Synthetic Studies Toward the Skipped 1,3-Polyol Natural Products and Some Pd-Mediated Reactions of Sugar Alkynols

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO
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BY
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Dr. M. N. Deshmukh

(Research Guide)

ORGANIC CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE-411008

MAY 2008

DEDICATED

TO

MY BELOVED PARENTS,
BROTHER, SIS-IN-LAW and NANDU,
WIFE.

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. N. Deshmukh**, Scientist F, Division of Organic Chemistry, National Chemical Laboratory, Pune - 411 008. 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
May 2008

(Mr. Srinivas Burgula)

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic Studies Toward the Skipped 1,3-Polyol Natural Products and Some Pd-Mediated Reactions of Sugar Alkynols**" has been carried out under my supervision and is a bonafide work of **Mr. Srinivas Burgula**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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- Srinivas

DEFINITIONS AND ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
AIBN	-	Azoisobutyronitrile
Ac_2O	-	Acetic anhydride
Ag_2O	-	Silver oxide
Bn	-	Benzyl
BnBr	-	Benzyl bromide
9-BBN	-	9-Borabicyclo[3,3,1]nonane dimer
$BF_3.Et_2O$	-	Boron trifluoride diethyl ether complex
n-BuLi	-	*n*-Butyl lithium
Bu_3SnH	-	Tributyltin hydride
Bu_2SnO	-	Dibutyltin oxide
CS_2	-	Carbon disulfide
$(COCl)_2$	-	Oxalyl chloride
DCM	-	Dichloromethane
DDQ	-	2,3-dichloro-5,6-dicyano 1,4-benzoquinone
DEAD	-	Diethyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DET	-	Diethyl tartrate
DIPT	-	Diisopropyl tartrate
DMP	-	2,2'-Dimethoxypropane
DMAP	-	4-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
Et_3N	-	Triethylamine
Et_3SiH	-	Triethylsilyl hydride
EtOH	-	Ethanol
Im	-	Imidazole
Ipc_2BH	-	Diisopinacamphenyl borane
KHMDS	-	Potassium 1,1,1,3,3,3-hexamethyldisilazane

K_2CO_3	-	Potassium carbonate
LDA	-	Lithium diisopropylamide
LAH	-	Lithium aluminium hydride
MeI	-	Methyl iodide
MeOH	-	Methanol
NaH	-	Sodium hydride
$NaBH_4$	-	Sodium borohydride
NaOMe	-	Sodium methoxide
NBS	-	N-bromosuccinimide
NIS	-	N-Iodosuccinimide
NMO	-	N-Methyl morpholine N-oxide
NH_4Cl	-	Ammonium chloride
$NiCl_2.6H_2O$	-	Nickel(II) chloride hexahydrate
ORTEP	-	Oak ridge thermal ellipsoid plot
PIFA	-	Phenyliodine(III) bis(trifluoroacetate)
Pd/C	-	Palladium on Carbon
$Pd/CaCO_3$	-	Palladium on Calcium carbonate
$Pd(PPh_3)_2Cl_2$	-	Bis(triphenylphosphine)palladium(II)dichloride
$Pd(OAc)_2$	-	Palladium(II) acetate
PCC	-	Pyridinium chlorochromate
$PdCl_2(MeCN)_2$	-	Bis(acetonitrile)dichloropalladium(II)
PMB-Cl	-	*para*-Methoxy benzyl chloride
PPTS	-	Pyridine *p*-Toluenesulfonate
THF	-	Tetrahydrofuran
TBAF	-	Tetrabutylammonium flouride
TBDMS-Cl	-	*tert*-Butyldimethyl chlorosilane
TFA	-	Trifluoroacetic acid
TPP	-	Triphenylphosphine
$TiCl_4$	-	Titanium(IV) chloride
TsCl	-	*para*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 MHz, and DRX-500 MHz spectrometer 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, AV-100 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 mA.
- 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 are 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 in ethanol as developing agents.
- 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 unless otherwise specified.
- Silica gel (60–120), (100-200), and (230-400) mesh were used for column chromatography.
- Different numbers were assigned for compounds in Abstract and Chapters.

CONTENTS

Abstract

ABSTRACT

The thesis entitled "**Synthetic Studies Toward the Skipped 1,3-Polyol Natural Products and Some Pd-Mediated Reactions of Sugar Alkynols**" consists of three chapters. First chapter describes total synthesis of Anti-Fungal 1,3-polyol/α-pyrone natural products, and second chapter discloses total synthesis of Aculeatin D and 6-*epi*-Aculeatin D. Third chapter deals with systematic investigation of electronic influence over 6-*exo*-dig *vs* 7-*endo*-dig cyclizations employing sugar alkynol substrates.

Chapter I

Total Synthesis of Anti-Fungal 1,3-Polyol/α-Pyrone Natural Products

Natural products **1** and **2**, (Figure 1) were recently isolated by Kurt Hostettmann et al. from *Ravensara anisata* by activity guided fractionation and shown to inhibit *C. cucumerinum* fungal growth as efficiently as the commercial antifungal compounds miconazole and propiconazole. The synthesis of **1** and **2** reported by Shibasaki and co-workers turned out to be their enantiomers. Herein, we document the first synthesis of the naturally occurring **1** and **2**, addressing the key *syn*, *syn*-polyol synthesis by adopting the chiral pool approach.

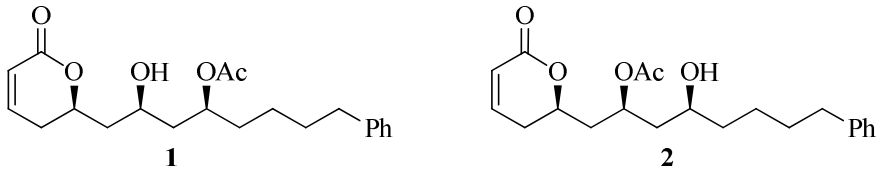
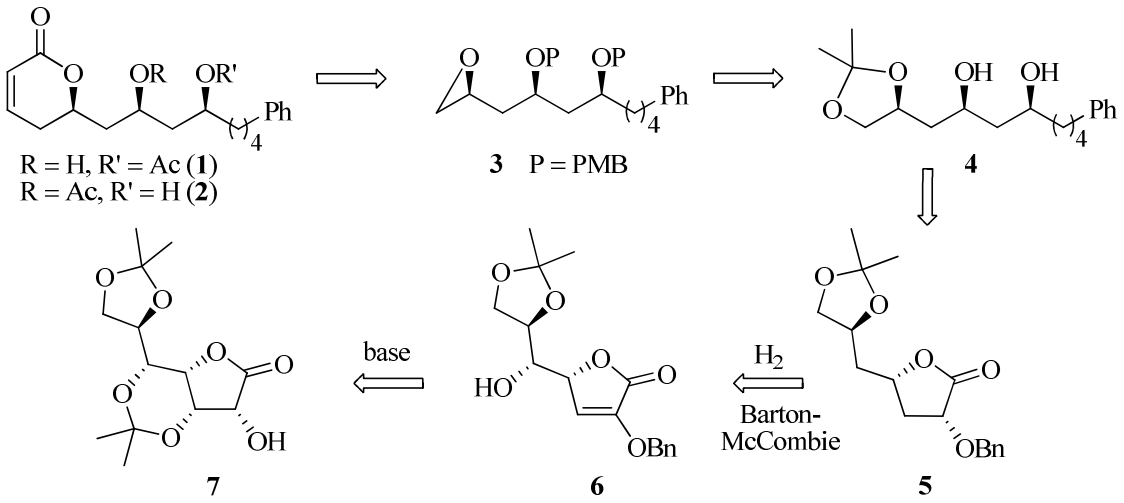


Figure 1: *1,3-polyol/α-pyrone natural products*

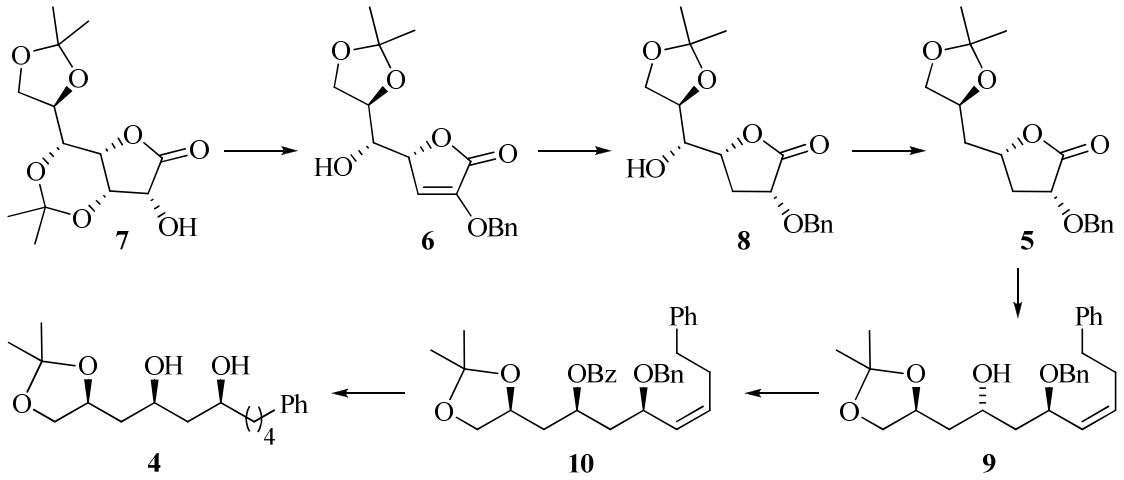
The structural analysis of **1** and **2** revealed that the diacetonide (**7**) of commercially available α-D-glucoheptonic-γ-lactone would be an ideal starting point as depicted in Scheme 1. The deoxygenation at *C*-3 by base mediated elimination and stereo-controlled reduction, and Barton-McCombie radical deoxygenation of *C*-5 followed by an inversion at *C*-4 after appending the required side chain are the key steps to secure the preparation of the key intermediate **4**. Coupling reaction between the

advanced intermediate **3** and methyl propiolate by Yamaguchi method, partial hydrogenation and lactonization should complete the total synthesis of the natural products **1** and **2**.



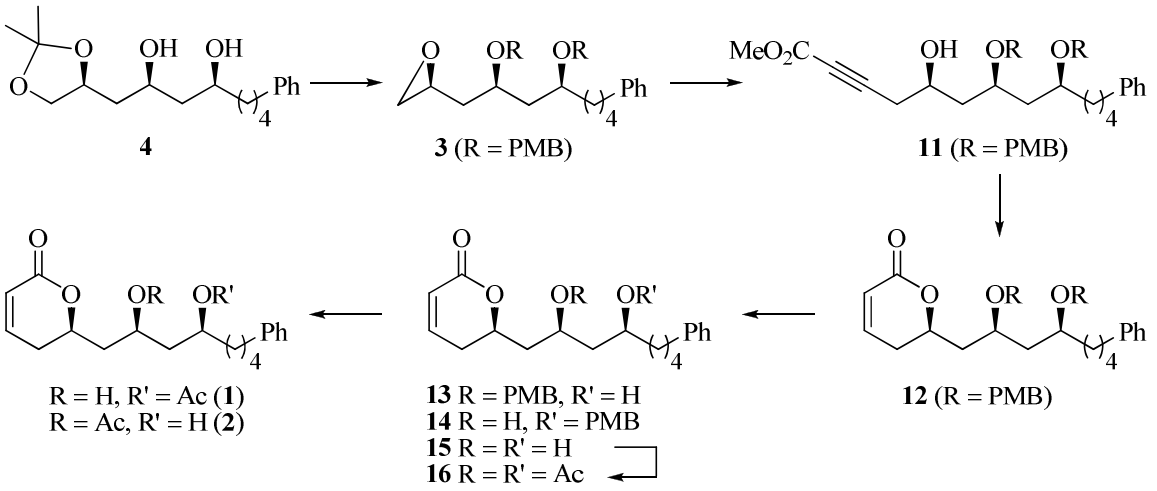
Scheme 1: Retrosynthetic strategy for 1,3-polyol/α-pyrone natural products

Protection of the hydroxyl group at *C*-2 of (**7**) with silver oxide and benzyl bromide, followed by subsequent elimination using potassium *t*-butoxide provided α,β-unsaturated lactone **6**. Selective conjugate reduction of the lactone **6** with benzyl ether intact was achieved with $NiCl_2$-$NaBH_4$ furnishing **8**. The spectral and analytical data of **8** were in agreement with the assigned structure which was further substantiated by the single crystal X-ray crystallography.



