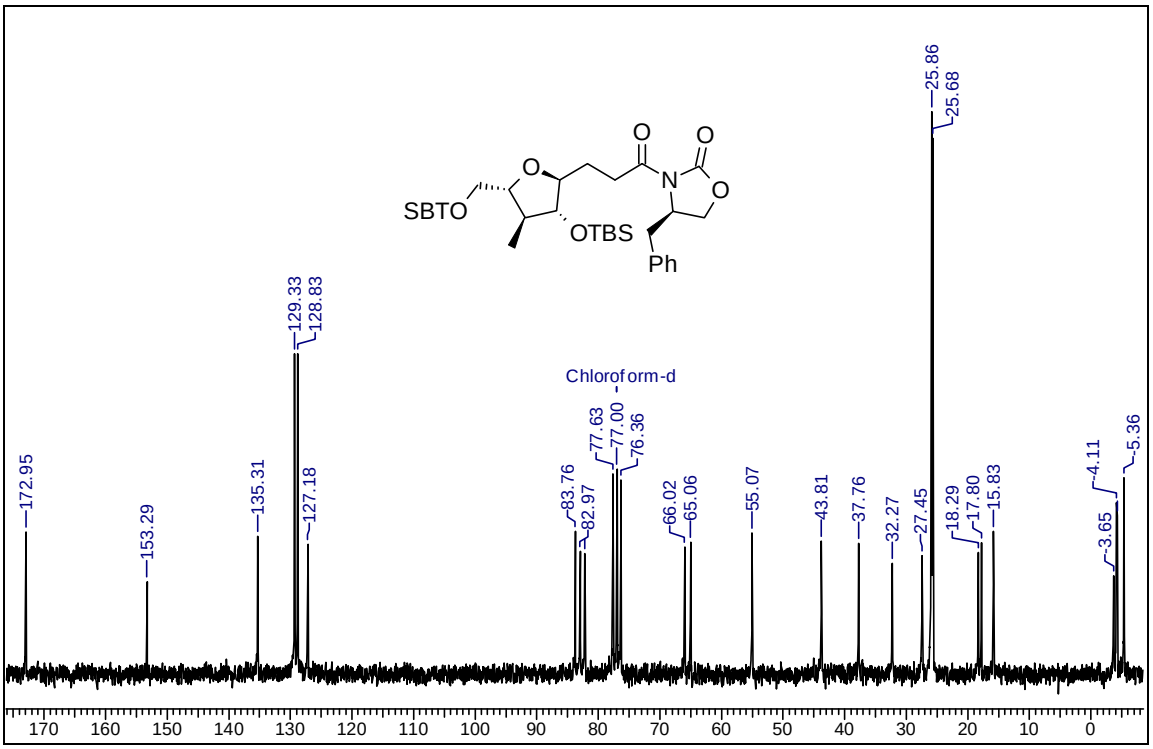
^{1}H NMR Spectrum of Iodo-TBS Aryl Nitro Evans adduct-OTMS 134 in $CDCl_3$



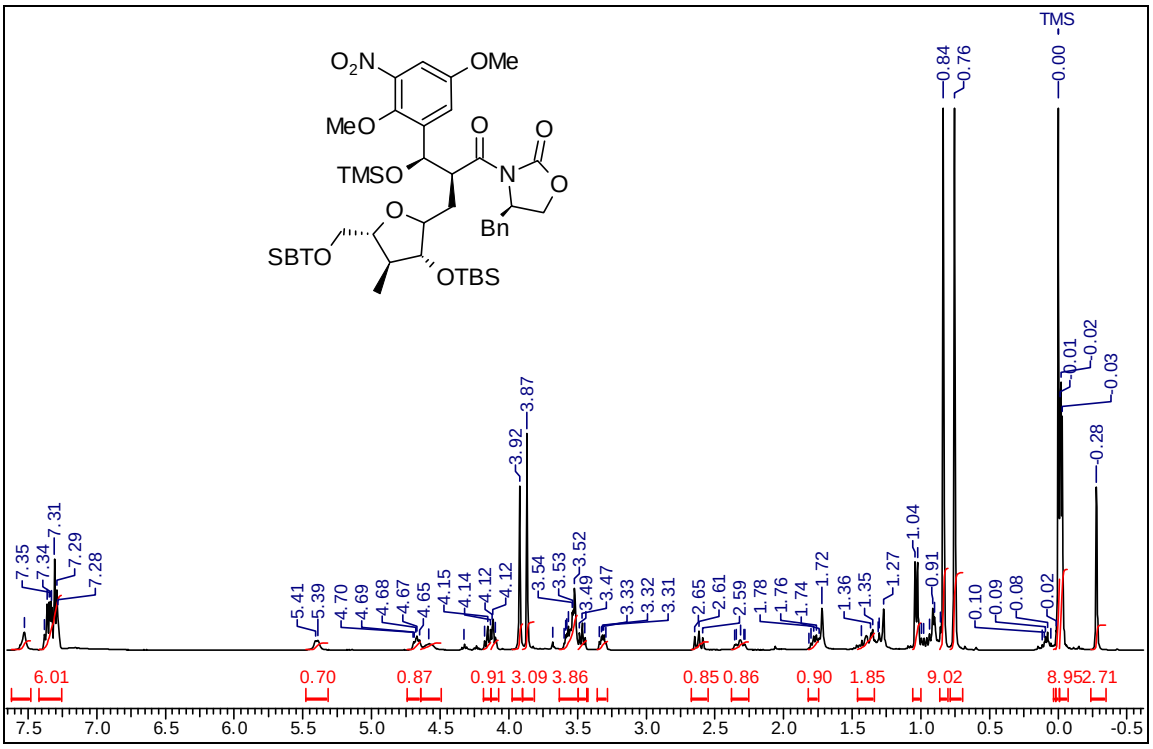
^{13}C NMR Spectrum of Iodo-TBS Aryl Nitro Evans adduct-OTMS 134 in $CDCl_3$



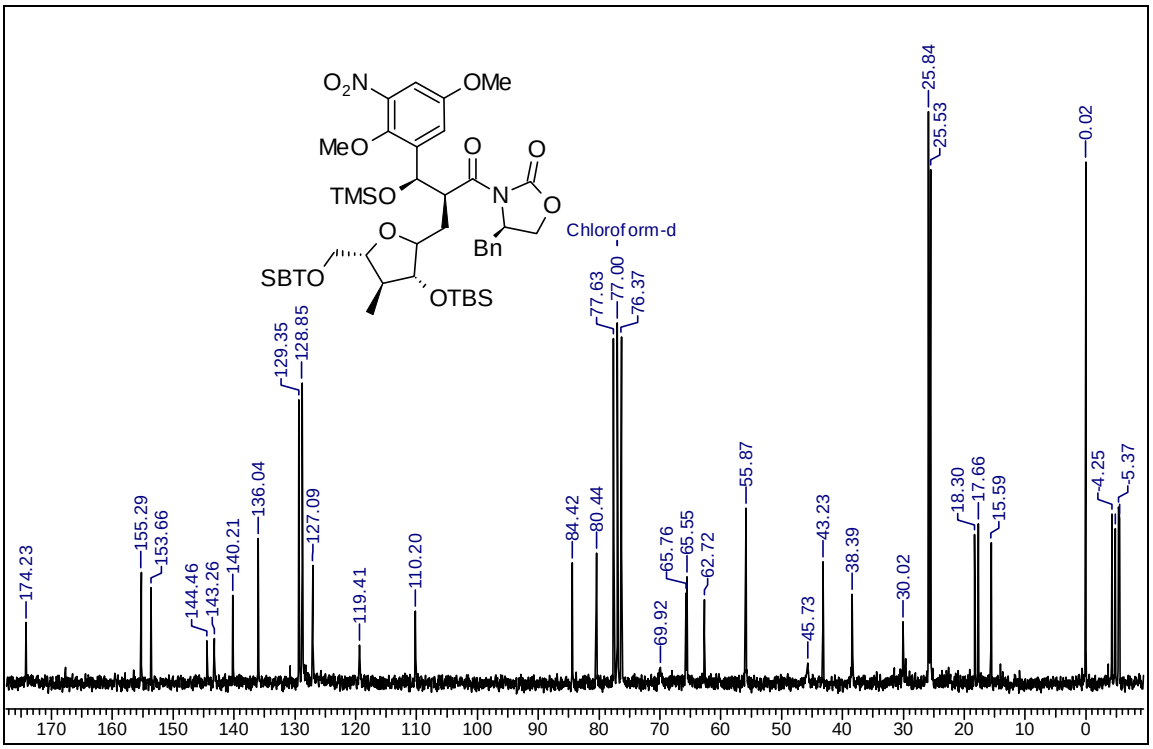
^{1}H NMR Spectrum of Di-TBS Oxazolidinone-137 in $CDCl_3$



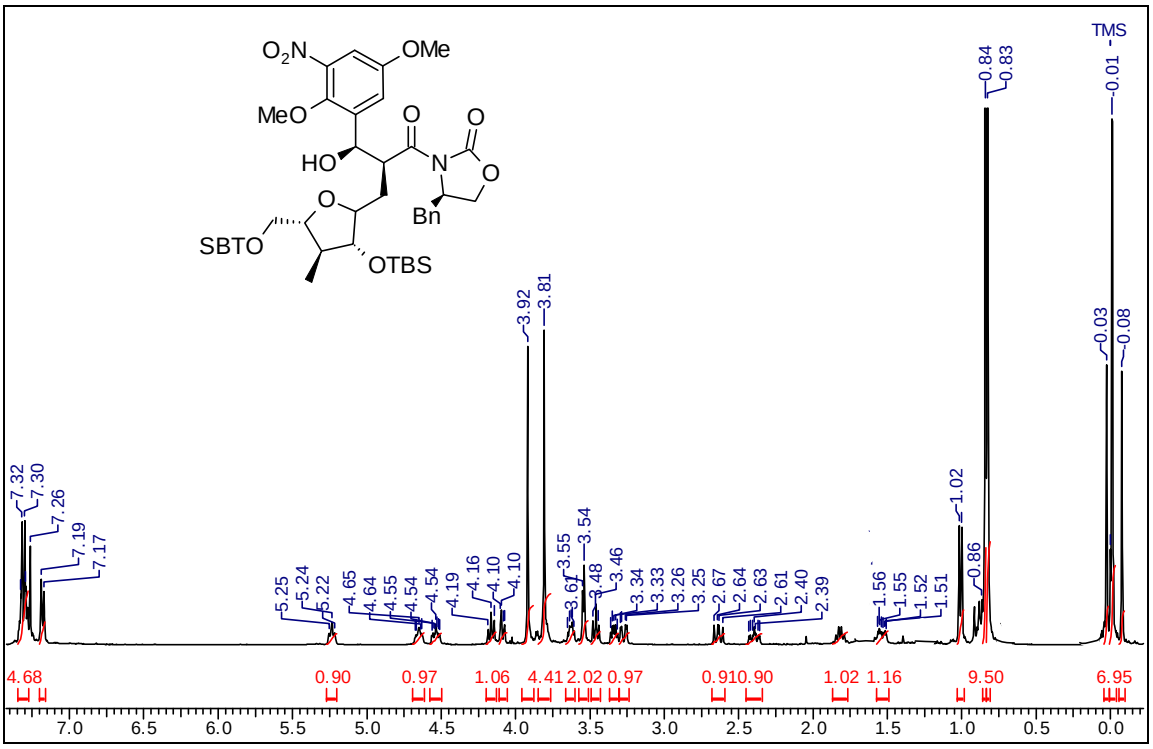
^{13}C NMR Spectrum of Di-TBS Oxazolidinone-137 in $CDCl_3$



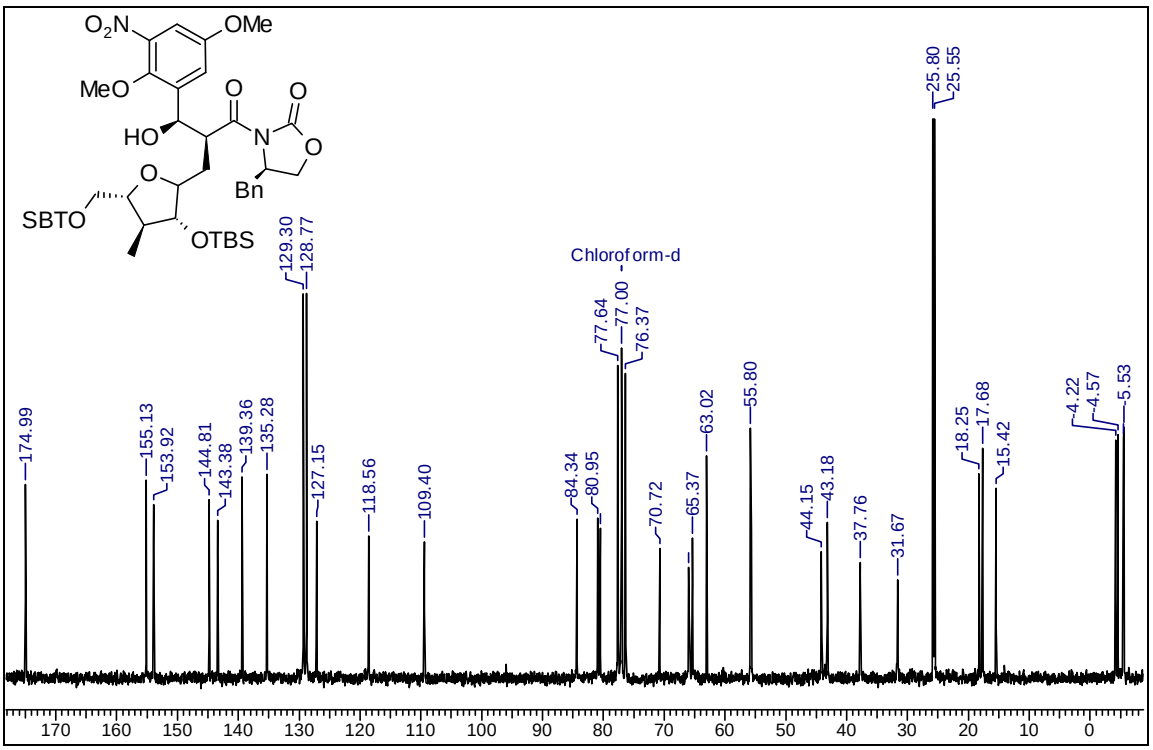
^{1}H NMR Spectrum of Di-TBS Aryl Nitro Evans adduct-OTMS 138 in $CDCl_3$



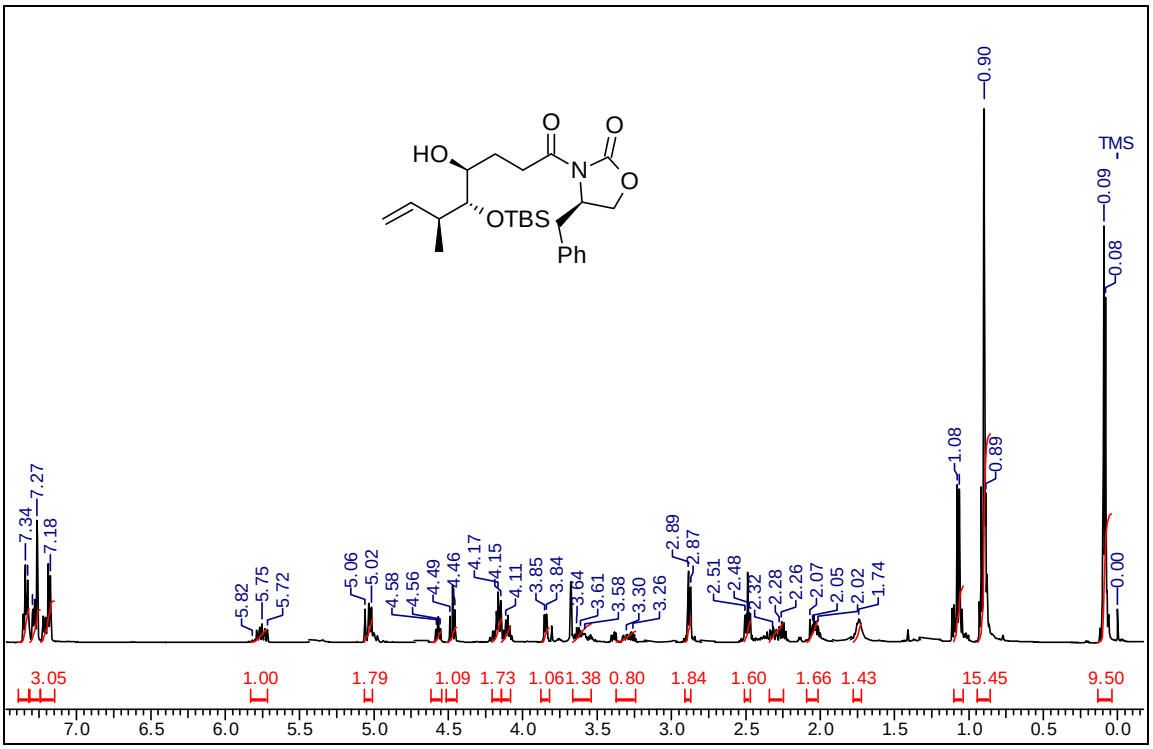
^{13}C NMR Spectrum of Di-TBS Aryl Nitro Evans adduct-OTMS 138 in $CDCl_3$



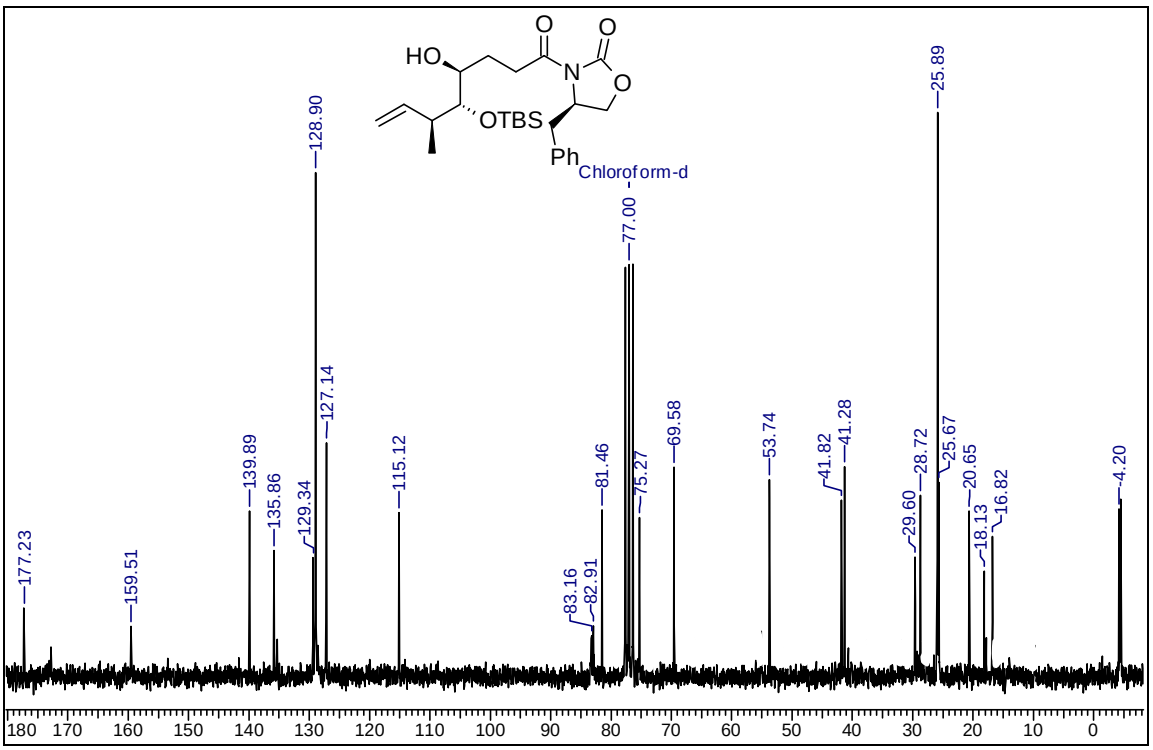
^{1}H NMR Spectrum of Di-TBS Aryl Nitro Evans adduct-OH 139 in $CDCl_3$



^{13}C NMR Spectrum of Di-TBS Aryl Nitro Evans adduct-OTMS 139 in $CDCl_3$



^{1}H NMR Spectrum of Hydroxy Olefine-141 in $CDCl_3$



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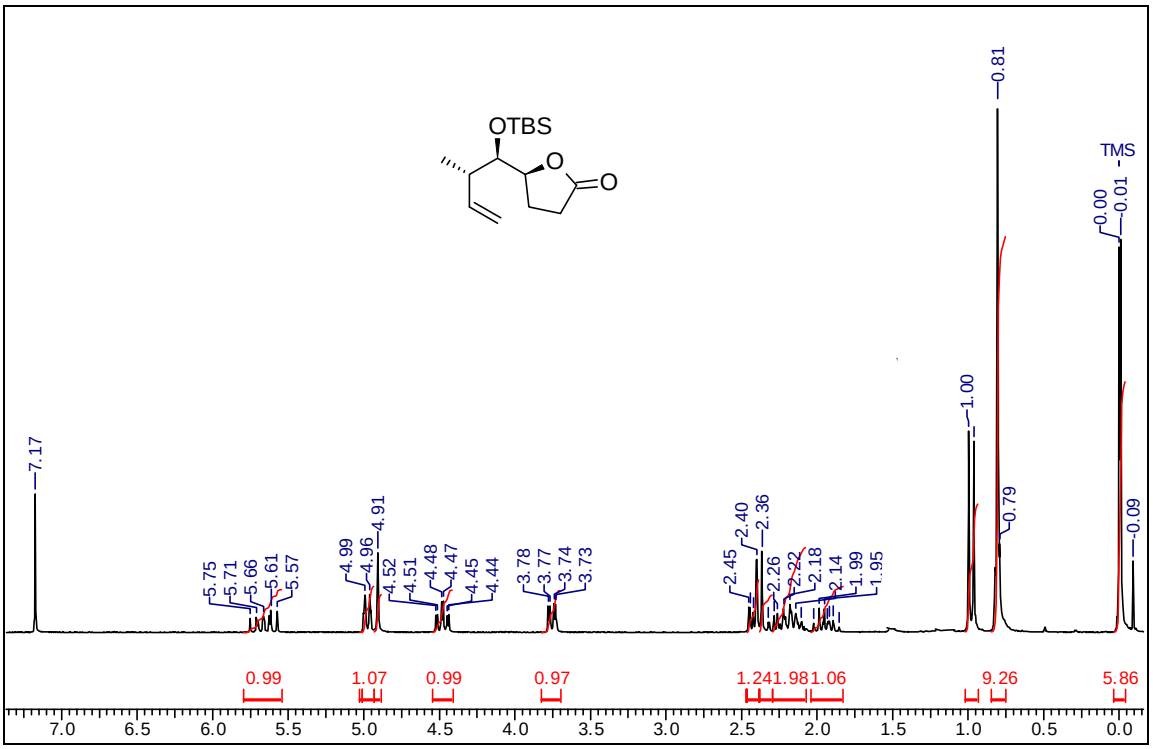
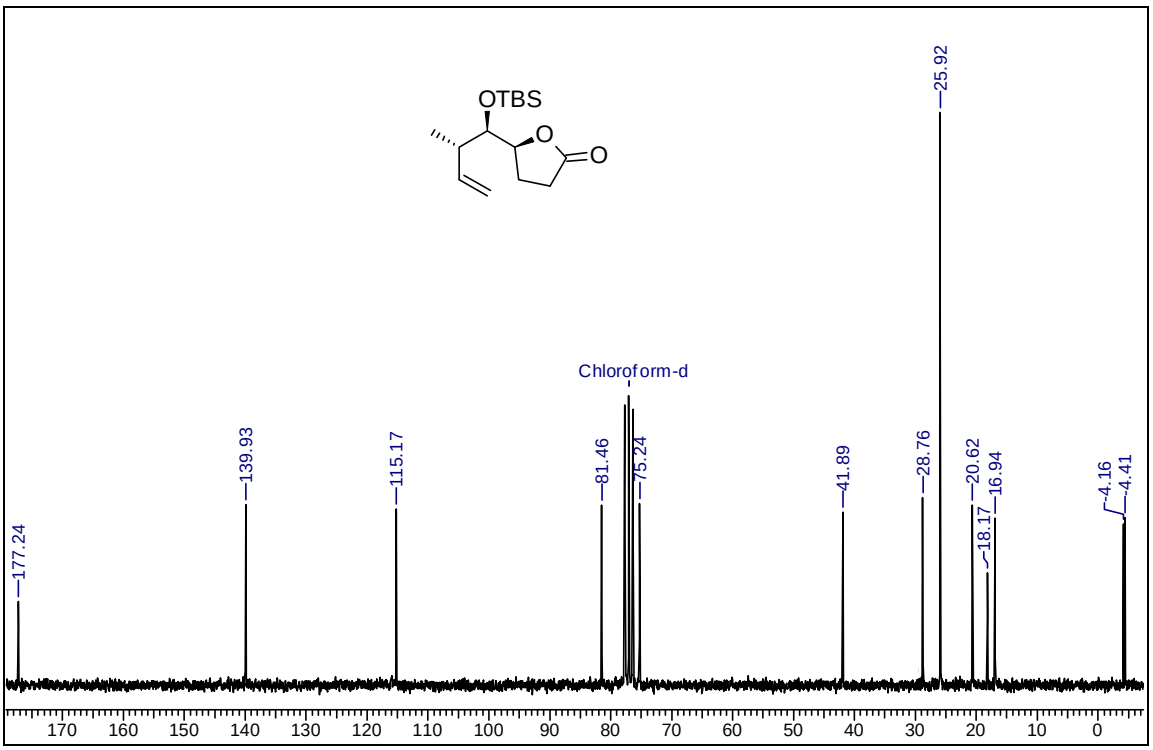
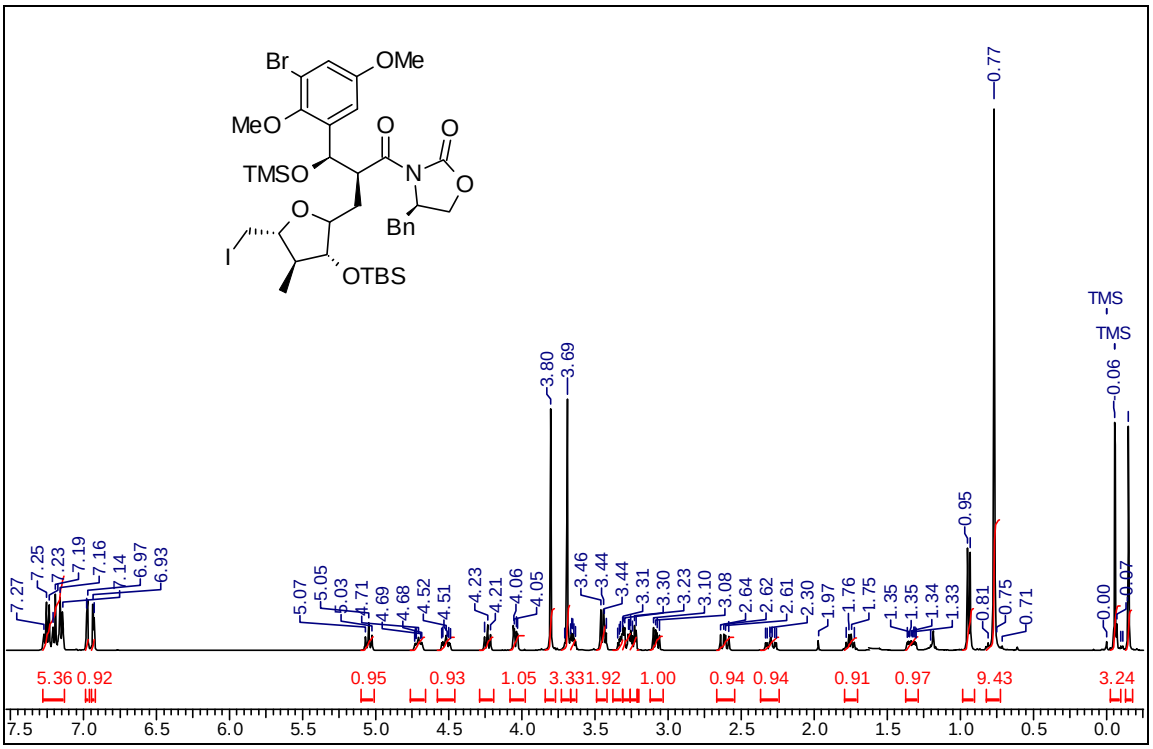


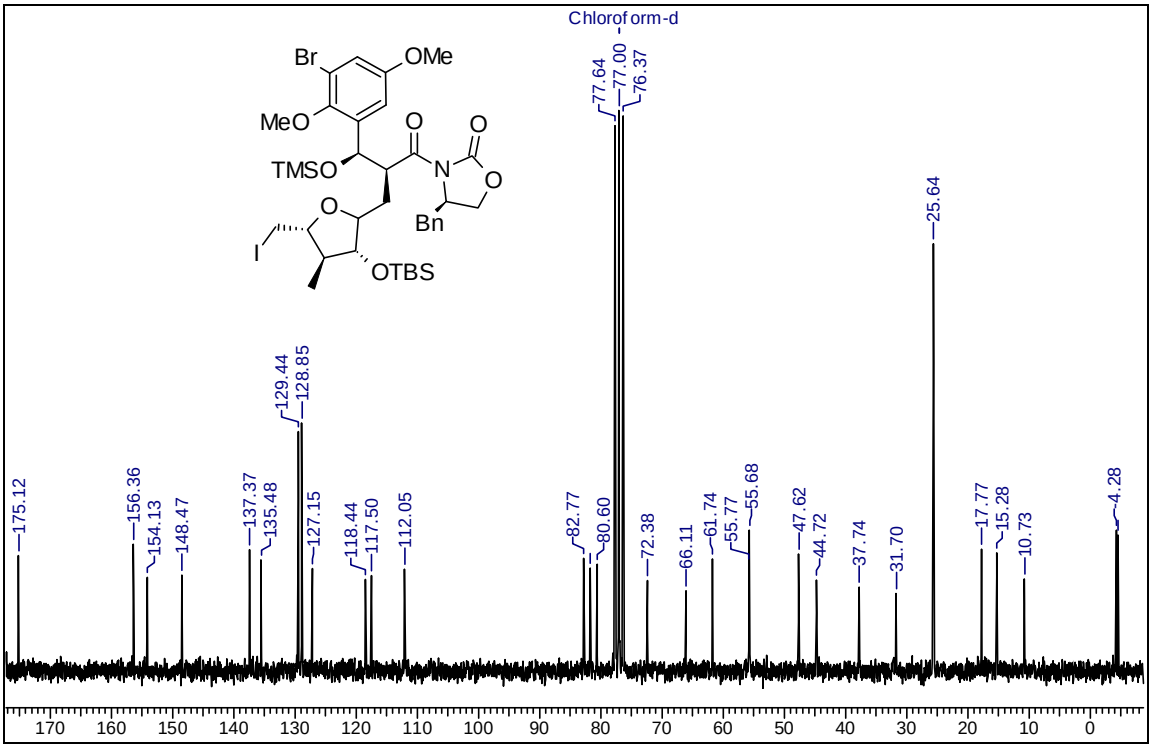
^{1}H NMR Spectrum of lactone-142 in $CDCl_3$



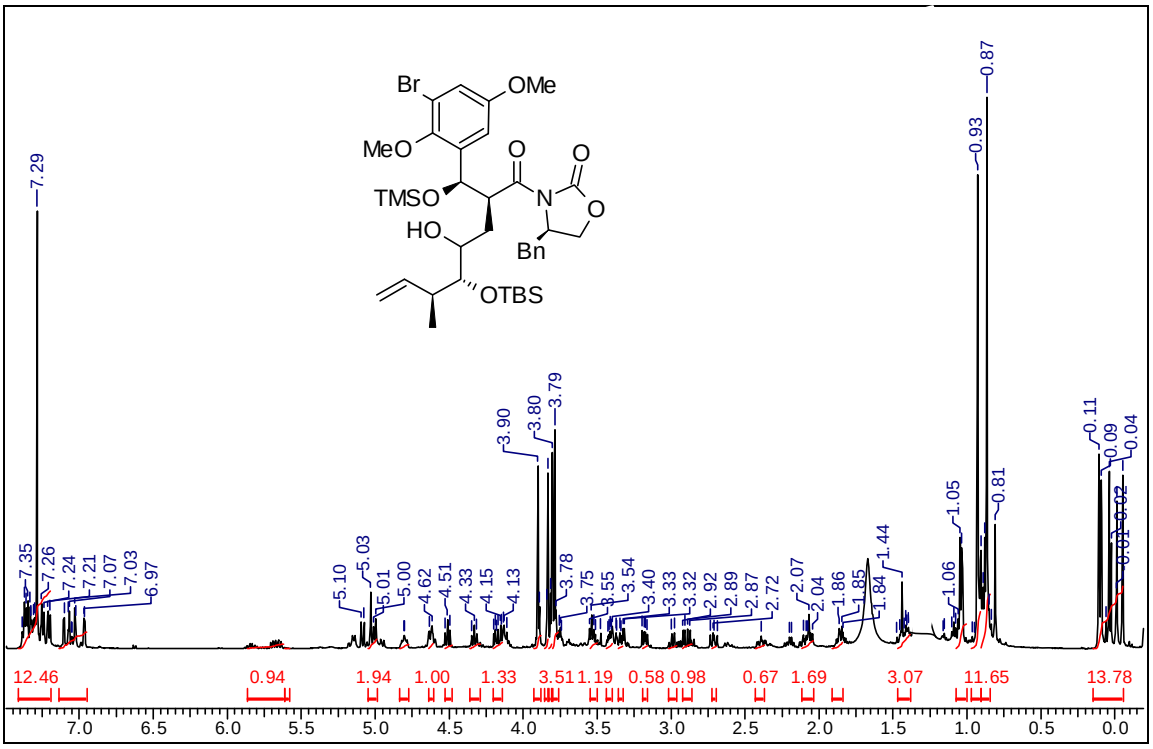
^{13}C NMR Spectrum of lactone-142 in $CDCl_3$



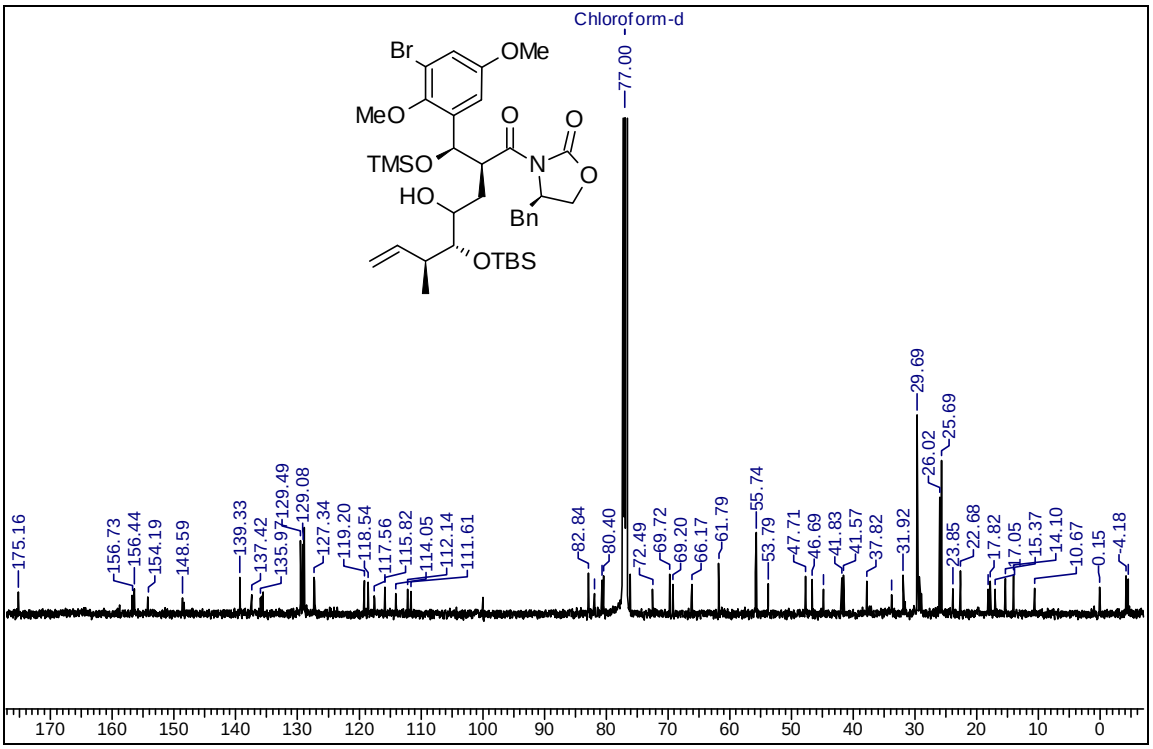
^{1}H NMR Spectrum of IodoTBS Aryl Bromo Evans adduct-OTMS 145 in $CDCl_3$



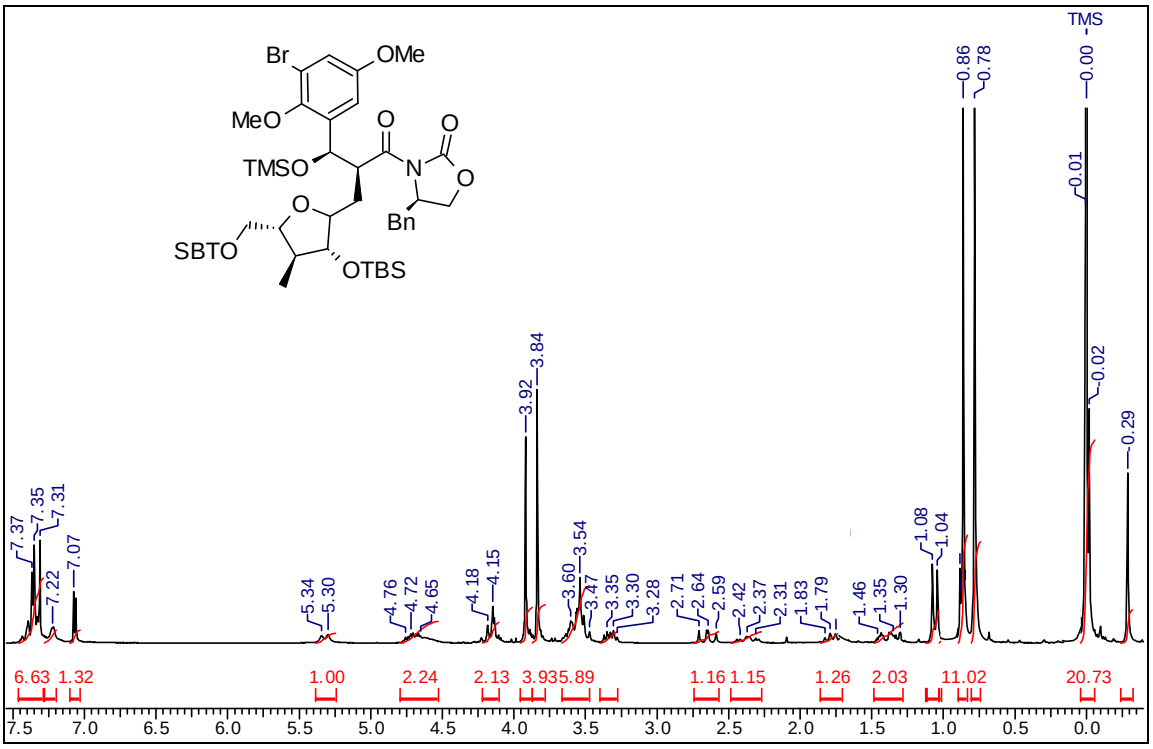
^{13}C NMR Spectrum of IodoTBS Aryl Bromo Evans adduct-OTMS 145 in $CDCl_3$



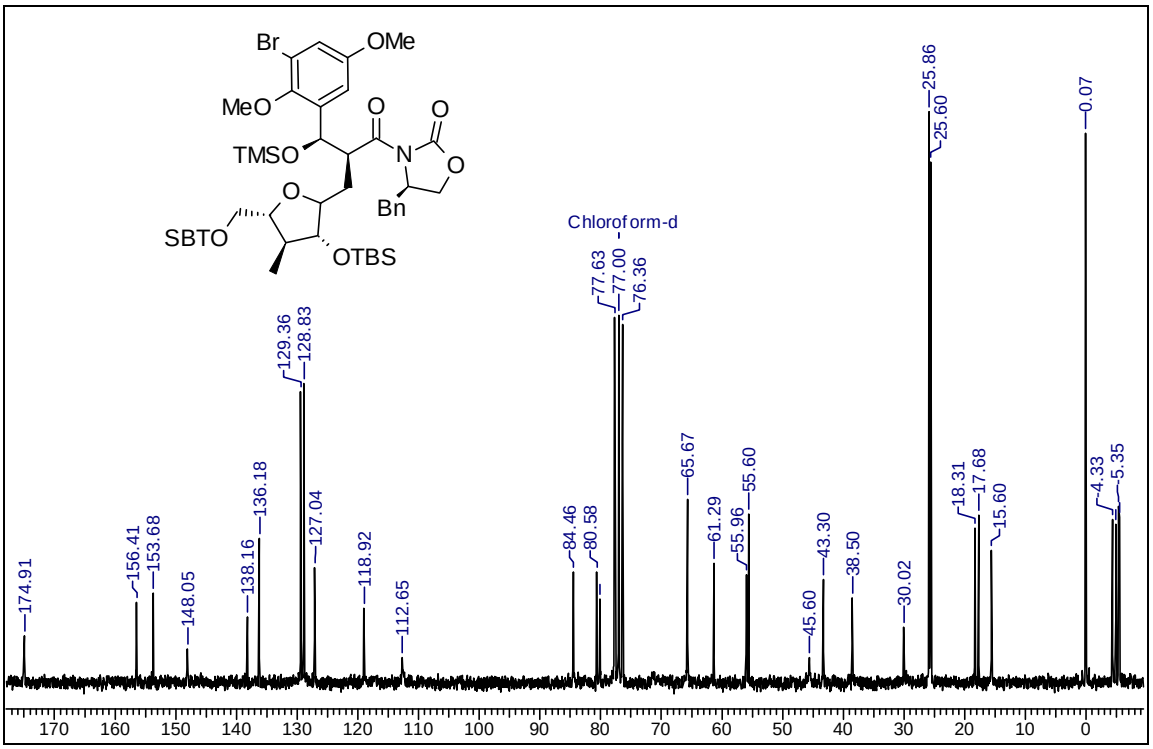
^{1}H NMR Spectrum of olefinic product 147 in $CDCl_3$



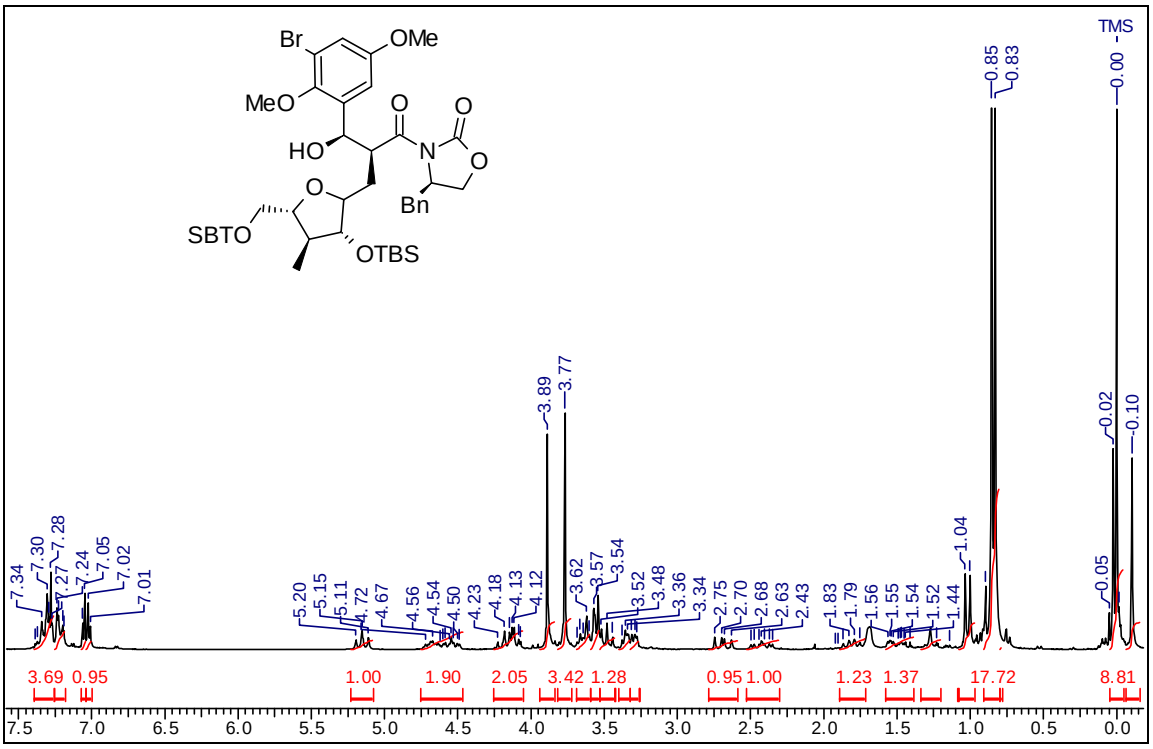
^{13}C NMR Spectrum of olefinic product 147 in $CDCl_3$