Scheme 2: Synthesis of *syn*, *syn*-1,3-diol **4**

Deoxygenation at *C*-5 of hydroxylactone **8** was achieved by employing Barton-McCombie protocol, transforming the lactone (**8**) to xanthate derivative followed by treatment with *n*-Bu_3SnH and catalytic AIBN to afford **5**. The controlled reduction of **5** with DIBAL-H and Wittig olefination with 3-phenylpropyl-triphenylphosphorane furnished **9**. The *Z*-configuration of **9** was evident from the relatively lower coupling constant (J = 10.3 Hz). Mitsunobu reaction of **9** using DEAD and benzoic acid was facile to give the benzoate derivative **10**. Hydrogenation of the double bond present in **10** by using Raney-Ni followed by saponification with catalytic NaOMe gave the key *syn*, *syn*-1,3-diol **4** (Scheme 2).



Scheme 3: Synthesis of 1,3-polyol/α-pyrone natural products

The diol **4** was protected as its PMB-ethers, subsequently the 1,2-isopropylidene group was hydrolyzed in the presence of PPTS in methanol to obtain terminal diol. The primary hydroxyl group was selectively tosylated by using TsCl, Bu_2SnO and triethylamine in dichloromethane, which was further transformed to oxirane by treating with K_2CO_3 in methanol to afford **3**. Our next concern is the construction of the key pyrone ring for which lithium salt of methyl propiolate was treated with the epoxide **3** in THF at −78 °C to furnish the β-hydroxy alkyne derivative **11**. Partial reduction of **11** in the presence of Lindlar's catalyst ($Pd/CaCO_3$) in benzene and acid catalyzed lactonization with PPTS in refluxing chloroform resulted in the formation of the δ-pyrone intermediate **12** (Scheme 3).

Attempted deprotection of PMB ethers of **12** using TFA in dichloromethane provided a (1:1) regiomeric mixture of mono PMB ethers **13** and **14** along with the diol **15**. The diol **15** was converted to the diacetate **16** which showed spectral data identical with the reported values. The acetylation of **13**/**14** followed by treatment with TFA furnished a mixture of **1** and **2** (3:1), separated by preparative HPLC. The spectral and analytical data of pure **1** and **2** were identical with the data reported for the natural products. Notably, a periodic examination of ^{1}H NMR spectra of pure isomers **1** and **2** indicated the migratory aptitudes of acetyl group in these compounds, however with different rates of migration. For example, the inter-conversion of **2**→**1** was substantially faster than **1**→**2**.

In summary, we developed a simple strategy for the synthesis of *anti*,*anti*- and *syn*,*syn*-1,3,5-polyol systems using a chiral pool approach. This study enabled us to carry out the first total synthesis of antifungal natural 1,3-polyol/α-pyrones **1** and **2**.

Chapter II

Total Synthesis of Aculeatin D and 6-*epi*-Aculeatin D

Aculeatins A – D are the spiroketals isolated from the terrestrial plant species *Amomum aculeatum*. They were assigned structures **1** – **4** respectively (Figure 2). Aculeatins were found to display antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species. In addition, they showed potential antibacterial activity and cytotoxicity against the KB cell line. Their promising biological activity taken together with the presence of structurally fascinating 1,7-dioxadispiro[5.1.5.2]-pentadecane spirocyclic architecture, aculeatins A – D aroused substantial interest culminating in several total syntheses.

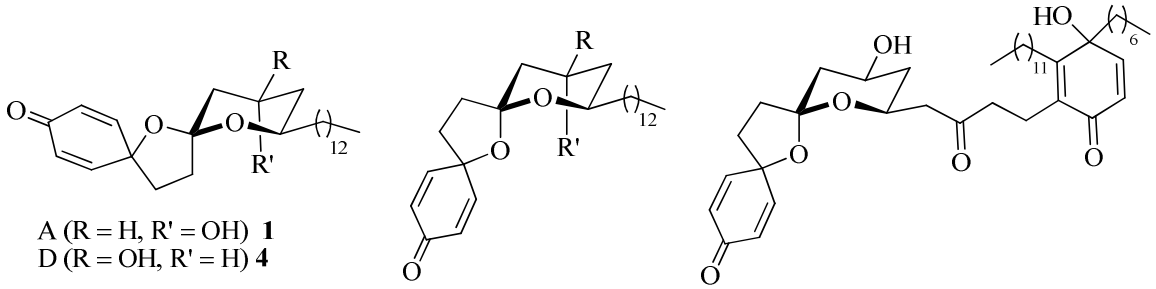
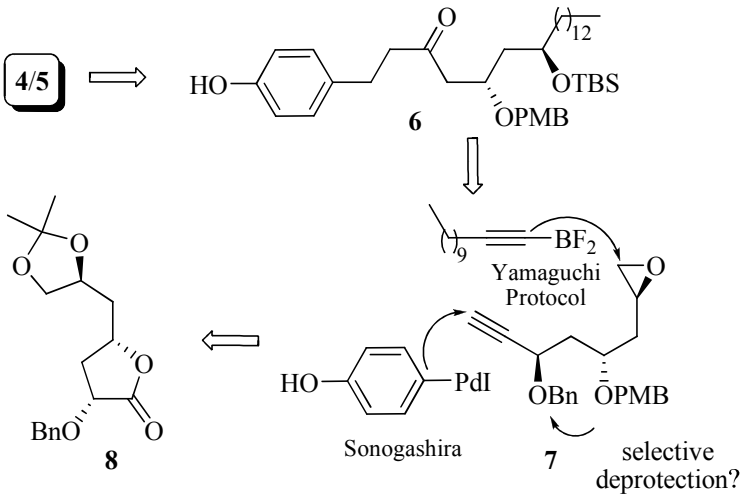


Figure 2: *Aculeatin A – D and 6-epi-Aculeatin D*

A flexible total synthesis that would allow access to modified aculeatins like functional group addition to cyclohexadienone unit and/or the alterations on the aliphatic side chain should give access to various synthetic analogues for structure activity studies. It was reasoned that addition of these units at a late stage in the synthesis would suffice this criteria. Herein we document a concise approach by selecting aculeatin D (**4**) as a target considering its documented superior cytotoxicity (IC_{50} = 0.38 μg/mL).

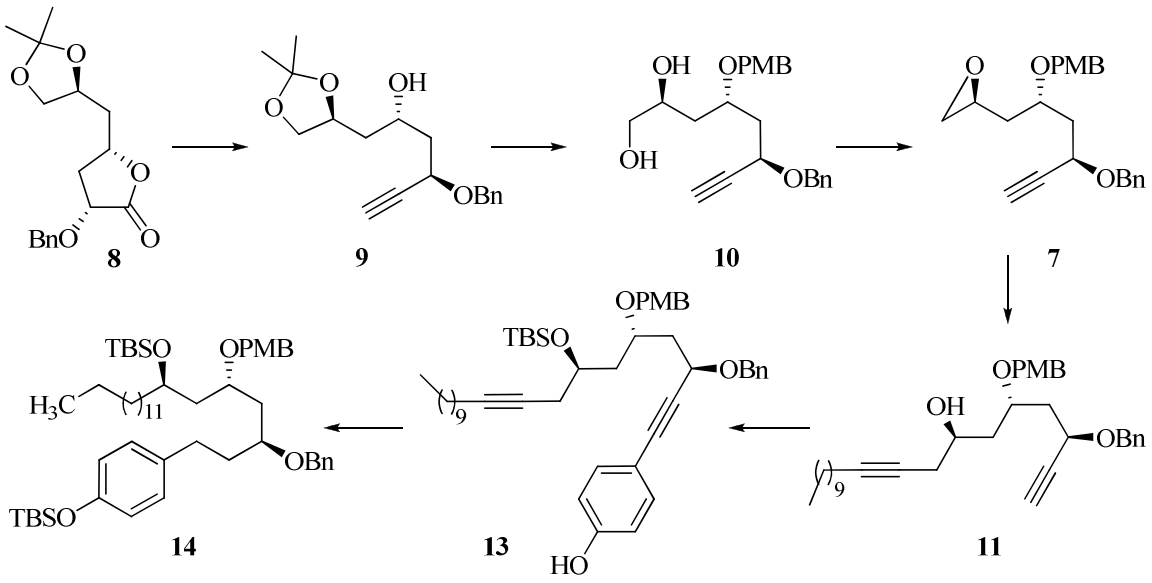


Scheme 4: Retrosynthetic strategy for Aculeatin D and 6-*epi*-Aculeatin D

As outlined in Scheme 4, the retrosynthetic disconnection identified an alkyne epoxide **7** as the key intermediate which can be extended to the advanced keto 3,5-diol unit **6** by Yamaguchi protocol at one end and the Sonogashira coupling on the alkyne end thus keeping flexibility at both sides. Keeping our previous observation, we hypothesized a selective propargylic–OBn cleavage during the Raney-Ni hydrogenation of the alkyne units. Oxidation of the released free C6-OH and subsequent global deprotection and phenolic oxidation should complete the total synthesis of aculeatin D (**4**) and its 6-epimer (**5**). The alkyne epoxide **7** could be obtained from the intermediate lactone **8**, upon successive controlled reduction, Ohira-Bestmann alkynylation and oxirane formation. The intermediate lactone **8** inturn could be secured following our established procedure from commercially available glucoheptono-1,4-lactone.

To explore in this direction, commercially available glucoheptono-1,4-lactone was advanced to the key intermediate lactone **8** following our established procedure.

Controlled reduction of lactone **8** with DIBAL-H and subsequent Ohira-Bestmann alkynylation of intermediate lactol afforded the alkyne **9**. Treatment of **9** with *p*-methoxybenzyl chloride in the presence of NaH in DMF followed by acetonide hydrolysis of resulting product, by using PPTS in MeOH afforded the diol **10**. The diol **10** was transformed to the oxirane **7** by selective 1°-OH tosylation using TsCl, Bu_2SnO and triethylamine in dichloromethane followed by cyclization with K_2CO_3 in methanol.

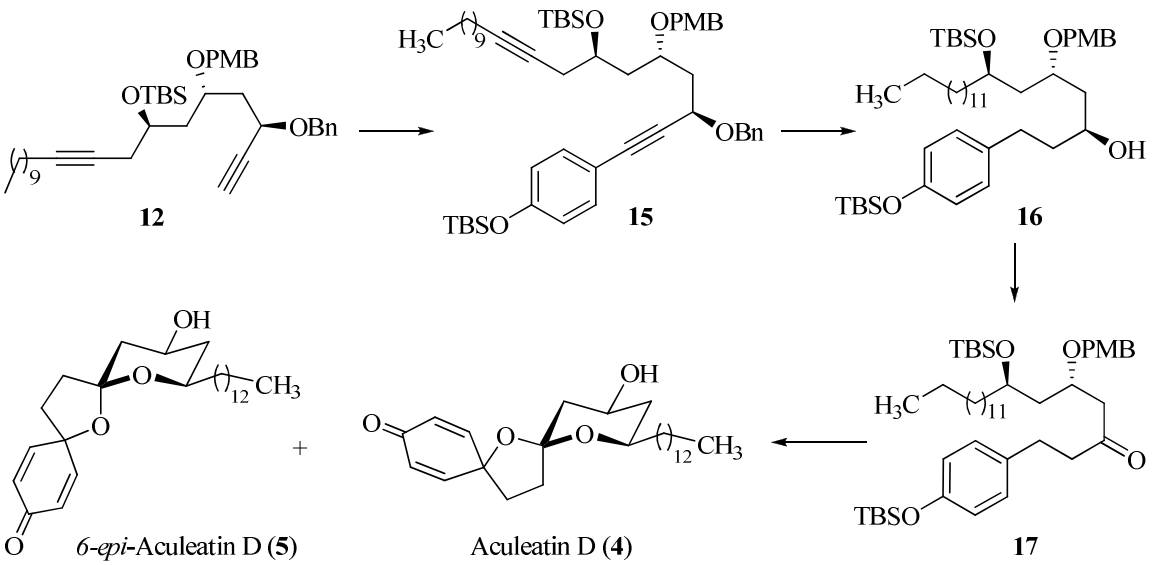


Scheme 5: Ohira-Bestmann alkynylation, Yamaguchi protocol and Sonogashira coupling

After having the epoxide **7**, we next focused our efforts on the synthesis of the keto-3,5-diol unit **6**. Thus the projected opening of **7** with dodec-1-nyl lithium in the presence of $BF_3{\cdot}Et_2O$ delivered the diyne **11** in near quantitative yield. Protection of the free hydroxyl group in **11** as its TBS ether, followed by Sonogashira coupling with *p*-iodophenol afforded the required coupling product **13** along with small amounts of self dimerized product. Our next concern was the hydrogenation of diyne **13** along with the desired selective propargyl-*O*-debenzylation. To our surprise, hydrogenation of **13** was facile, but resulted exclusively in diyne reduction to afford product **14** (Scheme 5).

After careful experimentation by employing protected *p*-iodophenol derivatives for Sonogashira coupling and subsequent Raney Ni hydrogenation, we concluded that TBS was the optimal protecting group that improved the yield in Sonogashira coupling

and, to our delight, the anticipated *O*-debenzylation during the hydrogenation of respective intermediate **15** affording **16**. Oxidation of **16** under Swern conditions afforded the keto-3,5-diol unit **17** (Scheme 6).



Scheme 6: Synthesis of Aculeatin D and 6-*epi*-Aculeatin D

Having the keto-3,5-*anti*-diol **17**, the stage was set for the global deprotection and subsequent phenol oxidation. Attempted global deprotection of PMB, TBS-ethers in acidic conditions (TFA, PTSA or PPTS) in solvents like methanol or dichloromethane yielded an unidentified complex mixture. Sequential deprotection of PMB-ether by using DDQ in dichloromethane under buffered conditions followed by TBS-ether deprotection in presence of TBAF in THF produced the free diol. Oxidative spiroacetalization of intermediate ketodiol by using phenyliodine(III) bis(trifluroacetate) (PIFA) in acetone/water (10:1, v/v solution) completed the synthesis of epimeric aculeatins (**4** and **5**) (Scheme 6). Physical and spectral data of these compounds were in agreement with the data reported for natural aculeatin D (**4**) and synthetic 6-*epi*-aculeatin D (**5**) respectively.

In conclusion, a chiral pool approach employing an easily accessible *anti*,*anti*-1,3-polyol unit for the total synthesis of naturally occurring aculeatin D (**4**) and its 6-epimer (**5**) was documented. As such, this route employs the addition of the both the terminal units (phenol and side chain) at the late stage of the synthesis thus provide sufficient flexibility for related analogues synthesis.

Chapter III

Cycloisomerization of Sugar Alkynols

The intramolecular addition of carbon and heteroatom nucleophiles across the alkynes falls under the broad category of cycloisomerization reactions. The key issue of the cycloisomerization reactions is the mode of cyclization *i.e. exo*-dig *vs. endo*-dig. After employing a broad set of substrates, it has been shown from our group that competition between 5-*exo*-dig *vs* 6-*endo*-dig modes of cyclization is substantially influenced by the electronic factors if the cyclization is not sterically demanding. In continuation, our investigations dealing with electronic control over competitive 6-*exo*-dig *vs* 7-*endo*-dig mode of cyclizations employing 3-*C*-propargyl-*ribo*-furanosyl derivatives (Figure 3) **4**–**8** form the objectives of the present chapter.

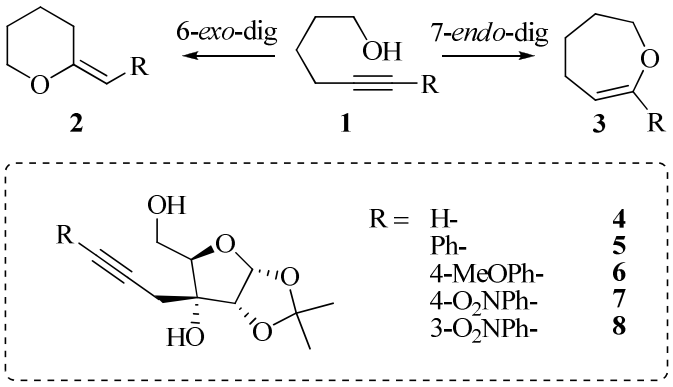
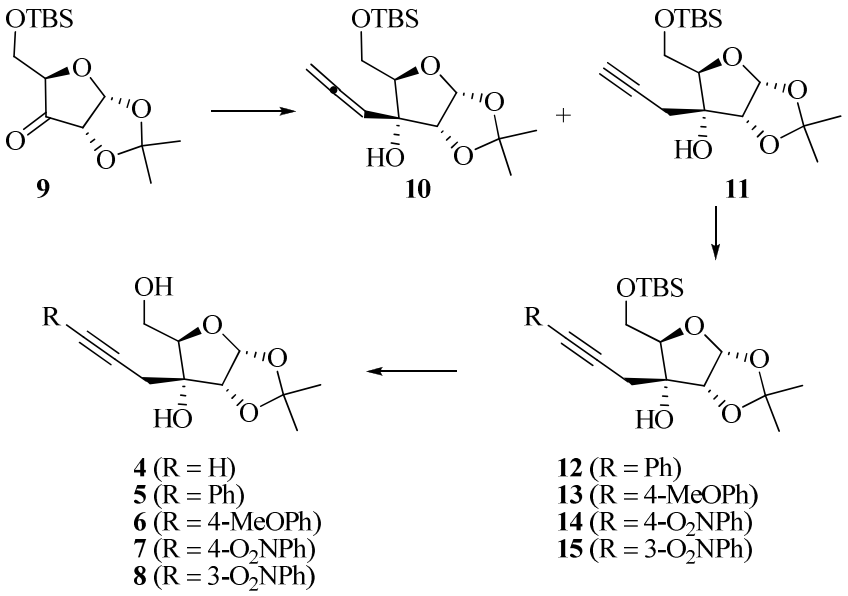


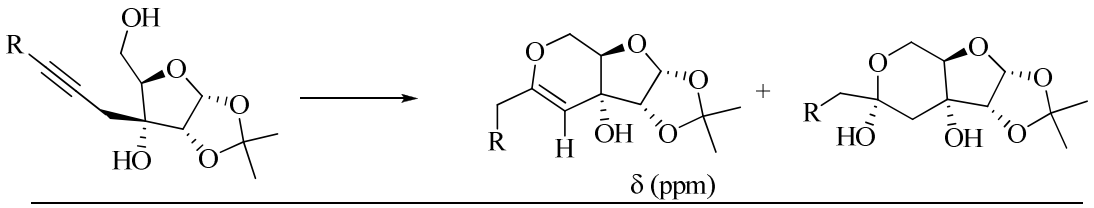
Figure 3: *Designed substrates for projected cycloisomerization*

The synthesis of the requisite model 3-*C*-propargyl-*ribo*-furanose derivatives **4**–**8** was started with propargylation of the known 3-ulose derivative **9** under Barbier conditions to afford **11** along with the allene **10** (1:0.6). To prepare the other proposed substrates, the Sonogashira coupling reaction of **11** with different aryl iodides was carried out in presence of $Pd(PPh_3)_2Cl_2$ to obtain compounds **12**–**15**. The TBS group present at *O*-5 of **11**–**15** was subsequently removed by using TBAF-THF to give the cycloisomerization substrates **4**–**8** (Scheme 7).



Scheme 7: Synthesis of cycloisomerization substrates **4**–**8**

The palladium-catalyzed cycloisomerization reactions of model 3-*C*-propargyl-*ribo*-furanose derivatives **4**–**8** were carried out in the presence of $Pd(CH_3CN)_2Cl_2$ in MeCN at room temperature. The results are summarized in Scheme 8. The parent compound **4** gave exclusively the fused dihydropyran **16** resulting from the double bond isomerization of the intermediate *exo*-methylene derivative.



		δ (ppm)		
4	R = H-	**16** (64%)	4.40	--
5	Ph-	**17** (60%)	4.40	**18** (19%)
6	4-MeOPh-	**19** (16%)	4.40	**20** (55%) Keto
7	4-O_2NPh-	**21** (60%)	4.51	**22** (14%)
8	3-O_2NPh-	**23** (53%)	4.53	**24** (13%)

Scheme 8: Cycloisomerization of alkynols **4**–**8**

Cycloisomerization of alkynol **5** afforded the *endo*-product **17** along with small amounts of the hemiketal **18** resulting from the hydrolysis of **17**. Whilst the cycloisomerization of the alkynol **6** gave dihydropyran **19** and the major product was found to be the keto derivative **20**. Formation of hemiketals **22**, and **24** was also noticed with the cycloisomerization of alkynols **7** and **8** respectively, along with the major dihydropyran derivatives **21** and **23** (Scheme 8). The similar NMR spectral pattern noticed for **16**, **17**, **19**, **21** and **23** confirmed the assigned structures. The structures of hemiketals **18**, **22** and **24** were proposed based on ^{1}H, ^{13}C, mass and elemental analysis. The single crystal X-ray study of *endo*-product **17**, **22** and **24** unambiguously proved its structure.

In summary, electronic control over the 6-*exo*-dig *vs.* 7-*endo*-dig modes of cyclizations in Pd-mediated cycloisomerization reaction has been studied in detail. 3-*C*-propargyl-*ribo*-furanose derivatives with systematic variation of functional groups at the other side of alkyne were employed to understand the competitive balance between inductive effect of furanose ring and mesomeric effect of aryl substituent. Unlike with 3-*C*-alkynyl-*allo*- and *ribo*-furanose derivatives where the regioselectivity of the cyclization were inline with the electronic control, with 3-*C*-propargyl-*ribo*-derivatives we observed complete 6-*exo*-dig selectivity without an electronic interference. However, intermediate exocyclic enol ethers isomerized to more stable endocyclic enol ethers.

Chapter I

Total Synthesis of Anti-Fungal 1,3-Polyol/α-Pyrone Natural Products

Introduction

Fungi are plant-like organisms that lack chlorophyll and are one of the five kingdoms of life. There are over 15,00,000 species of fungi, only 72,000 are known.[1] Fungal infections have emerged as a significant clinical problem in recent years. Due to the increasing frequency of fungal infections and development of resistance to the current treatment, mycology is today undergoing a true renaissance. The term **mycosis** (plural: *mycoses*) refers to conditions in which fungi invade the resistance barriers of the human body and establish infections. These mycoses can manifest themselves in a variety of ways. Infections can be superficial, that is situated at or close to the surface of the skin, or systemic, which means they can affect the body as a whole rather than individual parts or organs.

Fungal infections represent a serious problem for patients with immune systems compromised either by HIV infection, or administration of immunosuppressive drugs during cancer therapy and organ transplantation. High dissemination and proliferation rates of many pathogenic fungi along with their insusceptibility to common antimicrobial drugs urge implementation of efficient and reliable antifungal therapy. Till date, the macrolide polyene antibiotic amphotericin B (AmB) has long been recognized as a powerful fungicidal and leishmanicidal drug due to its potent fungicidal activity, broad spectrum, and relatively low frequency of resistance among the fungal pathogens. A conventional intravenous dosage form of AmB, AmB-deoxycholate (Fungizone or D-AmB), is the most effective clinically available method for treating mycotic and parasitic (leishmaniasis) infections. However, polyene macrolides are rather toxic, causing serious side effects such as renal failure, hypokalemia and thrombophlebitis, especially upon intravenous administration. Efforts to lower the toxicity are based on synthesis of AmB analogues. The newer formulations are substantially more expensive, but allow patients to receive higher doses for longer periods of time with decreased renal toxicity than conventional AmB.

Efforts to utilise combinations of amphotericin B with other agents were best realized with amphotericin B/flucytosine in cryptococcal meningitis, and to a lesser

degree in systemic candidiasis. More recently, the introduction of new imidazoles has extended the range of applications of these drugs to fungal diseases. Two members of this group, miconazole and ketoconazole, are promising agents. Miconazole is a parenterally administered agent for patients acutely ill with candidiasis and other mycotic infections. It may be the drug of choice for Petriellidium boydii infections and it is an attractive alternative to amphotericin B for intrathecal administration to patients with fungal meningitis. Ketoconazole offers much less toxicity, the advantage of oral administration, and the possibility of indefinite prolonged therapy. However, it does not attain high concentrations in either the urine or cerebrospinal fluid. Antifungals can be grouped into three classes based on their site of action: polyenes, which interact with fungal membrane sterols physicochemically; azoles, which inhibit the synthesis of ergosterol (the main fungal sterol); and 5-fluorocytosine, which inhibits macromolecular synthesis.