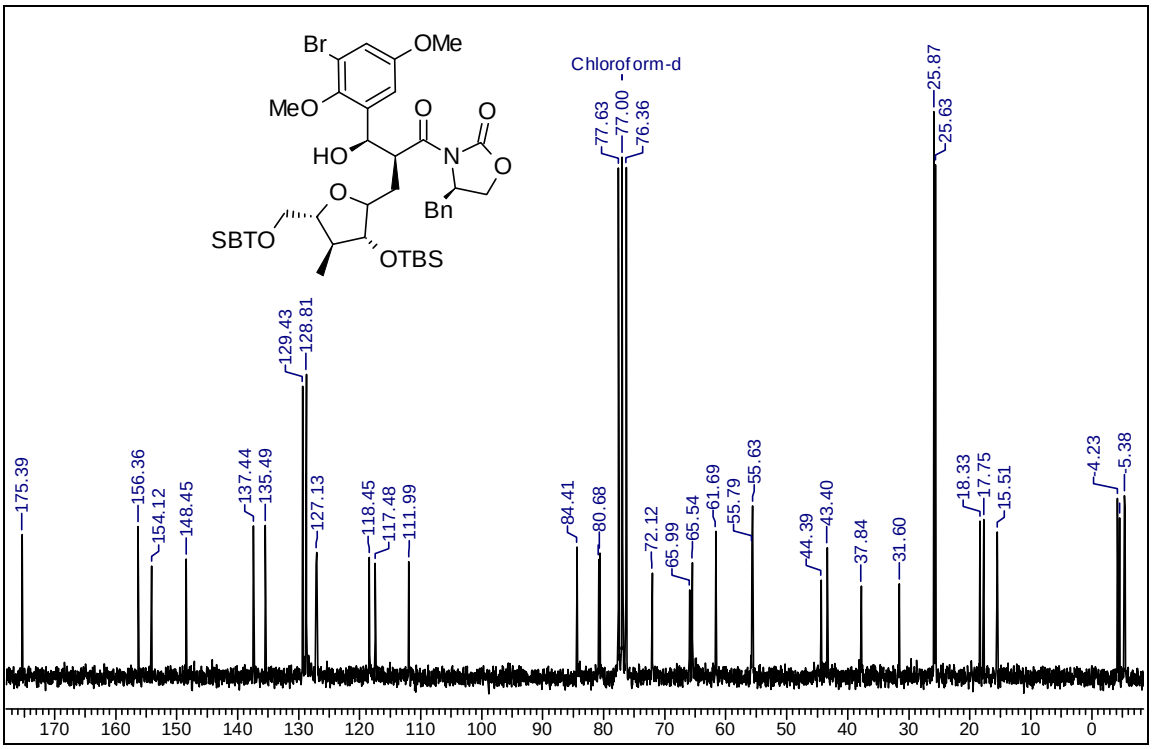
^{1}H NMR Spectrum of Di-TBS Evans anti aldol adduct-OTMS 149 in $CDCl_3$



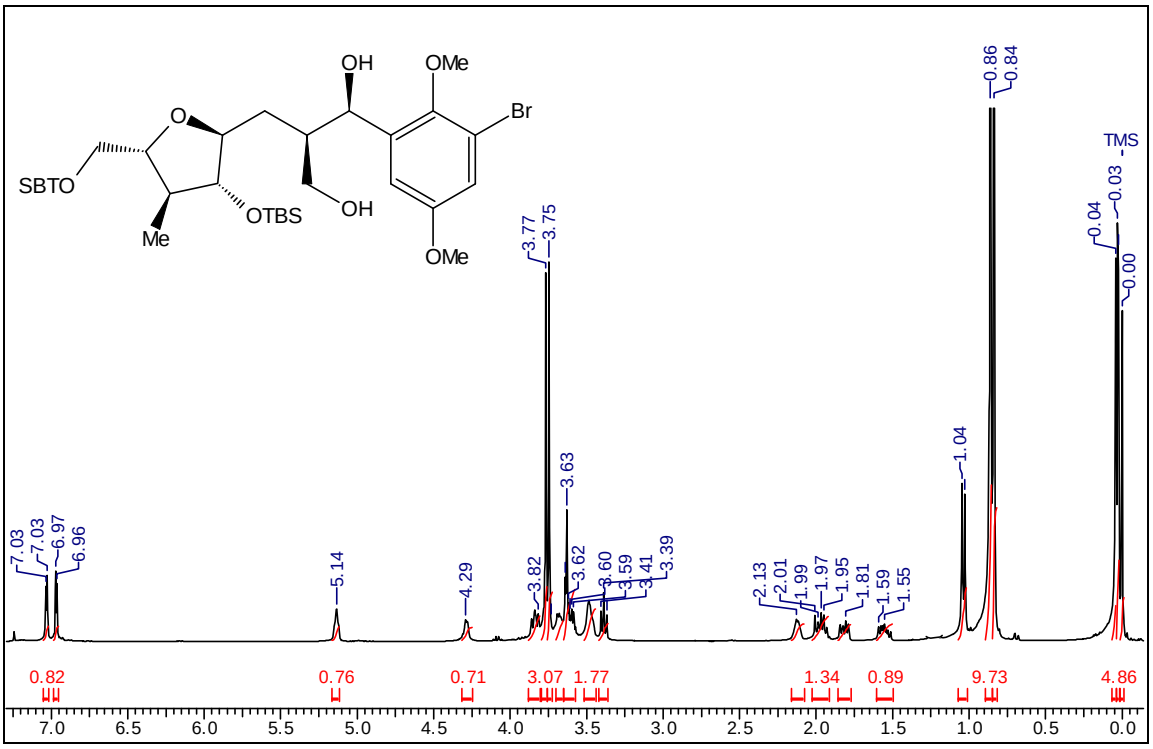
^{13}C NMR Spectrum of Di-TBS Evans anti aldol adduct-OTMS 149 in $CDCl_3$



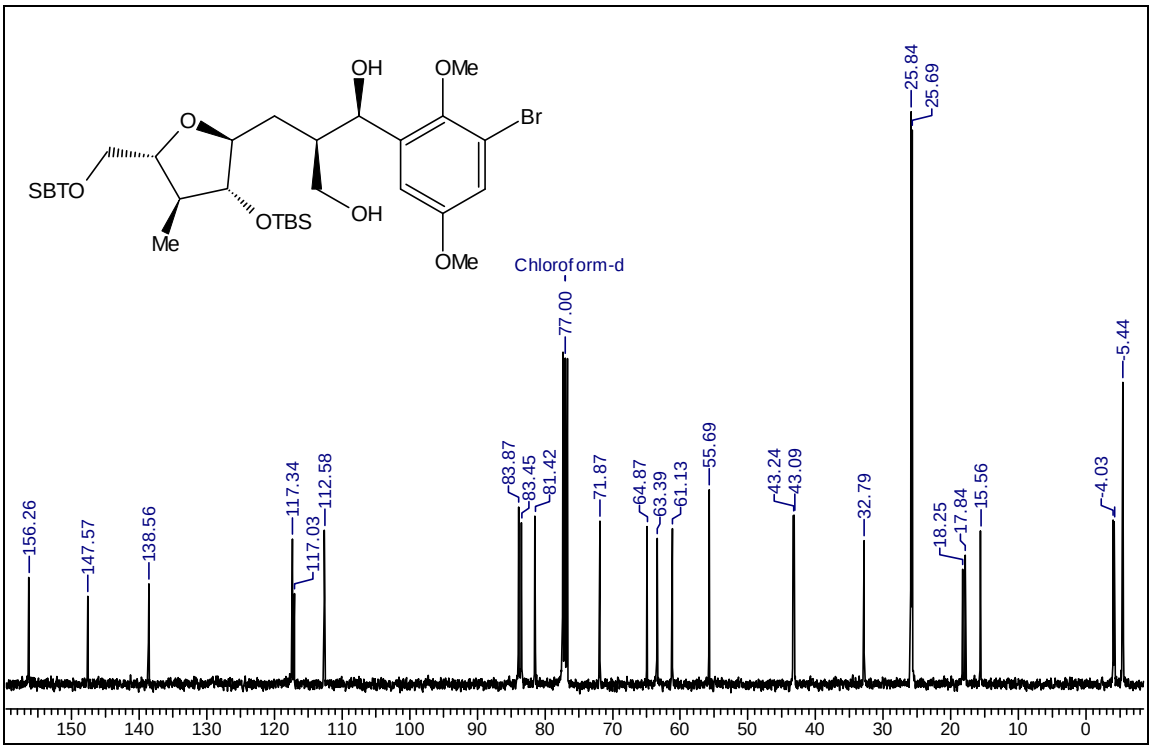
^{1}H NMR Spectrum of Evans anti aldol adduct-OH 150 in $CDCl_3$



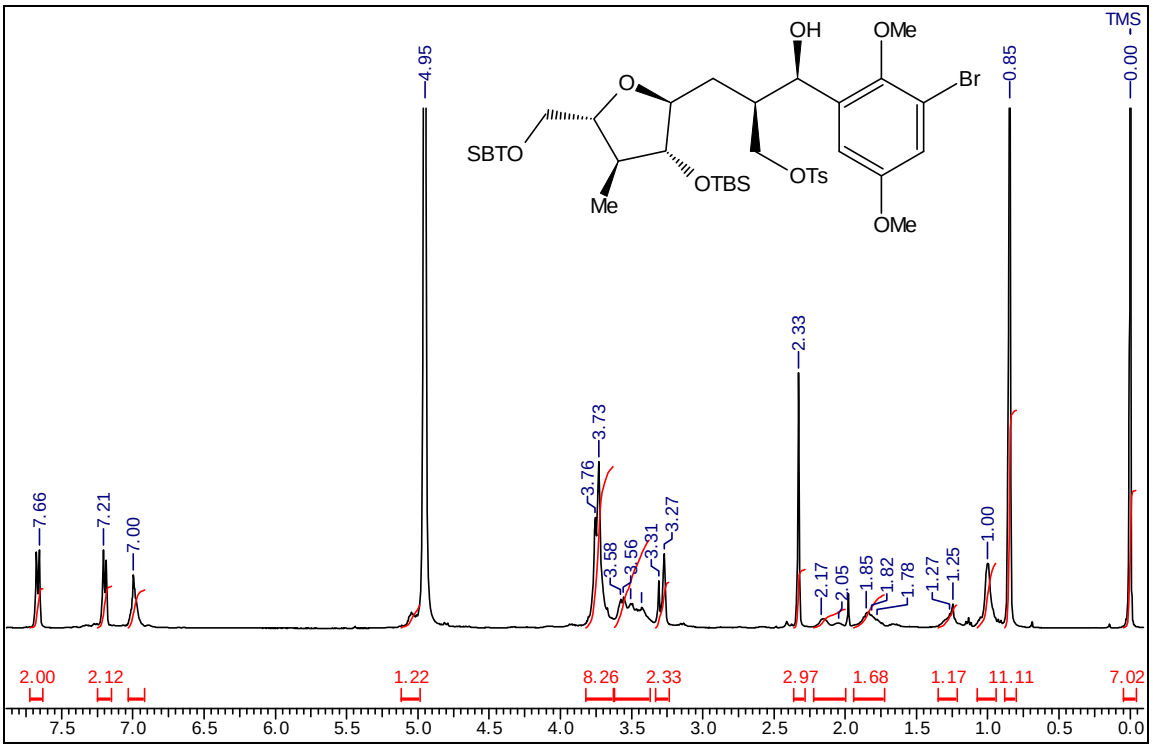
^{13}C NMR Spectrum of Evans anti aldol adduct-OH 150 in $CDCl_3$



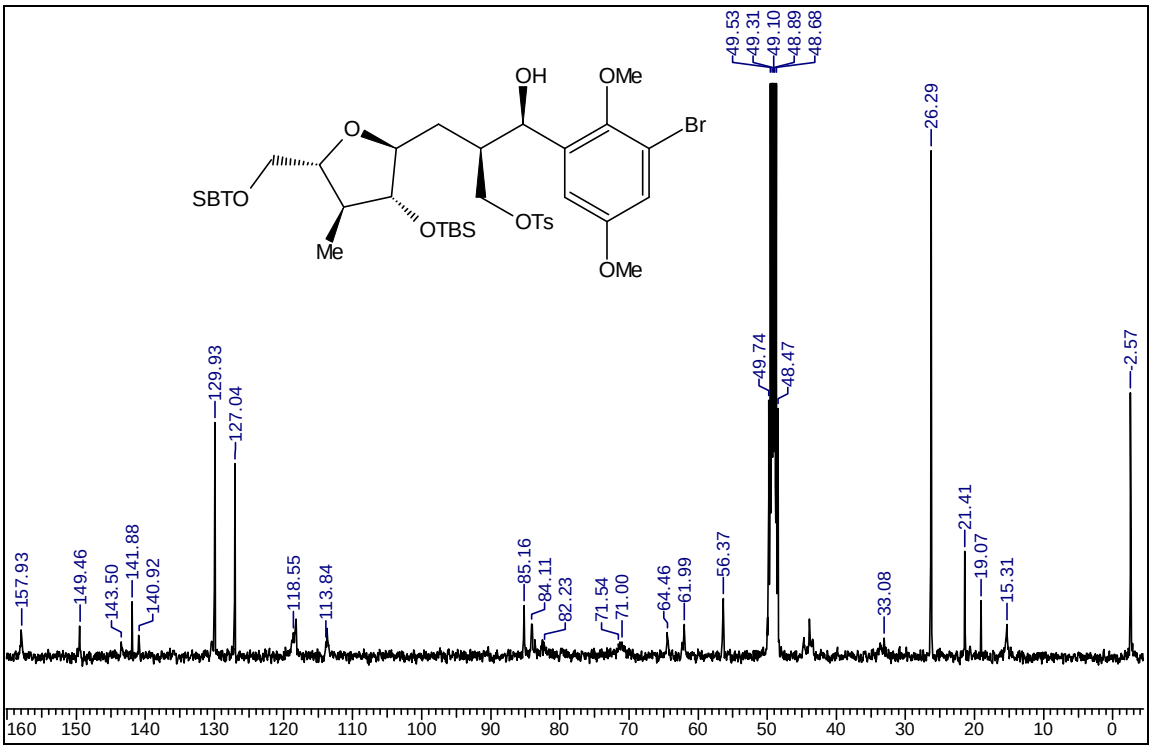
^{1}H NMR Spectrum of Diol 151 in $CDCl_3$



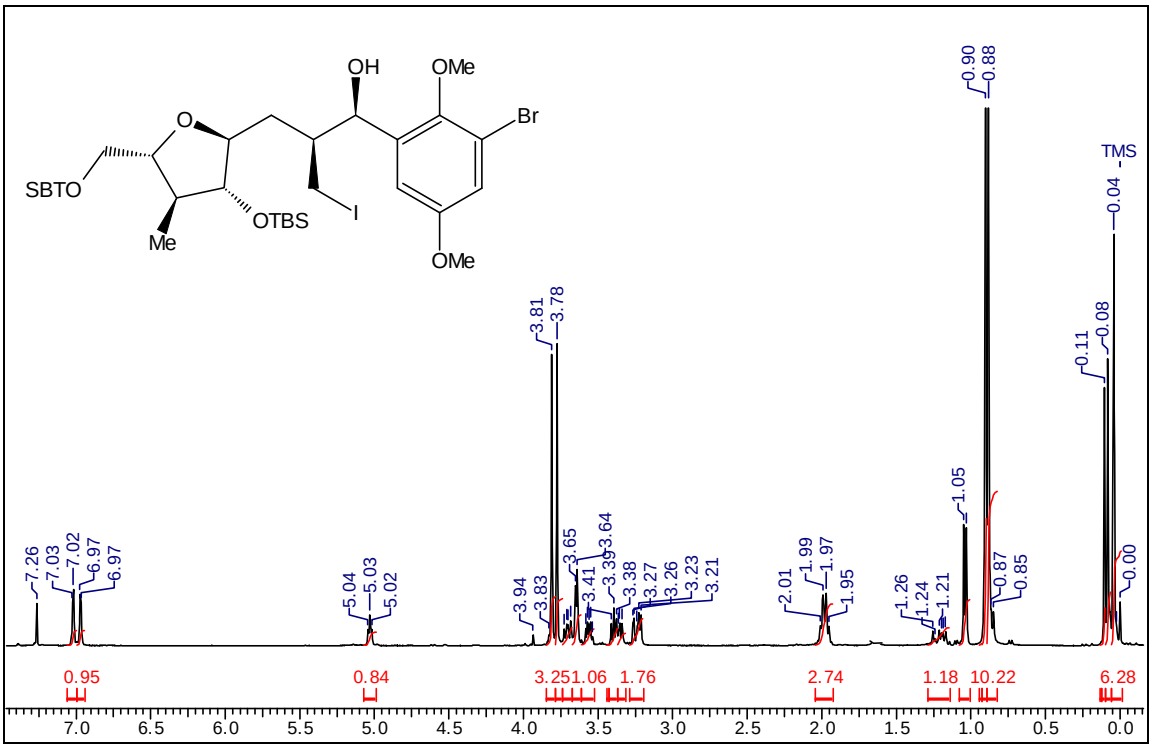
^{13}C NMR Spectrum of Diol 151 in $CDCl_3$



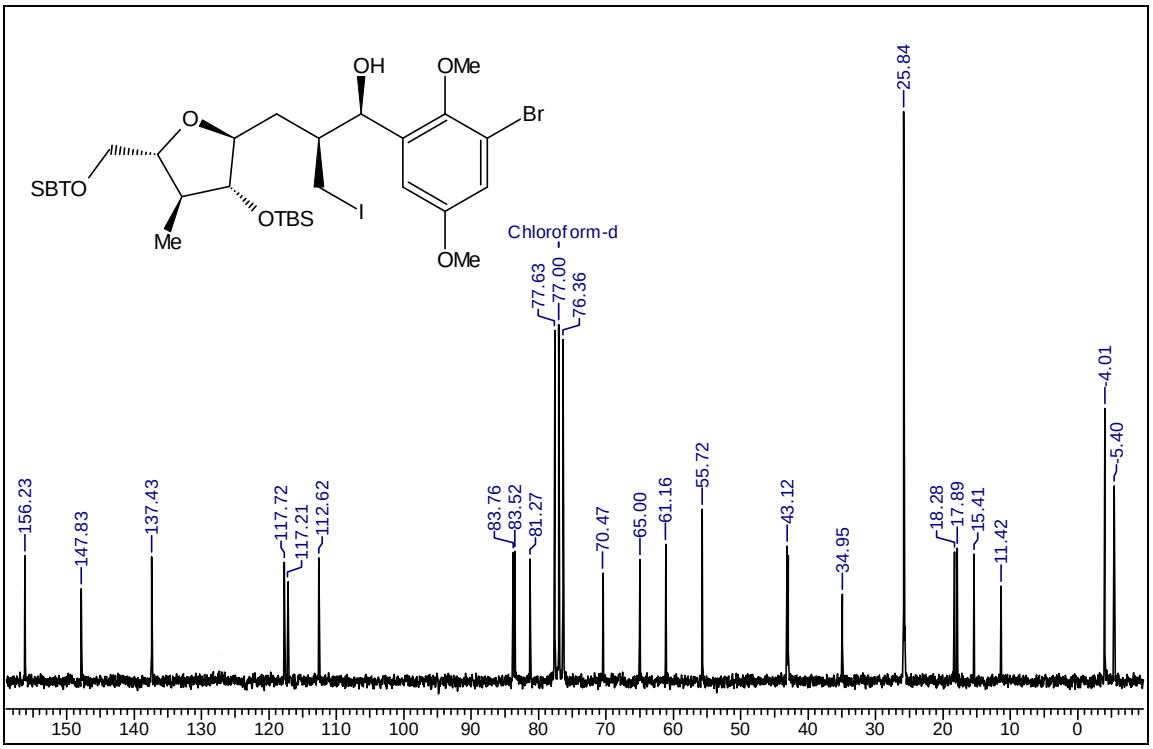
^{1}H NMR Spectrum of tosyl derivative 152 in $MeOD_4$



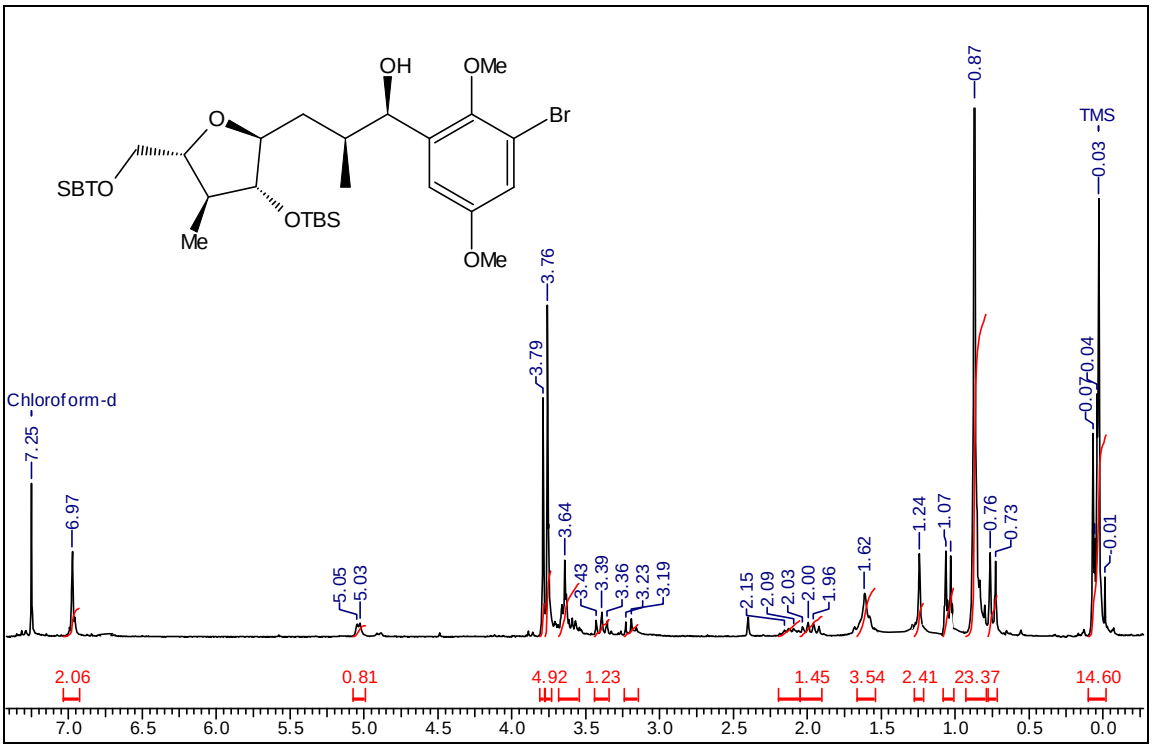
^{13}C NMR Spectrum of tosyl derivative 152 in $MeOD_4$



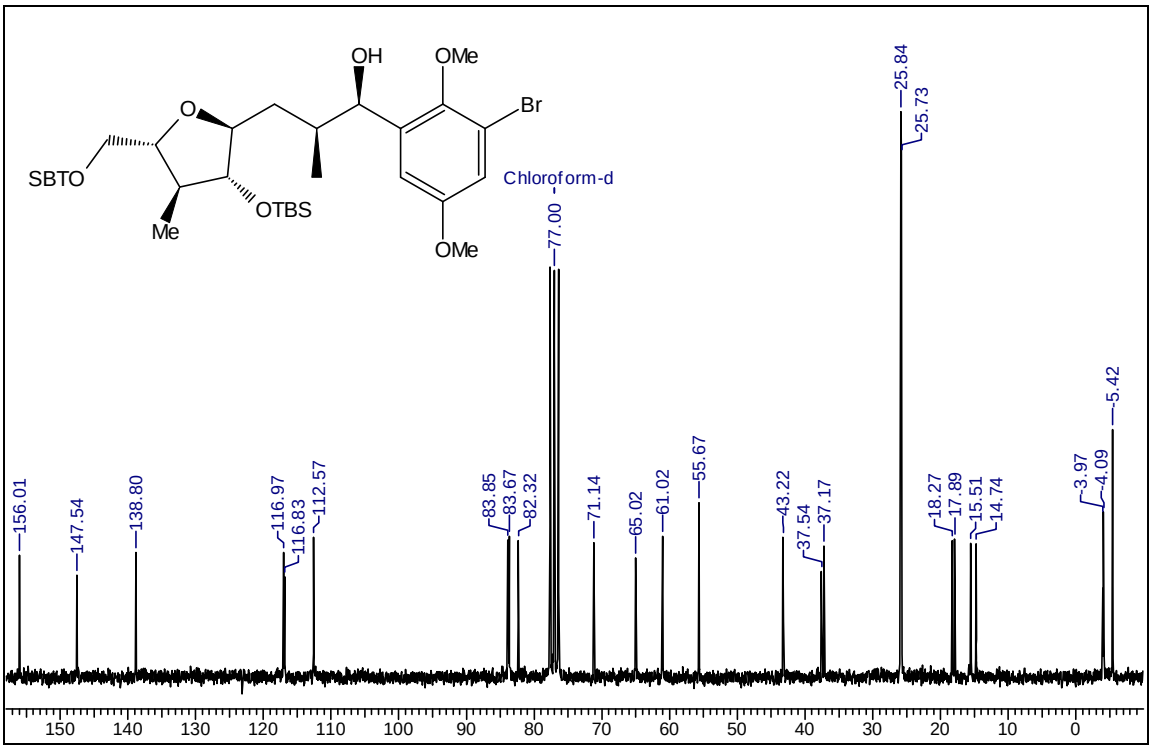
^{1}H NMR Spectrum of iodo derivative 153 in $CDCl_3$



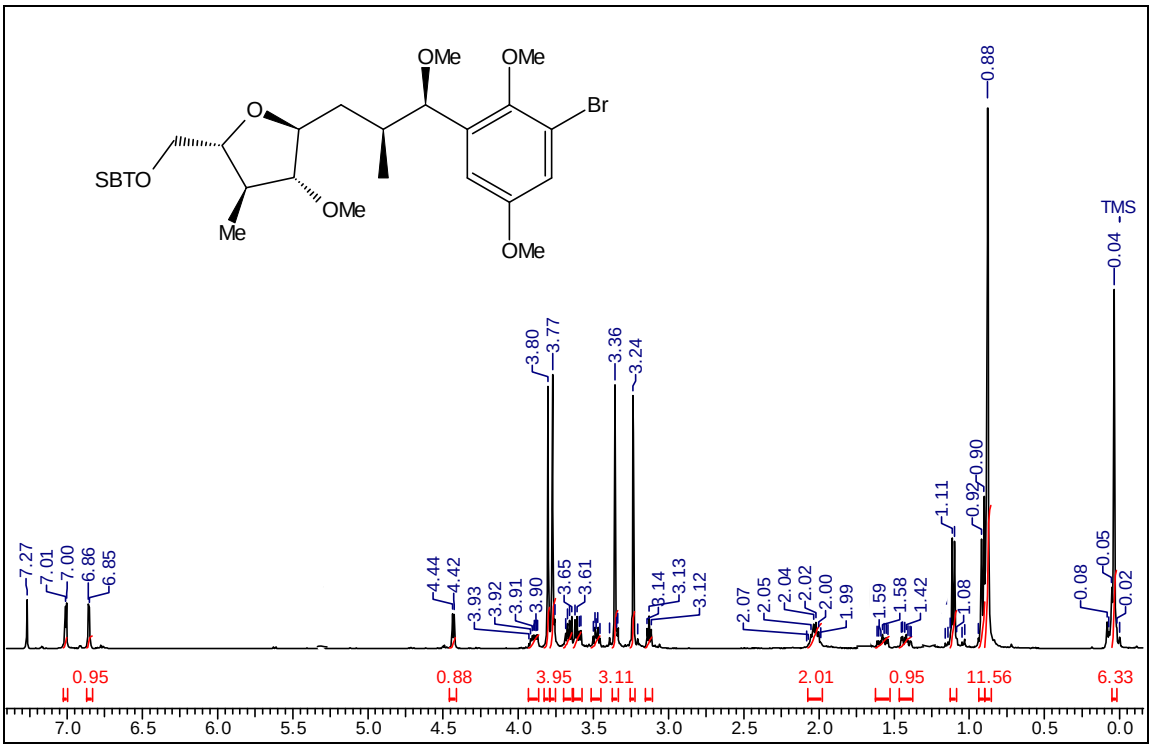
^{13}C NMR Spectrum of iodo derivative 153 in $CDCl_3$



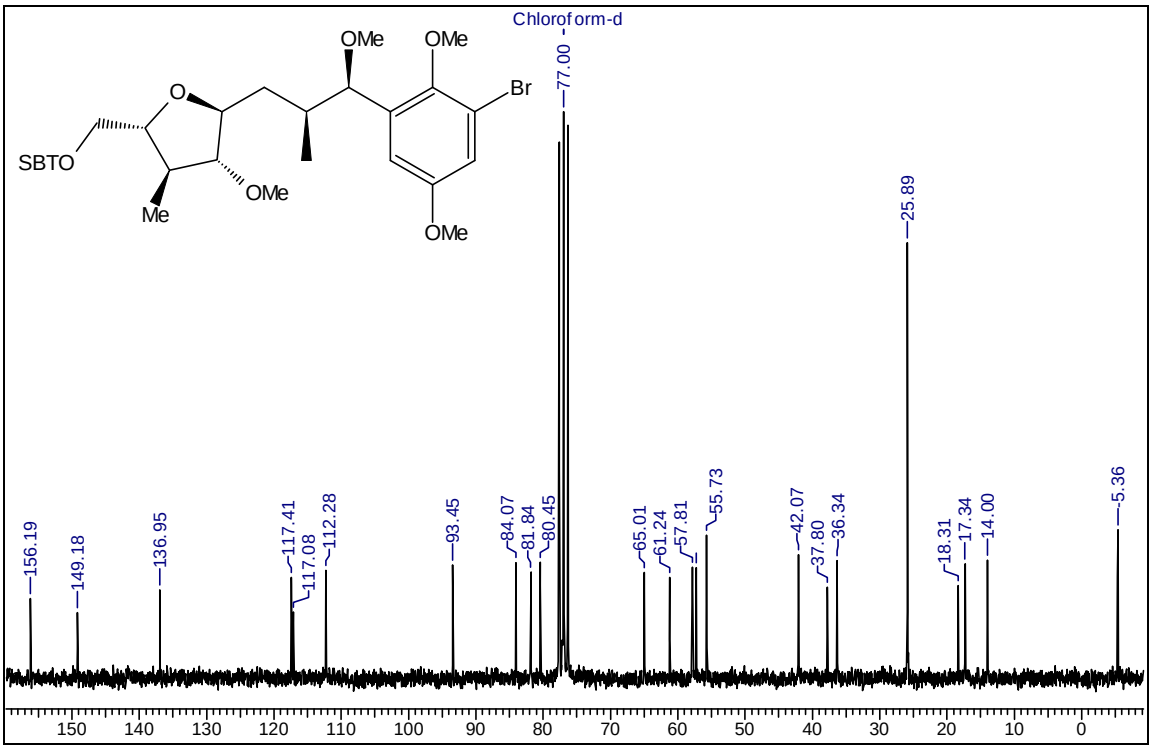
^{1}H NMR Spectrum of Deiodo product 154in $CDCl_3$



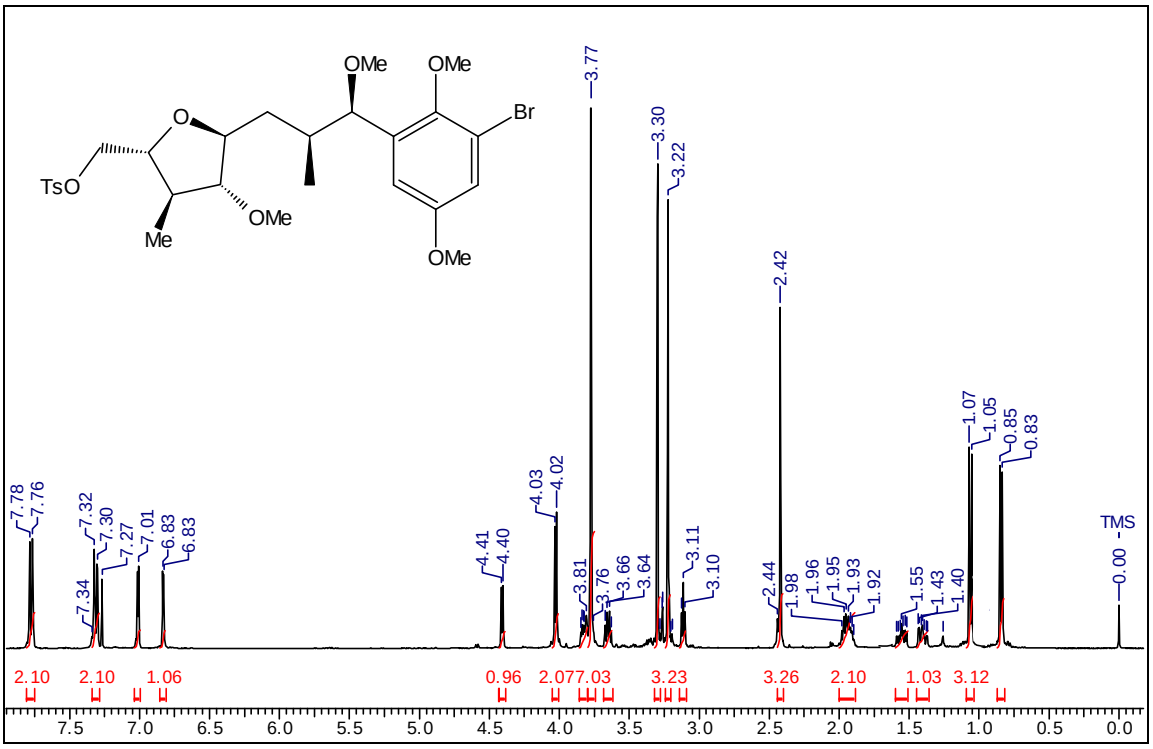
^{13}C NMR Spectrum of Deiodo product 154 in $CDCl_3$



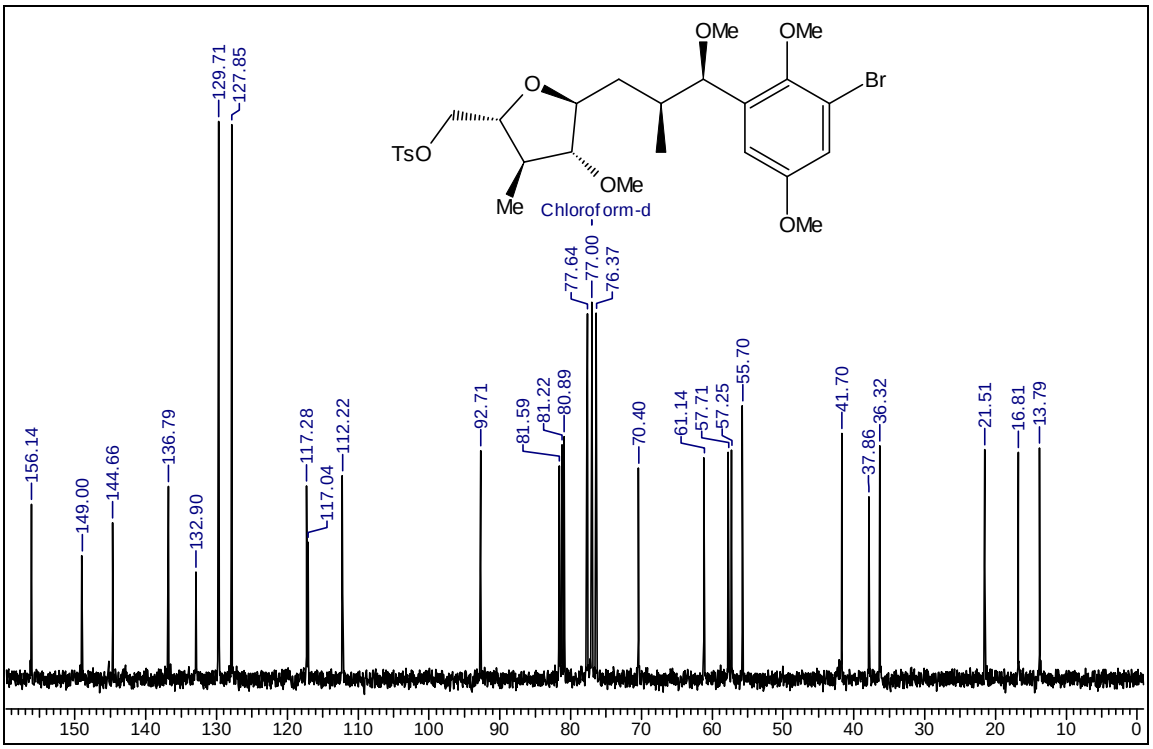
^{1}H NMR Spectrum of TBS-protected 157 in $CDCl_3$



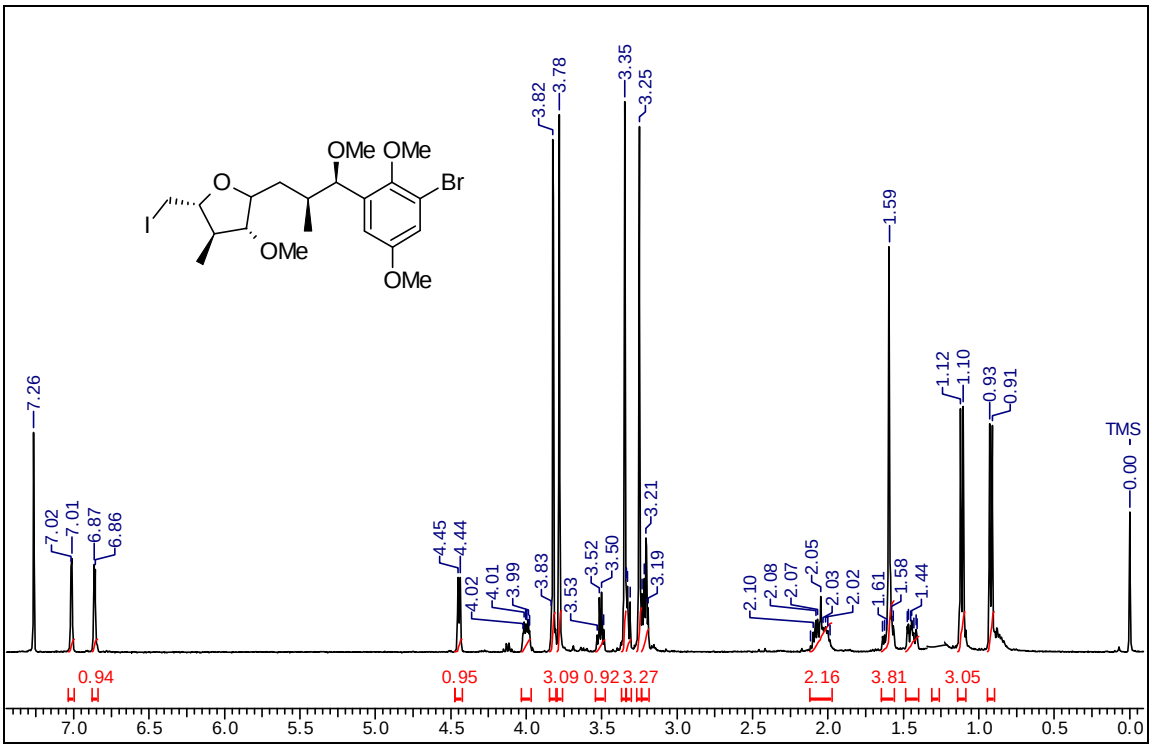
^{13}C NMR Spectrum of TBS-protected 157 in $CDCl_3$



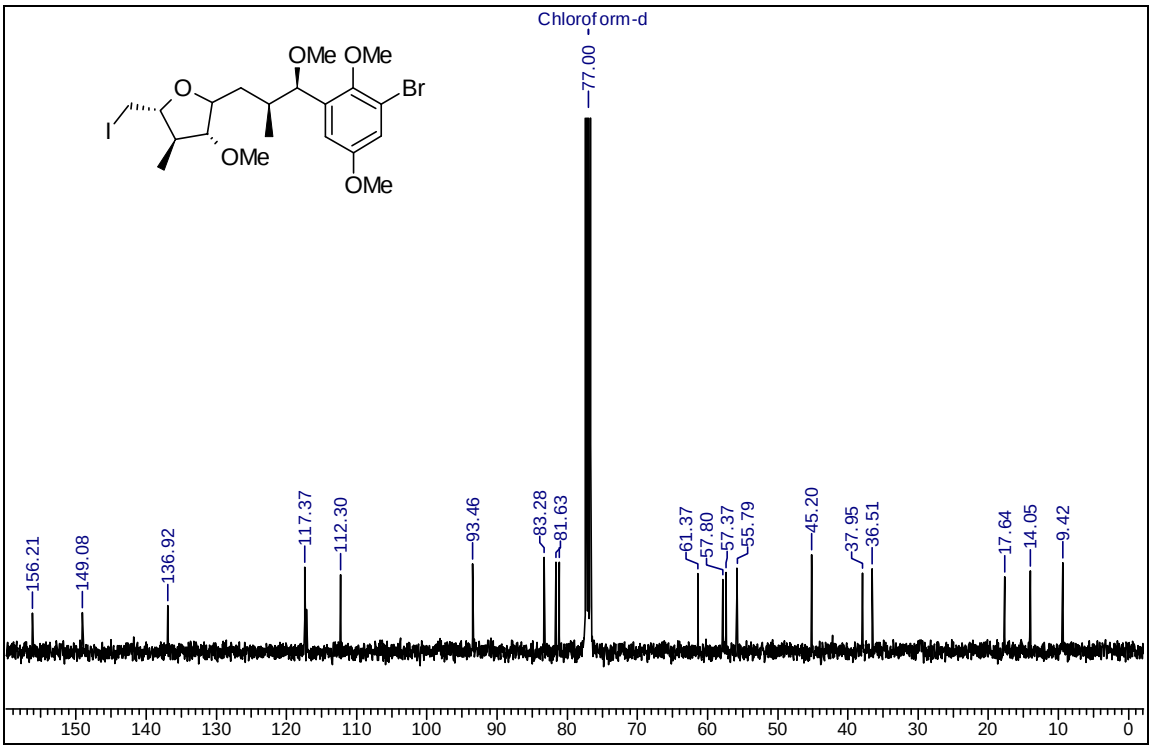
^{1}H NMR Spectrum of Tosylate 159 in $CDCl_3$