Azole antifungal agents, and especially fluconazole, have been used widely to treat oropharyngeal candidiasis in patients with AIDS. An increasing number of cases of clinical resistance against fluconazole, often correlating with *in vitro* resistance, have been reported. The analysis of sequential isogenic *C. albicans* isolates with increasing levels of resistance to fluconazole from five AIDS patients showed that over expression of the gene encoding 14DM either by gene amplification or by gene deregulation was not the major cause of resistance among these clinical isolates. However, that fluconazole-resistant *C. albicans* isolates failed to accumulate 3H-labelled fluconazole. This phenomenon was reversed in resistant cells by inhibiting the cellular energy supply with azide, suggesting that resistance could be mediated by energy-requiring efflux pumps such as those described as ATP-binding cassette (ABC) multidrug transporters. In fact, some but not all fluconazole-resistant clinical *C. albicans* isolates exhibited up to a 10-fold relative increase in mRNA levels for a recently cloned ABC transporter gene called *CDR1*. In an azole-resistant *C. albicans* isolate not over expressing *CDR1*, the gene for another efflux pump named *BEN*r was massively over expressed. This gene was cloned from *C. albicans* for conferring benomyl resistance in *Saccharomyces cerevisiae*. Therefore, at least the over expression or the deregulation of these two genes potentially mediates resistance to azoles in *C. albicans* clinical isolates from AIDS patients with oropharyngeal candidiasis. Involvement of ABC transporters in azole resistance was

further evidenced with *S. cerevisiae* mutants lacking specific multidrug transporters which were rendered hypersusceptible to azole derivatives including fluconazole, itraconazole, and ketoconazole.

Risk factors responsible for development of Fungal infections:

- Use of drugs that suppress the immune system, *ex*. Anticancer drugs, Corticosteroids.
- Diseases and conditions, such as AIDS, Kidney failure, Diabetes, Lung diseases, Leukemia, Organ transplantation etc.
- Difficulty in diagnosis of fungal infections and hence delay in initiation of treatment.

Need for further research in Antifungal Agents:

There are mainly three challenging problems for researchers in development of an effective antifungal drug in combating severely invasive mycosis.

1. Toxicity of currently used antifungal agents

The currently administered drugs are only fungistatic and cause severe side effects such as Nephrotoxicity (polyenes) and hepatotoxicity (azole), as the fungi shares similar cellular components and mechanism, as that of mammalian cell.

2. Resistance of yeasts to clinically useful antifungal agents

The molecular basis of resistance to azole antifungals, there are three different resistance mechanisms known in pathogenic yeasts.

- First, the reduced access of the agents to the target cytochrome P450 enzyme because of increased efflux of antifungals, caused by the action of resistance gene products.
- Second, the over production of cytochrome P450 enzyme, possibly by gene amplification.
- Third, a structural alteration in cytochrome P450 enzyme which results in lower susceptibility to azole antifungals.

3. Emergence of newer strains by mutation

The treatment of immunosuppressed and immunocompromised patients such as in Cancer and AIDS patient needs long term administration of antifungal drugs to treat the invasive infection caused by opportunistic pathogenic fungi. The consequence leads to the development of resistance of fungi to these drugs by mutation in the genes leading to the birth of newer resistant strains.

Nature synthesizes innumerable organic compounds using its own artillery. Understanding the structure of nature's creations and attempting to clone them in laboratory by means of chemical synthesis has fascinated the synthetic organic community. With the origin and development of modern science, our understanding about the constitution of any given material has improved immensely, natural products not being an exception. With the advancements in the area of natural product isolation and characterization, it has become possible to isolate and identify the active compound responsible for the observed biological activity. As they are present in minute quantities, often it is not practicable to isolate these natural products from their original resources for the commercial purposes. The solution for this problem is to synthesize them in laboratory by means of chemical synthesis.

The 1,3-skipped polyol systems with *anti*- or *syn*- configuration are the basic structural units of several important natural products including clinically valuable polyene macrolide antibiotics.[2] The polyene macrolide antibiotics are a large group of natural products constituting over 200 members. Several members of this class, such as amphotericin B, nystatin, and pimaricin, are important antifungal agents and have been used extensively in medicine. The resurgence of life-threatening fungal infections has renewed the interest in antifungal agents,[3] and polyene macrolides are still some of the most effective clinical antifungal agents known. All of these natural products are macrolides that incorporate a conjugated polyene ranging from three to seven double bonds in length. They also contain a polyol section made up of a sequence of l,2- 1,3-, and 1,4-diols, with 1,3-diols being the most common. Several members of this class have a sugar, usually the amino sugar D-mycosamine, attached by a β-linkage to one of the alcohols in the macrolide ring. The polyene macrolide antibiotics can be further divided into two groups: those having the polyene across the ring from the lactone carbonyl i.e.

amphotericin B (**1**), candidin (**2**), pentamycin (**3**) and filipin III (**4**) (Figure 1) whereas those having the polyene in conjugation with the lactone, generally described as the oxo polyene macrolides i.e. roxaticin (**5**), roflamycoin (**6**), mycoticin A (**7**) and mycoticin B (**8**) (Figure 2).

The biological activity of amphotericin B and other polyene macrolides has been extensively reviewed.[4] Polyene macrolide antibiotics such as amphotericin B are believed to exert their antifungal activity by formation of ion channels in cell membranes. Small polyene macrolide antibiotics do not form ion channels but rather disrupt membranes through less specific interactions. Most of the oxo polyene macrolides fall into this category with the notable exception of roflamycoin, which has been shown to form sterol-dependent ion channels similar to those observed with amphotericin B.

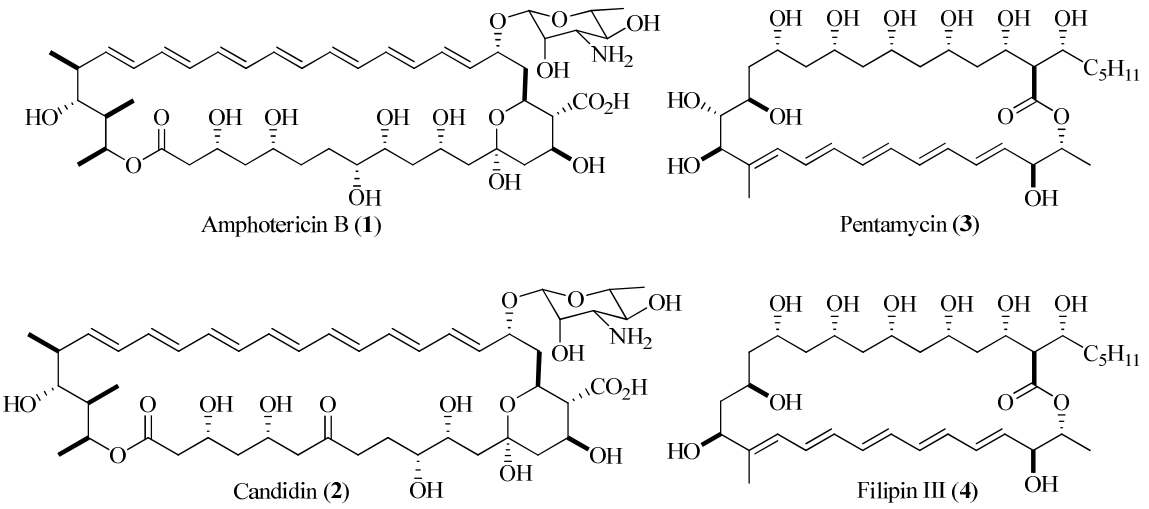


Figure 1: *Structures of Polyene Macrolide Antibiotics*

The structure and especially the stereochemical configuration of the polyene macrolides has been an area of active research since Omura et al. review.[5] At that time amphotericin B was the only polyene macrolide for which a complete three-dimensional structure was known; its X-ray crystal structure was reported in 1970. By 1984 the constitution of approximately 40 other polyene macrolides had been established through classic degradation studies, NMR spectroscopy, and analyses of mass spectra fragmentation patterns.[5]

The polyene macrolide antibiotics are challenging targets for synthetic chemists. The early work in this area focused exclusively on amphotericin B because it was the only polyene macrolide with a completely established structure from 1970 until 1987. Many groups worked on the synthesis of amphotericin B, but the only total synthesis was reported by Nicolaou et al. in 1987.[6] Another notable achievement in this area was the total synthesis of amphoteronolide B by Masamune's group in 1988.[7]

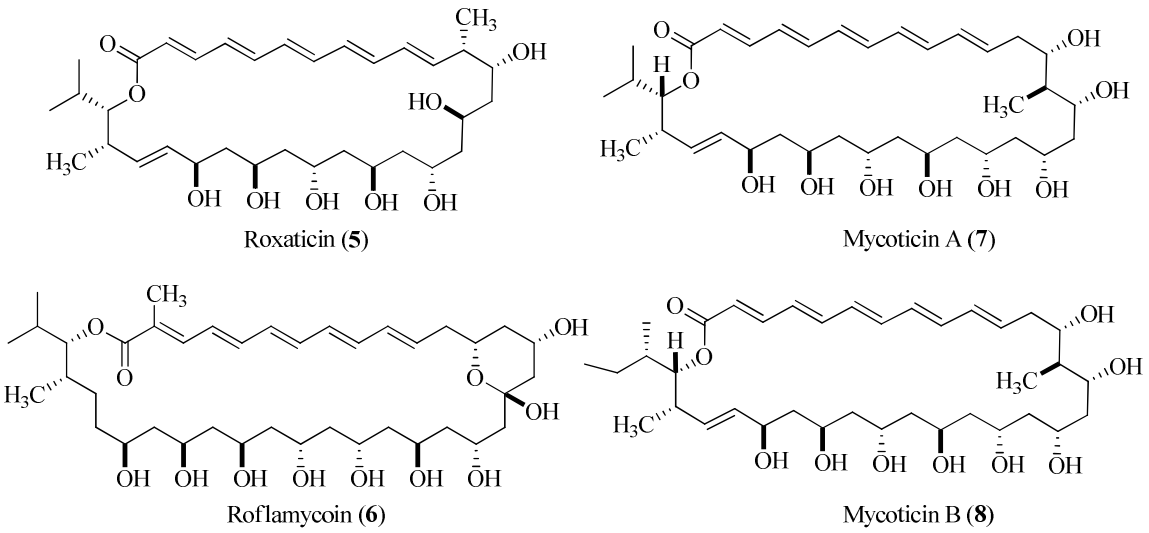


Figure 2: *Structures of Oxo Polyene Macrolide Antibiotics*

The intriguing structural complexity and often potent biological activity exhibited by many polyol-derived natural products has generated a continuing interest in the development of efficient, stereoselective approaches to the assembly of repeating 1,3-diol subunits. Stereocontrolled syntheses of polyether-, ansa-, and polyoxomacrolide antibiotics have developed remarkably in recent years, which are obviously linked to the rapid progress of stereocontrolled reactions in acyclic systems. On the other hand, chemistry of polyenemacrolide antibiotics has remained relatively undeveloped, although they exhibit effective antifungal properties. The structural feature of this class of antibiotics is that they contain a complex array of 1,3-polyhydroxyl functions. The seemingly simple structure of 1,3-polyol systems provides, on the contrary, very few clues for determining the stereostructure and constructing the chiral centers, which has

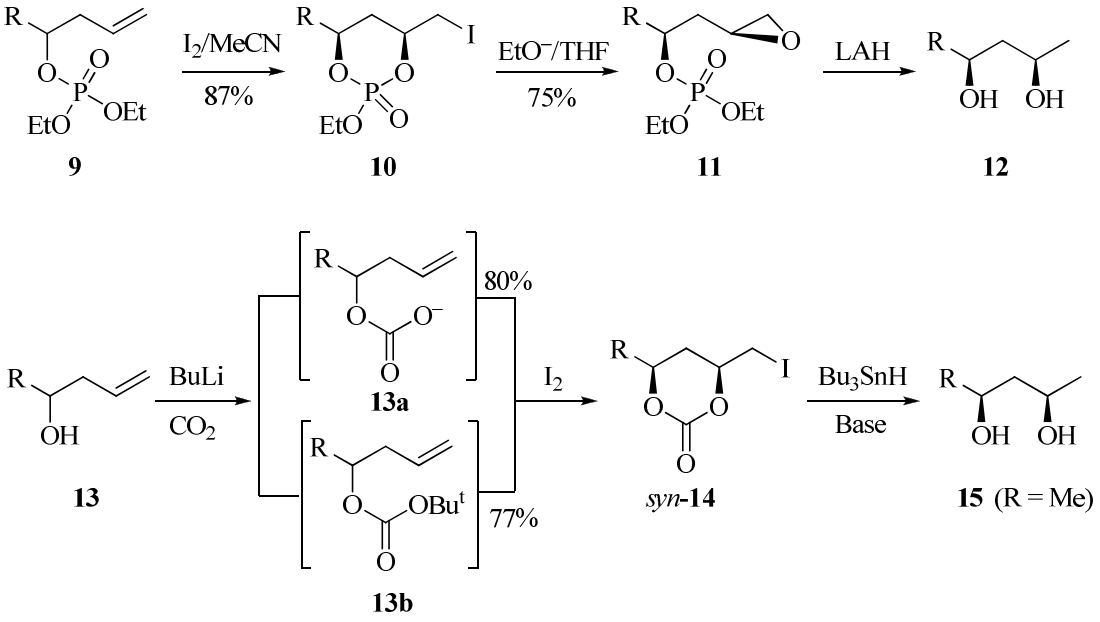
prevented progress in the chemistry of this field. This difficulty is amplified in the higher members of the 1,3-polyols. However, with progress in the chemistry of related acyclic systems, it has become possible to approach this hitherto inaccessible field and excellent work has begun to appear in recent years.