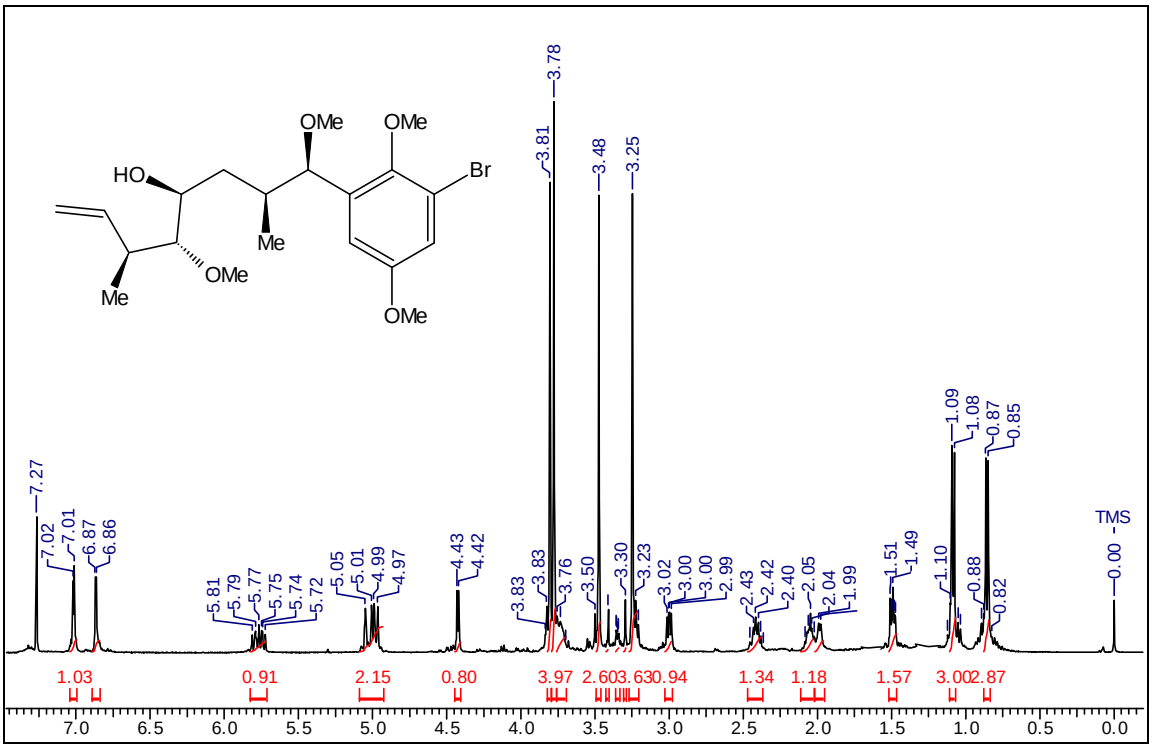
^{13}C NMR Spectrum of Tosylate 159 in $CDCl_3$



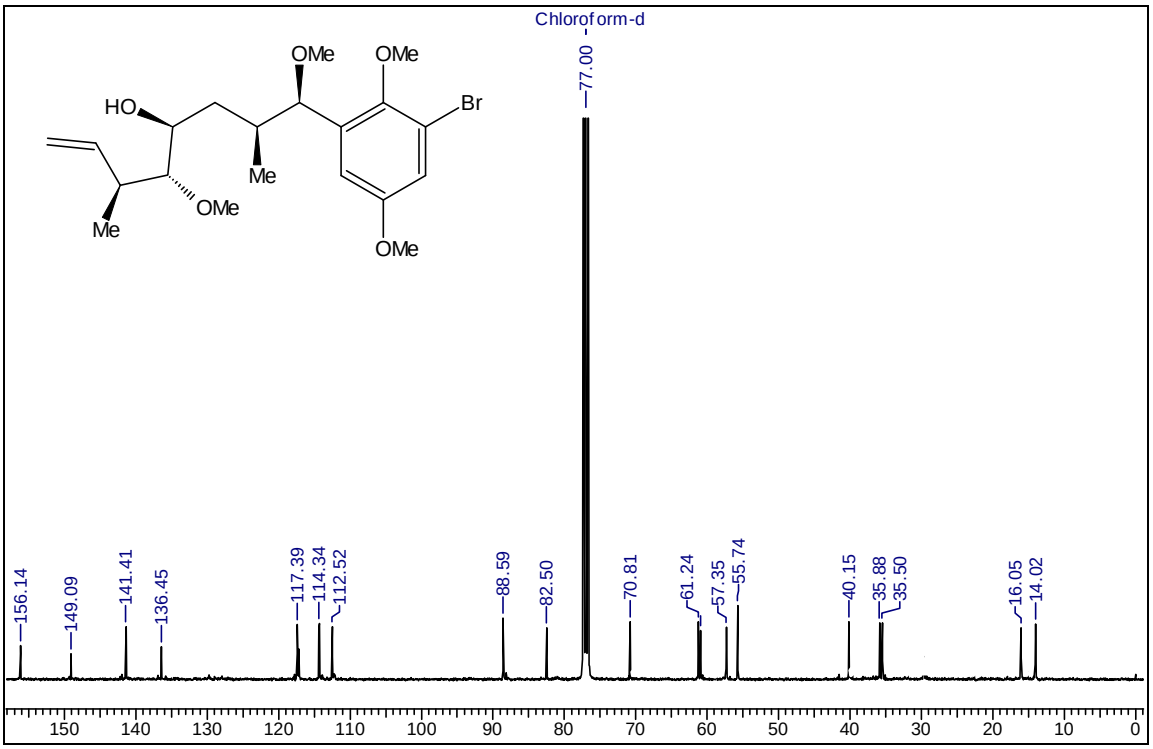
^{1}H NMR Spectrum of Iodo product 100 in $CDCl_3$



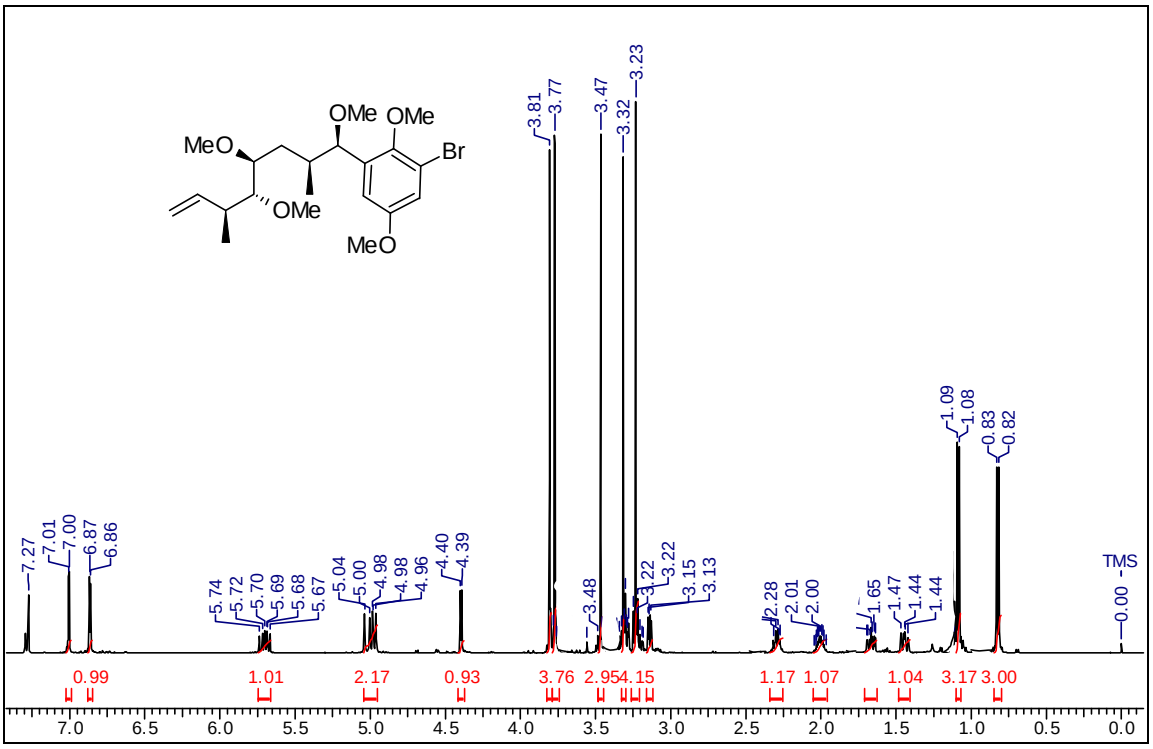
^{13}C NMR Spectrum of Iodo product 100 in $CDCl_3$



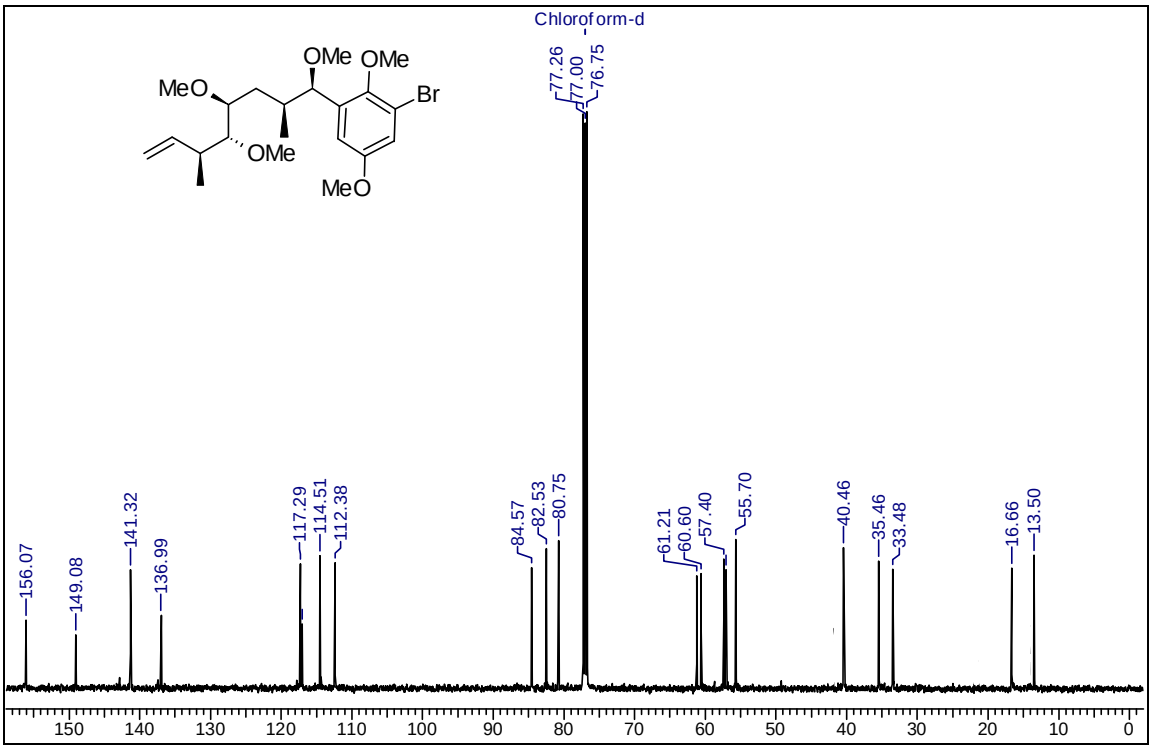
^{1}H NMR Spectrum of hydroxy olefin 160 in $CDCl_3$



^{13}C NMR Spectrum of hydroxy olefin 160 in $CDCl_3$



^{1}H NMR Spectrum of final fragment 98 in $CDCl_3$



^{13}C NMR Spectrum of final fragment 98 in $CDCl_3$

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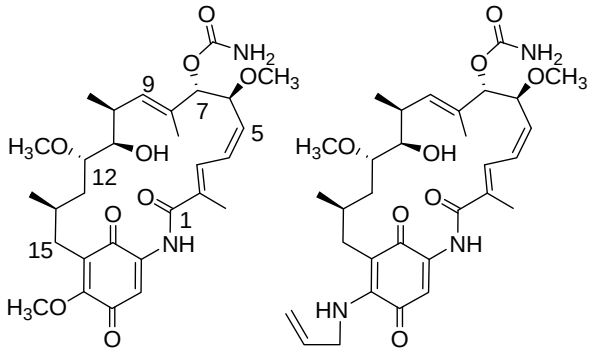
Section-II:Towards the total synthesis of 15- Hydroxy geldanamycin

INTRODUCTION AND PRESENT WORK

Section-II:Towards the total synthesis of 15- Hydroxy geldanamycin

Introduction:

Geldanamycin was isolated (from streptomyces hygroscopicus var. geldanus) in 1970 by workers at Upjohn and the structure was determined by Rinehart and co-workers shortly thereafter[1]. Geldanamycin belongs to benzoquinone anasamycin family. Benzoquinone containing ansa-bridged macrocyclic lactams have a significant range of antitumor, antibacterial, antifugal and antiprotozoa activies. Hsp90-geldanamycin complex were studied by X-ray crystallography,[2] absolute stereochemistry was determined by its total synthesis by Andus *et.al*.[3] The greatest drawback of biologically active geldanamycin is its cytotoxicity and low solubility in water for any formulation that can be used to administer it. To rectify this problem, derivatization of geldanamycin with ionisable or polar groups was explored. The 17-allyl amino geldanamycin prepared in this context, was currently in phase-II clinical trial[4].



Geldanamycin **17-allylaminoGeldanamycin**

Isolation and Characterization of 15-Hydroxygeldanamycin

The 15-Hydroxygeldanamycin[5] was formed as the major product when geldanamycin was added to the fermentation with *streptomyces hygroscopicus* AM-3672 along with a minor compound, a tricyclic geldanamycin (KOSN-1633) [5] was isolated. It has been established that the -OH group at 15-position of geldanamycin does not interfere in binding with Hsp90 but increase the lypophilicity of it. The structure of 15-hydroxy geldanamycin was elucidated by comparing the similarities of its spectral data with that of geldanamycin which are similar in all aspects (^{1}H, ^{13}C, HSQC, and COSY) except at the 15- position. High-resolution MS measurements for 15-hydroxy

geldanamycin were consistent with a formula of $C_{29}H_{40}N_2O_{10}$ for a monohydroxylated geldanamycin. However, signal for C-15 methylene were absent in its ^1H NMR; instead a new doublet at 4.58 ppm for a methine group was observed. ^1H and ^{13}C chemical shifts (except for the quaternary carbons) were assigned from multiplicity-edited HSQC and COSY. Chemical shifts for the quaternary carbons were assigned by comparison with those of geldanamycin. The stereochemistry of 15–OH group was assumed to be the same as in Herbimycin A.

Biological Activity Of Ansamycin family members and its derivatives:

compounds	SKBr3 IC_{50}
Geldanamycin	37
Herbimycin A	160
Reblastatin	600
15-hydroxygeldanamycin	710
KOSN-1633	1533
KOSN-1645	2559
KOSN-1646	3163

Table 1: **Cytotoxicity of geldanamycin analogues against SKBR3 cell line.**

The cytotoxicity of 15-hydroxygeldanamycin is same as that of reblastatin and 20 times lower than that of geldanamycin.[5] Though it was isolated in 2004, no attempt has yet been made to prepare this molecule. The unusual structural parameters coupled with cytotoxic activity of 15-hydroxygeldanamycin motivated us towards the total synthesis.

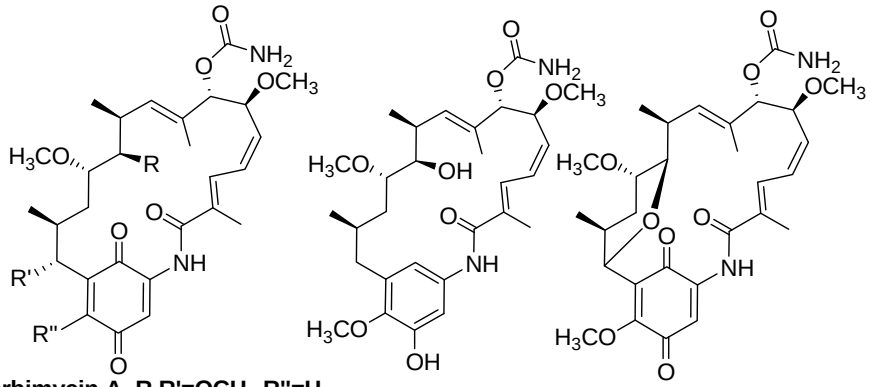


Figure -14 structure of novel natural products and its derivatives

Retrosynthetic analysis:

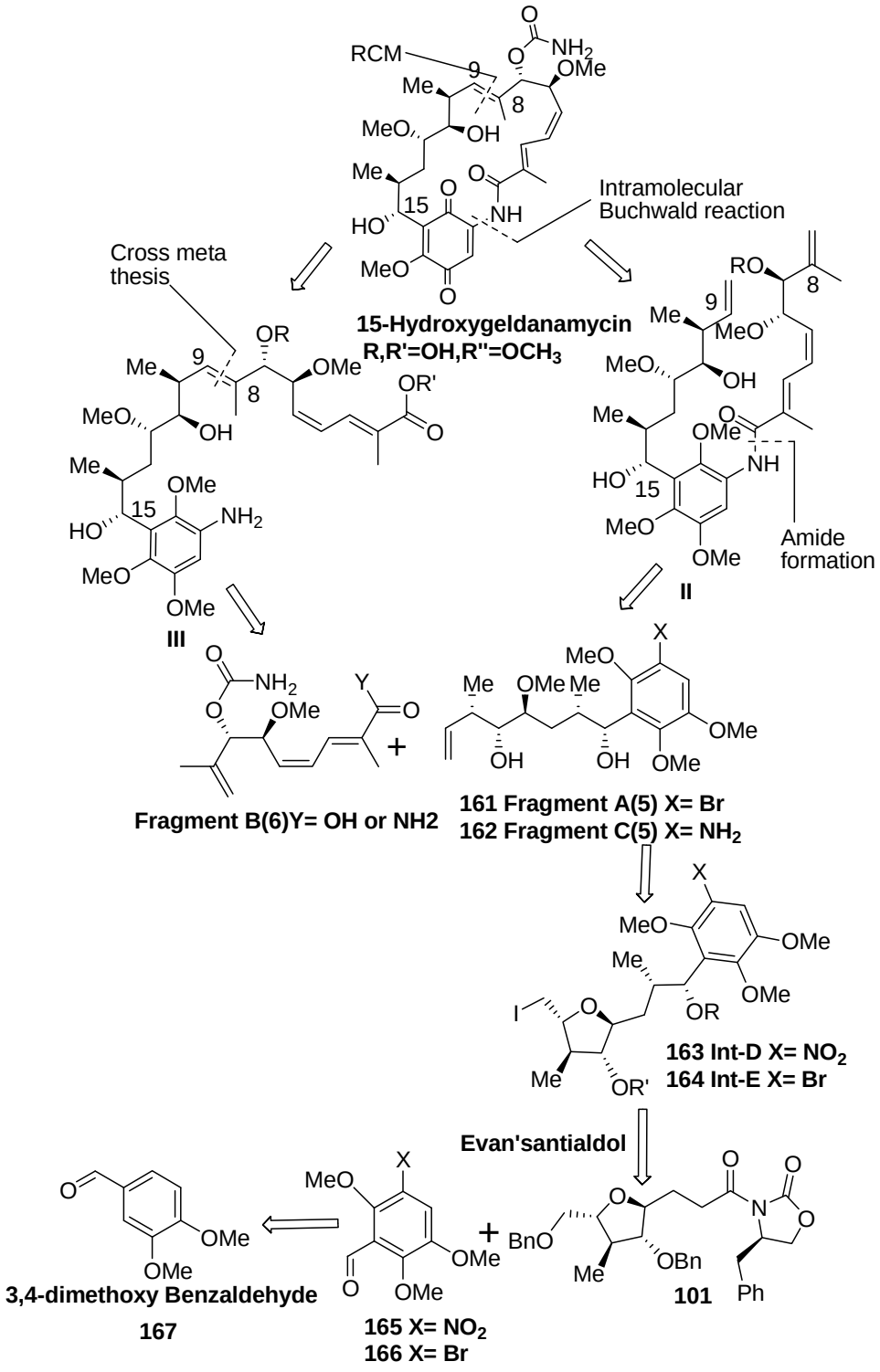


Figure 15. Retrosynthetic strategy for advanced right hand segment

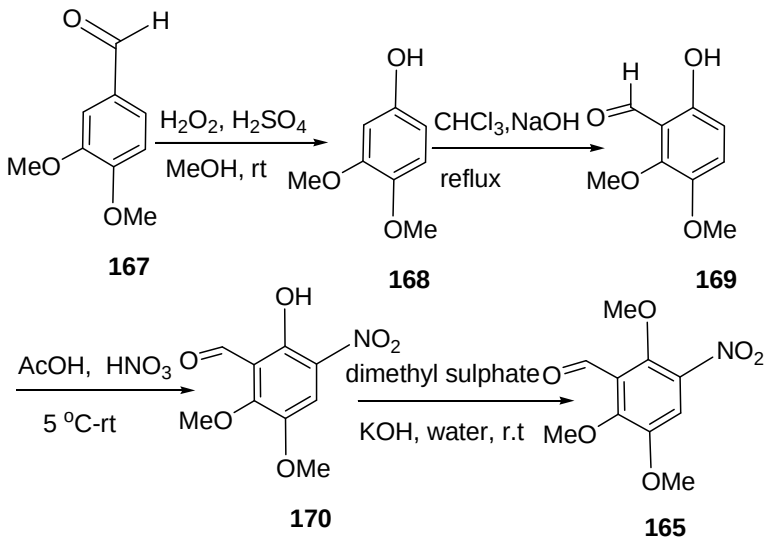
Our Retrosynthetic strategy for synthesis of the architechurally complex natural product, as depicted in Figure 15 is very similar to that of the Herbimycin A (previous section) and includes two strateges; first one involves intermolecular amidation of fragments A and B to get **II,** followed by RCM approach which would lead to our target molecule. Second strategy deals with assembling of the key fragments A and B by crossmetathesis which would result **III,** followed by intramolecular amidation to provide the target molecule. The key fragment A would be obtained by functional group manipulation using Evans anti aldol reaction of int-**101** and aryl aldehyde **165** or **166**. The int-**101** can be obtained by chemical manipulation of D-Glucose.

Once the retrosynthetic plan was finalized, started our synthesis by preparing the masked quinine **165** as described below (Scheme-50).

Synthesis of Masked Quinone Aryl Aldehyde 165:

Synthesis of masked quinine aryl aldehyde **165** was achieved following reported methods.[3] p-Methoxy benzaldehyde, under acid catalysed Dakin rearrangement afforded p-methoxy phenol **168**.[6]

Scheme 50



167 **168** **169** **170** **165**

Ortho-formylation of **168** under Reimer-Tiemen reaction conditions using $CHCl_3$ and NaOH provided aryl aldehyde **169**. Nitration of aldehyde **169** by using HNO_3 : AcOH in 1:1 ratio to afford nitroarylaldehyde **170,** which on methyaltion by using MeI

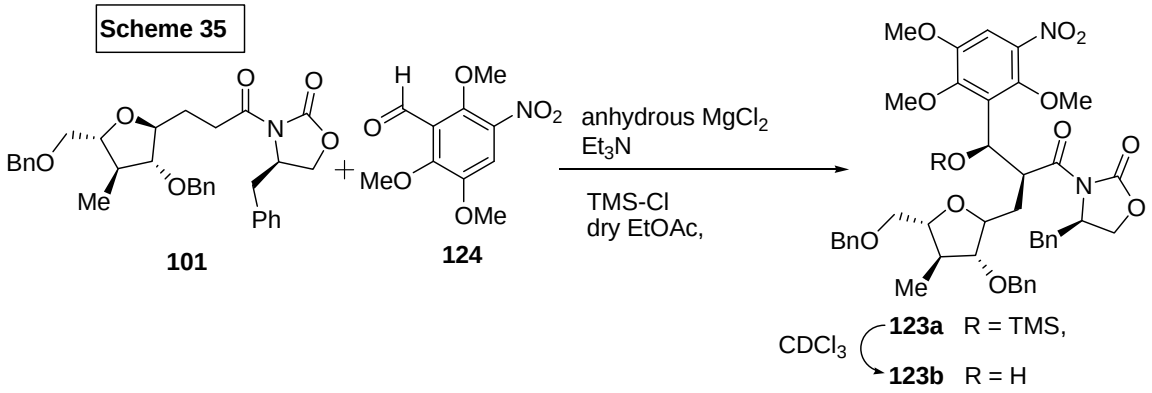
and K_2CO_3 in DMF afforded masked quinine arylaldehyde **165** (Scheme 50). The structure of **165** was determined by its ^1H NMR, ^{13}C NMR and other analytical data including M.P. are in complete agreement with the reported values. [3]

The other fragment for the Evan's anti aldol reaction was already in hand (**101**, prepared in the previous section). Having both the key intermediates for aldol reaction in hand, we then attempted asymmetric Evans' *anti* aldol reaction under reported/standard conditions.

Synthesis of Key fragment of 15-Hydroxygeldanamycin:

Our first attempt was the Evan's *anti* aldol reaction between the carbohydrate derived oxazolidinone (**101**) with highly substituted arylaldehyde (**124**) by using standard condition.[7]

Scheme 35



101 **124**

Using this reaction condition, oxazolidinone (**101**) was treated with $MgCl_2$, triethylamine, benzaldehyde (**124**) and chlorotrimethylsilane in dry ethylacetate at rt for 20h to give TMS ether derivative **(123a**), and free hydroxyl compound (**123b**), as a single isomer with excellent yield (light yellow color liquids and the aldol adducts **123a** (OTMS) : (**123b**) OH in 1:1 ratio) (Scheme 35). The OTMS aldol adduct was confimed from ^1H and ^{13}C NMR spectra. In which, the characteristic OTMS protons resonances at δ 0.01 ppm integrating nine protons, benzylic proton was appeared as multiplet at δ 5.65 ppm integrating one proton. Rest of the spectrum complete agreement with the excepted values. ^{13}C NMR Spectrum showed –OTMS carbon resonance at δ -0.21 ppm and benzylic carbon appeared at δ 79.34 ppm indicating the assigned structure. In addition, the mass spectral analysis showed *m/z* at 879.78 $[M+Na]^+$ which further confirmed it's formation. The elemental data also confirmed the structure **123a**. Finally the

stereochemical assignment was completed from its single X-ray crystal analysis (Figure 9). The OH aldol adduct (**123b**) showed the characteristic benzylic proton resonance at δ 5.26 ppm integrating for one proton and rest of the protons had expected chemical shift values in the ^{1}H NMR spectrum. The ^{13}C spectrum showed characteristic benzylic carbon resonance at 71.30 ppm. All other chemical shift values appeared at their respective positions. In addition, the mass spectral analysis showed an *m/z* 808.2 $[M+Na]^{+}$ was corroborated the structure of **123b**. The **123a** (OTMS) aldol adduct was unstable which was immediately transformed into **123b** (OH) aldol adduct in $CDCl_3$ or mild acidic conditions.

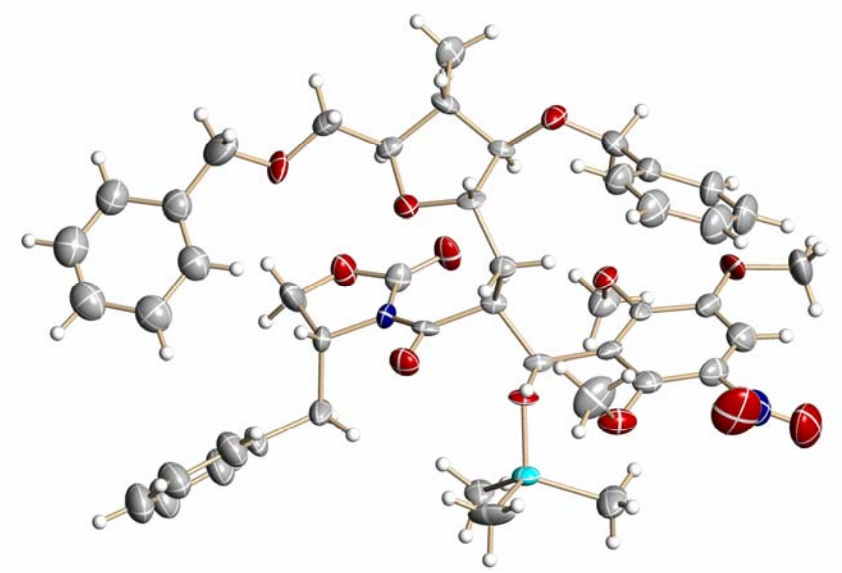


Figure 9: Crystal structure of 123a (Evans' anti aldoladduct).

Observation of restricted conformational isomers:

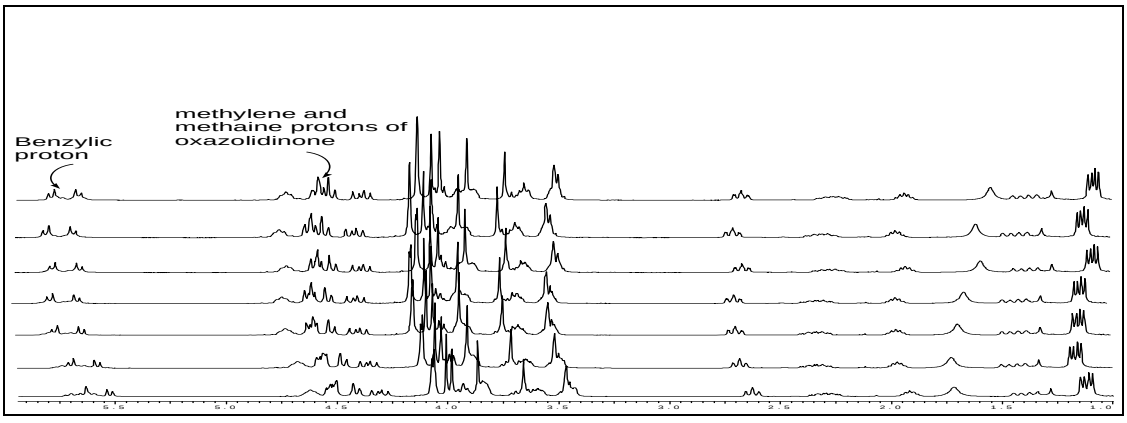


Figure10:High Temperature NMR Experiments on Evans' anti aldol adduct (123a).

A very interesting observation was made from the ^{1}HNMR experiments of the TMS derivative of Evans *anti* aldol adduct showing broad signal for benzylic protons and oxazolidinone methylene protons along with a slightly less-broad signal for the aromatic protons in the ^{1}H NMR Spectrum. Two sets of signal patteren were observed in the ^{13}C NMR spectrum. These phenomena were attributed to dynamic effects, and indeed, a temperature-dependent ^{1}H NMR study of OTMS aldol adduct **123a** revealed that at higher temperature the benzylic protons sharpened to the doublet with a coupling constant (J = 10.7 Hz). The oxazolidinone methane and methylene protons were sharpened and merged. Other proton signals did not changed at higher temperature. These results indicated that the presence of rigid conformers and hence these dynamic effects were assigned to a restricted sp^2-sp^3 rotation resultant due to restricted conformational isomers.

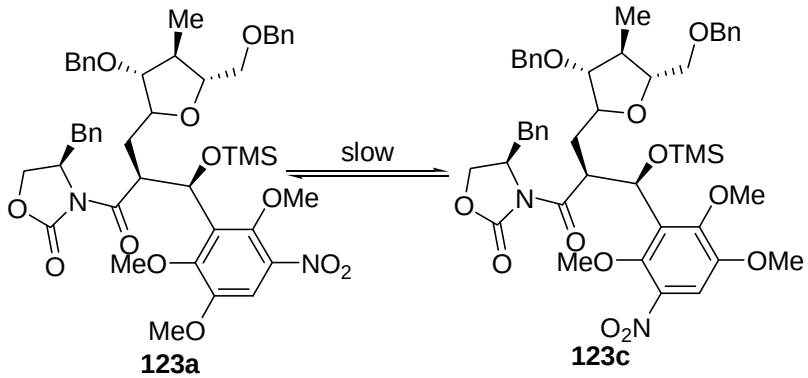


Figure 11:Conformers of OTMS ether derivative of Evans' anti aldol adduct.

This type of observation due to presence of rigid conformers like **123a** and **123c** at room temperature as shown above figure **11**. This was further confirmed by extensive NMR studies including COSY, NOESY experiments. Fortunately we were able to isolate one of conformer and obtained the single X-ray analysis which showed that the aryl moiety was perpendicular to C-OTMS group, and it was rigidly surrounded by benzyl groups of densly functionalized carbohydrate moiety and oxazolidinone moiety. This type of restricted environment leads to arrest one of the stable conformer; where as the other less stable conformer (due to spatial interactions between nitro group and benzyl group of carbohydrate moiety and due to less availability of this conformer we couldn't isolate it). Similar type of observation was reported by Mulzer. *et.al*. in the synthesis of advanced fragment of kendomycin.[8]

Scheme 52

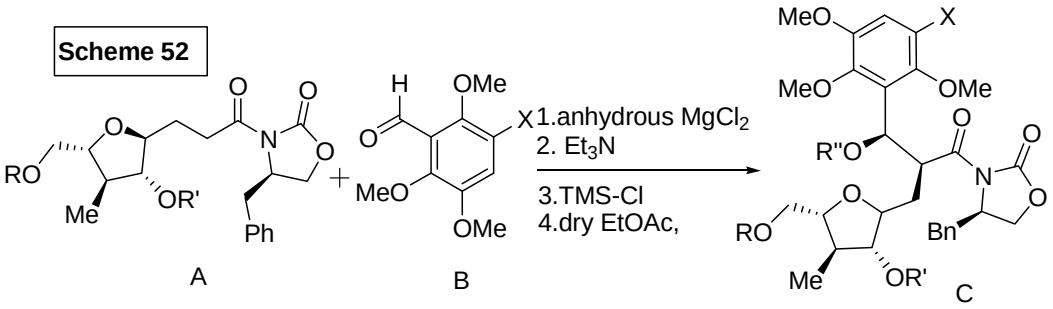
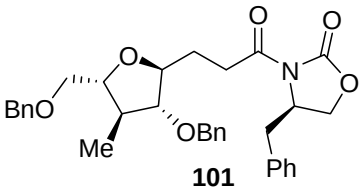
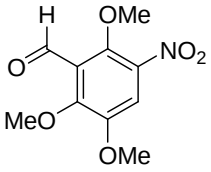
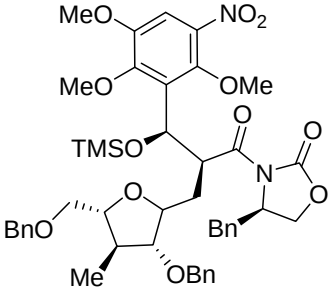
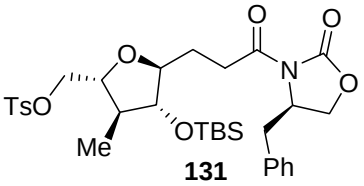
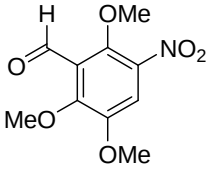
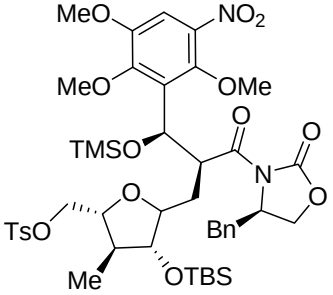
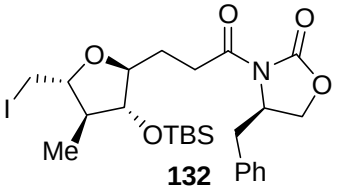
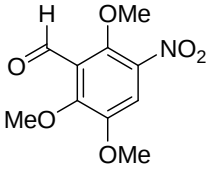
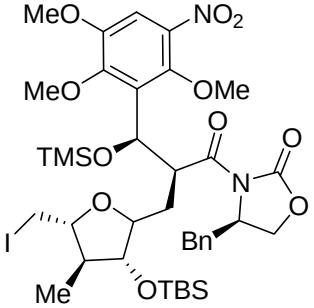
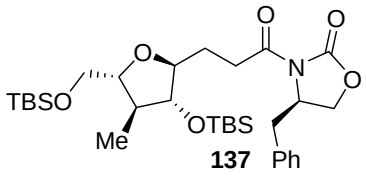
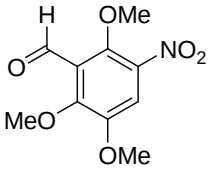
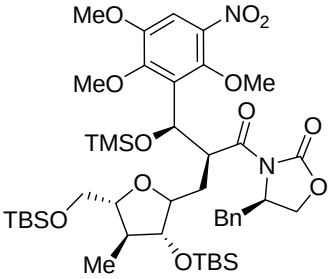
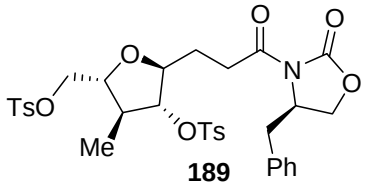
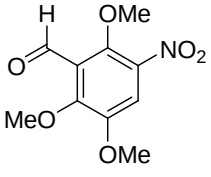
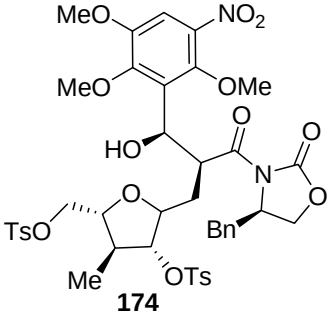
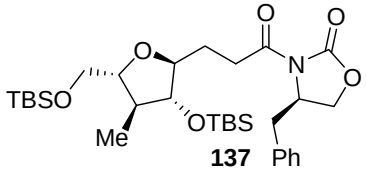
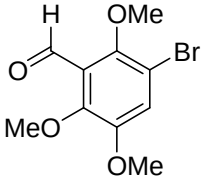
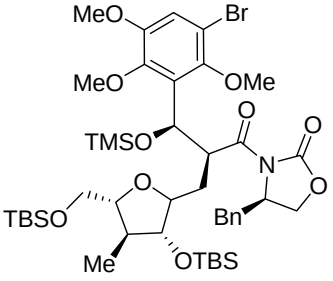


Table 4 :List of Aldol adducts showing restricted conformational isomers:

S. No	Oxazolidinone (A) derivative	Arylaldehyde (B)	OTMS Aldol adduct	
1	 **101**	 **124**	 **123a**	√
2	 **131**	 **124**	 **171**	√
3	 **132**	 **124**	 **172**	√

4	 **137**	 **124**	 **173**	√
5	 **189**	 **124**	 **174**	X
6	 **137**		 **175**	√

All the above oxazolidinone derivatives were prepared in the previous section-I

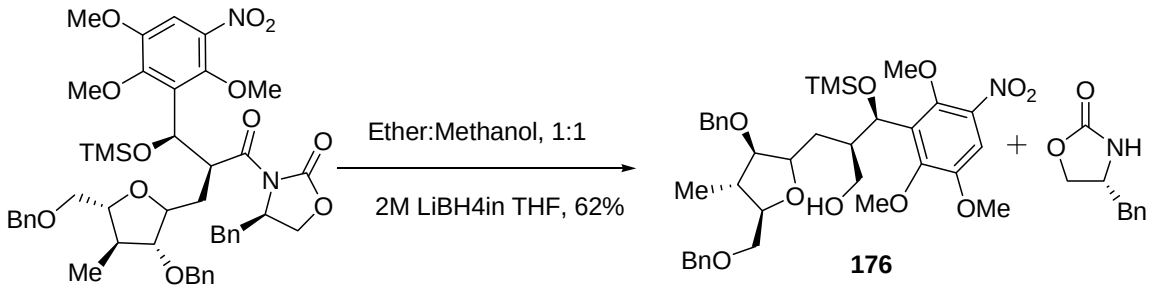
S.No	R	R'	X	R''= OTMS	remark
1.	Bn	Bn	NO_2	√	
2.	Ts	TBS	NO_2	√	
3.	Ts	Ts	NO_2	x	
4.	Iodo	TBS	NO_2	√	
5.	TBS	TBS	NO_2	√	
6.	Iodo	TBS	Br	√	
7.	TBS	TBS	Br	√	

For further confirmation, we prepared different types of aldol adducts (Table 4) by applying same reaction conditions to different coupling synthons. All these aldol adducts showed similar splitting patteren in ^{1}H NMR and ^{13}C NMR spectrum. These observations evidently confirmed that these aldol adducts exhibit restricted conformational isomers (may be called as atropisomers).

Syntheis of advanced fragment of 15-hydroxy geldanamycin:

Having Evans anti aldol adduct with all required stereocenters 10*S*, 11*R*, 12*S*, 14*S*,15*R* in hand, our next endeavor was to construct the key fragment of 15-hydroxy geldanamycin.

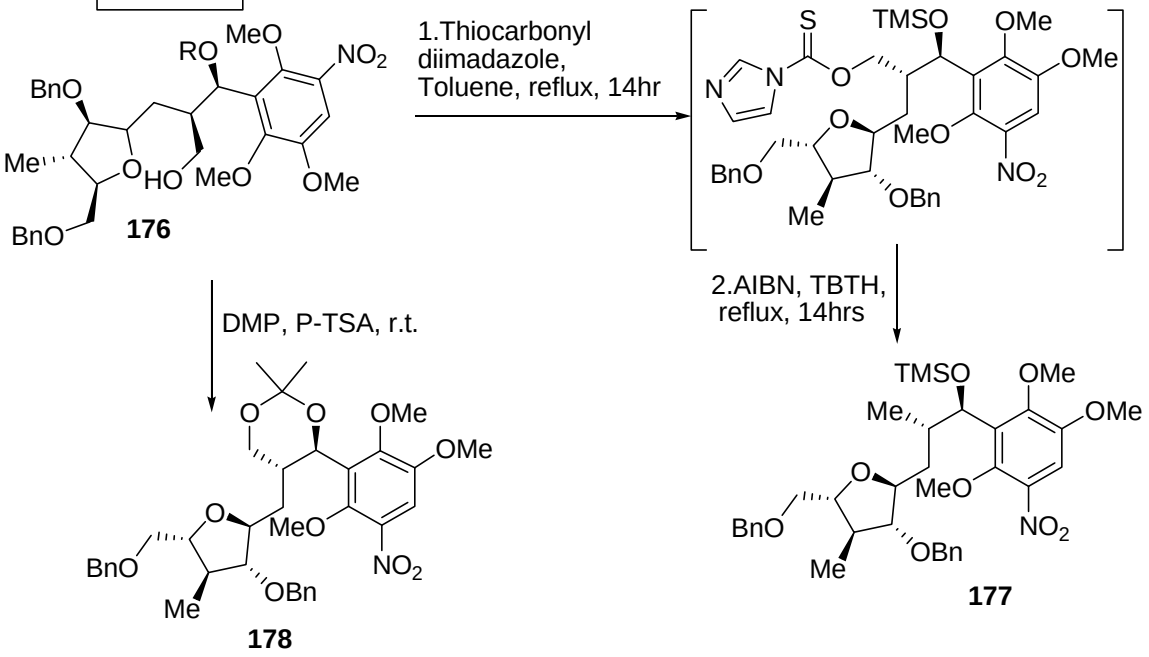
Scheme 53



123a **176**

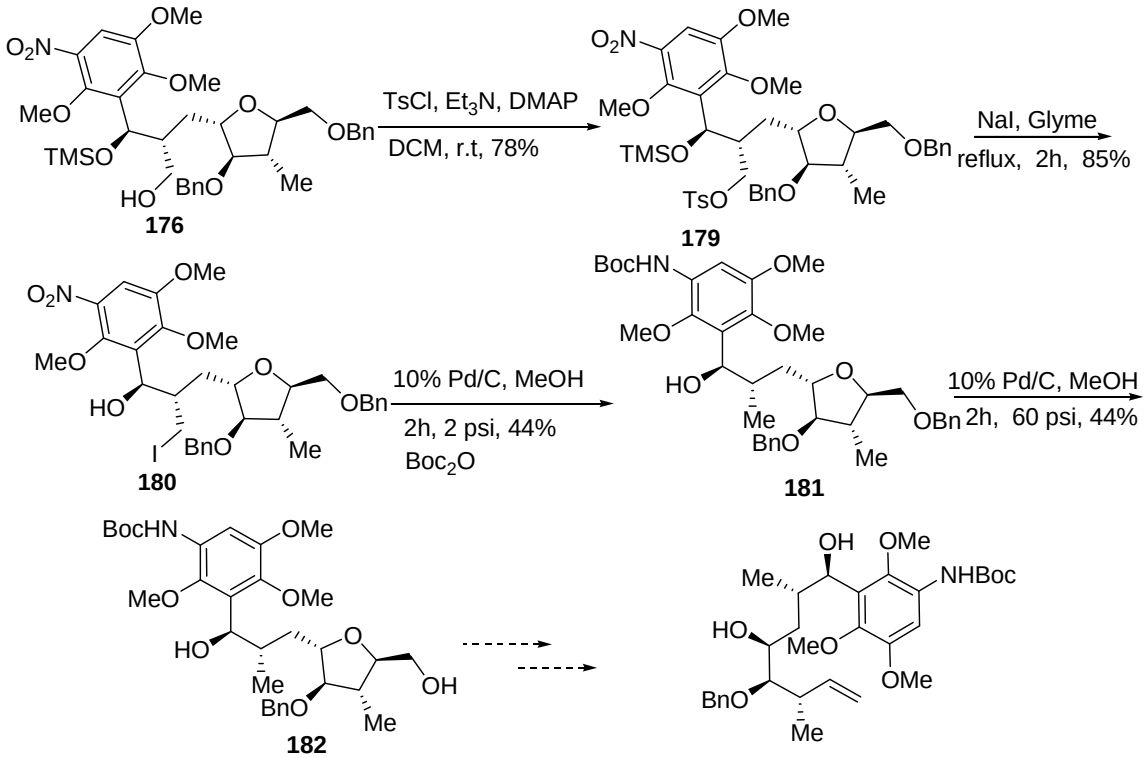
To achieve this target, the oxazolidinone of Int-**125** was reductively removed with 2M lithiumborohydride in THF to afford **176** as a sole product (Scheme 53). The product was confirmed by its ^{1}H NMR in which appearance of new methylene protons as a multiplet at δ 3.55 and rest of the protons were in good agreement with the excepted values.The ^{13}C NMR spectrum showed a new peak at δ 71.18 ppm which further supported the structure of **176.**

Scheme 54



The next critical transformation was deoxygenation of **176** which would result in the formation of methyl group at C-14 of key fragment. For this prupose, we applied Barton deoxygenation method, in which **176** was converted into a thiocarbonyl diimidazole derivative in dry toluene which was converted into **177** via radical scissoring method using Bu_3SnH and AIBN; unfortunately the yield of **177** was very low.

Scheme 55



176 **179** **180** **181** **182**

To overcome this problem, we redesigned our strategy, in which the primary hydroxyl group of **176** was selectively protected as its Tosyl ester **179** by using p-TsCl and Et_3N in CH_2Cl_2 at room temperature which was confirmed by ^1H NMR. A signal at δ 2.37 ppm due to $-CH_3$ group and two A_2B_2 doublets at δ 7.22 and 7.79 ppm confirmed the presence of *P*-toluene sulphonyl group. The structure was further confirmed by the ^{13}C NMR spectrum. The tosylate **179** was refluxed with NaI in glyme for 2h to afford iodo derivative **180** which was confirmed with the help of ^1H and ^{13}C NMR spectra. For instance, the ^1H NMR spectrum showed the presence of new peak in the up field region of spectrum at δ 1.70-1.95 ppm for methylene group and rest of the protons appeared at their expected chemical shifts. The ^{13}C NMR spectrum showed new peak at δ 14.48 ppm due to methylene carbon which confirmed the structure of **180**. The iodo product **180** was hydrogenated by exposed to 10% Pd/C and Boc anhydride in MeOH to afford NH-Boc protected compound **181** with low yield (Scheme 55). The ^1H NMR spectrum of **181** showed doublet at δ 0.98 ppm integrating for three protons, which was assigned to the newly created methyl group, a sharp singlet at δ 1.53 ppm integrating for nine protons for Boc group, a broad singlet appeared at 6.80 ppm due to N-H proton resonance integrating

for one proton and rest of the protons were complete agreement with excepted chemical shift values. In the ^{13}**C NMR** spectrum the appearance of methyl group resonance at δ 15.96 ppm, tert-methyl carbon of Boc group at δ 28.37 ppm further confimed the structure of **181**. In addition, the mass spectral analysis showed an *m/z* 688.54 $[M+Na]^+$ for molecular ion which supported the structure of **181**.[9]

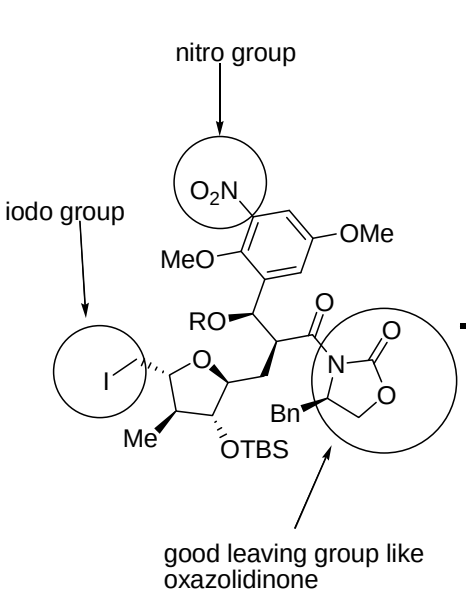


Figure 5: Iodoaldol adduct

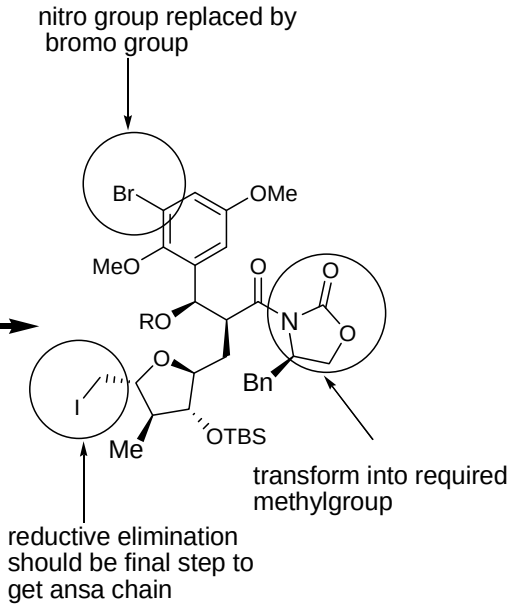


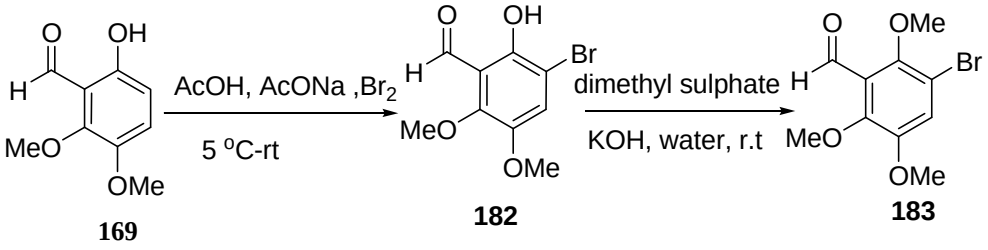
Figure 5: Revised Iodoaldol adduct

From our experience the previous section, we decided to replace the NO_2 group with a bromo group and remove the oxazolidinone moiety from the Evan's anti-aldol product and convert it the desired C-14 methyl group prior to attempting the Vassela-Bernet reaction.

Synthesis of Aryl Bromo Aldehyde 183:

According to redesigned strategy we prepared 3-bromo-2,5-dimethoxy benzaldehyde by reported method.[10] .

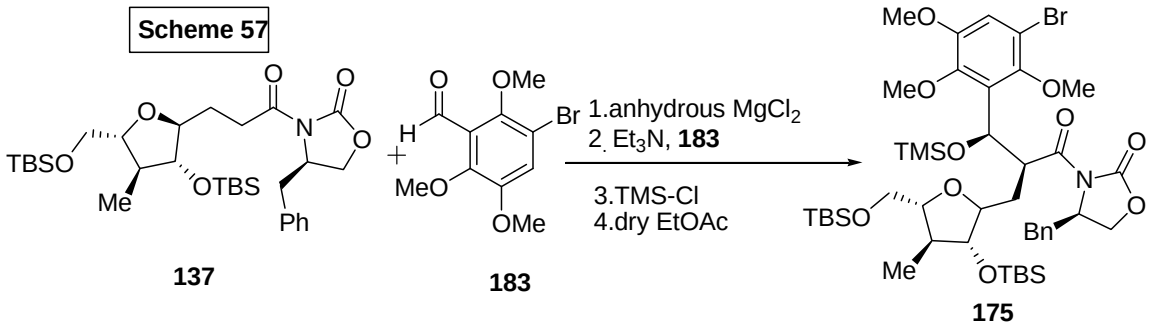
Scheme 56



169 **182** **183**

3-Bromo-2,5-dimethoxybenzaldehyde from **182** was prepared from aldehydes (25) by using bromine in AcOH, AcONa. Methylation using dimethyl sulphate and KOH as a base afforded required product **183** in quantitative yield (Scheme 56). The structure of 3-bromo-2,5-dimethoxybenzaldehyde was confirmed by comparing its spectral and other analytical data with reported data.

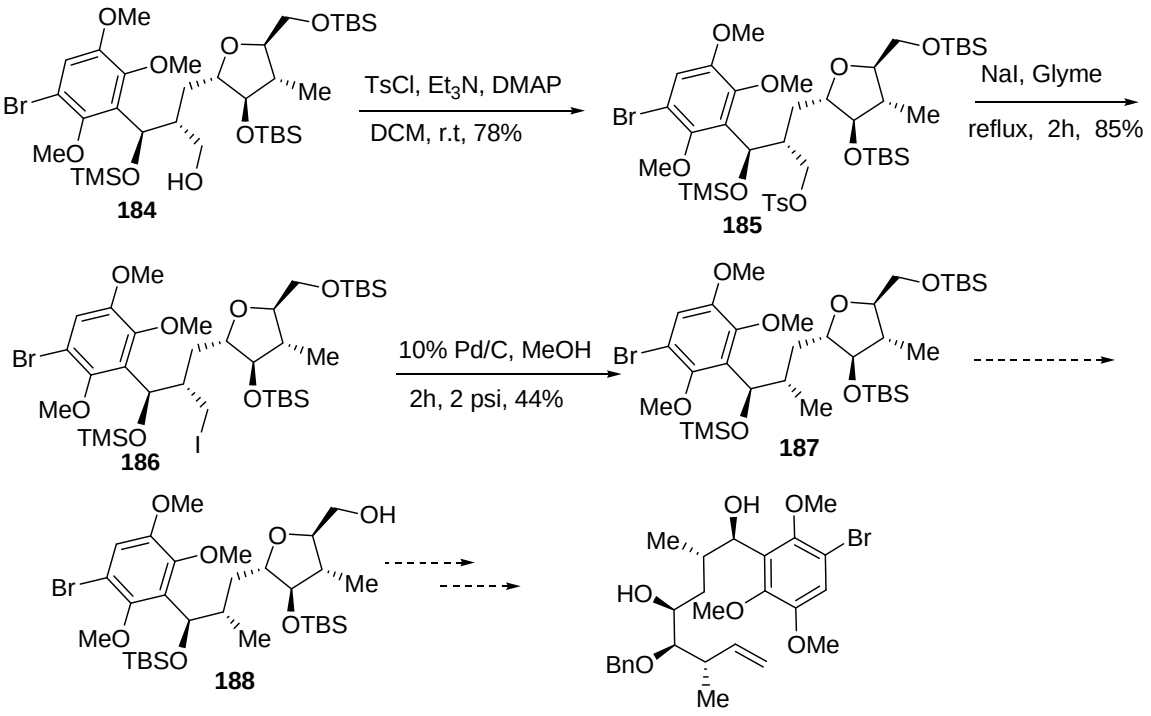
Scheme 57



137 **183** **175**

Under Evans anti aldol conditions oxazolidinone 137 was coupled with aldehydes 183 to afford the Evan's *anti* aldol adduct OTMS ether derivative **175** (Scheme 24). The ^{1}H NMR spectrum of OTMS aldol adduct **175,** showed characteristic trimethyl silane peak at δ 0.01 ppm integrating for nine protons, the characteristic benzylic proton resonating at δ 5.52 ppm and rest of the spectrum was in complete agreement with the excepted values. The characteristic trimethyl silane carbon resonance at δ -0.19 ppm, the characteristic benzylic carbon resonance at δ 84.70 ppm in the ^{13}C NMR spectra. The structure was further supported by the mass spectrum with the highest molecular ion peak at *m/z* 961.18 $[M+Na]^{+}$. The elemental analysis data further confirmed the structure **175.**

Scheme 58



Our next obtective was the reductive removal of oxazolidinone moiety of 175 which was successfully achieved by using 2M lithiumborohydride in THF to provide us primary alcohol **184.** The diol **184** was confirmed by ^{1}H NMR and other analytical data. In the ^{1}H NMR spectrum, the methylene group was deshielded and appeared as a multiplet at δ 3.64 ppm integrating for two protons. All other peaks were in complete agreement with the assigned structure (Scheme 58). The primary hydroxyl of **184** was selectively protected as Tosyl ester by using *p*-TsCl, Et_3N in CH_2Cl_2 at room temperature to furnish tosylate derivative **185** which was confirmed from ^{1}H and ^{13}C NMR spectra. The tosylate **185** was refluxed with NaI in glyme for 2h to afford iododerivative **186** whose structure was confirmed from ^{1}H and ^{13}C NMR spectra. For instance, in the ^{1}H NMR spectrum showed that the methylene protons were shielded and appeared in the up field region of the spectrum at δ 2.40 ppm integrating for two protons. All other protons signals appeared at their respective chemical shift values. The structure was further confirmed from ^{13}C NMR spectral study.

The iododerivative **186** was exposed to 10% Pd/c-H_2 in methanol to give exclusively the methyl derivative **187**. The spectroscopic and other analytical data were

in good agreement with the assigned structure **187**, for instance the ^{1}H NMR spectrum of **187** showed the methyl group was shielded and appeared in the up field region of the spectrum as doublet at δ 0.71 ppm integrating for three protons and rest of the protons appeared at excepted chemical shift values. In the ^{13}C NMR spectrum, the methyl carbon resonated at δ 15.63 ppm which confimed its structure (Scheme 58). Further work is in progress in our lab, to construct the crucial fragment of 15-hydroxygeldanamycin.

In conclusion, the critical part of the synthesis towards the key fragment of 15-hydroxy geldanmycin was completed by using Evans anti aldol reaction for construction of critical stereocenters C14-Methyl and C15-Hydroxy groups and rare restricted conformational isomerism was observed in the Evans anti aldol adduct.

EXPERIMENTAL

Experimental section: Analytical data of 15-Hydroxy Geldanamycin

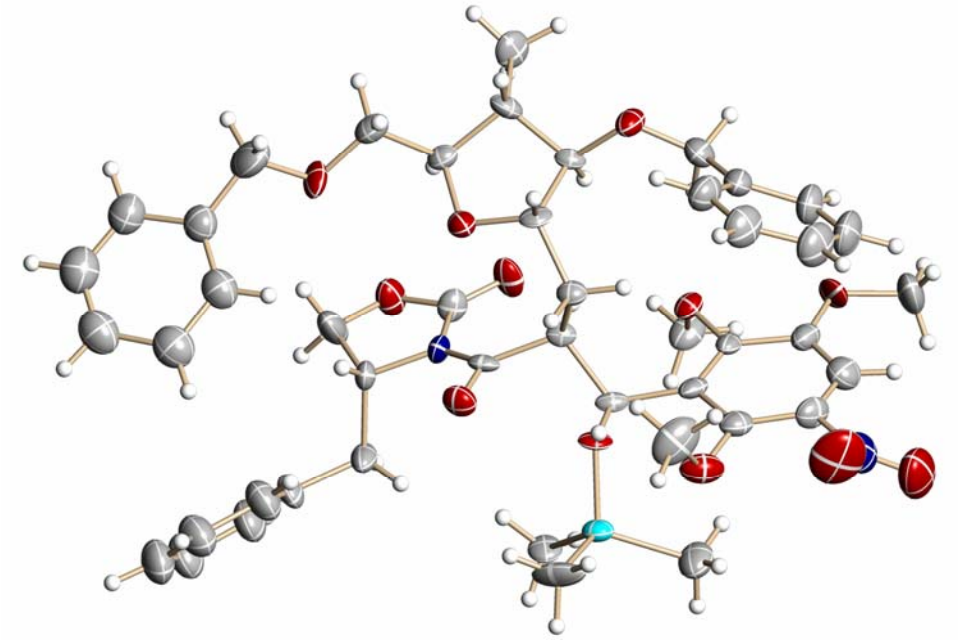
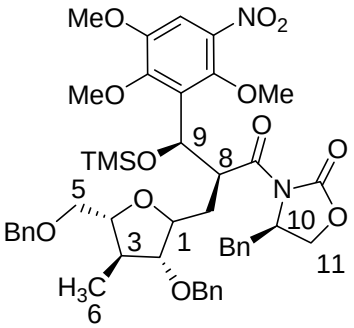


Table 1. Crystal data and structure for **123a**

Identification code	DiBn-Evan's anti OTMS- **123a**
Empirical formula	$C_{46}\ H_{56}\ N_2\ O_{12}\ Si$
Formula weight	857.02
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 9.171(3) A alpha = 90 deg. b = 17.037(6) A beta = 90 deg. c = 29.504(12) A gamma = 90 deg.
Volume	4610(3) A^3
Z, Calculated density	4, 1.235 Mg/m^3
Absorption coefficient	0.113 mm^-1
F(000)	1824

Crystal size	0.55 x 0.05 x 0.03 mm
Theta range for data collection	2.39 to 23.00 deg.
Limiting indices	-10<=h<=10, -18<=k<=14, -28<=l<=32
Reflections collected / unique	22886 / 6413 [R(int) = 0.1387]
Completeness to theta	= 23.00 99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9972 and 0.9404
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6413 / 304 / 557
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R1 = 0.1083, wR2 = 0.2061
R indices (all data)	R1 = 0.1823, wR2 = 0.2350
Absolute structure parameter	-0.5(5)
Largest diff. peak and hole	0.388 and -0.277 e.A^-3

(R)-4-benzyl-3-((2S,3R)-2-(((2S,3R,4S,5R)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,3,6-trimethoxy-5-nitrophenyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (123a).



123a

Oxazolidinone **101** (285 mg, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **124** (151 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^{o}C for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get

residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **123a** (262 mg), and free hydroxyl compound **123b** (61 mg), as a single isomers with excellent yeild (light yellowcolor liquid). OTMS : OH in 5:1 ratio, R_f 0.2: 0.5(10 % ethyl acetate/hexane).

Mol. Formula : $C_{46}H_{56}N_2O_{12}Si$

$[\alpha]_D^{25}$: +3.49 (*c* = 1.5, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 756, 1079, 1216, 1250, 1604, 1693, 1779, 2400, 3019 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.01 (s, 9H), 1.13 (dd, *J* = 6.7, 3H), 1.32-1.47 (m, 1H), 1.93 (hex, *J* = 6.7, 1H), 2.25-2.38 (m, 1H), 2.64 (t, *J* = 10.9, 1H), 3.44-3.51 (m, 2H), 3.58-3.65 (m, 1H), 3.65-3.67 (m, 1H), 3.84-3.86 (m, 2H), 3.88 (s, 3H), 3.95 (dd, *J* = 6.7, 10.7, 1H), 4.00 (s, 3H), 4.02 (s, 3H), 4.07-4.09 (m, 2H), 4.32 (dd, *J* = 10.7, 17.3, 1H), 4.42 (d, *J* = 10.7, 1H), 4.52 (q, *J* = 10.7, 17.3, 2H), 4.61-4.67 (m, 1H), 5.65 (ddd, *J* = 10.2, 22.7, 48.0, 1H), 7.06-7.40 (m, 16H) [2] ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -0.21 (q, TMS-**CH_3**), -0.16 (q, TMS-**CH_3**), 15.58 (q, CH-**CH_3** (**6**)), 15.74 (q, CH-**CH_3** (**6**)), 31.89 (t, CH-**CH_2**-CH), 31.99 (t, -CH-**CH_2**-CH (**7**)), 38.63 (t, Ph-**CH_2**), 41.72 (d, **CH**-CH_3(**3**)), 41.80 (d, O=C-**CH**-CH_2 (**8**)), 55.72 (d, OxazolidinoneCH_2-**CH (10)**), 56.00 (q, -O**CH_3**), 56.12 (q, -O**CH_3**), 61.38 (q, -O**CH_3**), 61.72 (q, -O**CH_3**), 63.58 (q, -O**CH_3**), 64.31 (d, -O**CH_3**), 65.41 (t, HCO-**CH_2**OBn (**5**)), 70.14 (d, -CH-**CH**O-CH_2OBn-(**4**)), 70.21 (d, -CH-**CH**O-CH_2OBn-(**4**)), 72.61 (t, Ph**CH_2-O**), 73.31 (t, Ph**CH_2-O**), 79.34 (d, aryl-**CH**-OTMS (**9**)), 79.54 (d, aryl-**CH**-OTMS (**9**)), 83.49 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 86.79 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 86.95 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.28 (d, Aryl**CH**), 108.63 (d, Aryl-**CH**), 127.00 (d, CH), 127.29 (d, CH), 127.53 (d, CH), 128.13 (d, CH), 128.82 (d, CH), 129.38 (d, CH), 131.28 (s, C), 136.13 (s, C), 138.06 (s, C), 138.47 (s, C), 138.53 (s, C), 146.81 (s, C), 148.09 (s, C), 148.63 (s, C), 149.45 (s, C), 151.85 (s, C), 153.48 (s, C), 153.84 (s, C), 176.81 (s, C)[1,2] ppm.

Hint : 1) In the ^{13}CNMR spectrum shows peak splitting indicates that "q" represents CH_3, " t" represents CH_2, "d" represents CH and "s" represents quatarnary carbon to make differeniate carbons which will appear in the DEPT Experiments.

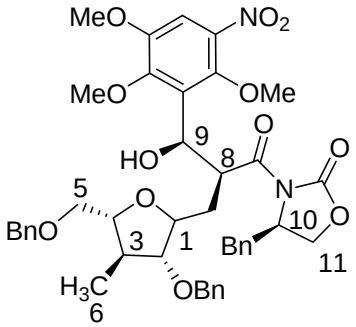
2). In the **^{1}H** and **^{13}CNMR** spectrum shows corresponding peaks in double splitting patteren indicates the presence of restricted conformational isomers.

ESI-MS (*m/z*) : 879.78 $[M+Na]^+$.

Elemental Analysis Calcd : C, 64.47; H, 6.59; N, 3.27 %

Found: C, 64.48; H, 6.60; N, 3.29 %

(R)-4-benzyl-3-((2S,3R)-2-(((2S,3R,4S,5R)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-hydroxy-3-(2,3,6-trimethoxy-5-nitrophenyl)propanoyl)oxazolidin-2-one (123b).



123b

Mol. Formula : $C_{43}H_{48}N_2O_{12}$

$[\alpha]_D^{25}$: -25.76 (*c* = 2.2, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1053, 1216, 1536, 1620, 1696, 1776, 3018, 3452 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.96 (d, *J* = 6.75, 3H), 1.21-1.34 (m, 2H), 1.90 (q, *J* = 6.7, 1H), 2.33 (ddd, *J* = 4.4, 9.7, 13.5, 1H), 2.76 (dd, *J* = 9.5, 13.5, 1H), 3.23 (t, *J* = 3.24, 1H), 3.33 (dd, *J* = 3.2, 8.5, 1H), 3.38-3.39 (m, 3H), 3.71 (s, 3H), 3.78 (d, *J* = 5.7, 1H), 3.82 (dd, *J* = 3.01, 5.7, 1H), 3.87 (s, 3H), 4.03 (s, 3H), 4.10 (d, *J* = 6.7, 1H), 4.30 (q, *J* = 11.1, 19.5, 2H), 4.38 (q, *J* = 11.1, 19.5, 2H), 4.47-4.55 (m, 1H), 4.78 (dt, *J* = 2.1, 11.07, 1H) 5.26 (t, *J* = 11.01, 1H), 7.04-7.31 (m, 15H), 7.33 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 15.84 (q, TMS-**CH_3**), 32.78 (t, CH-**CH_2**-CH (**7**)), 37.82 (t, -CH-**CH_2**Ph), 42.00 (d, **CH**-CH_3 (**3**)), 44.44 (d, O=C-**CH**-CH_2

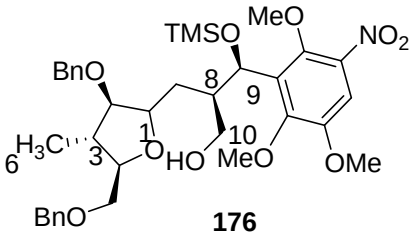
(**8**)), 56.15 (d, OxazolidinoneCH$_2$-**CH-(10)**), 56.36 (q, -O**CH$_3$**), 61.60 (q, -O**CH$_3$**), 63.31 (q, -O**CH$_3$**), 66.04 (t, HCO-**CH$_2$**OBn (**5**)), 71.03 (d, aryl-**CH**-OH (**9**)), 72.18 (t, Ph**CH$_2$-O**), 72.62 (t, Ph**CH$_2$-O**), 73.44 (t, Oxazolidinone**CH$_2$**-CH (**11**)), 79.70 (d, CHCH$_3$-**CH**O-CH$_2$OBn (**4**)), 83.32 (d, -$_2$HC-**HC**O-CH$_2$OBn (**1**)), 88.62 (d, CHO-**CH**OBn-CHCH$_3$(**2**)), 109.10 (d, Aryl**CH**), 127.09 (d, CH), 127.22 (d, CH), 127.61 (d, CH), 127.69 (d, CH), 128.27 (d, CH), 128.35 (d, CH), 128.79 (d, CH), 128.91 (d, CH), 129.58 (d, CH), 129.92 (s, C), 135.64 (s, C), 137.84 (s, C), 137.99 (s, C), 148.08 (s, C), 152.48 (s, C), 154.57 (s, C), 175.63 (s, C) ppm.

ESI-MS (*m/z*) : 807.89 $[M+Na]^+$.

Elemental Analysis Calcd : C, 65.80; H, 6.16; N, 3.57%

Found: C, 65.81; H, 6.18; N, 3.58%

(1R,2R)-2-(((2S,3R,4S,5R)-3-(benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)methyl)-1-(2,3,6-trimethoxy-5-nitrophenyl)propane-1,3-diol (176).



176

The aldol adduct **125** (1.8 g, 2.1mmol), 10 mL of drydiethylether and anhydrous methanol (0.04 mL) were added cooled to 0 ^oC. Lithium borohydrate (2.0M in THF , 0.51 mL, mmol) was added dropwise, and the mixture was stirred for 2h at 0 ^oC . The reaction was quenched with 15% NaOH and then concentrated in vacuo. The aqueous layer was extracted with ether , and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave **176** (0.92 g, 64%) of alcohol. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{36}H_{49}NO_{10}Si$

$[\alpha]_D^{25}$: +3.38 (*c* = 1.2, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1051, 1216, 1619, 1752,2402, 3019,3434 cm^{-1}

^{1}H NMR : δ 0.04 (s, 9H), 1.06 (d, *J* = 6.7, 3H), 1.26-1.33 (m, 2H), 1.55

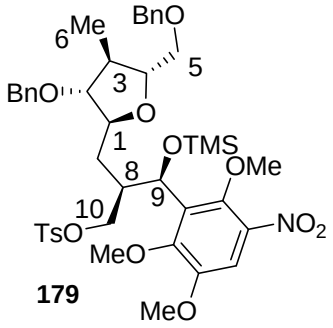
(500 MHz, $CDCl_3$) (brs, 1H), 2.12 (hex, *J* = 6.7, 1H), 2.76-2.78 (m, 1H), 3.29-3.35 (m, 1H), 3.51-3.56 (m, 3H), 3.73 (s, 3H), 3.84 (s, 3H), 3.85-3.89 (m, 2H), 3.92 (s, 3H), 4.19-4.22 (m, 1H), 4.32-4.44 (m, 2H), 4.52-4.55 (m, 2H), 5.17-5.32 (m, 1H), 7.14 (s, 1H), 7.25-7.34 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 0.09 (q, TMS-**CH_3**), 16.39 (q, CH-**CH_3** (**6**)), 32.05 (t, CH-**CH_2**-CH (**7**)), 41.59 (d, **CH**-CH_3 (**3**)), 41.94 (d, O=C-**CH**-CH_2(**8**)), 55.98 (q, -O**CH_3**), 61.30 (q, -O**CH_3**), 63.58 (t, -**CH_2**-CH **(10)**), 71.18 (t, HCO-**CH_2**OBn (**5**)), 72.19 (t, Ph**CH_2-O**), 73.31 (t, Ph**CH_2-O**), 79.68 (d, $CHCH_3$-**CH**O-CH_2OBn- (**4**)), 82.86 (d, $_2$HC-**HC**O-CH_2OBn (**1**)), 89.27 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.27 (d, Aryl**CH**), 127.26 (d, CH), 127.58 (d, CH), 128.31 (d, CH), 138.18 (s, C) ppm.

ESI-MS (*m/z*) : 706.08 $[M+Na]^+$.

Elemental Analysis Calcd : C, 63.23; H, 7.22; N, 2.05 %
Found: C, 63.25; H, 7.23; N, 2.03 %

(2R,3R)-2-(((2S,3R,4S,5R)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,3,6-trimethoxy-5-nitrophenyl)-3-(trimethylsilyloxy)propyl 4-methylbenzenesulfonate (179).

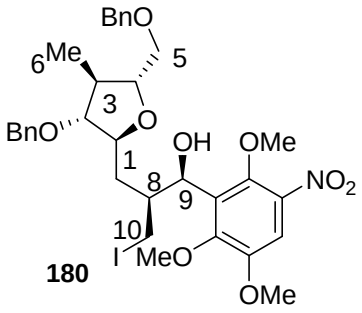


179

To a stirred solution of **176** (0.8 g,1.3 mmol), Et_3 N (0.22 mL, 1.57 mmol), and DMAP (20 mg), in dichloromethane (20 mL) was added p-toluenesulfonyl chloride (0.23 g, 1.57 mmol), at 0^{o}C. The reaction mixture was stirred for 6h at room temperature, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (2:1) to afford **179** (0.728 g, 79 %)as a syrup liquid. R_f 0.8(75 % ethyl acetate/hexane).

Mol. Formula	: $C_{43}H_{55}NO_{12}SSi$
$[\alpha]_D^{25}$	: +13.38 (*c* = 1.2, $CHCl_3$)
IR ($CHCl_3$) υ	: 666, 754, 1071, 1268, 1598, 1785, 2927, 3525 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 0.06 (s, 9H), 0.94 (m, 3H), 1.26-1.28 (m, 1H), 1.46-1.52 (m, 1H), 1.99 (hex, *J* = 6.7, 1H), 2.37 (s, 3H), 2.43-2.46 (m, 1H), 2.94 (t, *J* = 10.5, 1H), 3.18 (brs, 1H), 3.41-3.49 (m, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.22-4.28 (m, 1H), 4.37-4.38 (m, 2H), 4.49-4.60 (m, 3H), 5.14 (dd, *J* = 10.5, 38.2, 1H), 7.22-7.41 (m, 13H), 7.79 (d, *J* = 8.01, 2H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 1.91 (q, TMS-**CH_3**), 16.25 (q, CH-**CH_3** (**6**)), 21.58 (q, Ts-**CH_3**), 31.17 (t, CH-**CH_2**-CH (**7**)), 41.35 (d, **CH**-CH_3 (**3**)), 42.63 (d, O=C-**CH**-CH_2(**8**)), 56.22 (q, -O**CH_3**), 61.50 (q, -O**CH_3**), 63.21 (q, -O**CH_3**), 67.68 (d, $CHCH_3$-**CH**O-CH_2OBn- (**4**)), 68.63 (t, OTs-CH_2-**CH (10)**), 71.61 (t, HCO-**CH_2**OBn (**5**)), 71.88 (t, Ph**CH_2-O**), 73.26 (t, Ph**CH_2-O**), 79.57 (d, aryl-**CH**-OTMS (**9**)), 82.52 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 90.34 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.77 (d, Aryl**CH**), 127.56 (d, CH), 127.64 (d, CH), 127.93 (d, CH), 128.30 (d, CH), 128.37 (d, CH), 129.81 (d, CH), 130.47 (s, C), 132.98 (s, C), 138.04 (s, C), 138.18 (s, C), 144.66 (s, C), 146.89 (s, C), 148.19 (s, C), 152.24 (s, C) ppm.
ESI-MS (*m/z*)	: 861.05 $[M+Na]^+$.
Elemental Analysis	Calcd : C, 61.63; H, 6.61; N, 1.67 % Found: C, 61.65; H, 6.62; N, 1.66 %

(1R,2S)-3-((3R,4S,5R)-3-(benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)-2-(iodomethyl)-1-(2,3,6-trimethoxy-5-nitrophenyl)propan-1-ol (180)



180

A mixture of **179** (0.55 g, 0.72 mmol) and NaI (1.29 g, 8.62 mmol), was taken in a glyme. Reflux the reaction mixture for 2h, after complition of reaction mixture remove glyme under reduced pressure to get residue which was purified on silica gel by eluting with EtOAC-hexane (1:3) to give iododerivative **180** (0.412 g, 87 %), as a colorless liquid. R_f 0.4(25 % ethyl acetate/hexane).

Mol. Formula : $C_{33}H_{40}INO_9$

$[\alpha]_D^{25}$: -63.51 (*c* = 1.0, $CHCl_3$)

IR ($CHCl_3$) υ : 667,755, 1071, 1215, 1577, 2400, 3018, 3545 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.88 (d, *J* = 6.7, 3H), 1.18 (brs, 1H), 1.50 (ddd, *J* = 2.3, 10.5, 13.5, 2H), 1.70 (ddd, *J* = 2.3, 10.5 13.7, 1H), 1.95 (hex, *J* = 6.7, 1H), 3.13 (d, *J* = 11.4, 1H), 3.18 (dd, *J* = 5.01, 11.05, 1H), 3.30 (dq, *J* = 3.7, 6.2, 10.01, 1H), 3.35-3.42 (m, 2H), 3.55 (dd, *J* = 3.01, 10.5, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 3.93 (dd, *J* = 3.01, 10.5, 1H), 4.41 (q, *J* = 11.2, 2H), 4.42 (s, 2H), 4.78 (t, *J* = 10.5, 1H), 7.19-7.29 (m, 10H), 7.38 (s, 1H) ppm.

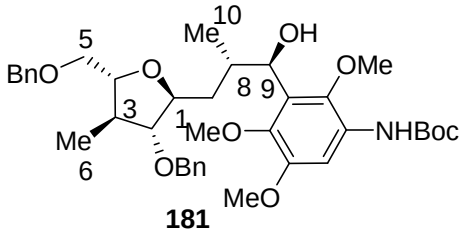
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.48 (t, I-**CH_2**-CH **(10)**), 15.98 (q, CH-**CH_3** (**6**)), 35.14 (t, CH-**CH_2**-CH (**7**)), 40.71 (d, **CH**-CH_3 (**3**)), 42.72 (d, O=C-**CH**-CH_2(**8**)), 56.26 (q, -O**CH_3**), 61.48 (q, -O**CH_3**), 63.28 (q, -O**CH_3**), 70.80 (d, $CHCH_3$-**CH**O-CH_2OBn- (**4**)), 71.60 (t, HCO-**CH_2**OBn (**5**)), 72.07 (t, Ph**CH_2-O**), 73.31 (t, Ph**CH_2-O**), 79.43 (d, aryl-**CH**-OTMS (**9**)), 82.54 (d, $_2$HC-**HC**O-CH_2OBn (**1**)), 90.16 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.78 (d, Aryl**CH**), 127.57 (d, CH), 127.71 (d, CH), 128.33 (d, CH), 130.69 (s, C), 138.19 (s, C), 146.96 (s, C), 148.22 (s, C), 152.31 (s, C) ppm.

ESI-MS (*m/z*) : 745.59 $[M+Na]^+$.

Elemental Analysis Calcd : C, 54.93; H, 5.59; N, 1.94%

Found: C, 54.94; H, 5.61; N, 1.95 %

tert-butyl 3-((1R,2S)-3-((2S,3R,4S,5R)-3-(benzyloxy)-5-(benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)-1-hydroxy-2-methylpropyl)-2,4,5-trimethoxyphenylcarbamate (181).



181

The iodocompound **180** (0.35 g, 0.485mmol) was taken in dry methnol in 50 mL RBF, to this 10% Pd/c (catalytic) and BOCanhydride (0.25 mL) was added and maintained at 2psi of hydrogen (balloon) for 6h. After completion of reaction mixture was filtered through celite, concentrate to get residue which on purification over silica gel column chromatography using EtOAc-hexane (1:6) to afford **181** (0.138 g, 43%) as a syrup liquid. R_f 0.6(20% ethyl acetate/hexane).

Mol. Formula : $C_{38}H_{51}NO_9$

$[\alpha]_D^{25}$: +41.32 (*c* = 0.6, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1067, 1216, 1599, 1693, 2401, 3017, 3434 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.98 (d, *J* = 6.7, 3H), 1.16 (d, *J* = 6.7, 3H), 1.22-1.28 (m, 2H), 1.53 (s, 9H), 2.04 (hex, *J* = 6.7, 1H), 2.11-2.19 (m, 1H), 3.10 (brs, 1H), 3.26 (t, *J* = 5.05, 1H), 3.41-3.51 (m, 3H), 3.69 (s, 3H), 3.77-3.81 (m, 1H), 3.84 (s, 6H), 4.01 (dt, *J* = 4.01, 10.08, 1H), 4.48 (s, 2H) 4.51 (s, 2H), 6.80 (s, 1H), 7.27-7.34 (m, 10H), 7.69 (s, 1H) ppm.

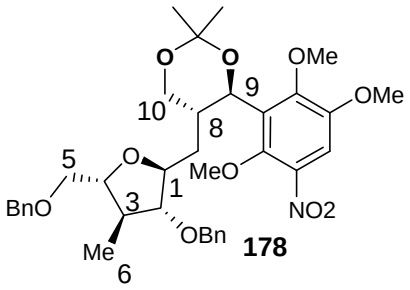
^{13}C NMR (125 MHz, $CDCl_3$) : δ 15.96 (q, CH-**CH_3** (**6**)), 16.41 (q, **CH_3**-CH **(10)**), 28.37 (q, Boc-**CH_3**), 37.55 (d, **CH**-CH_3 (**3**)), 42.63 (d, O=C-**CH**-CH_2(**8**)), 55.99 (q, -O**CH_3**), 61.08 (q, -O**CH_3**), 61.64 (q, -O**CH_3**), 71.65 (t, HCO-**CH_2**OBn (**5**)), 72.10 (t, Ph**CH_2-O**), 73.24 (t, Ph**CH_2-O**), 74.32 (d, aryl-**CH**-OTMS (**9**)), 80.28 (d, $CHCH_3$-**CH**O-CH_2OBn-(**4**)), 82.38 (d, $_2$HC-**HC**O-CH_2OBn (**1**)), 91.23 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 103.02 (d, Aryl**CH**), 127.57 (d, CH), 128.37 (d, CH), 129.10 (d, CH), 138.43 (s, C), 139.45 (s, C), 142.05 (s, C), 149.16 (s, C), 152.86 (s, C) ppm.

ESI-MS (*m/z*) : 688.74 $[M+Na]^+$.

Elemental Analysis Calcd : C, 68.55; H, 7.72; N, 2.10 %

Found: C, 68.56; H, 7.74; N, 2.11 %

(4*R*, 5*R*)-5-(((3*R*, 4*S*, 5*R*)-3-(Benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-4-methylfuran-2-yl)methyl)-4-(2,3,6-trimethoxy-5-nitrophenyl)-2,2-dimethyl-1,3-dioxane (178).



178

To the diol compound **176** (0.1 g, 0.163 mmol) in a dimethoxypropane added p-toluenesulphonicacid (catalytic) and maintained stirring at room temperature. After completion of reaction, neutralize the reaction mixture with triethylamine and remove DMP under reduce pressure to give residue which was purified by passing through silica gel column chromatography using EtOAc-hexane (1:8) to afford acetonide **178** (0.078 g, 82 %)as a syrup liquid. R_f 0.6(15% ethyl acetate/hexane).

Mol. Formula : $C_{36}H_{45}N_2O_8$

$[\alpha]_D^{25}$: +41.32 (*c* = 1.6, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 757, 1067, 1217, 1578, 1736, 2926 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.98 (d, *J* = 6.7, 3H), 1.19 (brs, 1H), 1.21-1.29 (m, 2H),1.38 (s, 3H), 1.51 (s, 3H), 2.02 (hex, *J* = 6.7, 1H), 2.89-2.99 (m, 1H), 3.21 (t, *J* = 6.7, 1H), 3.40 (d, *J* = 4.80, 2H), 3.54 (m, 1H), 3.70 (s, 3H), 3.82 (s, 3H), 3.83 (m, 1H), 3.88 (s, 3H), 4.03 (dd, *J* = 4.78, 11.5, 1H), 4.20 (m, 1H) 4.33 (d, *J* = 11.6, 1H), 4.48 (s, 2H), 5.05 (appd, 1H), 7.06 (d, *J* = 6.5, 2H), 7.16-7.27 (m, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 16.60 (q, **CH_3** (**6**)), 19.03 (q, **CH_3**), 29.74 (q, **CH_3**), 31.52 (t, CH-**CH_2**-CH (**7**)), 33.08 (d, O=C-**CH**-CH_2(**8**)), 42.19 (d, **CH**-CH_3 (**3**)), 56.05 (q, -O**CH_3**), 61.52 (q, -O**CH_3**), 63.50 (d, aryl-**CH**-OTMS (**9**)), 65.66 (t, -**CH_2**-CH **(10)**), 69.82 (q, -O**CH_3**), 71.39 (t, HCO-**CH_2**OBn (**5**)), 72.41 (t, Ph**CH_2-O**), 73.28 (t, Ph**CH_2-O**), 79.46 (d, $CHCH_3$-**CH**O-CH_2OBn- (**4**)), 82.76 (d, $_2$HC-**HC**O-CH_2OBn (**1**)), 89.59 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)),

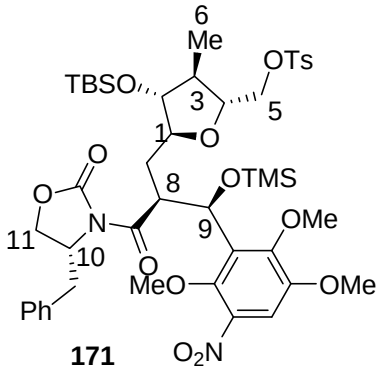
99.02 (s, Acetonide C), 108.67 (d, Aryl**CH**), 127.57 (d, CH), 129.78 (s, C), 138.42 (s, C) ppm.

ESI-MS (*m/z*) : 674.54 $[M+Na]^+$.

Elemental Analysis Calcd : C, 66.34; H, 6.96; N, 2.15%

Found: C, 66.36; H, 6.97; N, 2.17 %

((2R,3S,4R,5S)-5-((S)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-oxo-2-((R)-(2,3,6-trimethoxy-5-nitrophenyl)(trimethylsilyloxy)methyl)propyl)-4-(tert-butyldimethylsilyloxy)-3-methyltetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (171).



171

Oxazolidinone **131** (331 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **124** (151 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **171** (442 mg, 89 %)as a single isomers with excellent yeild (light yellowcolor liquid). R_f 0.2(10 % ethyl acetate/hexane).