Selected approaches for stereoselective construction of 1,3-Polyols:[8]

1) Stereoselective functionalization of homoallylic alcohols

Stereoselective introduction of an oxygen function into the β-position of a homoallylic alcohol should provide an efficient method for the synthesis of 1,3-diols. The most straightforward method is direct epoxidation of the double bond. However, only low 1,3-asymmetric induction is observed in the epoxidation of homoallyl alcohols. Thus, attention has been focused on the extension of nucleophilic character of the β-hydroxyl group by forming the ester bearing a proper functionality.

i) Route via a Cyclic Iodo Carbonate

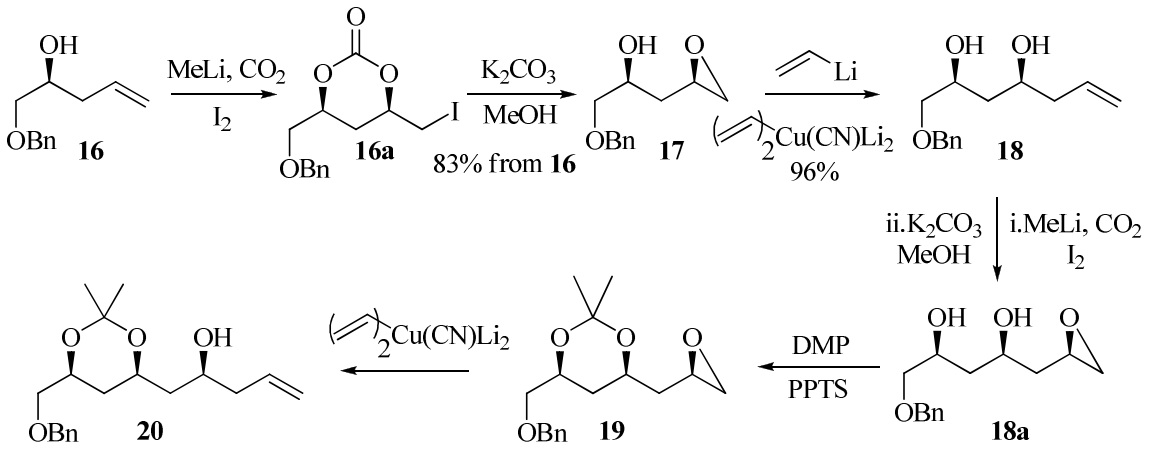


Scheme 1: Synthesis of *syn*-1,3-diol

The diethylphosphate of 4-pentene-2-ol **9** affords predominantly, on reaction with iodine, the corresponding *syn*-cyclic phosphate **10**.[9] Ethoxide-induced ring opening followed by LAH reduction of the resulting *syn*-epoxy diethyl phosphate **11** produces syn-1,3-diol (**12**) (*syn*/*anti* ratio, > 98%). The same type of reaction can be affected using the corresponding homoallylic carbonates **13a**, and **13b** giving cyclic *syn*-iodo carbonate **14**. Reduction of **14** with tributyl tin hydride followed by base-induced hydrolysis of the carbonate affords *syn*-diol (**15**) (Scheme 1). Same results were obtained with carbamates also.

ii) Homoallylic alcohol epoxidation followed by ring opening with Organocuprates

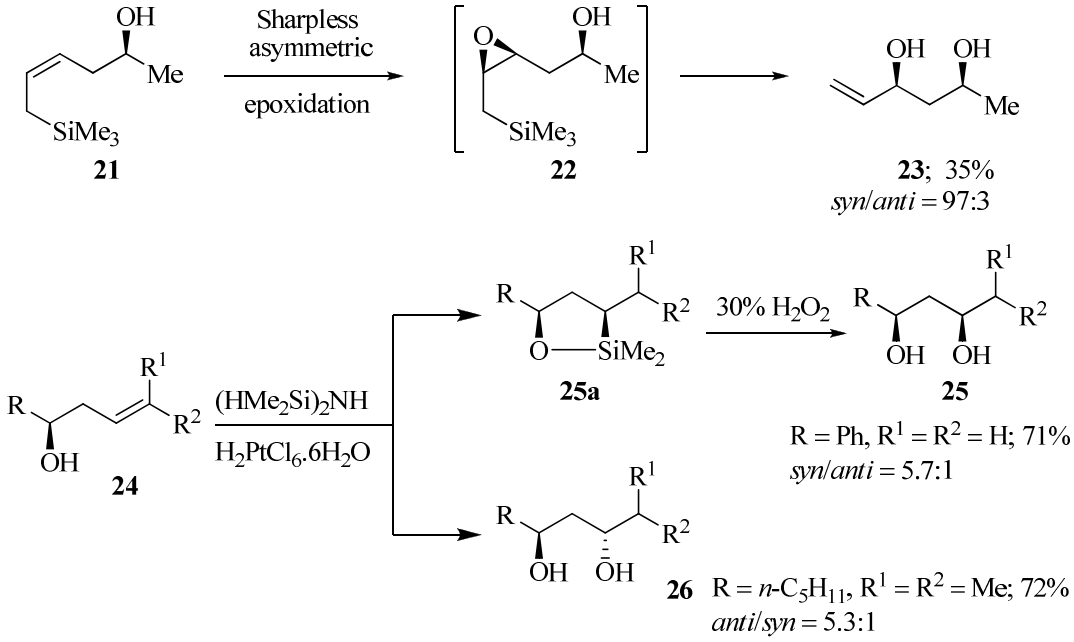
An elegant two-stage strategy for all 1,3-syn-1,3-polyols has been developed by Lipshutz et al.[10] The first stage is preparation of *syn*-β-epoxy alcohol **17** from the chiral homoallylic alcohol **16** based on the modified Cardillo procedure described above. The second stage is the two carbon elongation using a cuprate derived from vinyllithium and cuprous cyanide [i.e. $(CH_2{=}CH)_2Cu(CN)Li_2$]. The resulting 1,3-diol **18** contains the same homoallylic alcohol moiety as **16** and thus, the repetition of the sequences used for the preparation of **18** is possible producing all-*syn*-triol derivative (**20**) (Scheme 2). The intermediary epoxide **19** has been used as a building block in an approach to the synthesis of Roflamycoin.



Scheme 2: Synthesis of *syn*-1,3,5-triol

iii) Direct functionalization of homoallylic alcohols

When *cis*-homoallylic alcohol **21** containing the allylsilane subunit was subjected to the Sharpless asymmetric epoxidation, *syn*-1,3-diols (**23**) was obtained *via* intermediate *syn*-epoxy alcohol **22**. Although the yields are not satisfactory, the *syn*/*anti* ratios of the products are reported to be excellent. Synthesis of *syn*- and *anti*-1,3-diols (**25**, **26**) (Scheme 3) from homoallylic alcohol **24** *via* intramolecular hydrosilylation followed by oxidative cleavage of the carbon-silicon bond has been reported by Tamao and Ito et al.[11] The *syn/anti* ratio of diols is not satisfactory in these cases, while excellent selectivity is obtained in the synthesis of three isomeric triols having three consecutive chiral centers.



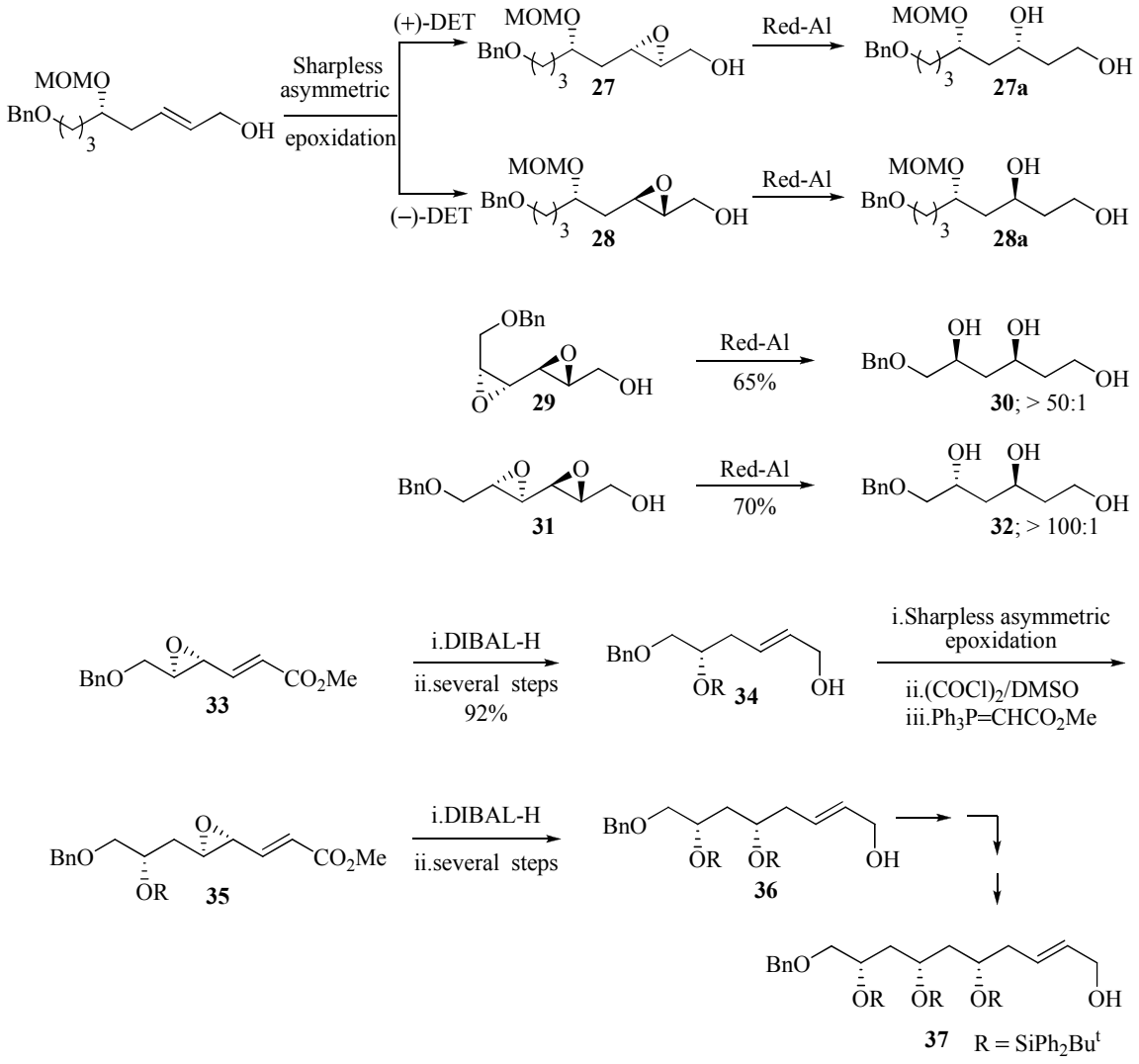
Scheme 3: Synthesis of *syn*- and *anti*-1,3-diol

2) Synthesis based on functionalization of allylic alcohols and related compounds

i) Sharpless asymmetric epoxidation followed by regioselective epoxide reduction

Reduction of epoxides prepared by oxidation of the corresponding allyl alcohol with Red-Al [$NaAlH_2(OCH_2CH_2OMe)_2$], proceeds with high regioselectivity giving 1,3-

diols. Based on these findings, combined with the Sharpless asymmetric epoxidation of allylic alcohols, a strategy for the synthesis of both *syn*-1,3-diol (**27a**) and *anti*-1,3-diol (**28a**) (Scheme 4) was developed by Kishi et al.[12] Since repetition of these sequences is possible in principle, the higher homologues of 1,3-polyols can be prepared. It has been demonstrated that Red-Al induced regioselective reductive ring opening of epoxides is not limited to monoepoxy alcohols, but the 2,3:4,5-diepoxy alcohols **29** and **31** can undergo clean double ring opening providing 1,3,5-triols (**30** and **32**) (Scheme 4) respectively.