Mol. Formula : $C_{45}H_{64}N_2O_{14}SSi_2$

$[\alpha]_D^{25}$: -8.19 (*c* = 1.4, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 756, 1079, 1215,1599, 1694, 1776,2400, 3020 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.39- -0.34 (s, 3H), 0.01-0.06 (s, 12H), 0.72 (s, 9H), 1.00 (dd, *J* = 6.7, 3H), 1.21-1.29 (m, 2H), 2.13-2.29 (m, 1H), 2.45 (s, 3H), 2.67 (dq, *J* = 5.6, 10.9, 1H), 3.53-3.64 (m, 4H), 3.91-4.08 (m, 4H), 3.91 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 4.25 (t, *J* = 8.1, 1H), 4.76-4.79 (m, 1H), 5.54 (ddd, *J* = 9.9, 20.3, 34.9, 1H), 7.30-7.34 (m, 5H), 7.37-7.41 (m, 2H), 7.49 (s, 1H), 7.75 (d, *J* = 7.78, 2H)

ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.01 (q, TBS-**CH_3**),-4.97 (q, TBS-**CH_3**),-4.61 (q, TBS-**CH_3**),-4.56 (q, TBS-**CH_3**),-0.20 (q, TBS-**CH_3**),-0.16 (q, TMS-**CH_3**), 14.63 (q, CH-**CH_3** (**6**)), 14.70 (q, CH-**CH_3** (**6**)), 17.69 (s, C), 21.59 (q, TBS-**CH_3**), 25.49 (q, TBS-**CH_3**), 25.56 (q, TBS-**CH_3**), 31.17 (t, CH-**CH_2**-CH (**7**)), 31.21 (t, CH-**CH_2**-CH (**7**)), 38.81 (t, -CH-**CH_2**Ph), 38.86 (t, -CH-**CH_2**Ph), 41.47 (d, **CH**-CH_3 (**3**)), 43.09 (d, **CH**-CH_3 (**3**)), 48.84 (d, O=C-**CH**-CH_2(**8**)), 49.00 (d, O=C-**CH**-CH_2(**8**)), 55.66 (d, OxazolidinoneCH_2-**CH (10)**), 55.90 (q, O**CH_3**), 56.30 (q, O**CH_3**), 61.36 (q, O**CH_3**), 61.52 (q, O**CH_3**), 63.46 (q, O**CH_3**), 64.46 (q, O**CH_3**), 65.67 (t, HCO-**CH_2**OBn (**5**)), 70.40 (d, aryl-**CH**-OTMS (**9**)), 70.48 (t, Oxazolidinone**CH_2**-CH (**11**)), 77.20 (d, -CH-**CH**O-CH_2OBn-(**4**)), 80.01 (d, -CH-**CH**O-CH_2OBn-(**4**)), 80.07 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 80.13 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 80.83 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 80.99 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.77 (d, Aryl**CH**), 112.85 (d, Aryl**CH**), 127.13 (d, CH), 127.91 (d, CH), 128.89 (d, CH), 129.36 (d, CH), 129.82 (d, CH), 131.20 (s, C), 131.42 (s, C), 132.66 (s, C), 136.04 (s, C), 138.15 (s, C), 139.60 (s, C), 144.81 (s, C), 147.01 (s, C), 148.03 (s, C), 149.27 (s, C), 149.56 (s, C), 152.04 (s, C), 153.43 (s, C), 154.31 (s, C), 176.27 (s, C) ppm.

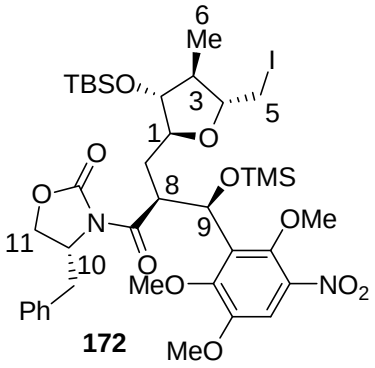
Hint: In the **^{1}H** and **^{13}CNMR** spectrum shows corresponding peaks in double splitting patteren indicates the presence of restricted conformational isomers.

ESI-MS (*m/z*) : 968.63$[M+Na]^+$.

Elemental Analysis Calcd: C, 57.18; H, 6.82; N, 2.96 %

Found: C, 57.19; H, 6.84; N, 2.97 %

(R)-4-benzyl-3-((2S,3R)-2-(((2S,3R,4S,5R)-3-(tert-butyldimethylsilyloxy)-5-(iodomethyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,3,6-trimethoxy-5-nitrophenyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (172).



172

Oxazolidinone **132** (308 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **124** (151 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^{o}C for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **172** (421 mg, 90 %)as a single isomers with excellent yeild (light yellowcolor liquid). R_f 0.2(10 % ethyl acetate/hexane).

Mol. Formula : $C_{38}H_{57}IN_2O_{11}Si_2$

$[\alpha]_D^{25}$: -9.14 (*c* = 0.2, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 758, 1053, 1252, 1698, 1776, 3088 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.29--003 (s, 3H), 0.01-0.06 (s, 12H), 0.78 (s, 9H), 1.11 (t, *J* = 6.7, 3H), 1.25-1.35 (m, 1H), 1.80 (hex, *J* = 6.7, 1H), 2.26 (dq, *J* = 4.3, 12.1, 16.2, 1H), 2.68 (dd, *J* = 10.5, 22.7, 1H), 3.18 (ddd, *J* = 1.6, 7.2, 9.4, 1H), 3.33 (dd, *J* = 3.8, 10.3, 1H), 3.44-3.51 (m, 1H), 3.60 (d, *J* = 12.3, 1H), 3.67-3.76 (m, 2H), 3.94-4.08 (m, 9H), 4.07-4.09 (m, 1H), 4.16 (dd, *J* = 2.7, 9.03, 1H), 4.35 (t, *J* = 8.3, 1H), 4.89 (q, *J* = 8.3, 1H), 5.55 (ddd, *J* = 9.8, 17.4, 27.9, 1H), 7.29-7.42 (m, 5H), 7.52 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -4.93 (q, TBS-**CH_3**), -4.90 (q, TBS-**CH_3**), -4.51 (q, TBS-**CH_3**), -4.42 ((q, TBS-**CH_3**), -3.63 (q, TBS-**CH_3**), -0.41 (q, TMS-**CH_3**), -0.15 (q, TMS-**CH_3**), 10.86 (t, HCO-**CH_2**OBn (**5**)), 10.90 (t, HCO-**CH_2**OBn (**5**)), 15.36 (q, CH-**CH_3** (**6**)), 15.44 (q, CH-**CH_3** (**6**)),

17.76 (s, C), 25.56 (q, TBS-**CH_3**), 25.62 (q, TBS-**CH_3**), 31.34 (t, CH-**CH_2**-CH (**7**)), 31.51 (t, CH-**CH_2**-CH (**7**)), 38.81 (t, -CH-**CH_2**Ph), 38.87 (t, -CH-**CH_2**Ph), 41.18 (d, **CH**-CH_3 (**3**)), 41.59 (d, **CH**-CH_3 (**3**)), 47.88 (d, O=C-**CH**-CH_2(**8**)), 47.93 (d, O=C-**CH**-CH_2(**8**)), 55.84 (q, -O**CH_3**), 55.94 (q, -O**CH_3**), 56.31 (d, OxazolidinoneCH_2-**CH (10)),** 61.39 (q, -O**CH_3**), 64.41 (d, -O**CH_3**), 61.48 (q, -O**CH_3**), 63.49 (d, -O**CH_3**), 65.73 (t, Oxazolidinone**CH_2**-CH (**11**)), 70.61 (d, aryl-**CH**-OTMS (**9**)), 70.71 (d, aryl-**CH**-OTMS (**9**)), 77.25 (d, -CH-**CH**O-CH_2OBn-(**4**)), 80.65 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 80.72 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 83.26 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.75 (d, Aryl**CH**), 108.83 (d, Aryl**CH**), 127.15 (d, CH), 128.85 (d, CH), 128.93 (d, CH), 129.41 (d, CH), 131.24 (s, C), 131.39 (s, C), 136.11 (s, C), 138.10 (s, C), 139.53 (s, C), 147.05 (s, C), 148.01 (s, C), 149.29 (s, C), 149.51 (s, C), 152.03 (s, C), 153.23 (s, C), 154.35 (s, C), 176.37 (s, C) ppm.

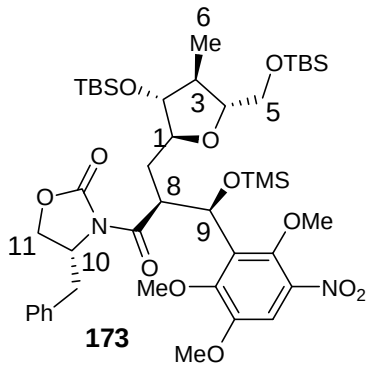
Hint: In the **^{1}H** and **^{13}CNMR** spectrum shows corresponding peaks in double splitting patteren indicates the presence of restricted conformational isomers.

ESI-MS (*m/z*) : 923.25$[M+Na]^+$.

Elemental Analysis Calcd : C, 50.66; H, 6.38; I, 14.09; N, 3.11 %

Found: C, 50.67; H, 6.39; I, 14.11; N, 3.13 %

(R)-4-benzyl-3-((2S,3R)-2-(((2S,3R,4S,5R)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(2,3,6-trimethoxy-5-nitrophenyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (173).



173

Oxazolidinone **137** (311 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **124** (152 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **173** (416mg, 87 %)as a single isomers with excellent yeild (light yellowcolor liquid). R_f 0.2(10 % ethyl acetate/hexane).

Mol. Formula : $C_{44}H_{72}N_2O_{12}Si_3$

$[\alpha]_D^{25}$: -16.31 (*c* = 0.77, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 757, 1078, 1251, 1604, 1693, 1735, 1780, 2401, 3021 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.29- -0.35 (s, 3H), 0.01-0.09 (s, 18H), 0.73 (s, 9H), 0.85-086 (m, 9H), 0.94 (d, *J* = 6.7, 13.9, 3H), 1.26-1.35 (m, 1H), 1.72-1.80 (m, 1H), 2.19-2.32 (m, 1H), 2.68 (dq, *J* = 5.7, 16.7, 1H), 3.33-3.41 (m, 1H), 3.51-3.54 (m, 1H), 3.61-3.71 (m, 2H), 3.88-3.99 (m, 9H), 3.99-4.04 (m, 4H), 4.18- 4.23 (m, 1H), 4.71 (t, *J* = 7.9, 1H), 5.55 (ddd, *J* = 10.1, 17.4, 23.9, 1H), 7.32-7.41 (m, 5H), 7.50 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.50 (q, TBS-**CH_3**), -5.36 (q, TBS-**CH_3**), -5.30 (q, TBS-**CH_3**), -5.09 (q, TBS-**CH_3**), -5.04 (q, TBS-**CH_3**), -4.58 (q, TBS-**CH_3**), -4.45 (q, TBS-**CH_3**), -0.21 (q, TMS-**CH_3**), -0.17 (q, TMS-**CH_3**), 15.58 (q, CH-**CH_3** (**6**)), 15.67 (q, CH-**CH_3** (**6**)), 17.73 (s, TBS-**C**), 18.34 (s, TBS-**C**), 25.53 (q, TBS-**CH_3**), 25.59 (q, TBS-**CH_3**), 25.88 (q, TBS-**CH_3**), 31.21 (t, CH-**CH_2**-CH (**7**)), 31.38 (t, CH-**CH_2**-CH (**7**)), 38.81 (t, -CH-**CH_2**Ph), 38.89 (t, -CH-**CH_2**Ph), 40.84 (d, **CH**-CH_3 (**3**)), 41.23 (d, **CH**-CH_3 (**3**)), 43.28 (d, O=C-**CH**-CH_2(**8**)), 43.31 (d, O=C-**CH**-CH_2(**8**)), 55.86 (q, -O**CH_3**), 56.29 (q, -O**CH_3**), 61.38 (q, -O**CH_3**), 61.42 (q, -O**CH_3**), 63.53 (d, OxazolidinoneCH_2-**CH (10)**), 64.42 (q, -O**CH_3**), 65.56 (t, Oxazolidinone**CH_2**-CH

(**11**)), 65.70 (t, Oxazolidinone**CH_2**-CH (**11**)), 70.59 (d, aryl-**CH**-OTMS (**9**)), 79.82 (d, - aryl-**CH**-OTMS (**9**)), 80.05 (d, CH-**CH**O-CH_2OBn-(**4**)), 80.68 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 80.76 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 84.74 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 108.69 (d, Ar-**CH**), 108.72 (d, Ar-**CH**), 127.11 (d, CH), 128.87 (d, CH), 129.40 (d, CH), 131.52 (s, C), 136.14 (s, C), 138.05 (s, C), 139.57 (s, C), 147.08 (s, C), 147.99 (s, C), 149.53 (s, C), 152.07 (s, C), 153.36 (s, C), 154.43 (s, C), 176.37 (s, C), 176.75 (s, C) ppm.

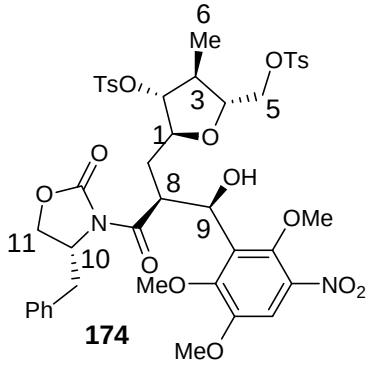
Hint: In the **^{1}H** and **^{13}CNMR** spectrum shows corresponding peaks in double splitting patteren indicates the presence of restricted conformational isomers.

ESI-MS (*m/z*) : 927.92 $[M+Na]^+$.

Elemental Analysis Calcd : C, 58.37; H, 8.02; N, 3.09 %

Found: C, 58.38; H, 8.04; N, 3.11 %

((2R,3S,4R,5S)-5-((S)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-oxo-2-((R)-(2,3,6-trimethoxy-5-nitrophenyl)(trimethylsilyloxy)methyl)propyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (174).



174

Oxazolidinone **189** (310 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **124** (173 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane

(1:12) to give OH-Evan's **174** (398 mg, 94 %)as a single isomers with excellent yeild (light yellowcolor liquid). R_f 0.4(10 % ethyl acetate/hexane).

Mol. Formula : $C_{44}H_{48}N_2O_{16}Si_2$

$[\alpha]_D^{25}$: -11.91 (*c* = 3.2, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 758, 872, 1070, 1251, 1604, 1696, 1736,1784, 2402, 3020 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.86 (d, *J* = 6.7, 3H), 1.20 (ddd, *J* = 2.7, 6.7, 14.7, 1H)1.22-1.24 (m, 1H), 1.26 (s, 1H), 2.00-2.05 (m, 1H), 2.23 (ddd, *J* = 4.6, 11.5, 15.5, 1H), 2.44 (s, 3H), 2.46 (s, 3H), 2.85 (dd, *J* = 9.5, 13.7, 1H), 3.42 (dd, *J* = 3.3, 13.7, 1H), 3.53 (ddd, *J* = 3.3, 6.7, 9.5, 1H), 3.78 (q, *J* = 6.07, 1H), 3.83-3.91 (m, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 4.11-4.15 (m, 1H), 4.17 (m, 3H), 4.25-4.31 (m, 1H), 4.76-4.83 (m, 2H), 5.23 (t, *J* = 11.3, 1H), 7.27-7.36 (m, 9H), 7.51 (s, 1H), 7.63 (d, *J* = 8.3, 2H), 7.71 (d, *J* = 8.3, 2H) ppm.

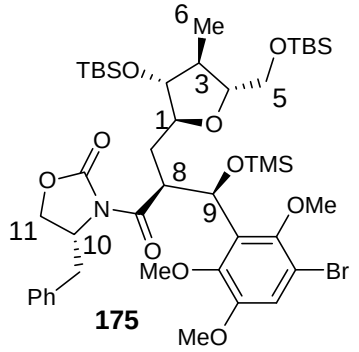
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.75 (q, CH-**CH_3** (**6**)), 21.62 (q, Ts-**CH_3**), 28.82 (q, Ts-**CH_3**), 31.02 (t, CH-**CH_2**-CH (**7**)), 37.87 (t, -CH-**CH_2**Ph), 41.10 (d, **CH**-CH_3 (**3**)), 44.30 (d, O=C-**CH**-CH_2(**8**)), 56.00 (q, -O**CH_3**), 56.43 (d, OxazolidinoneCH_2-**CH (10)**), 61.66 (q, -O**CH_3**), 63.21 (q, -O**CH_3**), 66.78 (t, HCO-**CH_2**OBn (**5**)), 69.78 (t, Oxazolidinone**CH_2**-CH (**11**)), 71.37 (d, aryl-**CH**-OTMS (**9**)), 79.12 (d, -CH-**CH**O-CH_2OBn-(**4**)), 81.03 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 86.45 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 109.53 (d, Aryl**CH**), 127.14 (d, CH), 128.71 (d, CH), 129.86 (d, CH), 129.94 (d, CH), 133.15 (s, C), 135.62 (s, C), 145.10 (s, C), 145.32 (s, C), 148.20 (s, C), 154.46 (s, C), 163.93 (s, C), 176.06 (s, C) ppm.

ESI-MS (*m/z*) : 936.55 $[M+Na]^+$.

Elemental Analysis Calcd : C, 56.57; H, 5.30; N, 3.07 %

Found: C, 56.58; H, 5.32; N, 3.08 %

(R)-4-benzyl-3-((2S,3R)-3-(3-bromo-2,5,6-trimethoxyphenyl)-2-(((2S,3R,4S,5R)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(trimethylsilyloxy)propanoyl)oxazolidin-2-one (175).



175

Oxazolidinone **137** (310 g, 0.52 mmol) was treated with $MgCl_2$ (5 mg, 0.052 mmol), triethylamine (106 mg, 0.146 mL, 1.05 mmol), benzaldehyde **183** (173 mg, 0.631 mmol) and chlorotrimethylsilane (85 mg, 0.10 mL, 0.789 mmol) in 6 mL of ethylacetate at 23 ^{o}C for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give TMS ether derivative **175** (448 mg, 91%)as a single isomers with excellent yeild (light yellowcolor liquid). R_f 0.2(10 % ethyl acetate/hexane).

Mol. Formula : $C_{44}H_{72}BrNO_{10}Si_3$

$[\alpha]_D^{25}$: +4.48 (*c* = 2.25, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 758, 872, 1070, 1251, 1604, 1696, 1736,1784, 2402, 3020 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.33 (s, 3H), -0.05-0.03 (s, 9H), -0.02 (s, 3H), -0.01 (s, 6H), 0.69 (s, 9H), 0.80 (s, 9H), 1.03 (d, *J* = 6.7, 3H), 1.30-1.37 (m, 1H), 1.71-1.73 (m, 1H), 2.28 (dt, *J* = 4.7, 12.7, 1H), 2.68 (dd, *J* = 11.2, 13.1, 1H), 3.38 (ddd, *J* = 4.3, 9.7, 14.0, 1H), 3.52-3.54 (m, 3H), 3.62 (dd, *J* = 4.7, 12.7, 1H), 3.68 (dd, *J* = 6.7, 11.2, 1H), 3.87 (s, 3H), 3.86-3.88 (m, 1H), 3.92 (s, 3H), 4.01 (s, 3H), 4.11 (d, *J* = 8.3, 1H), 4.19 (q, *J* = 7.8, 8.3, 1H), 4.70 (t, *J* = 7.8, 1H) 5.52 (ddd, *J* = 10.8, 22.8, 34.1, 1H), 7.00 (s, 1H), 7.24-7.35 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.50 (q, TBS-**CH_3**), -5.34 (q, TBS-**CH_3**), -4.84 (q, TBS-**CH_3**), -4.58 (q, TBS-**CH_3**), -4.39 (q, TBS-**CH_3**), -0.19(q, TMS-**CH_3**),

15.58 (q, CH-**CH_3** (**6**)), 15.64 (q, CH-**CH_3** (**6**)), 17.78 (s, TBS-**C**), 18.36 (s, TBS-**C**), 25.62 (q, TBS-**CH_3**), 25.68 (q, TBS-**CH_3**), 25.90 (q, TBS-**CH_3**), 31.31 (t, CH-**CH_2**-CH (**7**)), 31.56 (t, CH-**CH_2**-CH (**7**)), 38.83 (t, -CH-**CH_2**Ph), 38.90 (t, -CH-**CH_2**Ph), 40.83 (d, **CH**-CH_3 (**3**)), 40.90 (d, **CH**-CH_3 (**3**)), 43.35 (d, O=C-**CH**-CH_2(**8**)), 43.46 (d, O=C-**CH**-CH_2(**8**)), 55.72 (q, -O**CH_3**), 55.89 (q, -O**CH_3**), 56.26 (d, OxazolidinoneCH_2-**CH (10)**), 61.05 (q, -O**CH_3**), 61.13 (q, -O**CH_3**), 61.83 (q, -O**CH_3**), 62.10 (q, -O**CH_3**), 65.51 (t, HCO-**CH_2**OBn (**5**)), 65.80 (t, Oxazolidinone**CH_2**-CH (**11**)), 70.78 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 71.79 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 79.77 (d, -CH-**CH**O-CH_2OBn-(**4**)), 80.85 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 80.89 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 84.70 (d, aryl-**CH**-OTMS (**9**)), 84.88 (d, aryl-**CH**-OTMS (**9**)), 116.22 (d, Aryl**CH**), 116.50 (d, Aryl**CH**), 127.05 (d, CH), 128.84 (d, CH), 129.42 (d, CH), 130.74 (s, C), 136.28 (s, C), 147.06 (s, C), 148.75 (s, C), 149.04 (s, C), 149.19 (s, C), 150.86 (s, C), 153.35 (s, C), 176.77 (s, C) ppm.

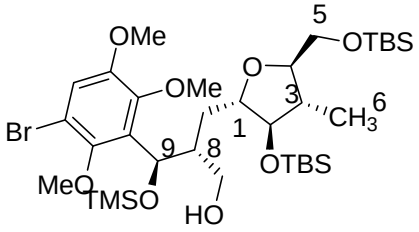
Hint: In the **^{1}H** and **^{13}CNMR** spectrum shows corresponding peaks in double splitting patteren indicates the presence of restricted conformational isomers.

ESI-MS (*m/z*) : 961.18 $[M+Na]^+$.

Elemental Analysis Calcd : C, 56.27; H, 7.73; Br, 8.51; N, 1.49 %

Found: C, 56.28; H, 7.75; Br, 8.52; N, 1.50 %

(2R,3R)-3-(3-bromo-2,5,6-trimethoxyphenyl)-2-(((2S,3R,4S,5R)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-(trimethylsilyloxy)propan-1-ol (184).



184

The aldol adduct **175** (1.2 g, 1.2 mmol), 10 mL of drydiethylether and anhydrous methanol (0.04 mL) were cooled to 0 ^{o}C. Lithium borohydrate (2.0M in THF , 0.51 mL mmol) was added dropwise, and the mixture was stirred for 2h at 0 ^{o}C . The reaction was quenched with 15% NaOH and then concentrated in vacuo. The aqueous layer was extracted with ether , and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave **184** (0.612 g, 63 %) of alcohol. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{34}H_{65}BrO_8Si_3$

$[\alpha]_D^{25}$: +4.66 (*c* = 0.95, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 756, 1062, 1252, 1559, 1654, 1718, 2402, 3378 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ -0.19 (s, 3H), 0.02 (s, 9H), 0.08 (s, 9H), 0.77 (s, 9H), 0.88 (s, 9H), 1.01 (d, *J* = 6.75, 3H), 1.30-1.50 (m, 2H), 1.91-1.93 (m, 1H), 2.72-2.76 (m, 1H), 3.30 (s, 1H), 3.51-3.53 (m, 1H), 3.53-3.70 (s, 5H), 3.73-3.75 (m, 1H), 3.80 (s, 3H), 3.84 (s, 6H), 5.08-5.21 (m, 1H), 6.98 (s, 1H) ppm.

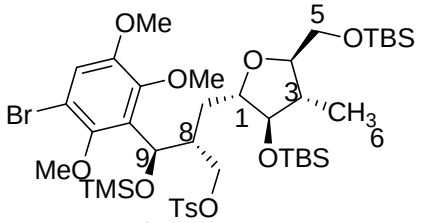
^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.39 (q, TBS-**CH_3**), -4.40 (q, TBS-**CH_3**), -4.23 (q, TBS-**CH_3**), -0.06 (q, TMS-**CH_3**), 15.77 (q, CH-**CH_3** (**6**)), 17.79 (s, TBS-**C**), 18.33 (s, TBS-**C**), 21.61 (s, TBS-**C**), 25.73 (q, TBS-**CH_3**), 25.92 (q, TBS-**CH_3**), 31.91 (t, CH-**CH_2**-CH (**7**)), 41.67 (d, **CH**-CH_3 (**3**)), 43.39 (d, O=C-**CH**-CH_2(**8**)), 56.01 (q, -O**CH_3**), 60.92 (q, -O**CH_3**), 61.82 (q, -O**CH_3**), 63.66 (t, CH_2(**10**)), 64.78 (t, HCO-**CH_2**OBn (**5**)), 69.17 (d, aryl-**CH**-OTMS (**9**)), 77.31 (d, -CH-**CH**O-CH_2OBn-(**4**)), 80.52 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)), 83.63 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 115.79 (d, Aryl**CH**), 127.88 (s, C), 128.19 (s, C), 129.77 (s, C) ppm.

ESI-MS (*m/z*) : 787.96 $[M+Na]^+$.

Elemental Analysis Calcd : C, 53.31; H, 8.55 %

Found: C, 53.32; H, 8.56 %

(2R,3R)-3-(3-bromo-2,5,6-trimethoxyphenyl)-2-(((2S,3R,4S,5R)-3-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methyl)-3-hydroxypropyl 4-methylbenzenesulfonate (185).



185

To a stirred solution of diol **184** (0.75 g, 1.08 mmol), Et_3 N (0.18 mL, 1.29 mmol) and DMAP (20 mg), in dichloromethane (30 mL) was added p-toluenesulfonyl chloride (0.189 g, 1.29 mmol), at 0^oC. The reaction mixture was stirred for 6h at room temperature, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (2:1) to afford **185** (0.826 g, 92 %)as a syrup liquid. R_f 0.8(75 % ethyl acetate/hexane).

Mol. Formula : $C_{41}H_{71}BrO_{10}SSi_3$

$[\alpha]_D^{25}$: -19.34 (*c* = 0.4, $CHCl_3$)

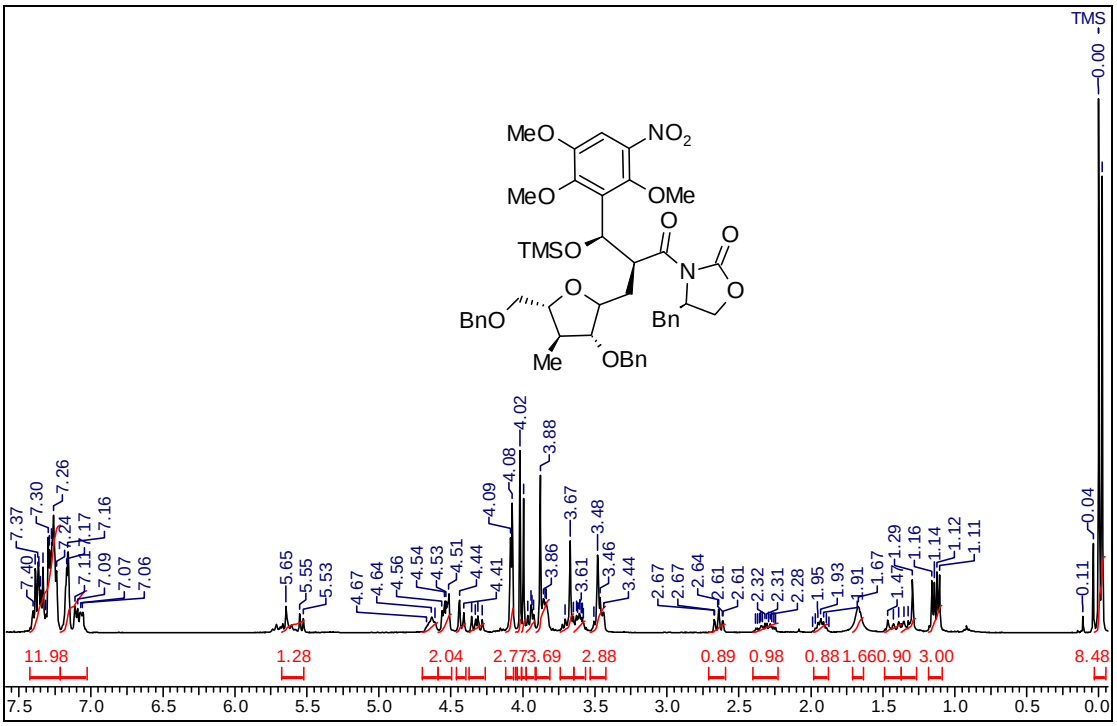
IR ($CHCl_3$) υ : 667, 756, 1066, 1252, 1598, 1666, 1731, 2401, 3017, 3453 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.01 (s, 3H), 0.04 (s, 9H), 0.06 (s, 3H), 0.10 (s, 6H), 0.88 (s, 9H), 0.93 (s, 9H), 1.02 (d, *J*= 6.7, 3H), 1.56 (ddd, *J*=1.6, 9.8, 14.3, 1H), 1.94 (hex, *J*=6.7, 1H), 2.34-2.42 (m, 1H), 2.48 (s, 3H), 3.05 (dt, *J* = 7.2, 13.4, 1H), 3.32 (t, *J* = 7.2, 1H), 3.46 (dt, *J* = 5.2, 9.7, 1H), 3.64 (dq, *J* = 5.5, 10.5,16.4, 2H), 3.74 (dq, *J* = 1.6, 6.7, 10.6, 1H), 3.82 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.00-4.06 (m, 1H), 5.07 (t, *J* = 9.5, 1H), 7.06 (s, 1H), 7.36 (d, *J* = 8.3, 2H), 7.80 (d, *J* = 8.3, 2H) ppm.

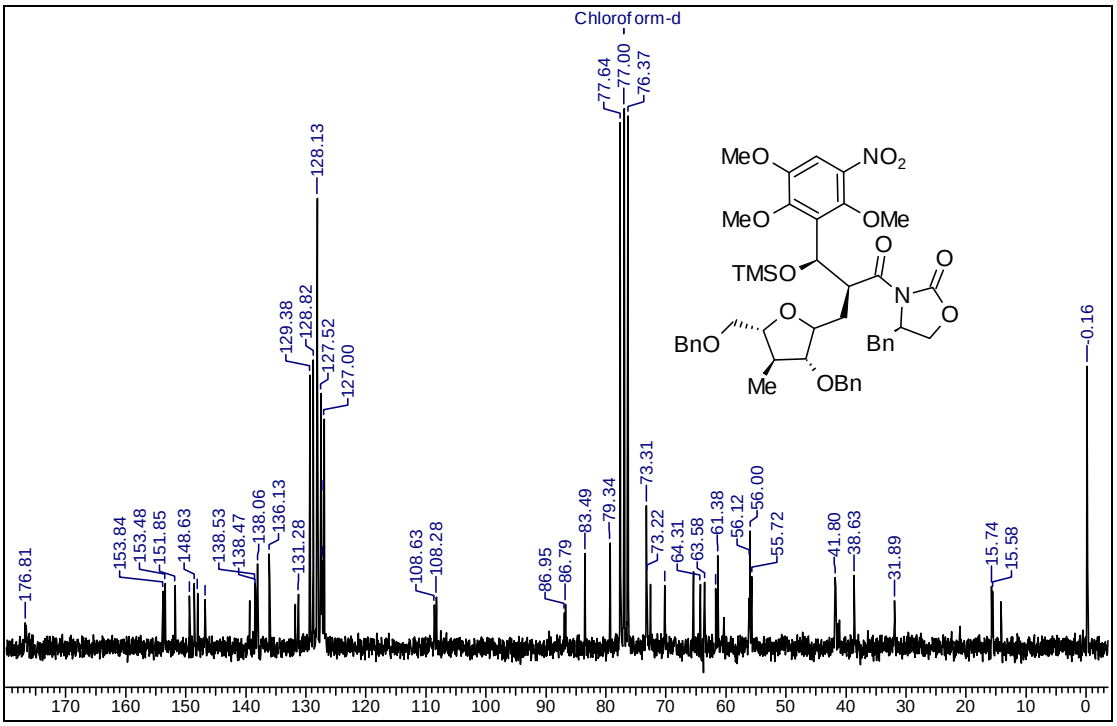
^{13}C NMR (125 MHz, $CDCl_3$) : δ -5.41 (q, TBS-**CH_3**), -4.37 (q, TBS-**CH_3**), -4.18 (q, TBS-**CH_3**), -0.19 (q, TMS-**CH_3**), 15.74 (q, CH-**CH_3** (**6**)), 17.79 (s, TBS-**C**), 18.27 (s, TBS-**C**), 21.46(q, Ts-**CH_3**), 25.69 (q, TBS-**CH_3**), 25.85 (q, TBS-**CH_3**), 32.20 (t, CH-**CH_2**-CH (**7**)), 43.65 (d, **CH**-CH_3 (**3**)), 43.86 (d, O=C-**CH**-CH_2(**8**)), 56.11 (q, -O**CH_3**), 61.06 (q, -O**CH_3**), 61.66 (q, -O**CH_3**), 64.33 (t, HCO-**CH_2**OBn (**5**)), 65.10 (t, -OTs-**CH_2**-CH (**10**)), 72.04 (d, aryl-**CH**-OTMS (**9**)), 77.32 (d, -CH-**CH**O-CH_2OBn-(**4**)), 80.48 (d, -$_2$HC-**HC**O-CH_2OBn (**1**)),

	83.65 (d, CHO-**CH**OBn-$CHCH_3$ (**2**)), 116.05 (d, Aryl**CH**), 125.87 (d, CH), 128.06 (d, CH), 129.60 (d, CH), 130.58 (s, C), 148.84 (s, C), 149.61 (s, C) ppm.
ESI-MS (*m/z*)	: 943.22 $[M+Na]^+$.
Elemental Analysis	Calcd : C, 53.51; H, 7.78 %
	Found: C, 53.53; H, 7.79 %

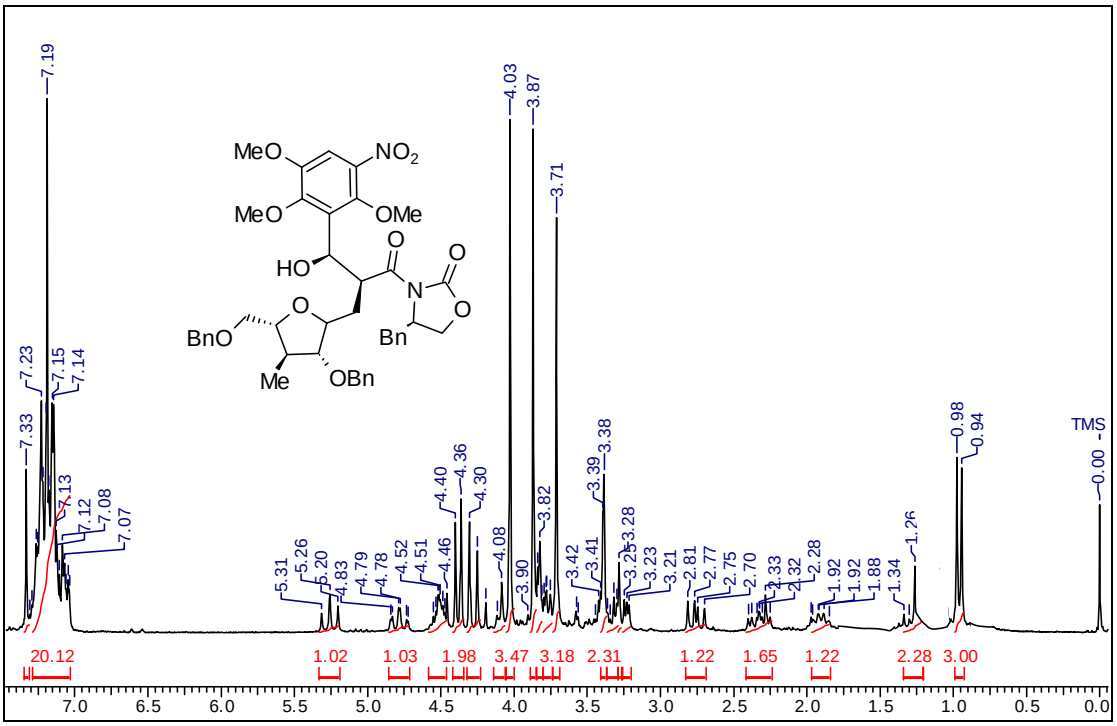
SPECTROSCOPIC DATA



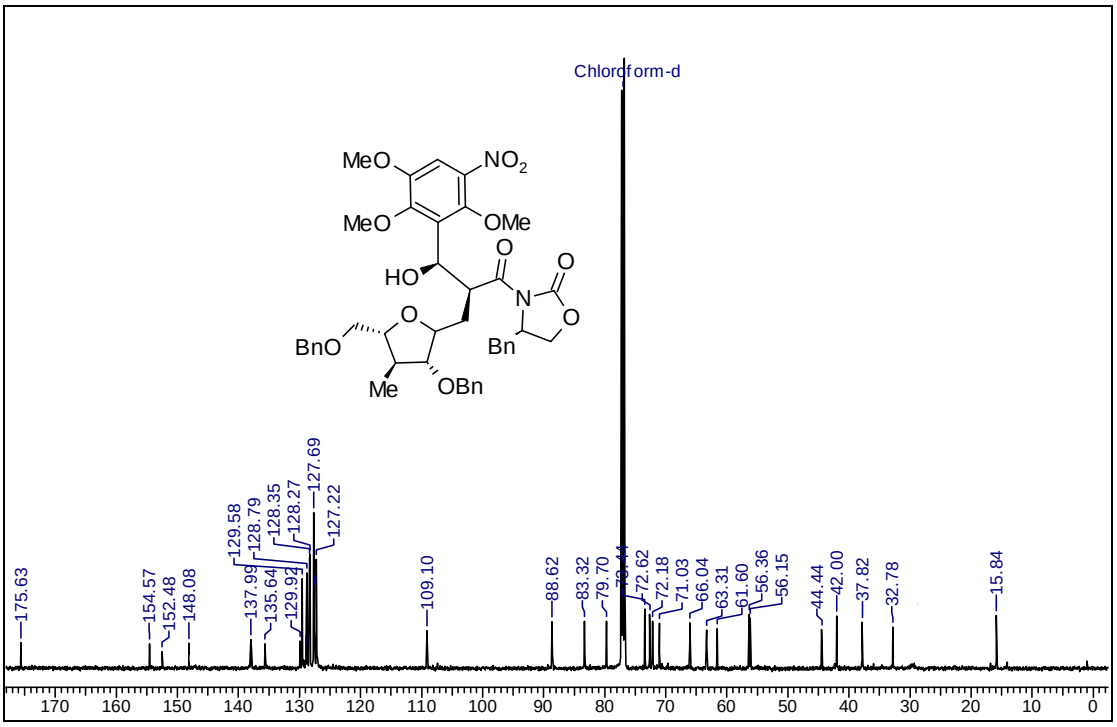
^{1}H NMR Spectrum of 123a in $CDCl_3$



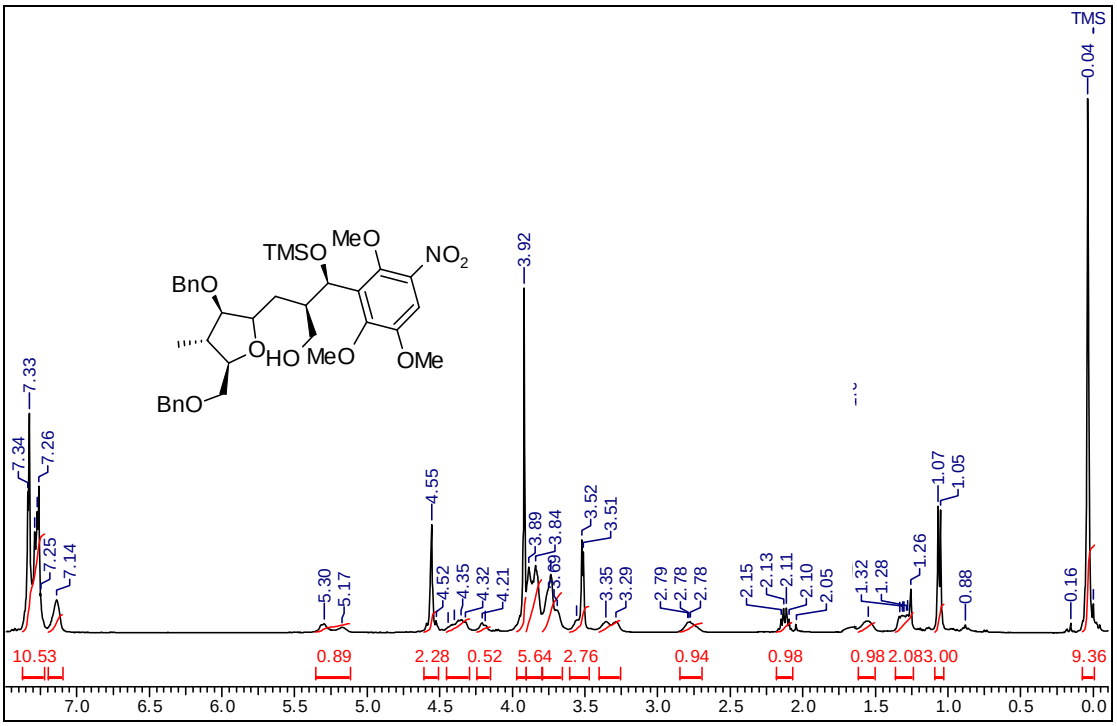
^{13}CNMR Spectrum of 123a in $CDCl_3$



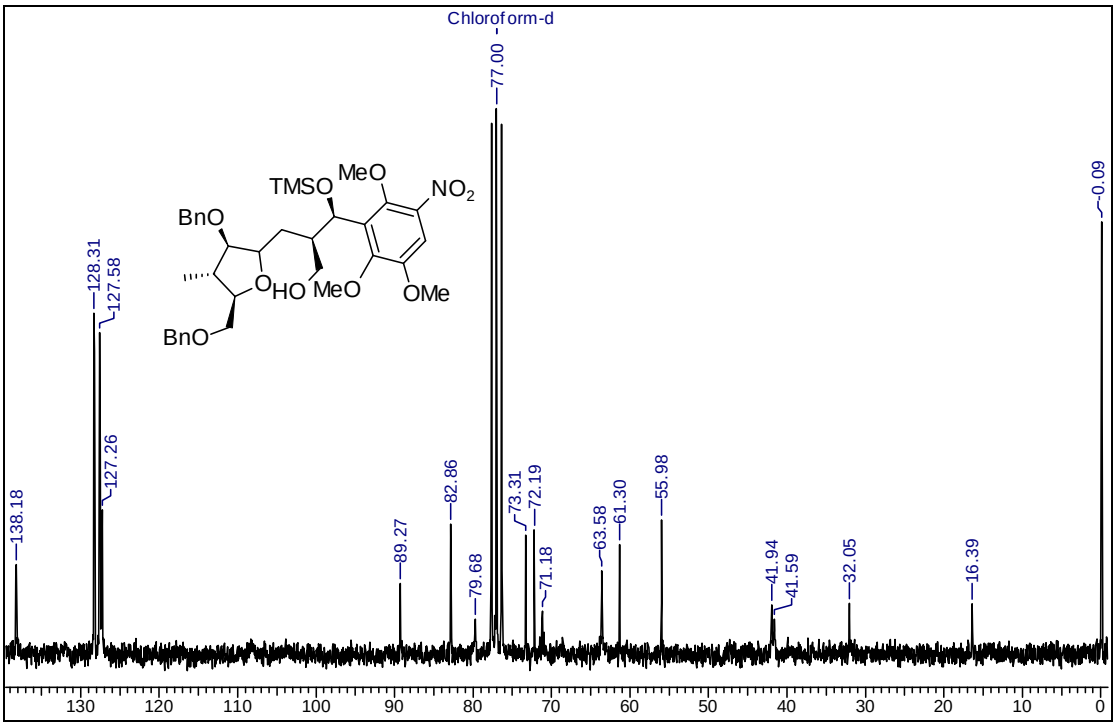
^{1}H NMR Spectrum of 123b in $CDCl_3$



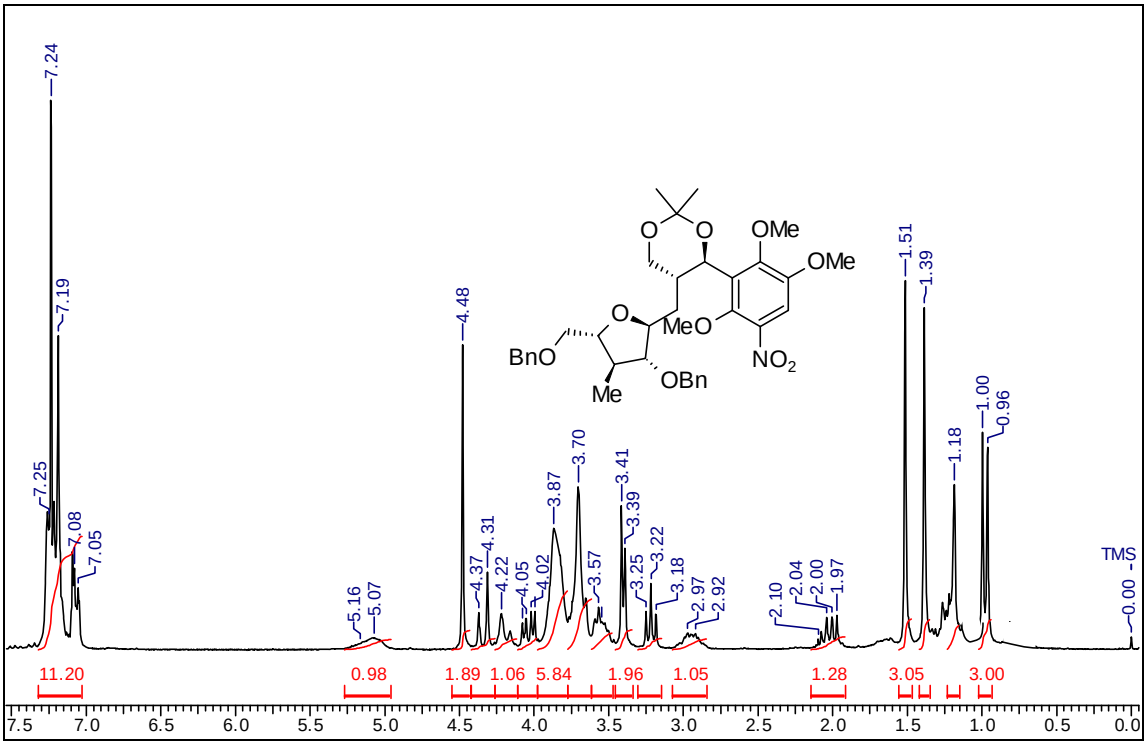
^{13}CNMR Spectrum of 123b in $CDCl_3$



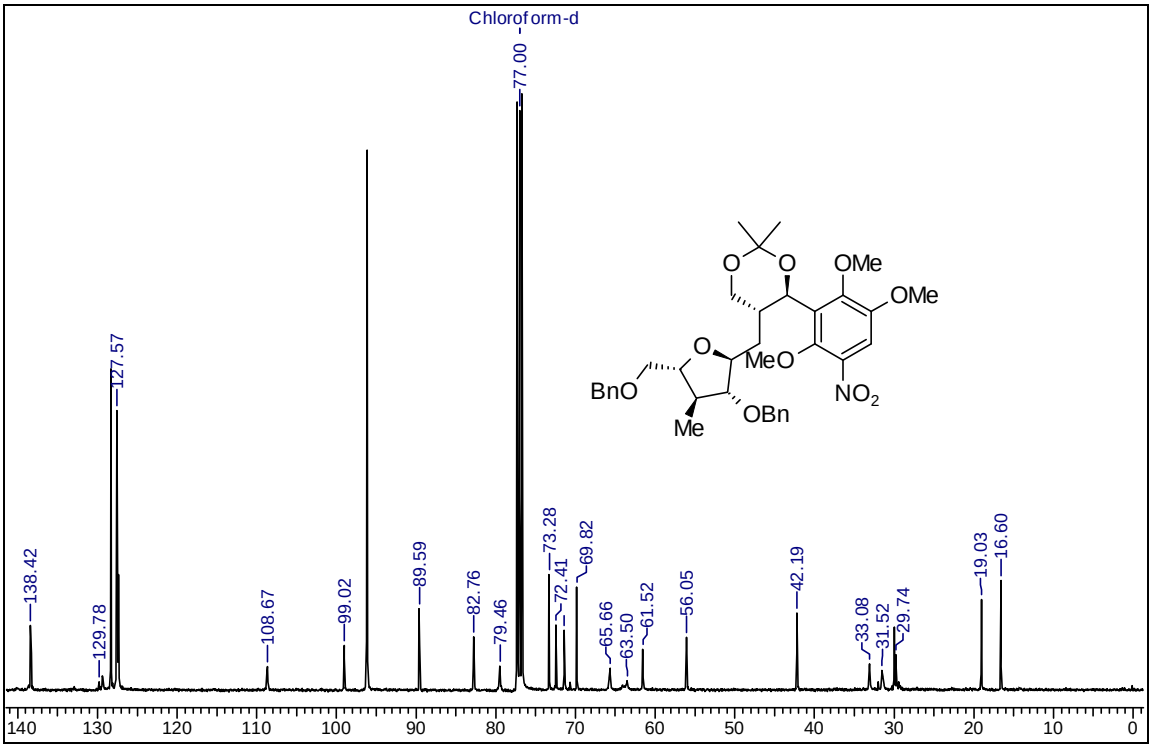
^{1}H NMR Spectrum of 176 in $CDCl_3$



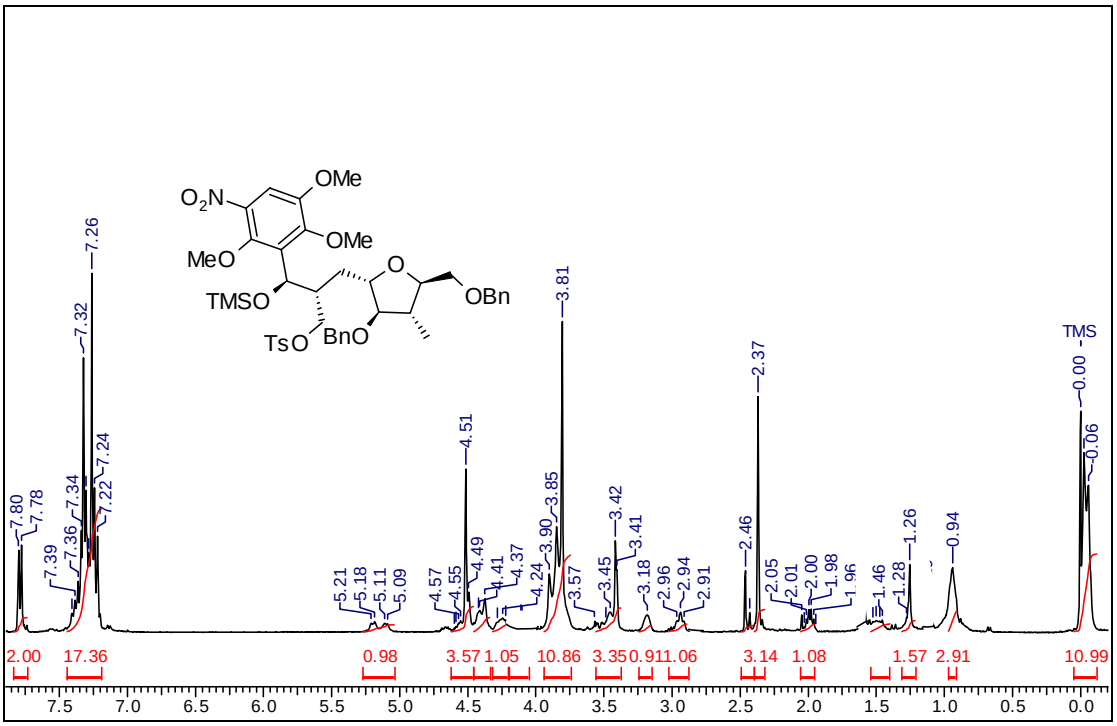
^{13}CNMR Spectrum of 176 in $CDCl_3$



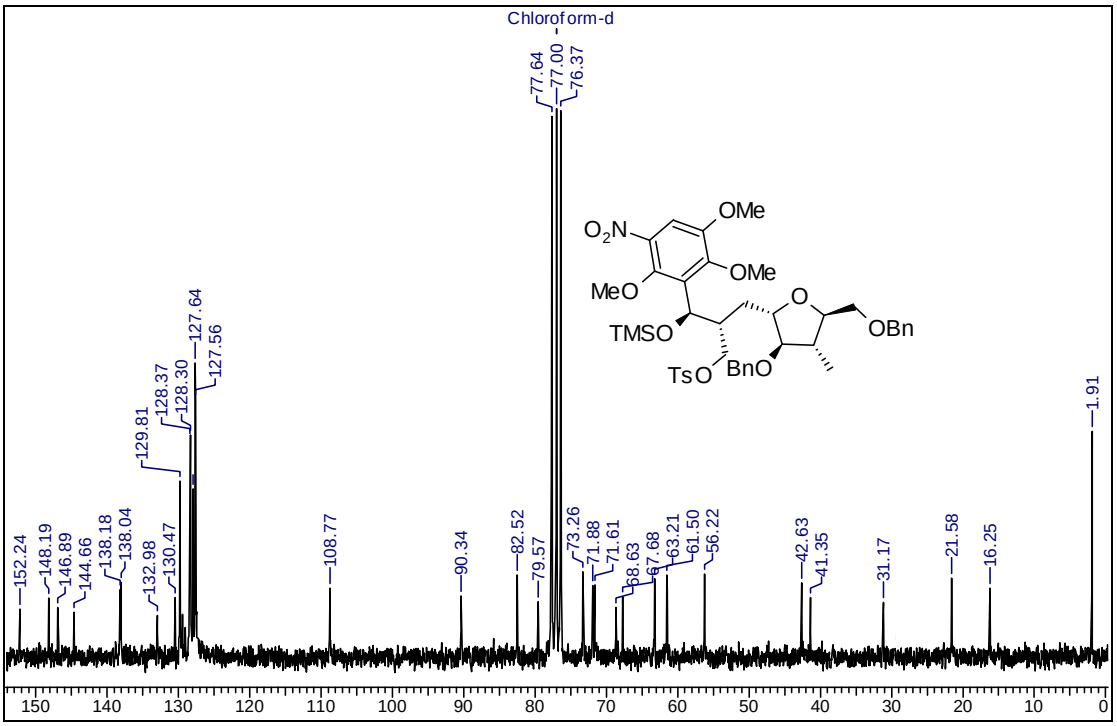
^{1}H NMR Spectrum of 178 in $CDCl_3$



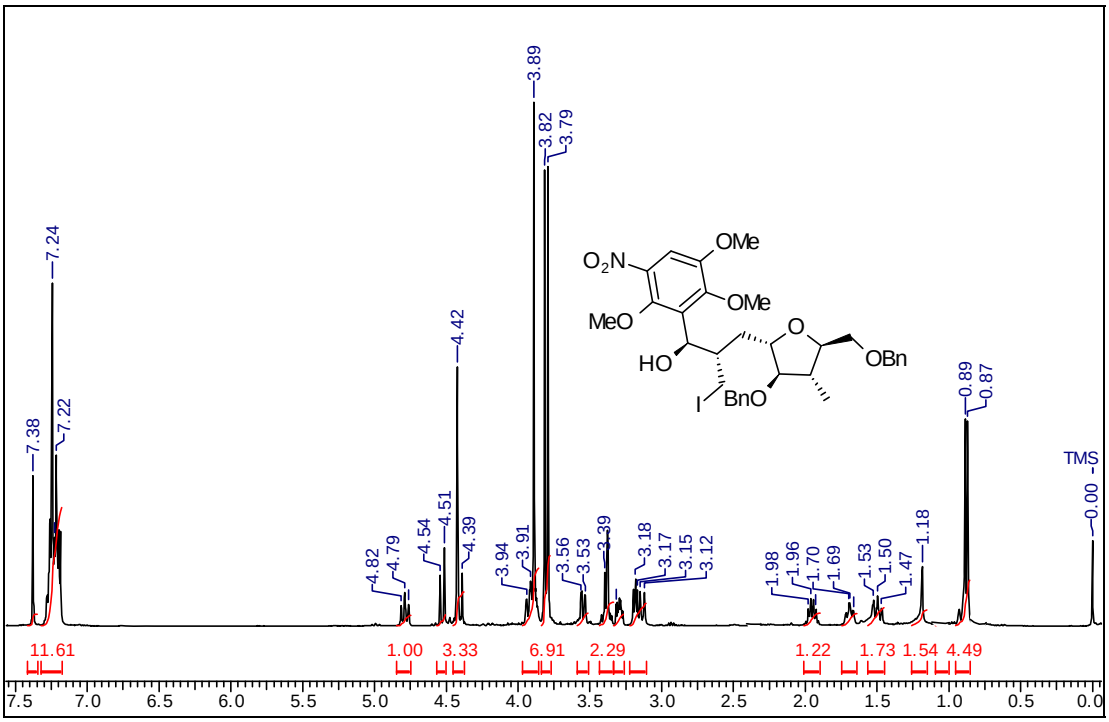
^{1}H NMR Spectrum of 178 in $CDCl_3/CCl_4$



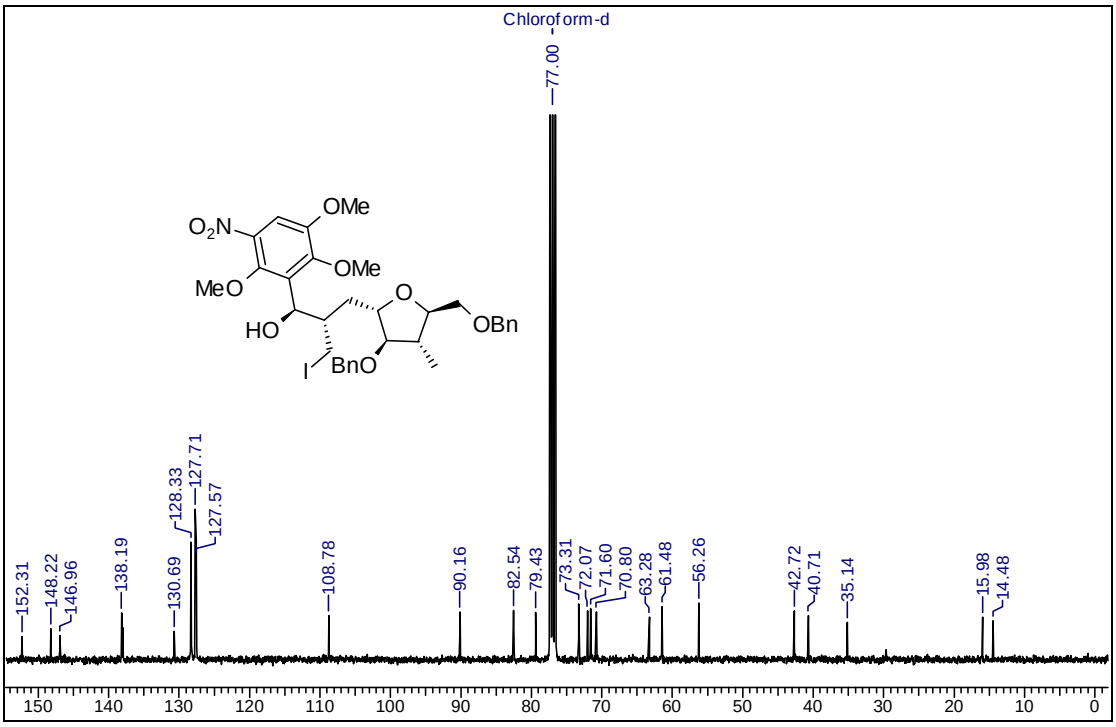
^{1}H NMR Spectrum of 179 in $CDCl_3$



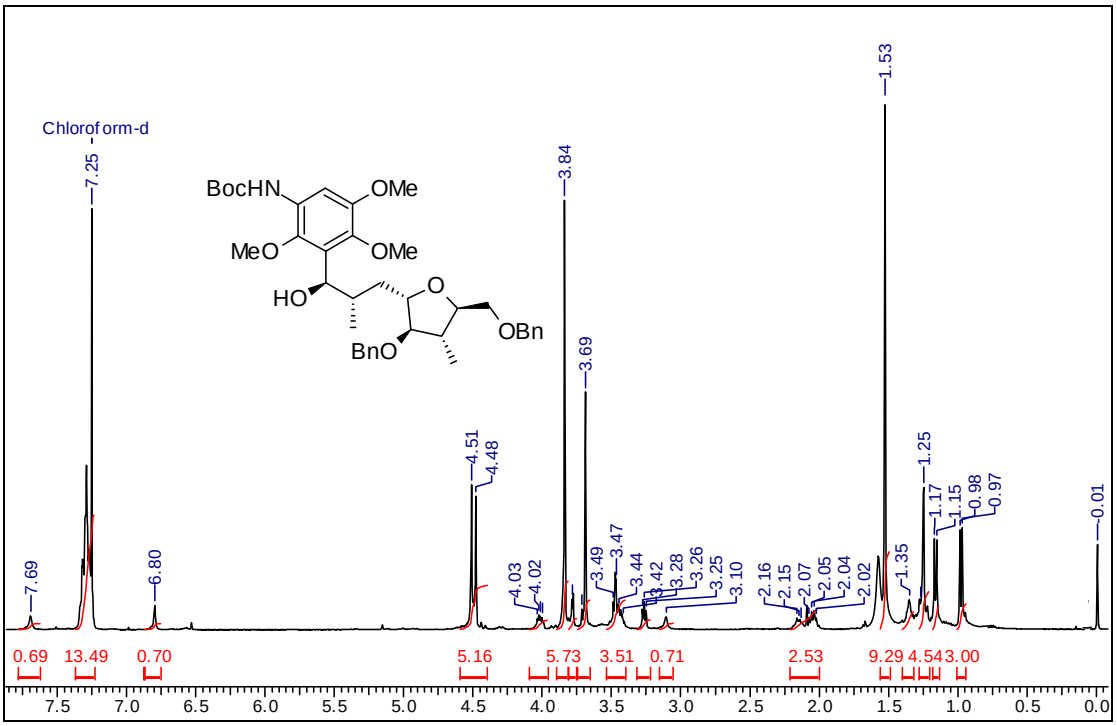
^{13}CNMR Spectrum of 179 in $CDCl_3$



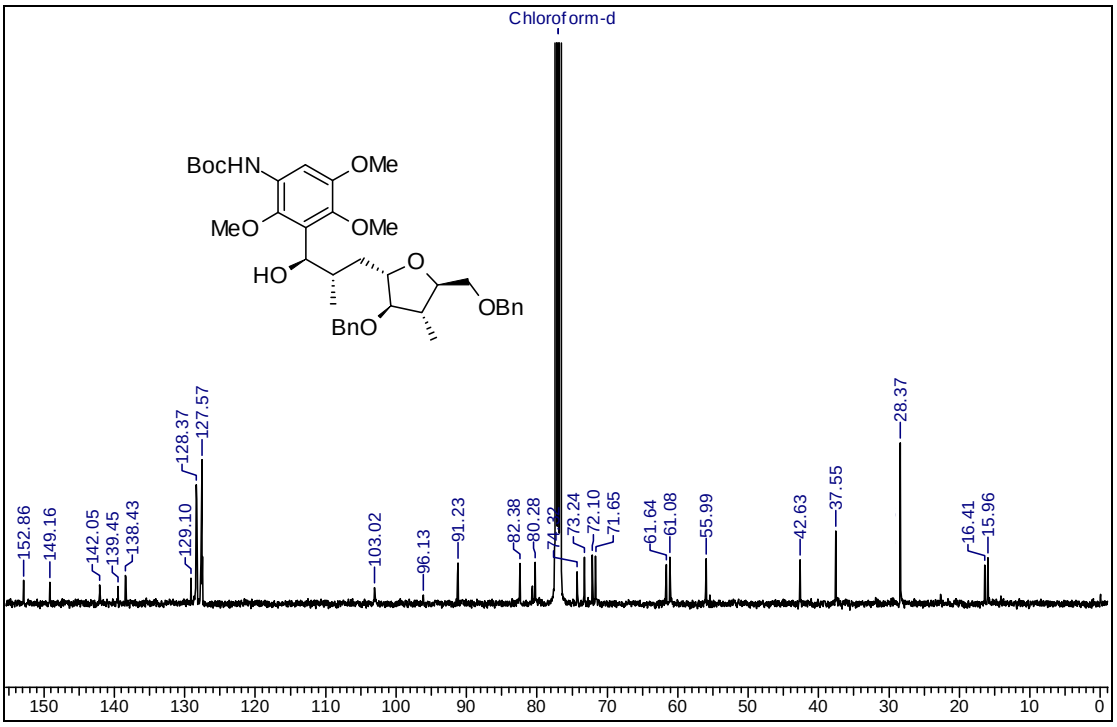
^{1}H NMR Spectrum of 180 in $CDCl_3$



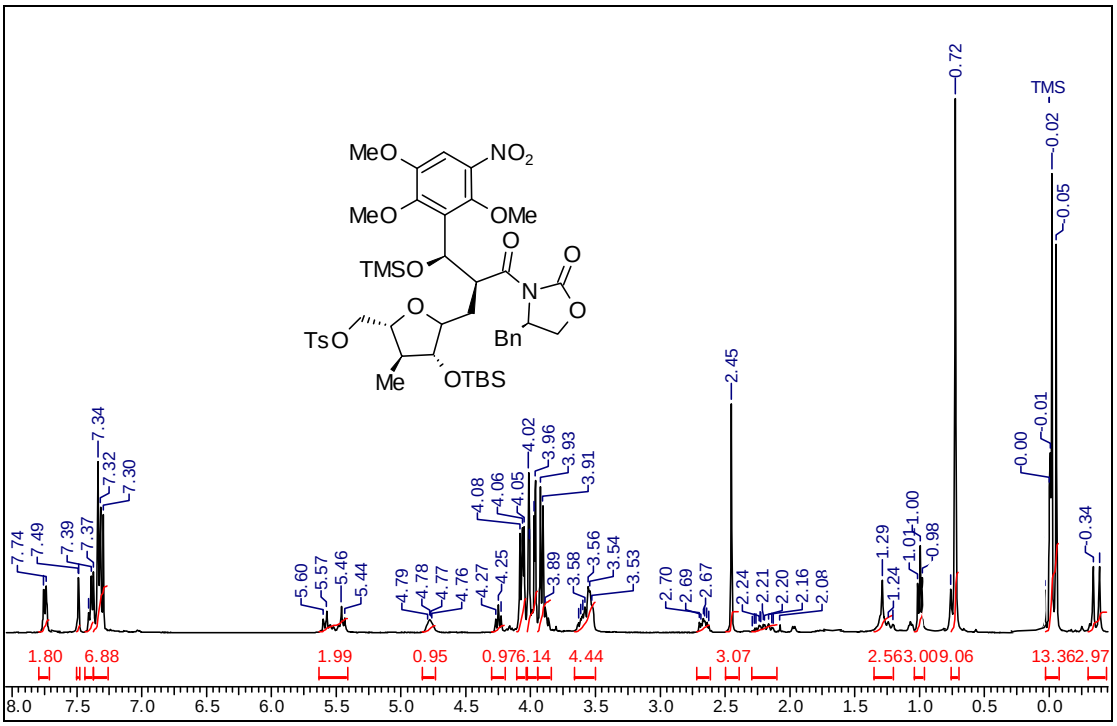
^{13}CNMR Spectrum of 180 in $CDCl_3$



^{1}H NMR Spectrum of 181 in $CDCl_3$



^{13}CNMR Spectrum of 181 in $CDCl_3$



^{1}H NMR Spectrum of 171 in $CDCl_3$

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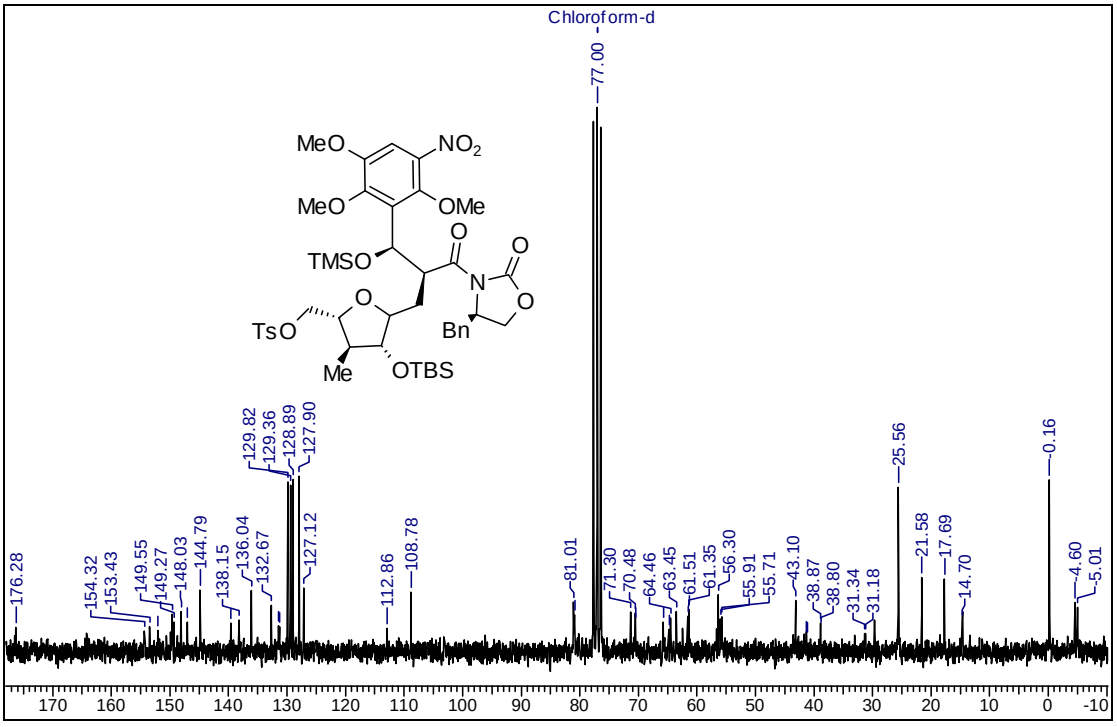
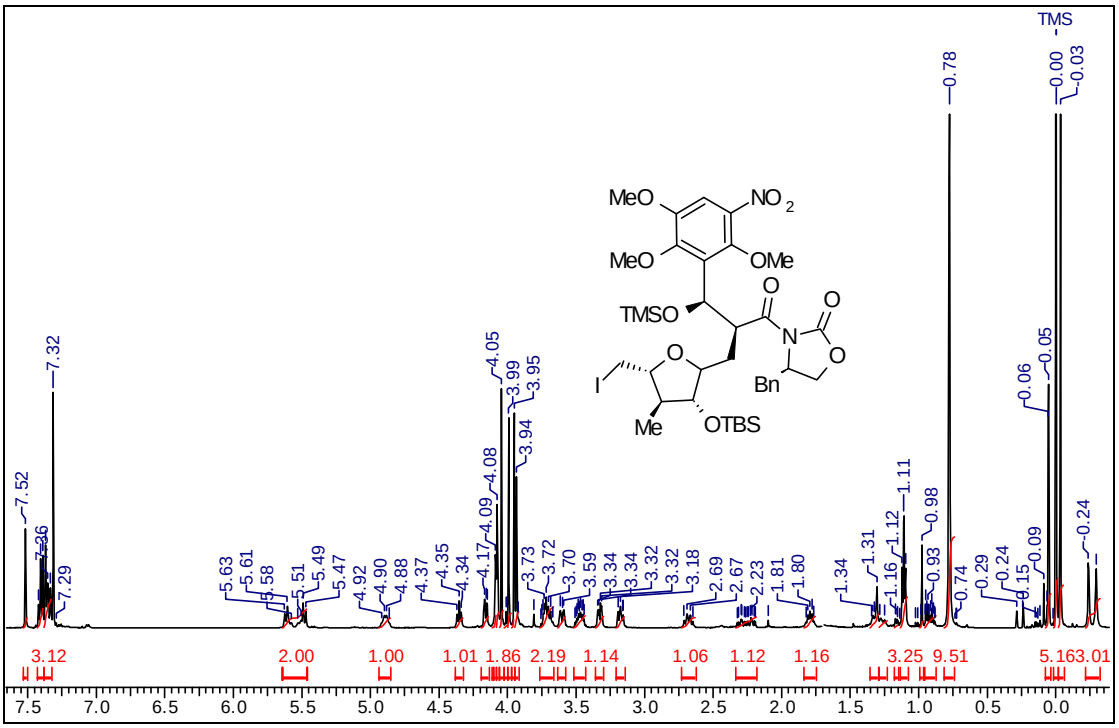
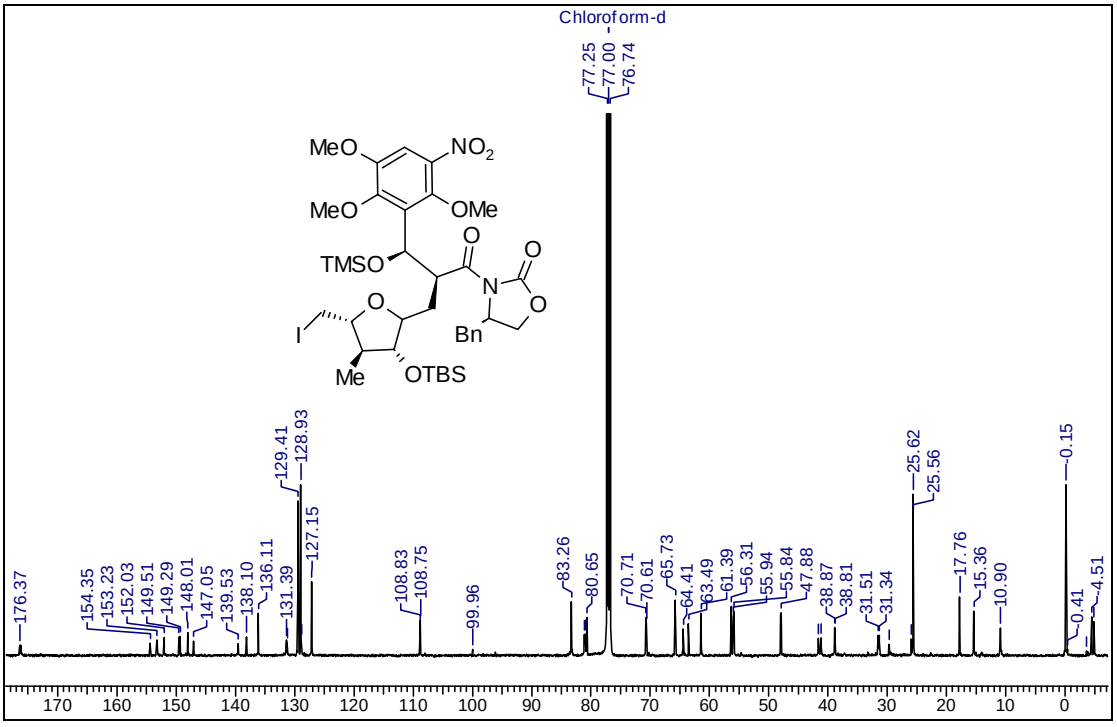