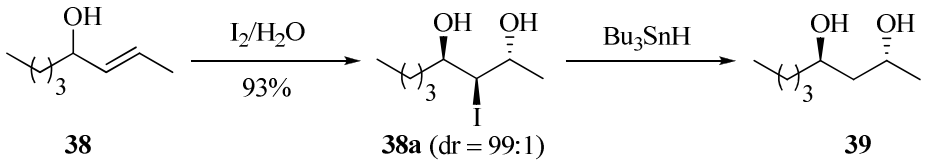


Scheme 4: Synthesis of *syn*- and *anti*-1,3-diol and polyol

Nicolaou et al.[13] reported the regiospecific reductive opening of γ,δ-epoxy-α,β-unsaturated ester **33** at the α-carbon of the double bond with DIBAL-H. The TBDPS derivative **34** is converted to **35**, further DIBAL-H reduction and successive protection of the secondary alcohol yields *syn*-diol derivative **36**. A similar sequence was explored by taking **36** as substrate and resulted in the triol derivative (**37**), a higher homologue of **36** (Scheme 4).

ii) Route *via* iodohydrins

Iodohydrin formation of disubstituted allylic alcohols proceeds with high regio- and stereoselectivity to give 2-iodo-1,3-diols **38a**, which upon reduction with tributyltin hydride affords *anti*-1,3-diols (**39**) (Scheme 5) has been documented.[14] The stereoselectivity of iodohydrin formation may be rationalized according to Houk's conformational and orbital overlap arguments.

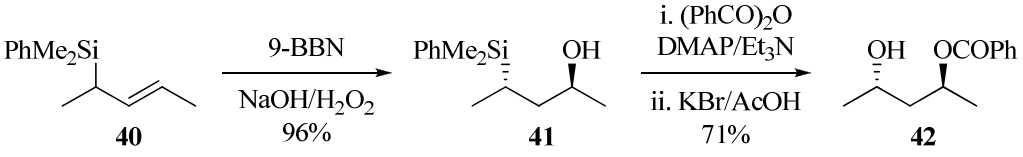


38 **38a** (dr = 99:1) **39**

Scheme 5: Synthesis of *anti*-1,3-diol

iii) Route *via* hydroboration of allylsilanes

The hydroboration of allylsilane **40** with 9-BBN as the hydroborating reagent proceeds in a highly stereoselective manner yielding γ-silyl alcohol **41**, which can be converted stereospecifically into the *anti*-1,3-diol derivative (**42**) (Scheme 6).

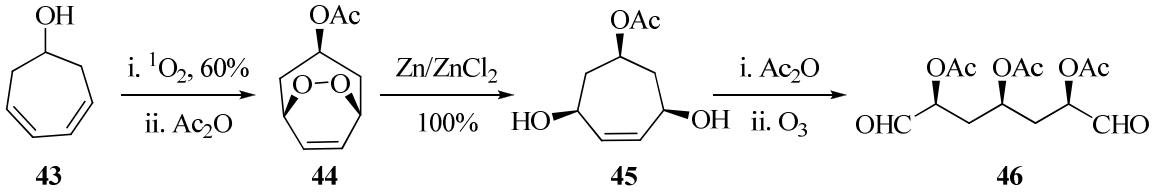


40 **41** **42**

Scheme 6: Synthesis of *anti*-1,3-diol

3) Synthesis of *syn*-1,3-polyols via peroxides

Addition of photo-generated singlet oxygen to 3,5-cycloheptadien-1-ol **43** followed by acetylation affords peroxide **44** as the main product. Cleavage of the peroxide moiety in **44** with $Zn/ZnCl_2$ yields the monoacetate of triol **45**, whose diacetylation followed by ozonolysis gives all-*syn*-1,3,5-triol derivative (**46**) (Scheme 7).



43 **44** **45** **46**

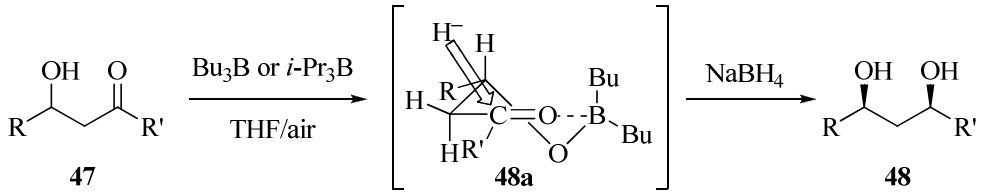
Scheme 7: Synthesis of *syn*-1,3,5-triol

4) Reduction of acyclic β-hydroxy ketones

Stereoselective reduction of acyclic β-hydroxy ketones is one of the general methods employed for 1,3-diols synthesis. It has been reported that chelation-controlled addition of hydride reagents affords *syn*-diastereoselectivity, while intramolecular delivery of hydride directed by the β-hydroxyl group leads to *anti*-diastereoselectivity. Thus, both *syn*- and *anti*-diols can now be synthesized from the same acyclic β-hydroxy ketones by changing the reagents and reaction conditions.

i) Synthesis of *syn*-1,3-diols

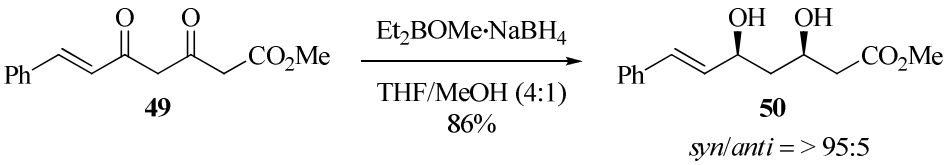
Initial treatment of β-hydroxy ketone **47** with tributyl- or triisopropylborane followed by sodium borohydride reduction of the resulting complex affords *syn*-1,3-diol (**48**) with excellent to moderate selectivity (Scheme 8). The stereochemical outcome of the present reduction may be explained by assuming that the intermediate dibutylboronic ester (**48a**) exists in a chelated transition state and then reducing reagents attack from the less hindered upper external face. The use of THF/MeOH (4:1) in this reduction was found to increase the rate of reduction without decreasing the reaction specificity.



48	R = R'	Temp °C	Yield (%)	*syn*/*anti*
a	Ph	−78	94	98:2
b	Bu	−100	74	96:4
c	cyclohexyl	−100	90	94:6

Scheme 8: Synthesis of *syn*-1,3-diol

Alkoxydialkylboranes (R_2BOR'; R = Et, Bu; R′ = alkyl) are reported to be still more effective complexing agents than trialkylboranes. The intermediary dialkylboronic esters are formed without air activation. In all cases examined, the diastereomeric ratios of *syn*- and *anti*-1,3-diols were more than 98:2. The same reagent system diethylmethoxy borane/sodium borohydride ($Et_2BOMe/NaBH_4$) has been used for the reduction of β,δ-dioxo ester **49** (Scheme 9).[15]

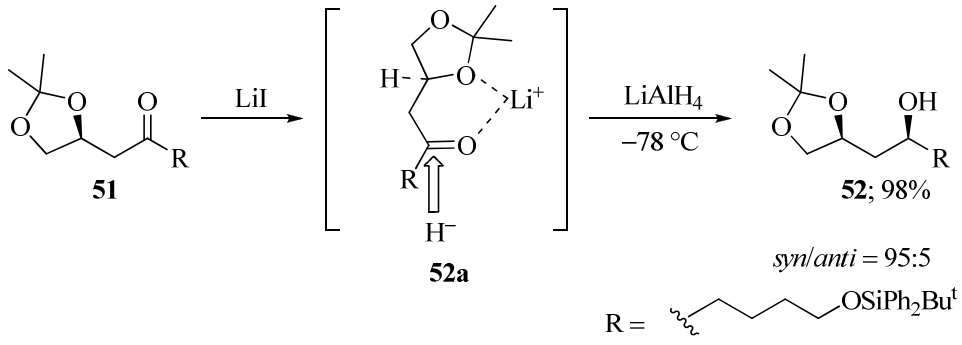


Scheme 9: Synthesis of *syn*-1,3-diol

A combination of titanium tetraisopropoxide/sodium borohydride/tetrahydrofuran [$Ti(OPr\text{-}i)_4/NaBH_4$/THF] has been used for the same purpose (**47** R = CH_2CH_2Ph, R′ = CH_2CH_2OBz, *syn*/*anti* = 87:13).[16a] Diisobutylaluminum hydride is reported to induce 1,3-

asymmetric induction without using complexing agents; an analogous chelation model to **48a** has been suggested by Kiyooka et al.[16b]

Lithium aluminum hydride reduction of β,γ-dihydroxy ketones **51** in the presence of lithium iodide affords the corresponding *syn*-l,3-diol (**52**) with high stereoselectivity. The high selectivity using lithium aluminum hydride/ lithium iodide may be attributed to the fact that the upper side of the carbonyl group in **52a** is highly hindered by the *gem*-dimethyl group of the acetonide thus hydride attack takes place from the lower side (Scheme 10).



Scheme 10: Synthesis of *syn*-1,3-diol

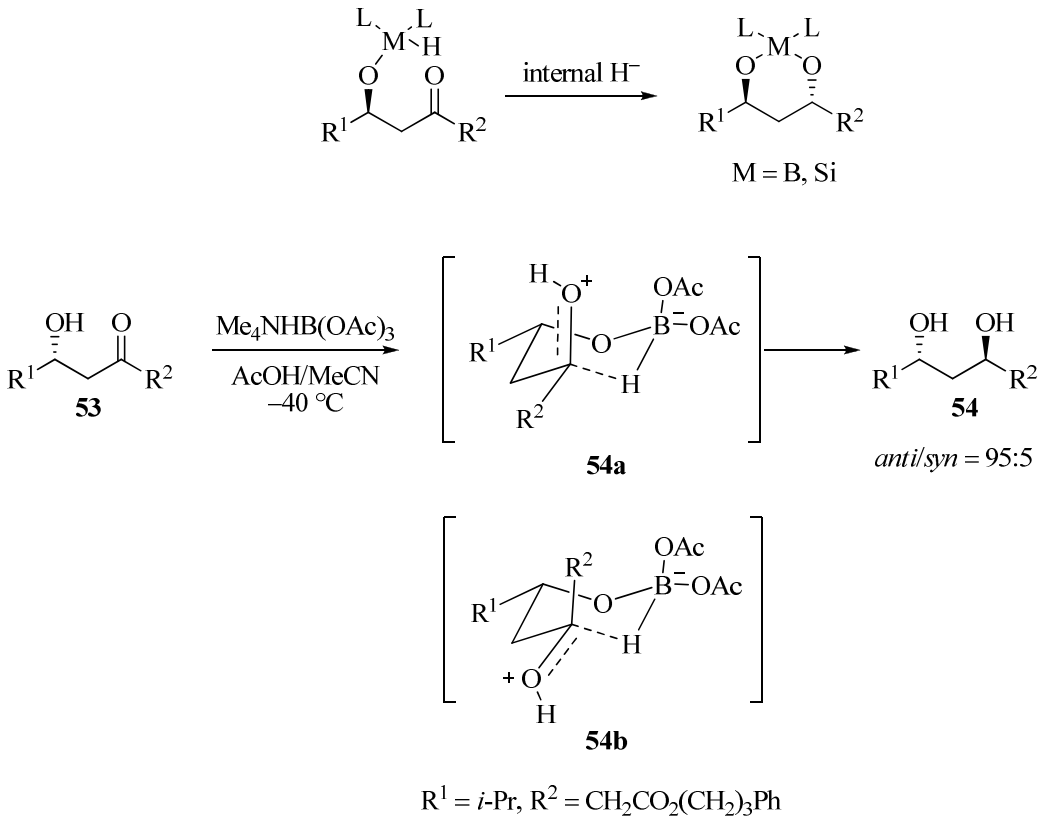
ii) Synthesis of *anti*-1,3-diols

In contrast with chelate-controlled external hydride addition to acyclic β-hydroxy ketones giving *syn*-1,3-diols, intramolecular delivery of hydride directed by the β-hydroxyl group leads to selective *anti*-reduction. The reducing reagent used in this type of reduction should satisfy the following two requirements.