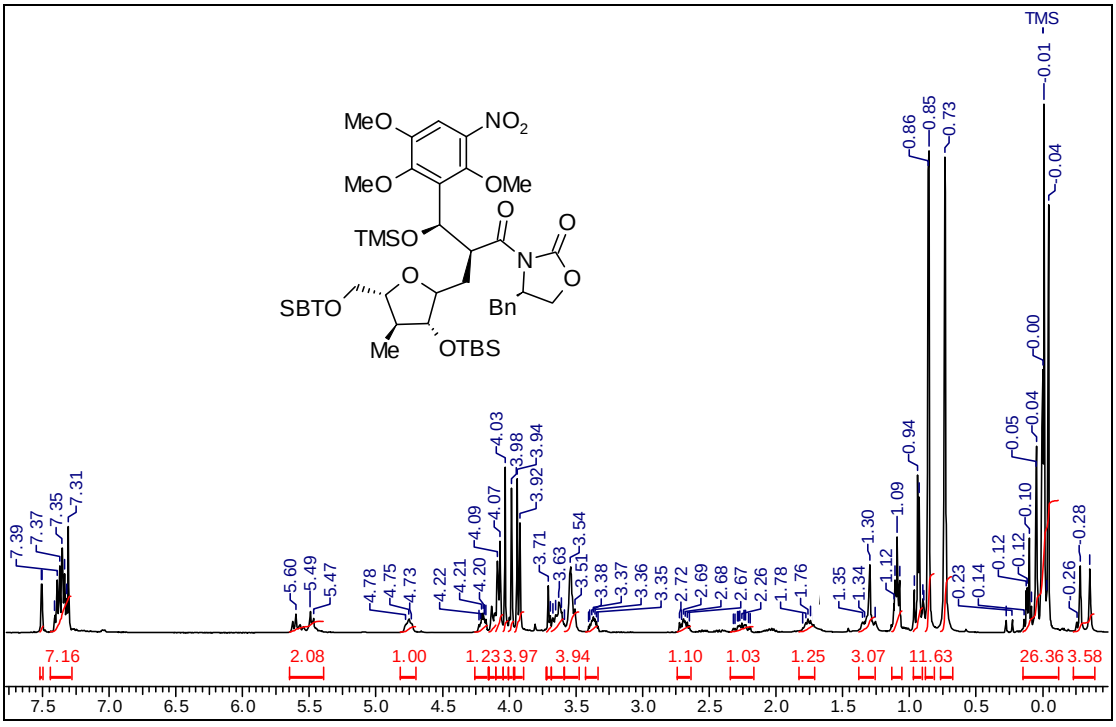
^{13}CNMR Spectrum of 171 in $CDCl_3$



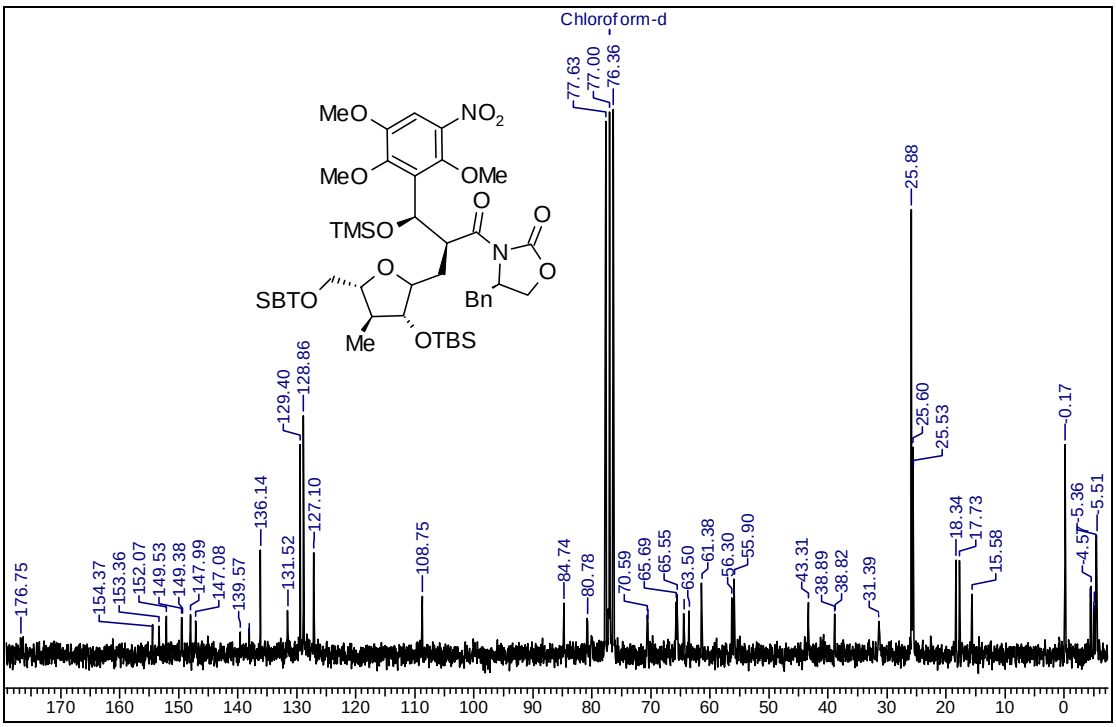
^{1}H NMR Spectrum of172 in $CDCl_3$



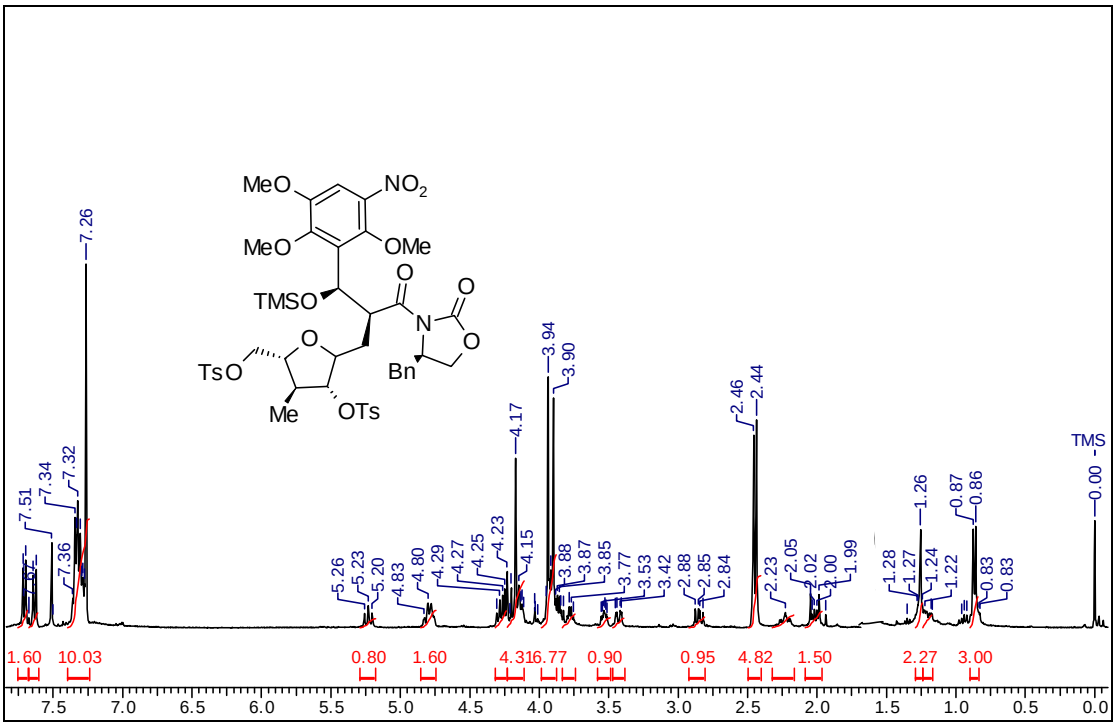
^{13}CNMR Spectrum of 172 in $CDCl_3$



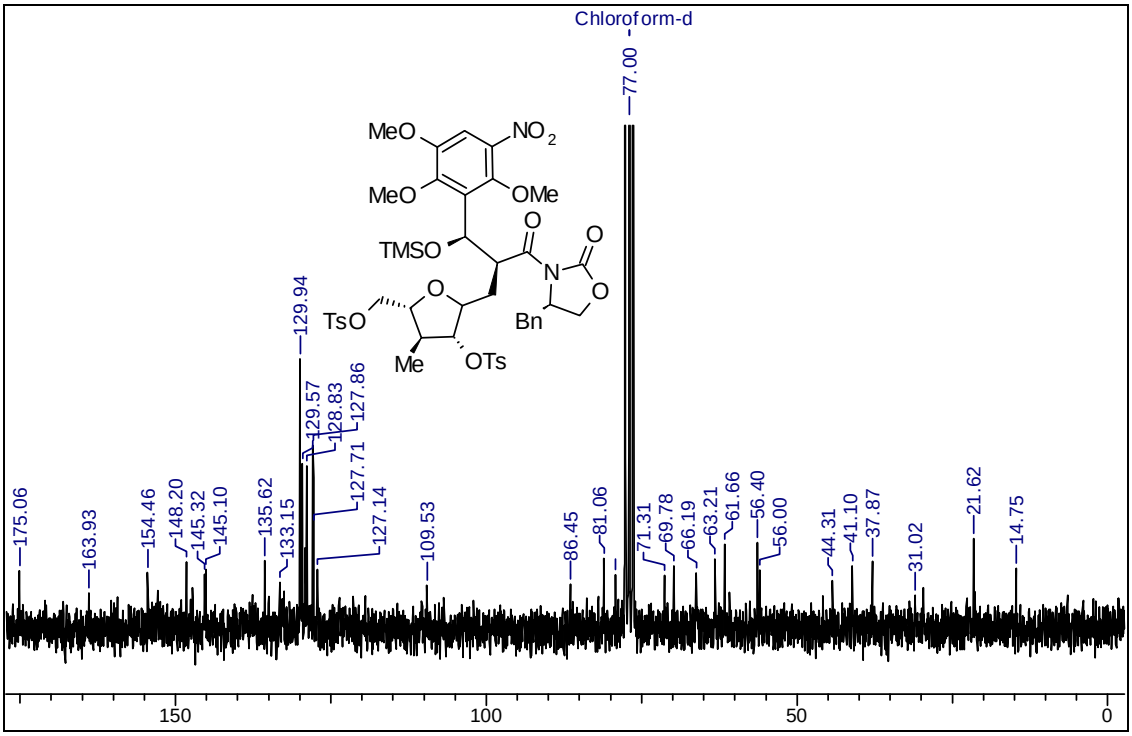
^{1}H NMR Spectrum of 173 in $CDCl_3$



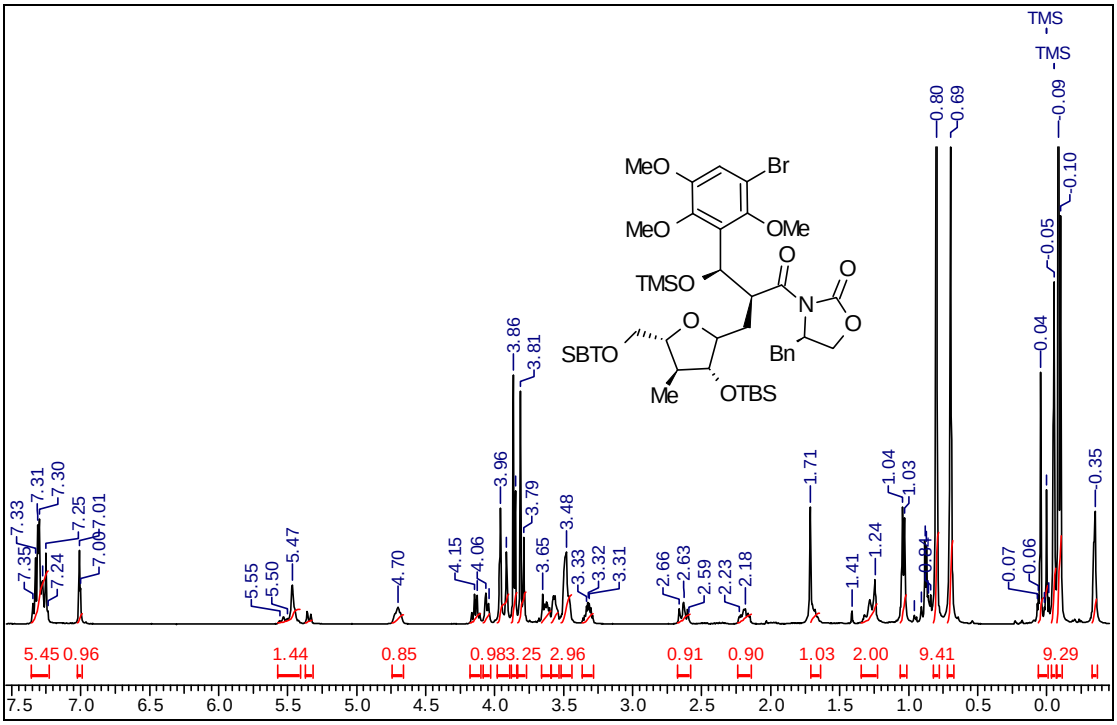
^{13}CNMR Spectrum of 173 in $CDCl_3$



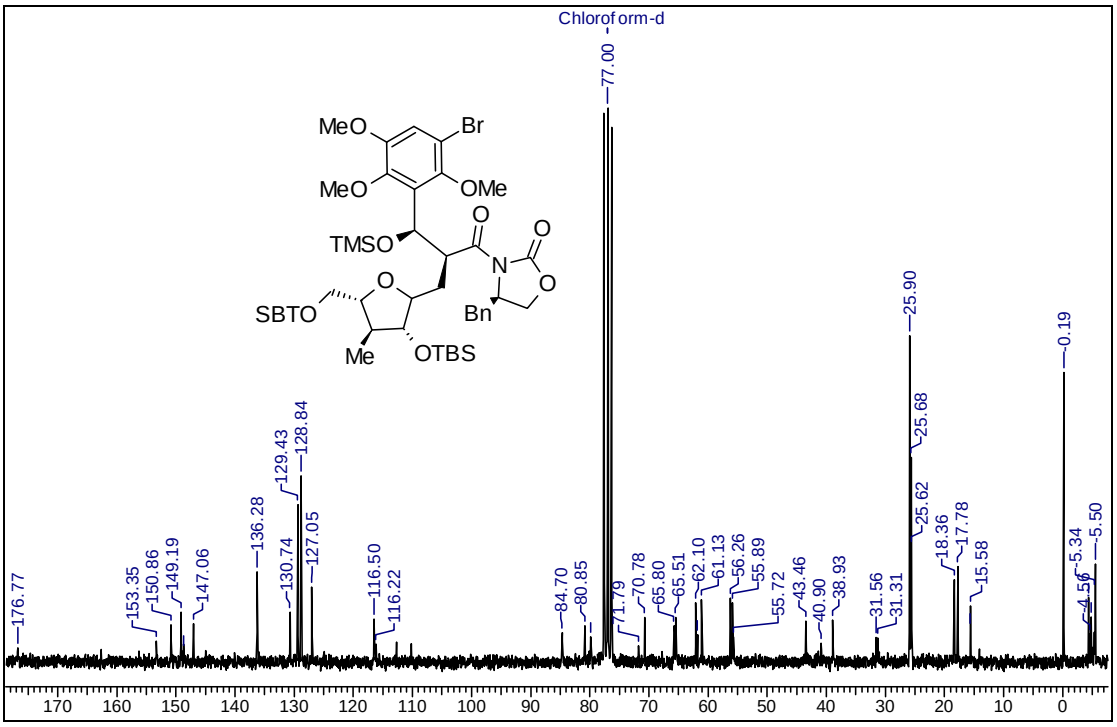
^{1}H NMR Spectrum of 174 in $CDCl_3$



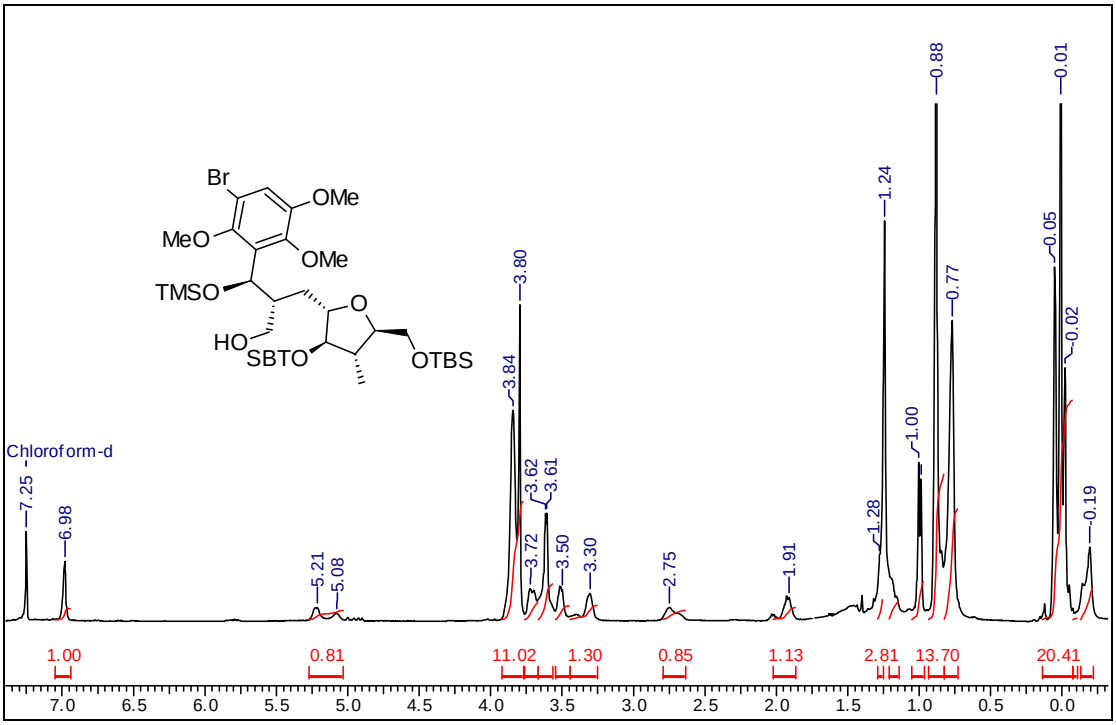
^{13}CNMR Spectrum of 174 in $CDCl_3$



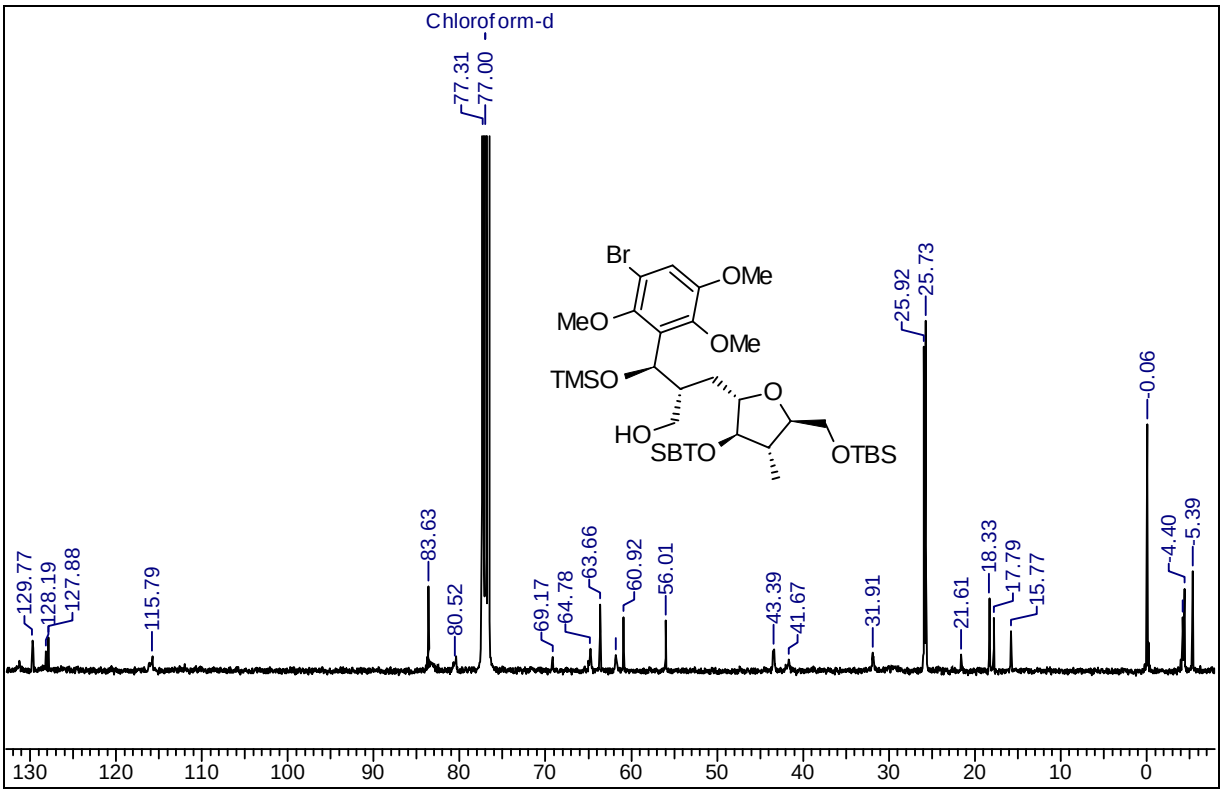
^{1}H NMR Spectrum of 175 in $CDCl_3$



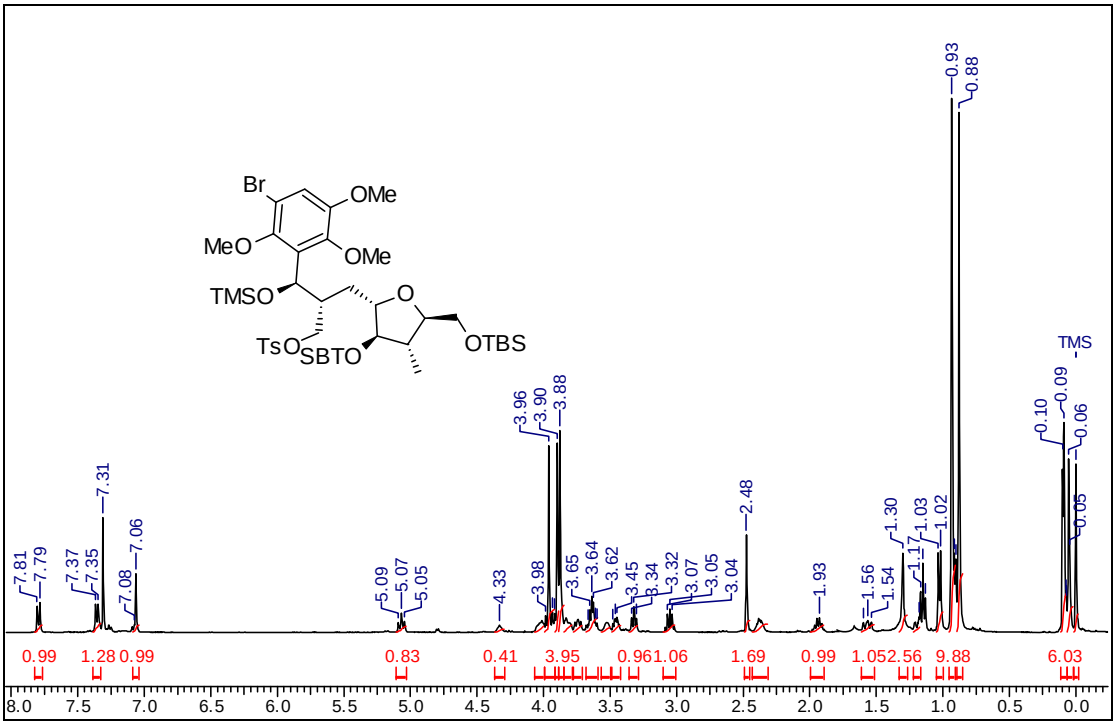
^{13}CNMR Spectrum of 175 in $CDCl_3$



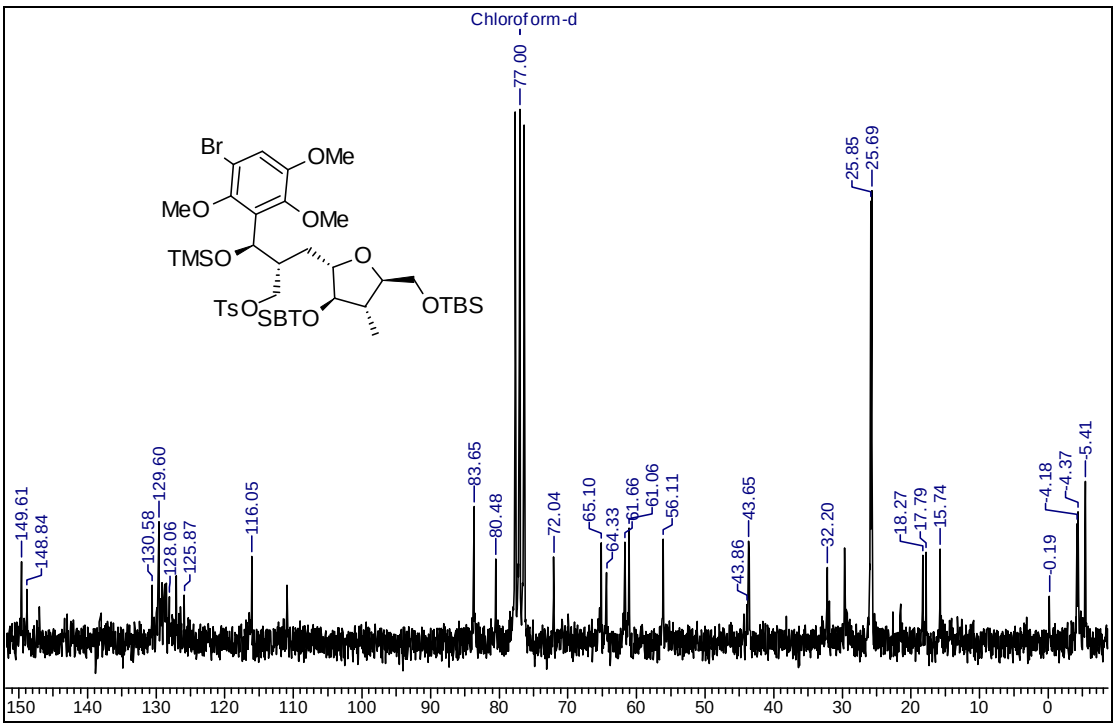
^{1}H NMR Spectrum of 184 in $CDCl_3$



^{13}CNMR Spectrum of 184 in $CDCl_3$



^{1}H NMR Spectrum of 185 in $CDCl_3$



^{13}CNMR Spectrum of 185 in $CDCl_3$

Reference:

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Section-III: Towards synthesis of key fragment of KOSN 1633

INTRODUCTION AND PRESENT WORK

Section-III: Towards synthesis of key fragment of KOSN 1633

Introduction:

In the search of most potent and biologically active molecules that deliver a drug, to cure different types of cancers. It has been identified that the geldanamycin was more potent biologically active Hsp90 inhibitor.[1] The greastest draw back is its low solubility and more cytotoxic. To rectify this problem, derivatisation of geldanamycin was necessary to improve lipophilicity and reduce cytotoxicity of it. For this purpose, different types of geldanamycin derivatives were obtained from direct microbial bioconversion and a genetically engineered geldanamycin producer were isolated and characterized. In this regard, 17-hydroxymethyl-17-demethoxygeldanamycin and 17-formyl-17-demethoxy-18-O,-dihydrogeldanamycin were isolated from S. hygroscopicus NRRL 3602/ Pkos279-78. another important geldanamycin derivative was KOSN-1633 (Figure 21).[2] All these geldanamycin derivatives exhibit reduced cytotoxicity against SKBr3 Cancer cells. KOSN-1633 has significantly two-fold less cytotoxic than 15-hydroxygeldanamycin.[2]

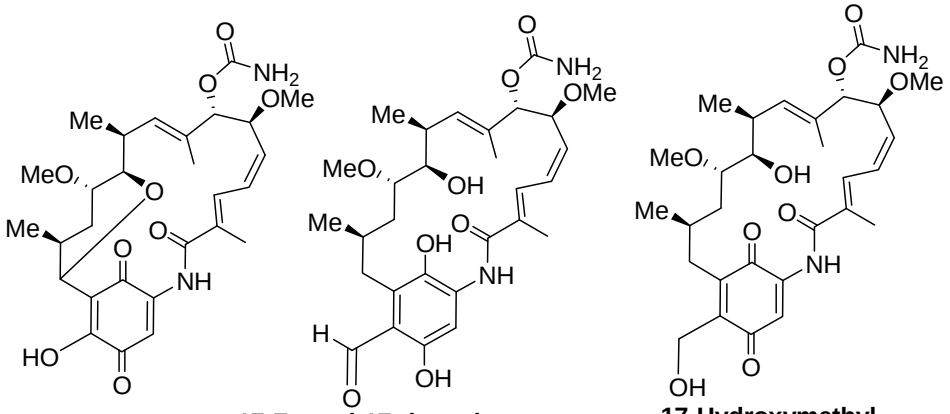


Figure-21: structures of KOSN-1633, KOSN-1645, KOSN-1646

Present Work:

Characterization of KOSN-1633

The tricyclic geldanamycin (KOSN-1633)[1] was isolated as a minor isomer-**I** when geldanamycin was added to the fermentation broth of the S. *hygroscopicus* AM-3672. The structure of KOSN-1633 possess (**I**) a tricyclic core (**II**) cyclization between

C15-OH and C11-OH leads to form highly substitueted tetrahydropyran of ansachain attached to the metaposition of benzoquinone (**III**) along with 17-O-demethylation of 15-hydroxy geldanamycin. A molecular formula of $C_{28}H_{36}N_2O_9$ was established for KOSN-1633 from ^{13}C NMR spectrum and high resolution mass spectral data (ESI TOF MS m/z 567.2303, calculated for $C_{28}H_{36}N_2O_9Na$ ($[M+Na]^+$) 567.2313. carbon-hydrogen connectivity was established using the multiplicity-edited HSQC spectrum, while gsCOSY and ctHMBC data allowed tracing of the carbon-oxygen skeleton. The molecular formula indicates that KOSN-1633 contains one carbon fewer than geldanamycin, and the proton NMR spectrum lacks the 17-methoxy signal displayed by geldanamycin (δ 4.12). the molecular formula also indicates an additional element of unsaturation with respect to geldanamycin, which is accounted for by a cyclic ether joining carbons 11 and 15. The location of this ether linkage is confirmed by an HMBC connecting H-15 (δ 4.51) and C-11 (δ 7.41). One and two-dimensional NMR data are consistent with the rest of the structure being identical to geldanamycin.

Retrosynthetic analysis:

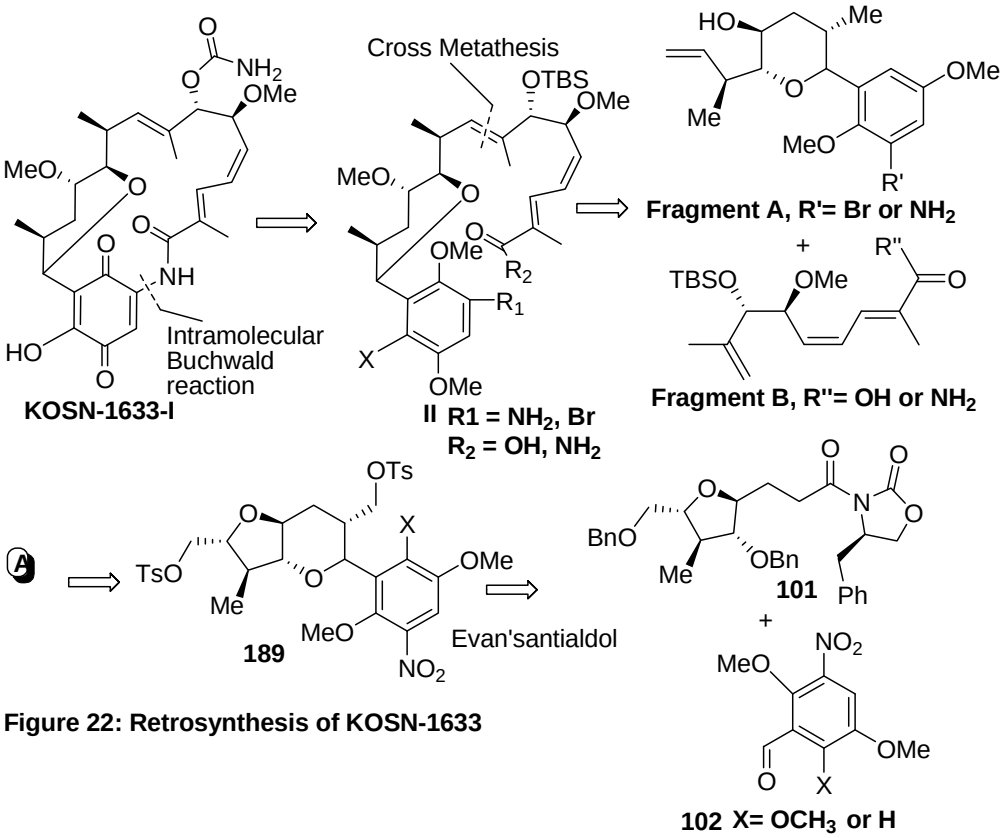


Figure 22: Retrosynthesis of KOSN-1633

As a part of our continuing efforts towards the total synthesis of these class of compounds and the unique structural features motivated us to take up the synthesis of critical fragment of KOSN-1633. The Retrosynthetic plan has been illustrated in Figure: 22, which involved the bond disconnection at C1-N22 resulting int-**II**, further intramolecular Buchwald reaction or intramolecular lactonization would lead to target molecule-I. The crucial Int-**II** can be obtained by assembling key fragments A and B through crossmetathesis. The critical fragment-A can be prepared by using Evans anti aldol protocol from aldehyde-**102** and carbohydrate precursor-**101**.

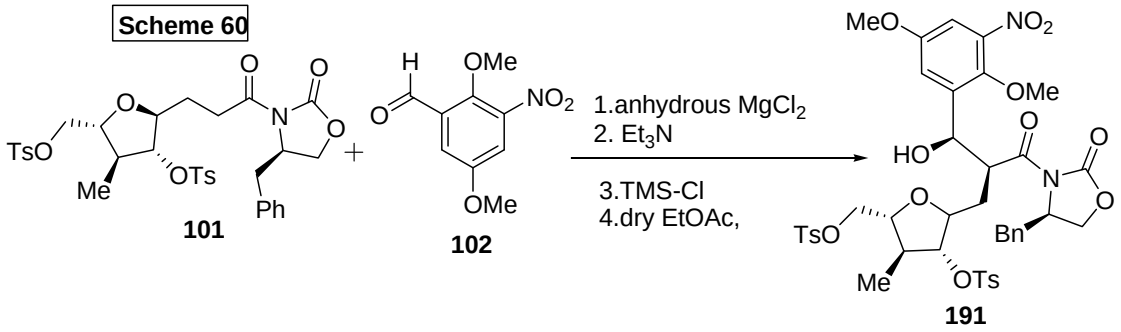
Synthesis of pyranofuranose derivative :

We envisaged that, synthesizing the suitably substituted pyranofuranose ring attached to the aryl ring could be the most challenging endevour in the total synthesis of this target molecule.

Scheme-59

To achieve the desired target, we started with the synthesis of ditosyl derivative-**190** from ealier synthesized dioloxazolidinone derivative-**129** by using TsCl, imidazole, and catalytic DMAP in DCM at rt. The ditosylate oxazolidinone-**190** was confirmed from it's ^{1}H NMR, ^{13} C NMR spectral studies. The characteristic signals of two tosyl groups were observed in ^{1} H NMR spectrum, at δ 2.40 , 2.43 ppm due to $-CH_3$ groups and four A_2B_2 doublets at 7.16, 7,18, 7.67 and 7.68 ppm confimed the structure of **190** (Scheme-59).

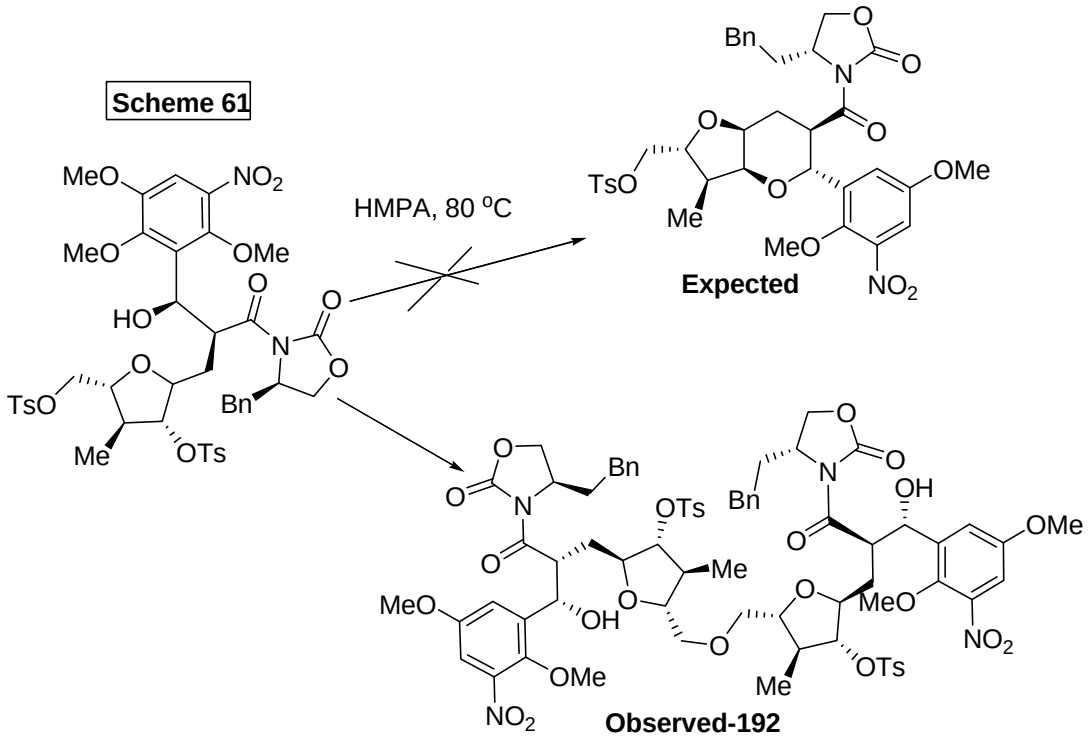
Scheme 60



101 **102** **191**

With the two key intermediates **101** and aldehydes **102** required for asymmetric anti aldol reaction were in hand, our next task was the Evan's anti aldol adduct by appling standard Evan's anti aldol reaction conditions by using $MgCl_2$, triethyl amine as base, chlorotrimethyl silane and dry ethyl acetate.[3] This experiment afforded the OTMS aldol adduct-**191** as a single isomer with excellent yield. The aldol adduct was confirmed by ^{1}H , ^{13}C NMR spectral analysis.

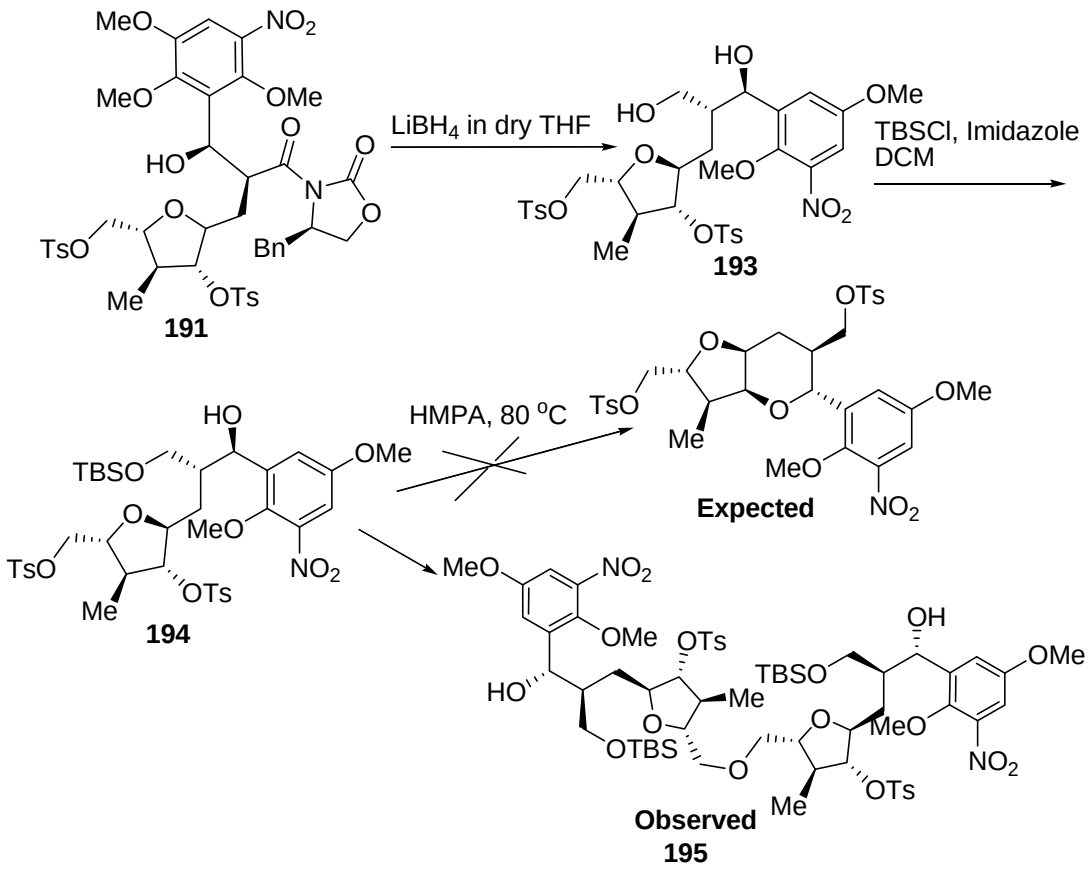
Scheme 61



Once we have the key int-191 with desired stereocenters in hand, our next objective was to make pyranofuranose core. To achieve this, the Evans anti aldol adduct was heated in dry HMPA for 6h. unfortunately, the experiment did not provide us the desired product rather provided an unexcepted dimerised product-**192**. The dimerised

product was formed may be due to presence of bulky oxazolidinone group in the Evans aldol adduct. So we then changed our strategy, accordingly oxazolidinone was removed by reductive hydrolysis using lithium borohydride in dry THF at 0 ^{o}C to give hydrolysed product-**193** (Scheme-62). The structure of hydrolysed product-**193** was confirmed from its ^{1} H NMR in which the peaks due to oxazolidinone were deported and rest of the protons appeared at their excepted chemical shift values. The ^{13} C NMR spectral studies further confirmed the structure of **193**.

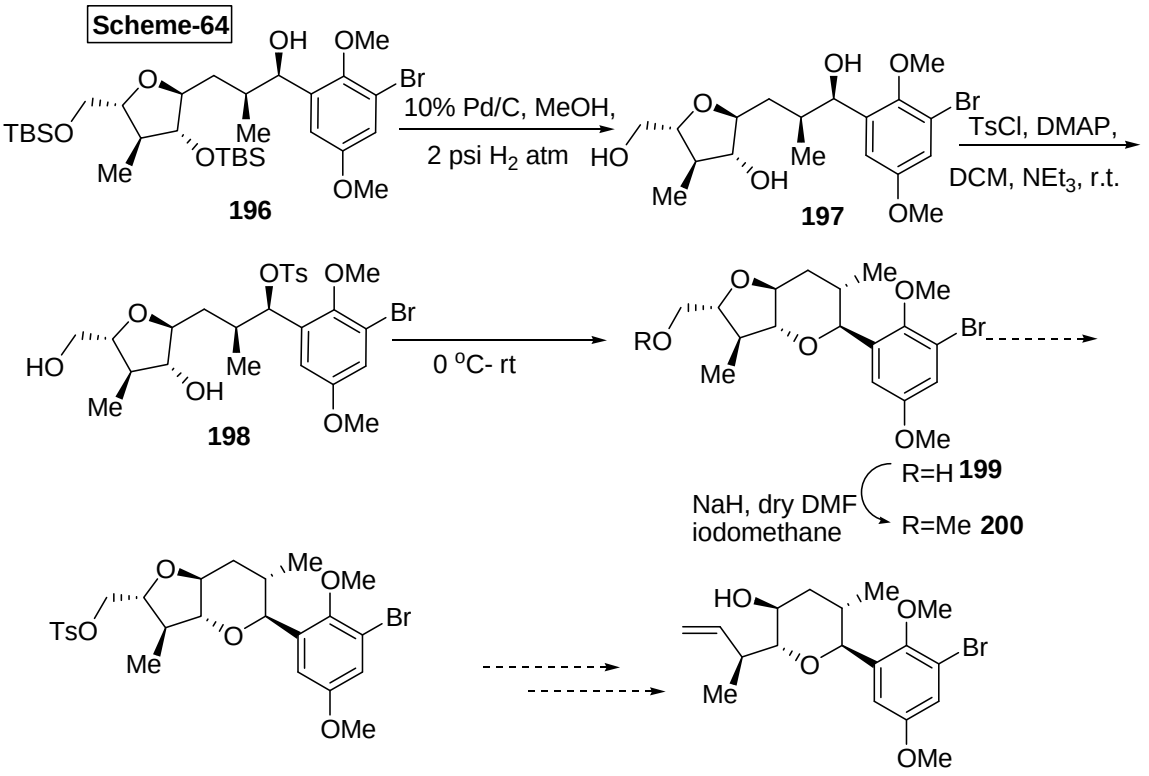
Scheme-62



Selective protection of primary alcohol of **193** by using TBDMSCl, imdazole in DCM to afforded TBS ether-**194**. The structure of **194** was confirmed by it's ^{1}H, ^{13} C NMR spectra. **194** under HMPA/80 ^{o}C condition again failed to give the desired pyranofuranose product, instead afforded a dimerised product **195** as a sole product.

The main cause for this observation is not yet clear; but may be due to bulky tosyl groups present in the aldol adduct. So we redesigned our synthetic strategy again and try the cyclization by keeping free hydroxyl group. .

Synthesis of Pyranofuranose unit:



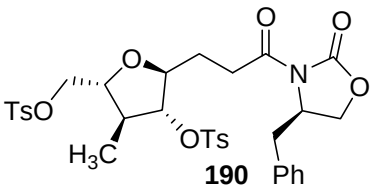
Accordingly, the benzylic OH group of triol-**197** was selectively protected as tosylate-**198** by using TsCl, Et_3N, DMAP, in DCM at r.t. The structure of **198** was confirmed from spectral and other analytical data.

At this stage the the tosylate derivative-**198** was treated with strong base (NaH in DMF) which fortunately affored the expected pyranofuranoside as a sole product-**199**. The structural conformation was done by extensive spectral studies (including ^{1}H ,^{13}C NMR, COSY, NOESY spectral studies) of its methyl derivative-**200**, which was prepared by using iodomethane, strong base NaH in DMF at $0^{o}C$. Further work was going on in our laboratory to complete the total synthesis of KOSN-1633.

EXPERIMENTAL

Experimental section: Analytical data of KOSN-1633

((2R,3S,4R,5S)-5-(3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-oxopropyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (190).



190

To a stirred solution of diol-**129** (3.2 g, 8.81 m.mol), Et_3 N (3.68 mL, 26.44 m.mol), and DMAP (30 mg), in dichloromethane (30 mL) was added p-toluenesulfonyl chloride (3.86 g, 26.44 m.mol), at 0^oC. The reaction mixture was stirred for 12h at room temperature, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:4) to afford di-tosyl derivative-**190** (5.2 g, 88 %)as a syrup liquid. R_f 0.5(25 % ethyl acetate/hexane).

Mol. Formula : $C_{33}H_{37}NO_{10}S_2$

$[\alpha]_D^{25}$: -25.69 (*c* = 1.4, $CHCl_3$)

IR ($CHCl_3$) υ : 667, 1019, 1216, 1701, 1781,2400, 3025,3436 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.95 (d, *J* = 6.8, 3H), 1.79 (qn, *J* = 7.5, 14.4, 1H), 1.87 (dq, *J* = 6.7,18, 1H), 2.18 (hex, *J* = 7.3, 14.1, 1H), 2.44 (s, 3H), 2.46 (s, 3H), 2.74 (dd, *J* = 9.8, 13.3, 1H), 2.88 (dt, *J* = 7.5, 17.1, 1H), 2.95 (dt, *J* = 7.5, 17.1, 1H), 3.27 (dd, *J* = 3.1, 13.1, 1H), 3.74 (q, *J* = 5.1, 9.3, 1H), 3.93 (qn, *J* = 4.45, 8.9, 1H), 4.01 (ddd, *J* = 4.26, 10.7, 2H), 4.17 (dd, *J* = 9.1, 16.7 , 2H), 4.33 (t, *J* = 5.37, 1H), 4.65 (ddd, *J* = 3.2, 6.9, 12.7, 1H), 7.21 (d, *J* = 7.04, 2H), 7.25-7.29 (m, 1H), 7.32-7.38 (m, 6H,), 7.76 (d, *J* = 8.34, 2H), 7.80 (d, *J* = 8.34, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 15.05 (q, CH_3), 21.55 (q, CH_3), 21.60 (q, CH_3), 26.68 (t, CH_2), 31.55 (t, CH_2),37.66(t, CH_2), 41.76 (d, CH), 55.10 (d, CH), 66.17 (t, CH_2), 69.39 (t, CH_2), 80.66 (d, CH), 81.06 (d, CH), 88.77 (d, CH), 127.22 (d, CH), 127.82 (d, CH), 127.87 (d, CH), 129.00 (d, CH), 129.34 (d, CH), 129.94 (d, CH), 131.06 (s, C),

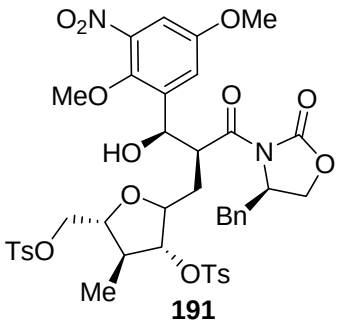
133.28 (s, C), 135.29 (s, C), 144.95 (s, C), 145.23 (s, C), 153.37 (s, C), 172.29 (s, C) ppm.

ESI-MS (*m/z*) : 694.52 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 59.00; H, 5.55; N, 2.09 %

Found: C, 59.03; H, 5.57; N, 2.06%

((2R,3S,4R)-5-((S)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-((R)-(2,5-dimethoxy-3-nitrophenyl)(hydroxy)methyl)-3-oxopropyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (191).



191

Oxazolidinone derivative-**190** (332g,0.52m.mol) was treated with $MgCl_2$ (5mg,0.052m.mol), triethylamine (106mg, 0.146mL, 1.05m.mol), benzaldehyde-**102** (133mg, 0.631m.mol) and chlorotrimethylsilane (85mg, 0.10mL, 0.789m.mol) in 6 mL of ethylacetate at 23 ^oC for 20h. The yellow slurry was pushed through a plug of silica (2cm x 10cm) with 100 mL of diethyl ether. The ether solution was concentrated *in vacuo* to get residue. The residue was purified on silica gel 230-400 by eluting with EtOAC-hexane (1:12) to give free hydroxyl aldol adduct-**191** (0.411g, 94 %), as a single isomer with excellent yeild (light yellowcolor liquid). R_f 0.5(10 % ethyl acetate/hexane).

Mol. Formula : $C_{42}H_{46}N_2O_{15}S_2$

$[\alpha]_D^{25}$: -24.62 (*c* = 0.3, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1051, 1216, 1694, 1778,2402, 3022,3454 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.76 (d, *J* = 6.75, 3H), 1.72 (dq, *J* = 3.3, 14.3, 1H), 2.03 (q, *J* = 6.7, 2H), 2.23 (td, *J* = 3.9, 10.5, 24, 1H), 2.44 (s, 3H), 2.47 (s, 3H), 2.58 (dd, *J* = 9.5, 13.6, 1H), 3.23 (dd, *J* = 2.3,13.5, 1H), 3.51-3.55 (m, 1H), 3.81 (s, 3H), 3.86-3.88 (m, 3H), 3.92 (s, 3H), 4.04 (dd, *J* = 2.3, 9.1, 1H), 4.21 (t, *J* = 8.2, 1H), 4.31 (t, *J* = 7.3, 1H), 4.61 (td, *J* = 2.7, 7.1, 17.3, 1H), 4.70 (t, *J* = 8.7, 1H), 5.18

(dd, *J* = 7.2, 9.1, 1H), 7.14 (d, *J* = 7.2, 2H), 7.26-7.33 (m, 7H), 7.38 (d, *J* = 8.1, 2H), 7.70 (d, *J* = 8.1, 2H), 7.79 (d, *J* = 8.1, 2H) ppm.

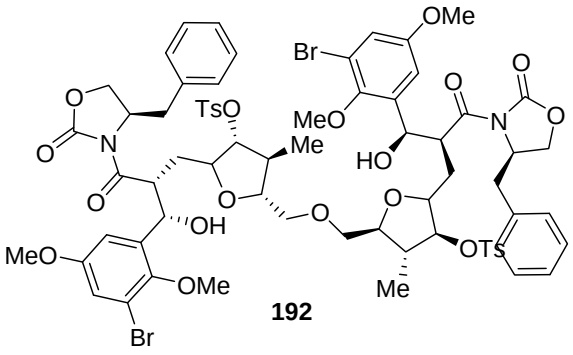
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.09 (q, CH_3), 14.26 (q, CH_3), 21.53 (q, CH_3), 21.58 (q, CH_3), 31.17 (t, CH_2), 37.71 (t, CH_2), 40.67 (d, CH), 43.85 (d, CH), 55.38 (d, CH), 55.92 (q, CH_3),60.30 (d, CH), 63.08 (q, CH_3),66.06 (t, CH_2), 69.65 (t, CH_2), 71.01 (d, CH), 78.88 (d, CH), 80.76 (d, CH), 86.09 (d, CH), 109.29 (d, CH), 118.67 (d, CH), 127.19 (d, CH), 127.72 (d, CH), 127.90 (d, CH), 128.80 (d, CH), 129.26 (d, CH), 129.86 (d, CH), 129.95 (d, CH), 132.46 (d, CH), 132.94 (s, C), 135.15 (s, C), 139.14 (s, C), 143.46 (s, C), 144.92 (s, C), 145.07 (s, C), 145.35 (s, C), 153.94 (s, C), 155.18 (s, C), 174.77 (s, C) ppm.

ESI-MS (*m/z*) : 905.45 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 57.13; H, 5.25; N, 3.17 %

Found: C, 57.15; H, 5.26; N, 3.19 %

(3R,4S,5R)-5-((((2S,3R,4S)-5-((S)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-((R)-(3-bromo-2,5-dimethoxyphenyl)(hydroxy)methyl)-3-oxopropyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methoxy)methyl)-2-((R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-((S)-(3-bromo-2,5-dimethoxyphenyl)(hydroxy)methyl)-3-oxopropyl)-4-methyltetrahydrofuran-3-yl 4-methylbenzenesulfonate (192).



192

The aldol adduct-**191** (0.14g, 0.15mmol) was taken in a HMPA and maintained temperature at 80^{o}C for 6h. the reaction mixture was worked up to give the residue, which was purified on silica gel by eluting with EtOAc-hexane (1:8) to give **192** (0.12g, 50 %)as a syrup liquid. R_f 0.5 (30 % ethyl acetate/hexane).

Mol. Formula : $C_{70}H_{78}Br_2N_2O_{21}S_{22}$

$[\alpha]_D^{25}$: +11.65 (*c* = 0.2, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 759, 1048, 1216, 1599, 1729, 2400, 3017 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.81 (d, *J* = 6.7, 3H), 0.78 (dq, *J* = 3.2,6.7, 14.3, 2H), 2.18 (hex, *J* = 6.7, 1H), 2.31 (ddd, *J* = 4.5, 10.3, 14.4, 1H,), 2.47 (s, 3H), 2.55 (dd, *J* = 9.8, 13.4, 1H), 3.24 (dd, *J* = 3.1, 13.5, 1H), 3.44 (dd, *J* = 6.1, 11.5, 1H), 3.50 (dd, *J* = 4.1, 11.5, 1H), 3.53-3.56 (m, 1H), 3.81 (m, 3H), 3.95 (s, 1H), 4.00 (dt, *J* = 6.1, 10.7, 1H), 4.07 (dd, *J* = 2.5, 9.2, 1H), 4.17 (t, *J* = 8.2, 1H), 4.40 (t, *J* = 6.7, 1H), 4.65-4.70 (m, 2H), 5.2 (d, *J* = 6.1, 1H), 7.15 (d, *J* = 7.1, 2H,), 7.25-7.35 (m, 5H), 7.38 (d, *J* = 8.1, 2H), 7.81 (d, *J* = 8.1, 2H) ppm.

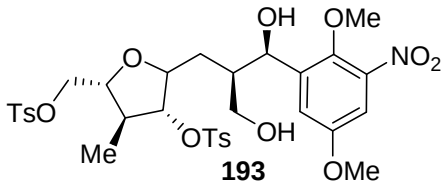
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.65 (q, CH_3), 21.68 (t, CH_2), 31.42 (q, CH_3), 37.90 (d, CH), 42.46 (d, CH), 43.84 (t, CH_2), 45.93 (d, CH), 55.55 (q, CH_3), 56.02 (q, CH_3), 63.20 (d, CH), 66.10 (t, CH_2), 71.27 (d, CH), 79.34 (t, CH_2), 82.99 (d, CH), 86.48 (d, CH), 109.35 (d, CH), 115.46 (s, C), 118.72 (d, CH), 127.36 (d, CH), 128.02 (d, CH), 128.96 (d, CH), 130.03 (d, CH), 133.14 (s, C), 135.15 (s, C), 139.18 (s, C), 143.56 (s, C), 145.07 (s, C), 145.40 (s, C), 153.81 (s, C), 155.25 (s, C), 175.09 (s, C) ppm.