- The reagent must combine with the hydroxyl group retaining the hydride in the molecule.
- The reducing ability of the reagent should be moderate to avoid the competing bimolecular reductions of ketones.

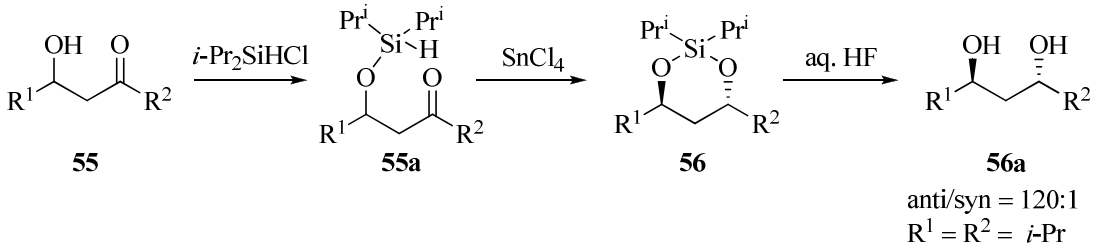
Under these general considerations, various combinations of sodium borohydride based reagents and solvents were tested and tetramethylammonium triacetoxyborohydride was found to be the reagent of choice. In fact, a variety of β-hydroxy ketones **53** (Scheme 11) are reduced with this reagent affording a mixture of 1,3-diols with the *anti* isomer being the

major isomer. The *anti*-stereochemistry of these reductions may be rationalized by considering chair-like transition state **54a**. The transition state **54b** leading to the *syn*-isomer is destabilized by the 1,3-diaxial interaction between R^2 and OAc.



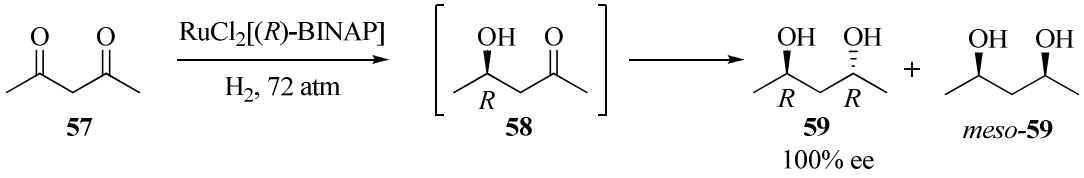
Scheme 11: Synthesis of *anti*-1,3-diol

The same *anti*-directed reduction of β-hydroxy ketones has been achieved by using chlorodiisopropylsilane:pyridine as a reducing agent.[17] The initially formed β-siloxy ketones **55a** are stable, but can be activated by Lewis acid catalysts causing intramolecular hydride transfer to the carbonyl group. The resulting siladioxanes **56** are stable under the reaction conditions, but easily desilylated with hydrogen fluoride in acetonitrile producing *anti*-diols (**56a**) with extremely high diastereoselectivity although the yields are moderate (Scheme 12).



Scheme 12: Synthesis of *anti*-1,3-diol

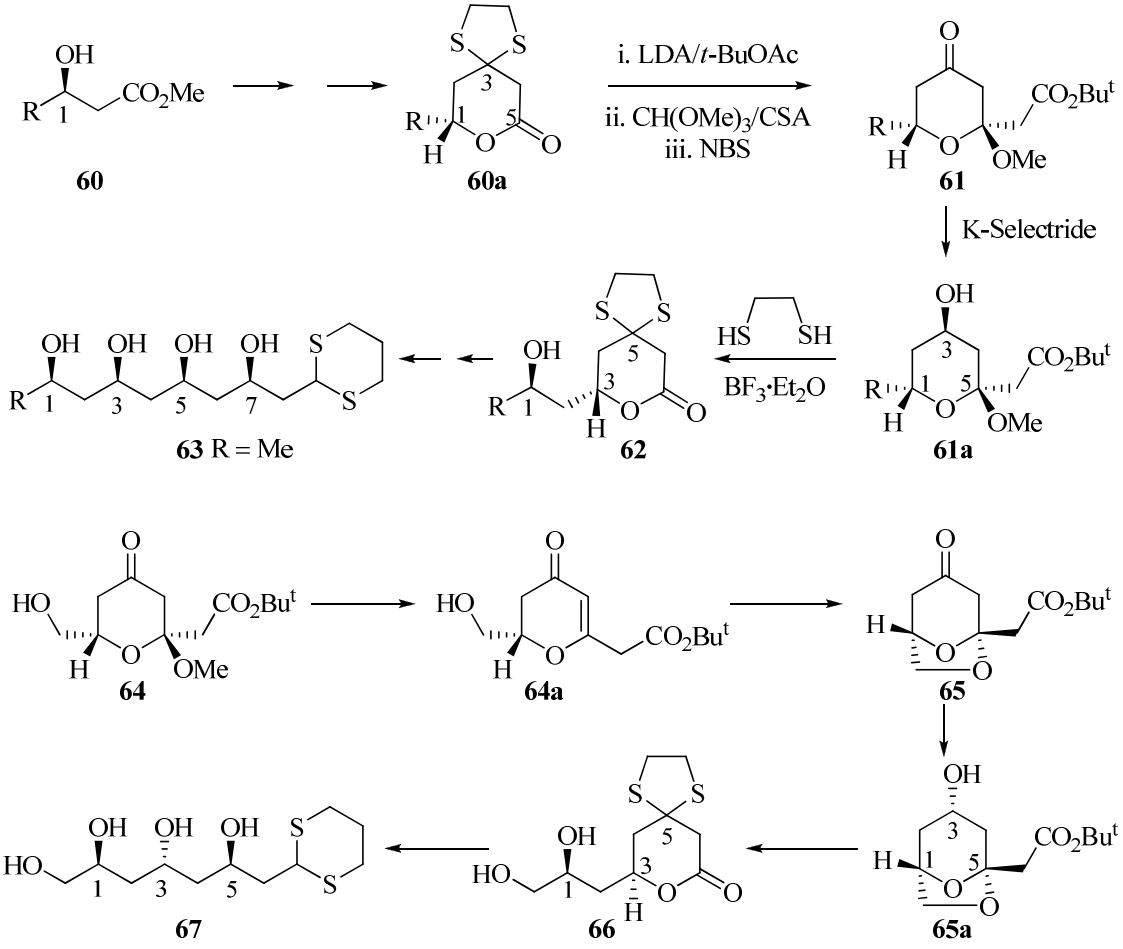
Noyori and Takaya et al. reported a remarkably high two-step diastereo- and enantioselective hydrogenation of 1,3-diketones (**57**) producing *anti*-1,3-diols **59** (Scheme 13) by using $RuCl_2$[(*R*)-BINAP] as a chiral catalyst.[18] The initial stage of the reduction is a chirality transfer from the catalyst. In the second stage, reduction is highly dependent on the chirality of the initially created hydroxyl group. It should be noted that hydrogenation of pure **58** with an (*S*)-BINAP based catalyst led to the isomeric diols (**59**) and (*meso*-**59**) in only 15:85 ratio, demonstrating that double stereodifferentiation is operative in the present $RuCl_2$[BINAP]-mediated reduction. Essentially the same results have been obtained using the dimeric triethylamine complex Ru_2CCl_4[(*R*)-BINAP]$_2$ (Et_3N).



Scheme 13: Synthesis of *anti*-1,3-diol

5) Reduction of cyclic ketone equivalents of acyclic β-hydroxy ketones

Stereoselectivity on reduction of acyclic ketones involving an oxygen function at the α- or β-positions is presumed to be dependent on the stability and the structural specificity of metal-mediated cyclic transition states. Thus, in principle, a well-established stereochemistry in cyclic systems is still valid even in these cases. So, if it is possible to design acyclic β-hydroxy ketones which are in equilibrium with the cyclic structure with the latter form predominating during the reduction, then, acyclic 1,3-diols would be produced with high selectivity. A general strategy for synthesizing both *syn*- and *anti*-1,3-polyols has been established by Nakata and Oishi et al. based on these considerations referring to their biogenetic pathway.[19]



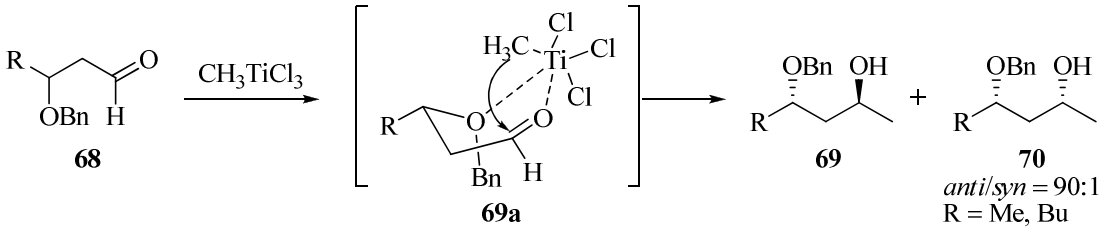
Scheme 14: Synthesis of *syn*- and *anti*-polyols

Reduction of **61** with K-Selectride/tetrahydrofuran afforded **61a** with a *syn*-l,3-diol exclusively, while **65** gave **65a** with an *anti*-l,3-diol. Acetal-thioacetal exchange reactions of **61a** and **65a** followed by δ-lactone formation between the newly produced C-3 hydroxyl groups and an ester afford **62** and **66**, and subsequently (**63**) and (**67**) (Scheme 14) respectively. The series of reactions used for this conversion are reiterative, and thus synthesis of their higher homologues (**63**) and (**67**) is possible. This strategy was successfully applied to the synthesis of the right half of Pederin[20] and naturally occurring all-*syn*-tetrol derivative.[21]

6) Synthesis of 1,3-diols by carbon-carbon bond formation

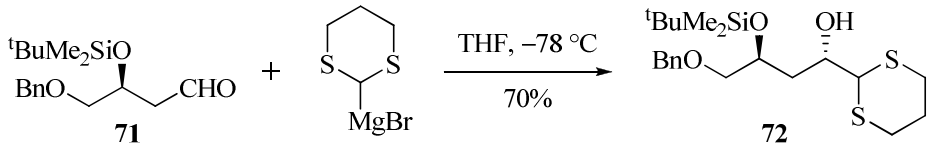
i) Alkylation of β-alkoxy aldehydes

Excellent chelation controlled 1,3-asymmetric induction has been demonstrated Reetz et al. in the alkylation of β-alkoxy aldehydes with Lewis acid titanium reagents of the type $RTiCl_3$, while lithium dimethylcuprate (Me_2CuLi) which causes high selectivity in 1,2-asymmetric induction gives unsatisfactory results.[22] The reaction of **68** with methyltrichlorotitanium ($MeTiCl_3$) in dichloromethane at −78°C yielded *anti*-1,3-alkoxy alcohol (**69**) and the *syn*-isomer (**70**) in a ratio of 90:1 (scheme 15). The intermediate leading to *anti*-**69** is thought to be **69a**. Complexation with titanium tetrachloride ($TiCl_4$) or tin tetrachloride ($SnCl_4$) followed by addition of allyltrimethylsilanes or dibutylzinc at −78 °C also resulted in *anti*-products with stereoselectivities of ≥ 90%. Reetz et al. reported that formation of cyanohydrins from **68** using tin tetrachloride/trimethylsilyl cyanide takes place with moderate *anti*-selectivity.