ESI-MS (*m/z*) : 1530.39 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 55.78; H, 5.22 ;N, 1.86%

Found: C, 55.79; H, 5.24; N, 1.88%

((2R,3S,4R)-5-((2R,3R)-3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxy-2-(hydroxymethyl)propyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (193).



193

The aldol adduct-**191** (0.35g,0.39m.mol), 10 mL of drydiethylether and anhydrous methanol (0.04 mL) were cooled to 0 ^{o}C. Lithium borohydrate (2.0M in THF , 0.51 mL 1quiv) was added dropwise, and the mixture was stirred for 2h at 0 ^{o}C . The reaction was quenched with 15% NaOH and then concentrated in vacuo. The aqueous layer was extracted with ether , and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave of diol **193** (0.186g, 66%). R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{32}H_{39}NO_{13}S_2$

$[\alpha]_D^{25}$: +1.71 (*c* = 0.96, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 1051, 1216, 1694, 1778,2402, 3022,3454 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.93 (d, *J* = 6.75, 3H), 1.58 (dq, *J* = 5.6, 14.7, 19.4, 1H), 1.73 (dd, *J* = 2.3, 8.2, 1H,), 1.76 (br.s, 1H), 1.99-2.02 (m, 1H), 2.18 (q, *J* = 6.7, 13.9, 1H,), 2.43 (s, 3H), 2.45 (s, 3H), 2.71 (br.s, 1H), 3.48 (dd, *J* = 3.1, 11.1, 1H,), 3.63 (dd, *J* = 2.3, 1.1, 1H,), 3.71 (qn, *J* = 4.9, 8.1, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 3.85 (d, *J* = 4.4, 1H), 4.02-4.04 (m, 2H), 4.25 (t, *J* = 5.8, 1H), 5.14 (br.s, 1H), 7.32-7.37 (m, 6H), 7.72-7.80 (m, 4H) ppm.

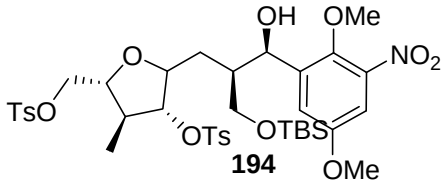
^{13}C NMR (125 MHz, $CDCl_3$) : δ 14.79 (q, CH_3), 21.55 (q, CH_3), 21.58 (q, CH_3), 31.22 (t, CH_2), 41.38 (d, CH), 41.78 (d, CH), 55.95 (q, CH_3), 62.38 (q, CH_3), 62.69 (t, CH_2), 69.34 (t, CH_2), 71.81 (d, CH), 80.33 (d, CH), 80.53 (d, CH), 89.50 (d, CH), 108.54 (d, CH), 118.76 (d, CH), 127.68 (d, CH), 127.78 (d, CH), 129.89 (d, CH), 129.97 (d, CH), 132.53 (s, C), 133.09 (s, C), 140.53 (s, C), 143.51(s, C), 143.98 (s, C), 145.13 (s, C), 145.43 (s, C), 155.20 (s, C). ppm.

ESI-MS (*m/z*) : 732.86 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 54.15; H, 5.54; N, 1.97 %

Found: C, 54.17; H, 5.57; N, 1.98 %

((2R,3S,4R)-5-((2R,3R)-2-((tert-butyldimethylsilyloxy)methyl)-3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxypropyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate(194).



194

A mixture of diol-**193** (0.15g, 0.211m.mol), imidazole (0.015 g, 0.232 m.mol), TBDMSCl (0.035g, 0.23m.mol) and DMAP (14mg) in CH_2Cl_2 (15 mL) was stirred for 6h at room temperature. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by eluting with EtOAC-hexane (1:4) to give TBS ether derivative-**194** (0.132g, 76 %), as a colorless liquid. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{38}H_{53}NO_{13}S_2Si$

$[\alpha]_D^{25}$: -2.85 (*c* = 2.1, $CHCl_3$)

IR ($CHCl_3$) υ : 666, 1051, 1216, 1719, 3020, 3412 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.10 (s, 6H), 0.90 (s, 9H), 0.93 (d, *J* = 7.2, 3H), 1.59 (dq, *J* = 5.6, 16.6, 1H,), 1.74 (dd, *J* = 7.1, 14.4, 1H,), 2.02-2.07 (m, 2H), 2.18 (q, *J* = 7.1, 14.4, 1H,), 2.43 (s, 3H), 2.46 (s, 3H), 3.48 (dd, *J* = 3.97, 11.3, 1H), 3.64 (dd, *J* = 2.5, 11.3, 1H), 3.71 (qn, *J* = 5.1, 8.5, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.00-4.08 (m, 3H), 4.25 (t, *J* = 5.75, 1H), 5.14 (d, *J* = 4.45, 1H), 7.32-7.37 (m, 6H), 7.72-7.80 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ -3.63 (q, CH_3), 14.86 (q, CH_3), 17.95 (s, C), 21.61 (q, CH_3), 25.61 (q, CH_3),), 25.76 (q, CH_3), 31.36 (t, CH_2), 41.42 (d, CH), 41.83 (d, CH), 56.02 (q, CH_3), 62.48 (t, CH_2), 62.73 (q, CH_3), 69.34 (t, CH_2), 71.93 (d, CH), 80.38 (d, CH), 80.62 (d, CH),

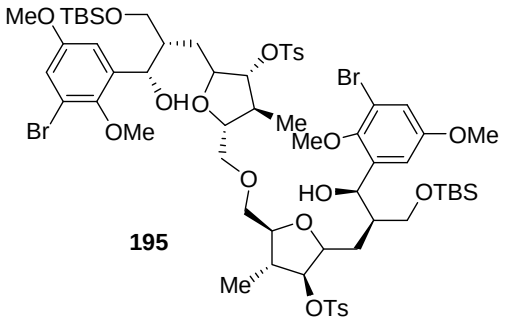
89.45 (d, CH), 108.61 (d, CH), 118.82 (d, CH), 127.87 (d, CH), 129.94 (d, CH), 130.02 (s, C), 132.60 (s, C), 133.14 (s, C), 140.52 (s, C), 143.57 (s, C), 144.02 (s, C), 145.17 (s, C), 145.47 (s, C), 155.27 (s, C) ppm.

ESI-MS (*m/z*) : 845.98 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 55.39; H, 6.48; N, 1.70 %

Found: C, 55.40; H, 6.50; N, 1.71 %

(3S,4R,5S)-2-((2R,3R)-3-(3-bromo-2,5-dimethoxyphenyl)-2-((tert-butyldimethylsilyloxy)methyl)-3-hydroxypropyl)-5-((((2R,3S,4R)-5-((2S,3S)-3-(3-bromo-2,5-dimethoxyphenyl)-2-((tert-butyldimethylsilyloxy)methyl)-3-hydroxypropyl)-3-methyl-4-(tosyloxy)tetrahydrofuran-2-yl)methoxy)methyl)-4-methyltetrahydrofuran-3-yl 4-methylbenzenesulfonate (195).



195

The compound-**194** (0.12g, 0.14mmol) was taken in a HMPA and maintained temperature at 80°C for 6h. the reaction mixture was worked up to give the residue, which was purified on silica gel by eluting with EtOAc-hexane (1:8) to give-**195** (0.11g, 54 %)as a syrup liquid. R_f 0.5(30 % ethyl acetate/hexane).

Mol. Formula : $C_{62}H_{92}Br_2O_{17}S_2Si_2$

$[\alpha]_D^{25}$: +7.41 (*c* = 0.25, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 759, 1048, 1216, 1599, 1729, 2400, 3017 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.07 (s, 6H), 0.92 (s, 9H), 0.97 (d, *J* = 6.7, 3H), 1.61-1.63 (m, 1H), 1.62 (s, 1H), 1.83 (dq, *J* = 2.5, 8.5, 14.3, 1H), 2.11-2.5 (m, 1H), 2.34 (qn, *J* = 6.7, 1H), 2.46 (s, 3H), 3.54 (dd, *J* =

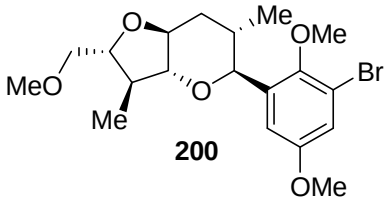
5.1, 11.5, 1H), 3.61 (dd, *J* = 5.1, 11.5, 1H), 3.67 (dt, *J* = 5.2, 7.2, 2H), 3.84 (s, 6H), 4.08 (dq, *J* = 2.8, 5.2, 11.1, 1H), 4.30 (t, *J* = 5.5, 1H), 4.56 (d, *J* = 6.6, 1H), 5.10 (dd, *J* = 5.2, 15.6, 1H), 7.35-7.37 (m, 4H), 7.79 (d, *J* = 8.3, 2H) ppm.

ESI-MS (*m/z*) : 438.42$[M+Na]^+$.

Elemental Analysis Calcd.: C, 53.59; H, 6.67 %

Found: C, 53.61; H, 6.69 %

(3S,6R)-5-(3-bromo-2,5-dimethoxyphenyl)-hexahydro-2-(methoxymethyl)-3,6-dimethyl-2H-furo[3,2-b]pyran (200).



200

The compound **198** (0.12g, 0.21mmol) in dry DMF (8mL) was cooled to 0°C and NaH (60% dispersion in oil,0.01g, 0.25mmol) was added portion-wise at 0°C. After 1h, again remaining NaH (60% dispersion in oil,0.01g, 0.25mmol) was added portion-wise at 0 °C followed by iodo methane 0.03g(0.016mL, 0.25mmol) was added . After 3 h, the reaction mixture was worked up to give the residue, which was purified on silica gel by eluting with EtOAc-hexane (1:7) to give **200** (0.058g, 67%)as a syrup liquid. R_f 0.5(20 % ethyl acetate/hexane).

Mol. Formula : $C_{19}H_{27}BrO_5$

$[\alpha]_D^{25}$: -9.53 (*c* = 0.7, $CHCl_3$)

IR ($CHCl_3$) υ : 668, 759, 1048, 1216, 1599, 1729, 2400, 3017 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.90 (d, *J* = 6.7, 3H), 0.98 (d, *J* = 6.7, 3H), 1.31 (ddd, *J* = 5.1, 8.7, 14.1, 1H), 1.57 (ddd, *J* = 5.1, 8.7, 14.1, 1H), 1.91-1.99 (m, 1H), 2.12 (q, *J* = 6.7, 1H), 3.23 (s, 3H), 3.74-3.75 (m, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 3.98 (dt, *J* = 2.1, 6.7, 10.1, 2H), 4.14 (s, 1H), 4.36 (d, *J* = 5.3, 1H), 6.84 (d, *J* = 3.1, 1H), 6.98 (d, *J* = 3.1, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 9.93 (q, CH_3), 14.18 (q, CH_3), 35.40 (t, CH_2), 36.41 (d, CH), 41.53 (d, CH), 55.76 (q, CH_3), 57.40 (q, CH_3), 61.16 (q, CH_3),

	73.54 (t, CH_2), 79.90 (d, CH), 81.56 (d, CH), 82.64 (d, CH), 83.11 (d, CH), 112.15 (d, CH), 117.11 (s, C), 117.42 (d, CH), 136.83 (s, C), 149.05 (s, C), 156.27 (s, C) ppm.
ESI-MS (*m/z*)	: 437.09$[M+Na]^+$.
Elemental Analysis	Calcd.: C, 54.95; H, 6.55 %
	Found: C, 54.96; H, 6.57 %

NOESYPH
ppm
MeO
Me
O
Me
OMe
Br
OMe
200

BRUKER
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PROCNO 1
F2 - Acquisition Parameters
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DE 6.00 usec
TE 296.2 K
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P1 10.50 usec
PL1 -2.00 dB
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TD 512
SFO1 500.1321 MHz
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SW 7.297 ppm
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SSB 0
LB 0.00 Hz
GB 0
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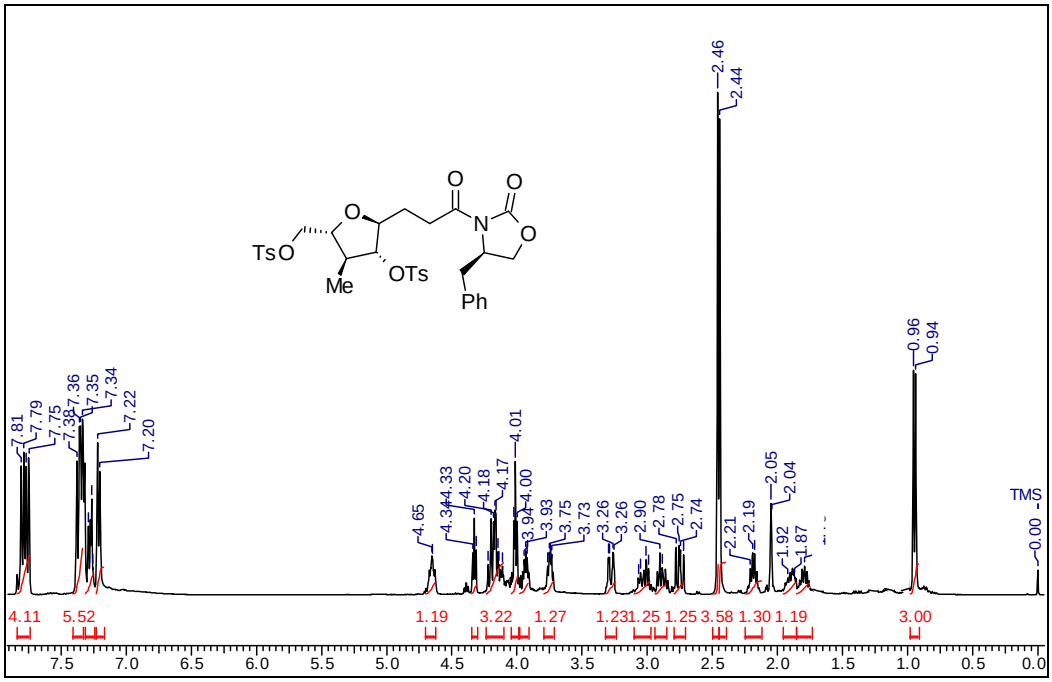
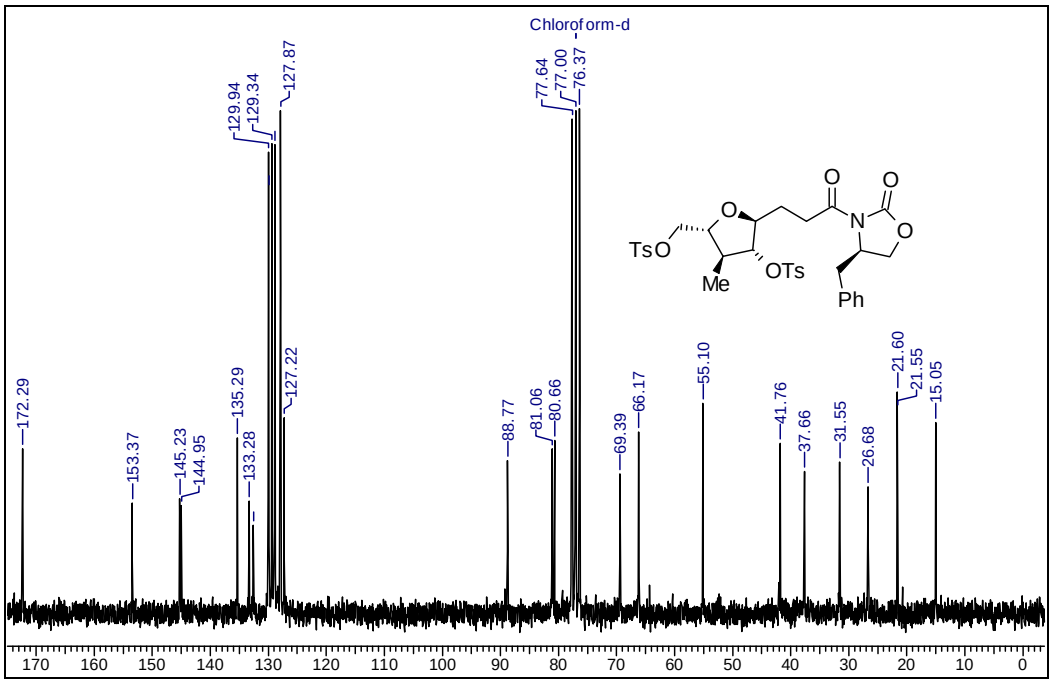
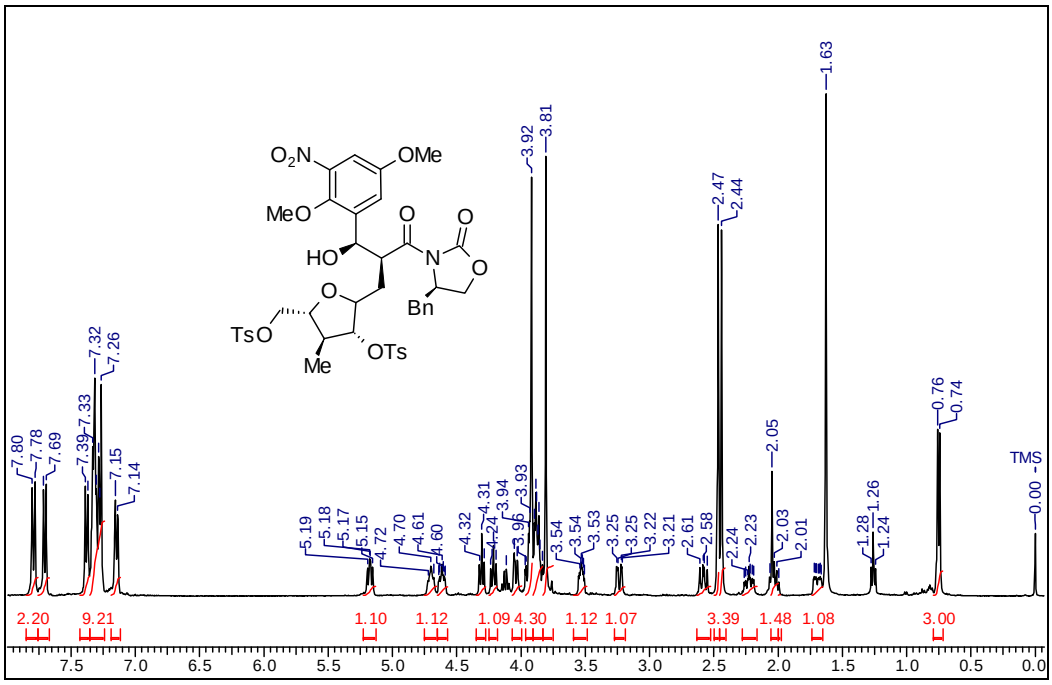
SPECTROSCOPIC DATA



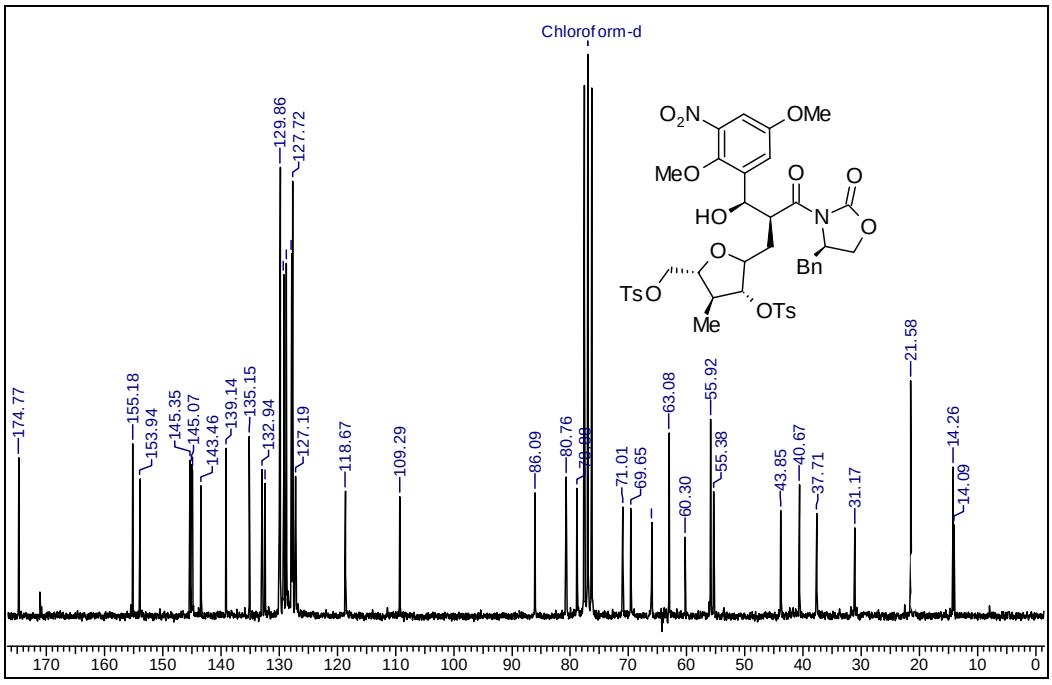
^{1}H NMR Spectrum of di-Tosyl oxazolidinone 190 in $CDCl_3$



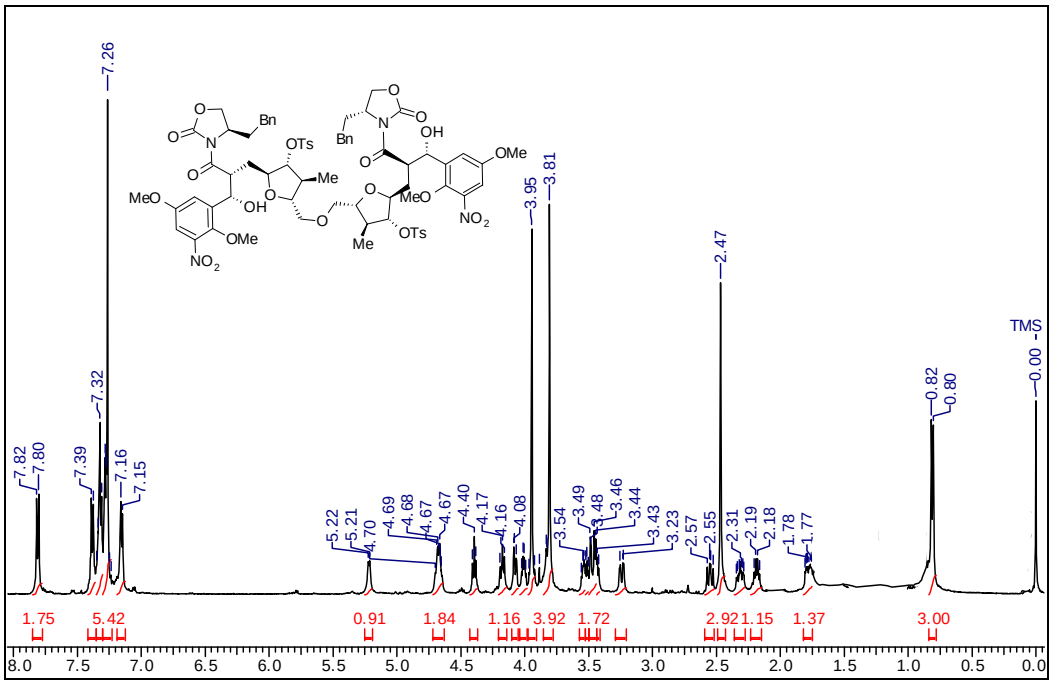
^{13}CNMR Spectrum of di-Tosyl oxazolidinone 190 in $CDCl_3$



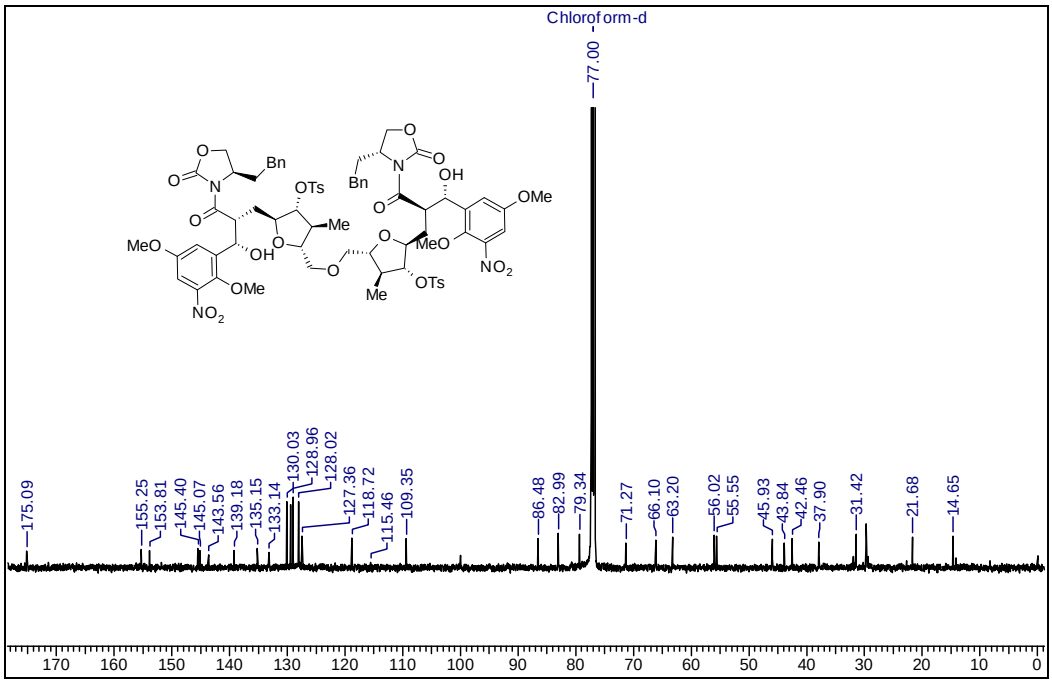
^{1}H NMR Spectrum of di-Tosyl aldol adduct 191 in $CDCl_3$



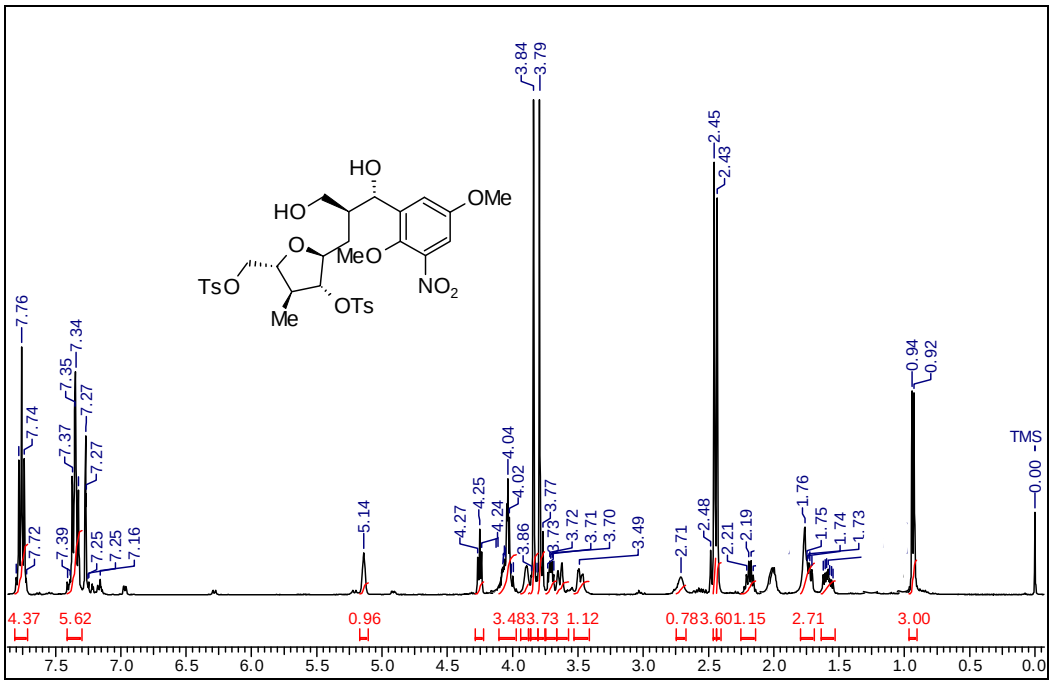
^{13}CNMR Spectrum of di-Tosyl aldol adduct 191 in $CDCl_3$



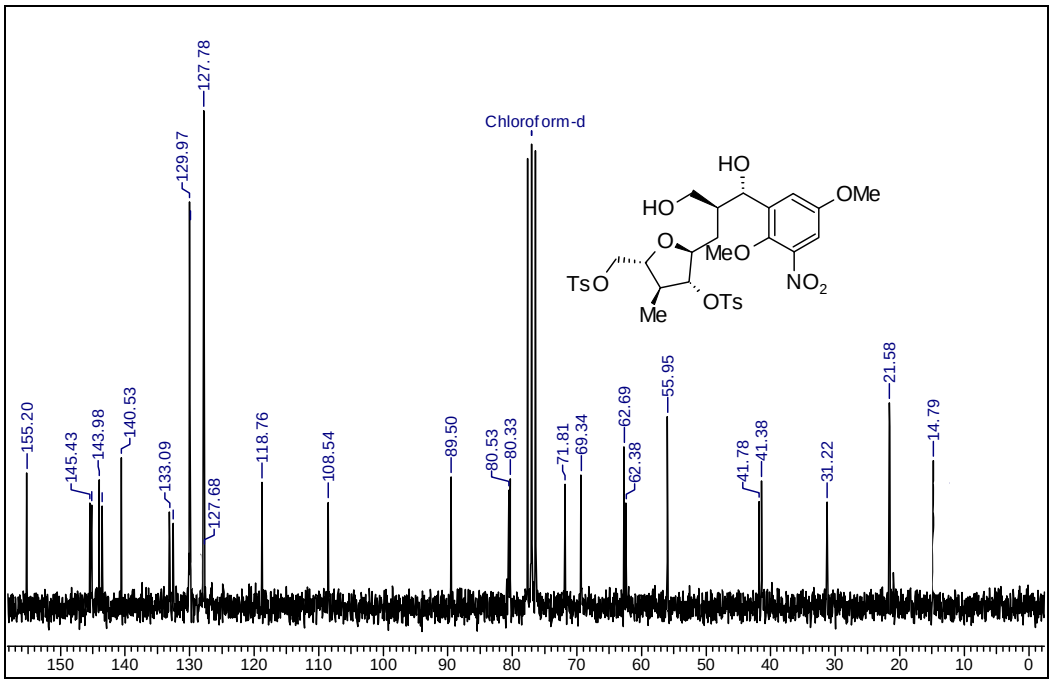
^{1}H NMR Spectrum of 192 in $CDCl_3$



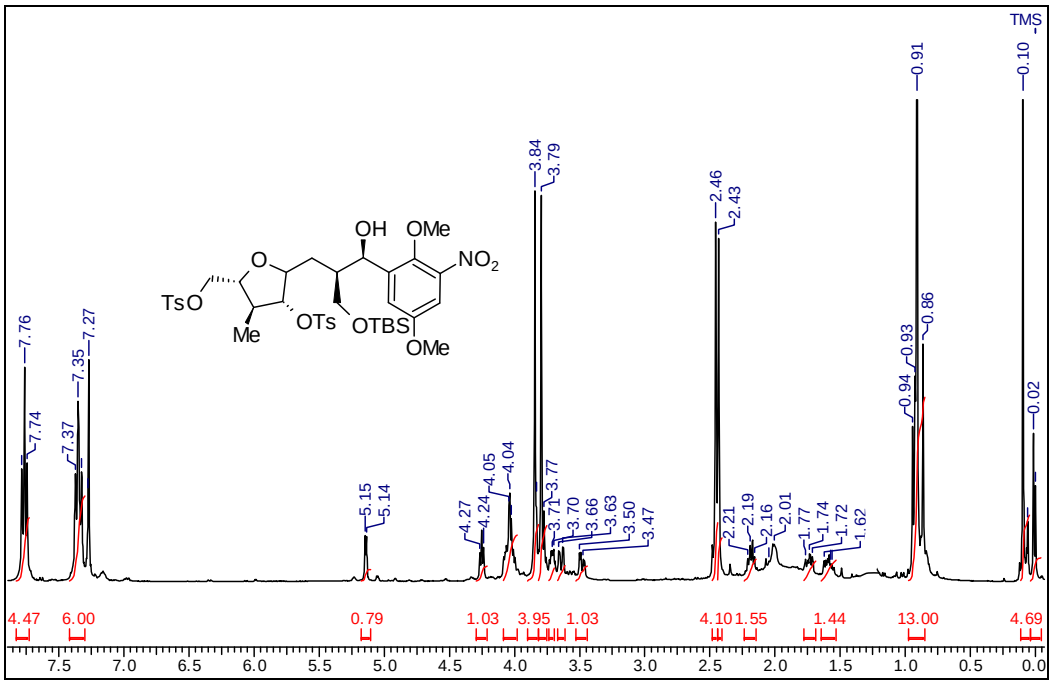
^{13}CNMR Spectrum of 192 in $CDCl_3$



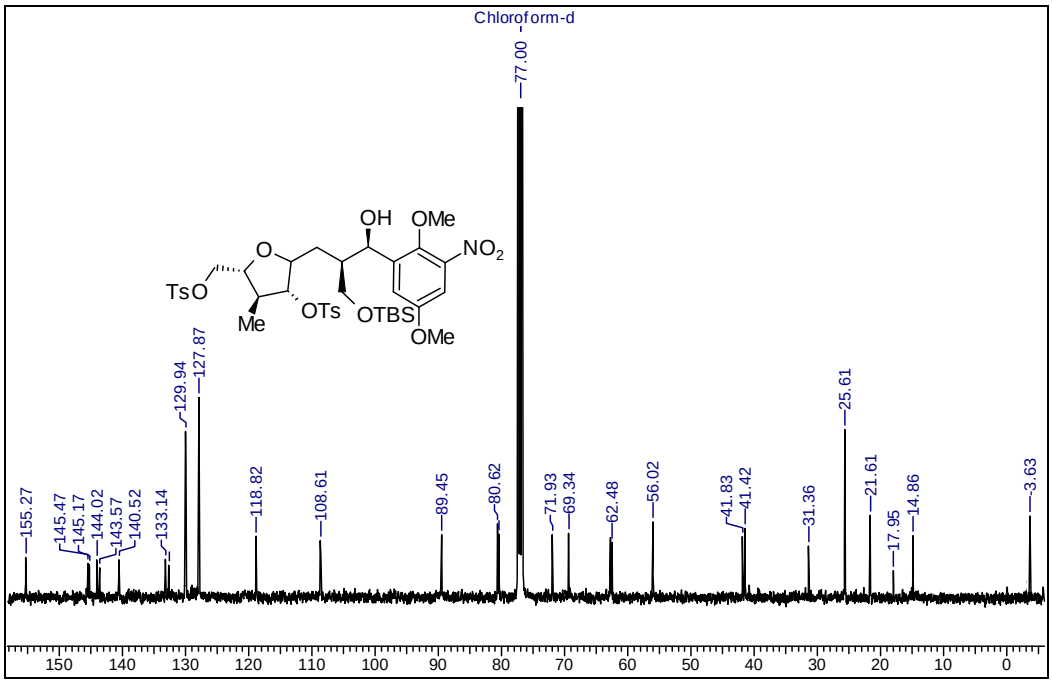
^{1}H NMR Spectrum of 193 in $CDCl_3$



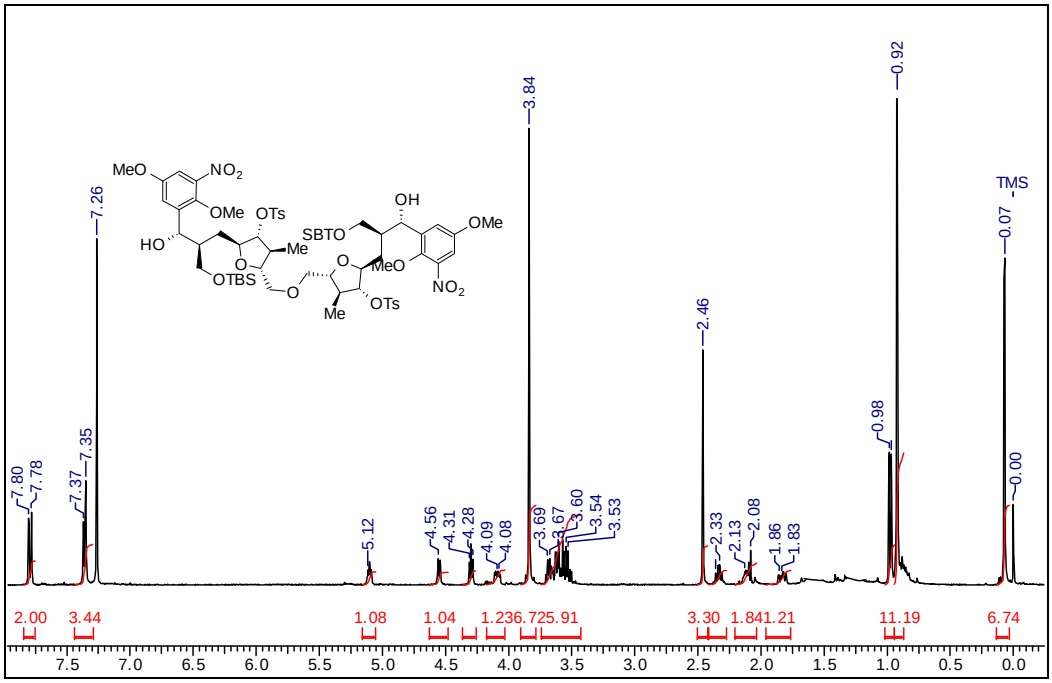
^{13}CNMR Spectrum of 193 in $CDCl_3$



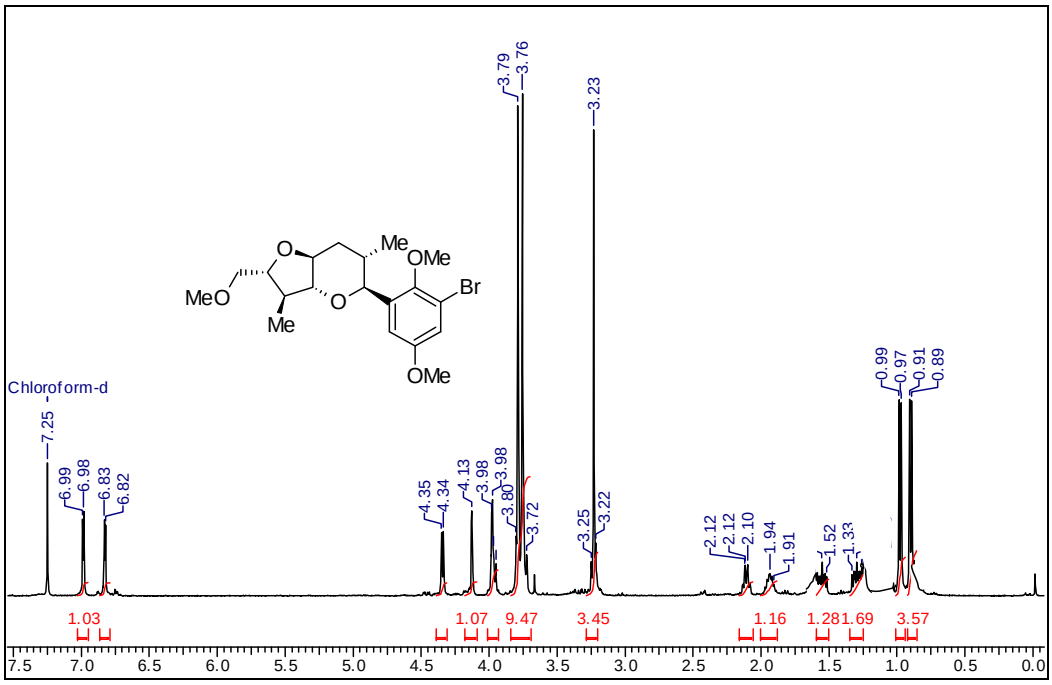
^{1}H NMR Spectrum of 194 in $CDCl_3$



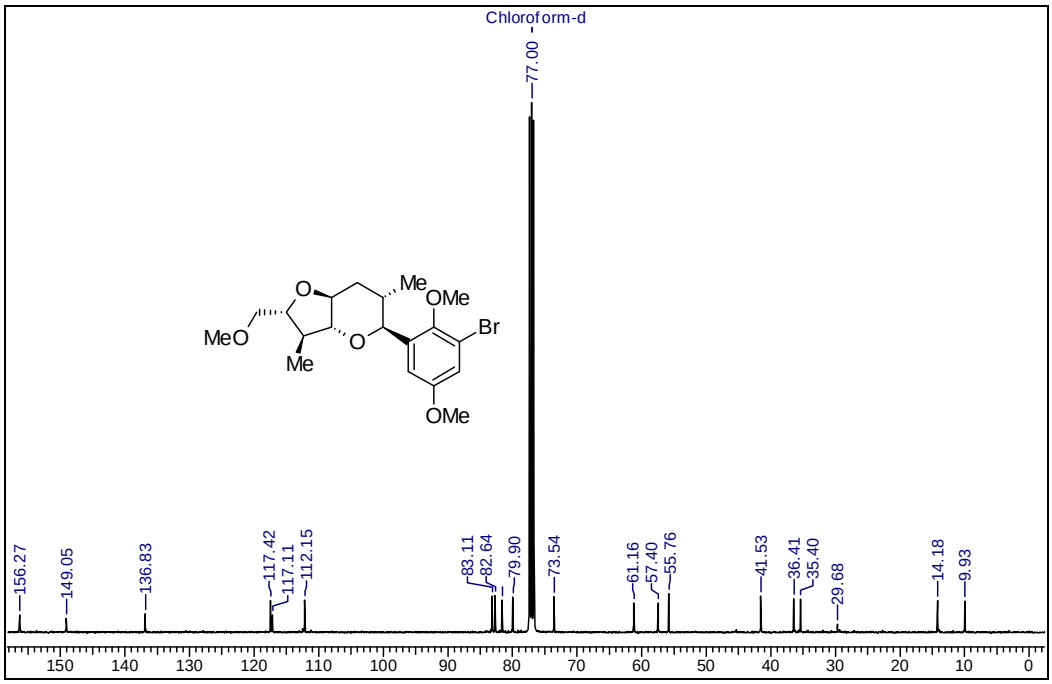
^{13}CNMR Spectrum of 194 in $CDCl_3$



^{1}H NMR Spectrum of di-Tosyl aldol adduct 195 in $CDCl_3$



^{1}H NMR Spectrum of 200 in $CDCl_3$



^{13}CNMR Spectrum of 200 in $CDCl_3$

Reference:

(1) Uehara, Y. *Curr*. *Cancer Drug Targets* **2003**, *3*, 325-330.

(2) Zhihao Hu, Yaoquan Liu, Zong-Qiangtian, Wei Ma, Courtney M Starks, Rika Regentin, Peter Licari, David C. Myles and C.Richard Hutchinson. *J. Antibiot.* **2004**, *57*, 421-428.

(3) (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc*. **2002**, *124*, 392-393 (b) David A. Evans,; C. Wade Downey,; Jared T. Shaw,; Jason S. Tedrow,; *Org. Lett.* **2002**, *4*, 1127-1130.

List of Publications

1. "Towards synthesis of subunits (C8-C21) of Herbimycin A and 15-Hydroxy geldanamycin by applying Anhydrous $MgCl_2$ catalysed Non-Evan's *anti* aldol reaction: Observation of a rare restricted conformational isomers" (manuscript under revision)

M.k.Gurjar, **Rambabu Dakarapu,** Narendra Tripathy, and Rajesh Gonnade.

2. "A Rare restricted Conformational isomerism exhibited by Carbohydrate derived Non-Evans anti aldol adducts" (manuscript under revision)**.**

M.k.Gurjar, **Rambabu Dakarapu,** Narendra Tripathy, and Rajesh Gonnade.

3. "Synthetic studies towards Central core of KOSN-1633 (synthesis of Pyranofuranose C8-C22 Fragment)" (manuscript under revision)**.**

M.k.Gurjar, **Rambabu Dakarapu,** Narendra Tripathy, and Rajesh Gonnade.