Scheme 15: Synthesis of *anti*-1,3-diol

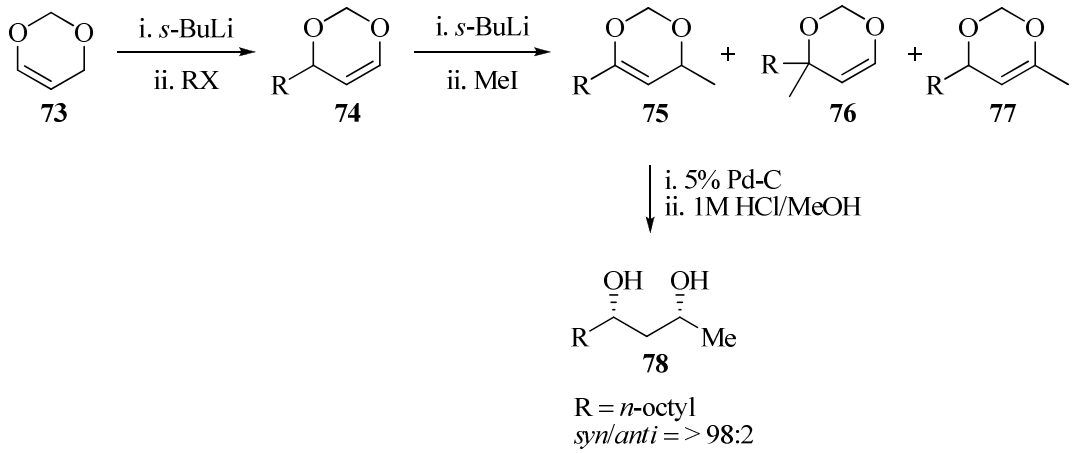
Solladie and coworkers[23] has been reported that treatment of **71** with bromomagnesium l,3-dithian-2-ide produced *anti*-l,3-glycol derivative (**72**) exclusively (Scheme 16). The selectivity is remarkably high in this case.



Scheme 16: Synthesis of *anti*-1,3-diol

ii) Dialkylation of 1,3-dioxins

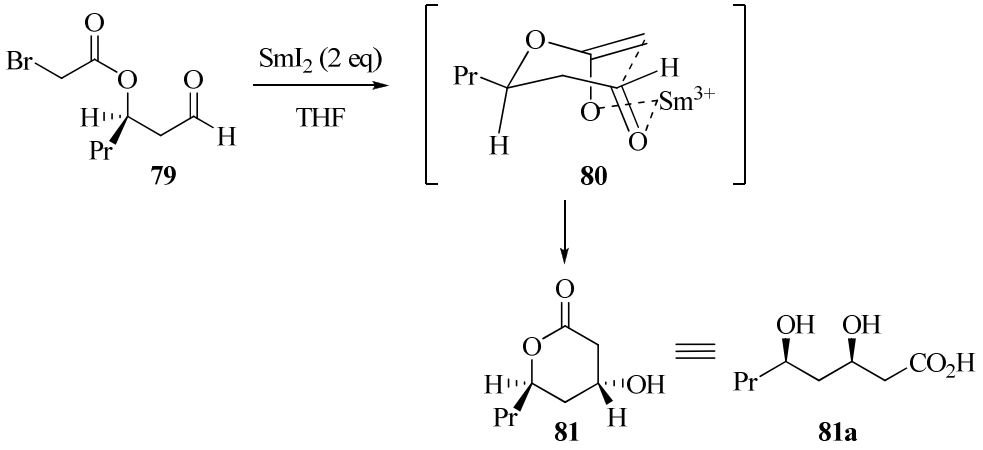
Allylic deprotonation of 4*H*-l,3-dioxins (**73**) with *sec*-butyllithium followed by alkylation provides the monosubstituted dioxins **74**, which after deprotonation and successive methyl iodide treatment yields a mixture of three disubstituted dioxins **75**–**77** with **75** predominating was studied by Funk and coworkers.[24] Hydrogenation of the main product **75** with 5% palladium on carbon yielded *syn*-1,3-diol (**78**) (> 98:2) after hydrolysis (Scheme 17).



Scheme 17: Synthesis of *syn*-1,3-diol

iii) Intramolecular Reformatsky-type reaction

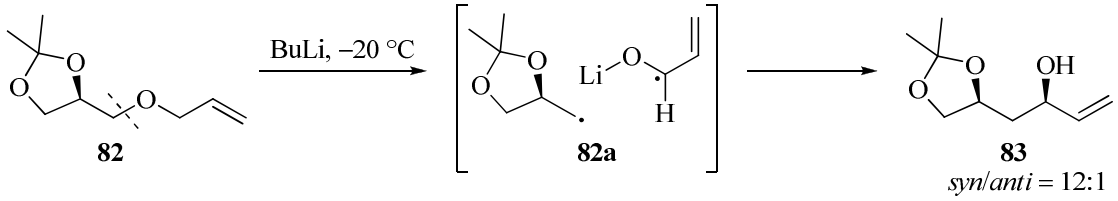
Molander et al.[25] reported that samarium diiodide (SmI_2) promoted intramolecular Reformatsky-type reaction of bromoacetoxy carbonyl substrate **79** affords 5-pentanolide derivative (**81**) corresponding to *syn*-1,3-diol (**81a**). Initially Sm^{3+} ester enolates may be generated and the following cyclization is expected to ensue through a rigid cyclic transition state **80** (Scheme 18). Various *syn*-1,3-diol derivatives can be prepared by this methodology.



Scheme 18: Synthesis of *syn*-1,3-diol

iv) [1,2]-Wittig rearrangement of β-alkoxyalkyl allyl ethers

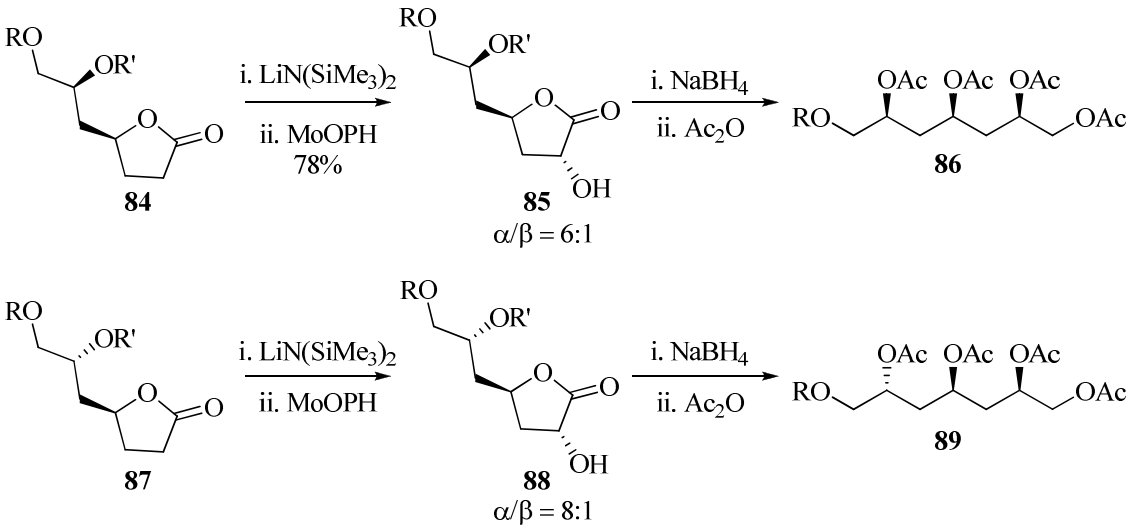
β-Alkoxyalkyl allyl ethers **82** on treatment with butyllithium undergo [1,2]-Wittig rearrangement to give *syn*-1,3-diol (**83**) (Scheme 19) *via* a radical intermediate **82a** along with [1,4]-Wittig products was studied by Schreiber et al.[26]



Scheme 19: Synthesis of *syn*-1,3-diol

7) Hydroxylation of 4-butanolides with bulky substituents in position 4

Treatment of the enolates liberated from 4-butanolide **84** and its isomer **87** with MoOPH [MoO_5.Py.HMPA] produces 2-hydroxy derivatives **85** and **88** respectively, which can be converted into the triol derivatives (**86**) and (**89**) (Scheme 20). The degree of stereoselection in the hydroxylation of 4-butanolide enolates is dependent on the bulkiness and nature of the C-4 side chain was documented by Hanessian et al.[27]



Scheme 20: Synthesis of polyols

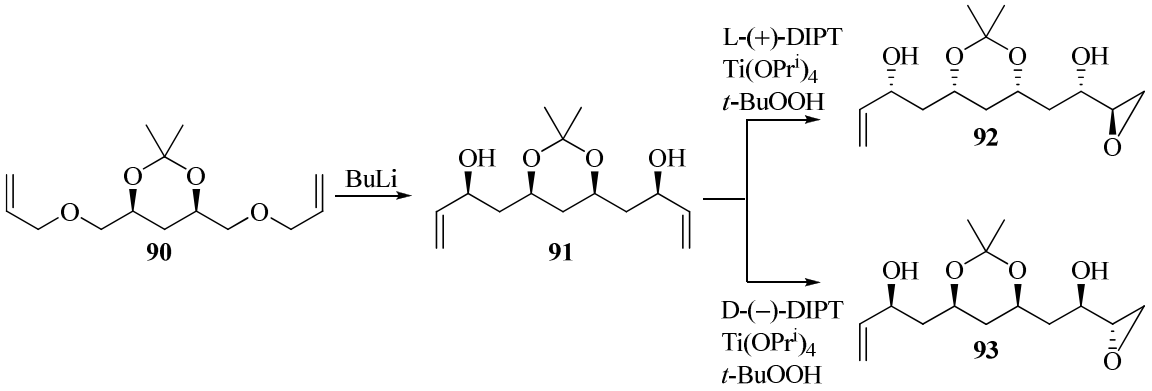
8) A strategy for the synthesis of extended 1,3-polyol chains

Excellent methodologies for the synthesis of 1,3-diols, 1,3,5-triols or 1,3,5,7-tetrols have recently appeared. However, new technology is still required for the construction of further extended 1,3-polyol chains.

i) Two-directional 1,3-Polyol chain extension strategy

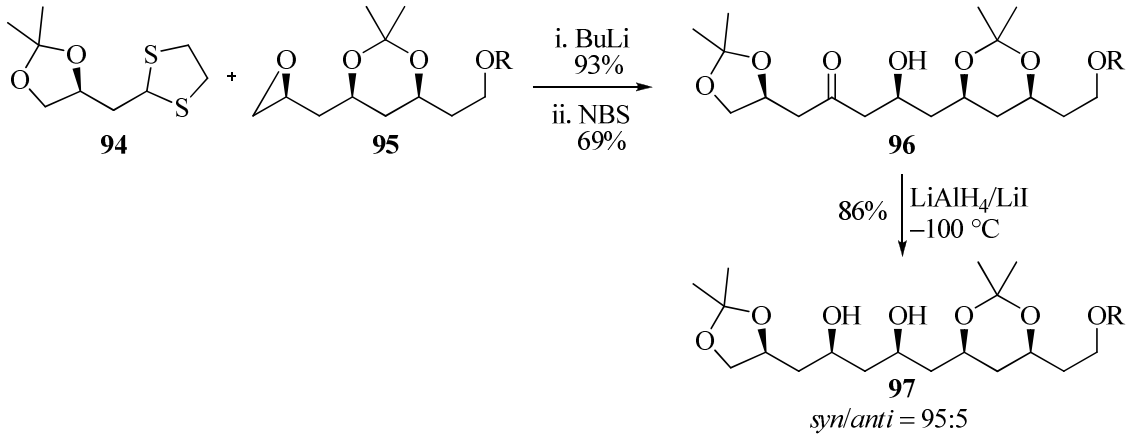
Two-directional extension of 1,3-polyol chains by the terminus differentiation of *meso* precursors based on group and face selective Sharpless asymmetric epoxidation has been developed by Schreiber and coworkers.[28] The 1,3-tetraol derivative **91** prepared from **90** by using the [1,2]-Wittig rearrangement of β-alkoxyalkyl allyl ethers undergoes epoxidation with group and face selectivity affording **92**, $[a]_D$ – 0.86° (*c* = 1.51, $CHC1_3$),

or **93**, $[a]_D$ + 0.80° (*c* = 1.50, $CHC1_3$), respectively, by using the pro-*S* and pro-*R* selective Sharpless reagents (Scheme 21). The minor isomers produced in these reactions are further epoxidized by a fast second epoxidation giving rise to diepoxides. Thus, the enantiomeric excess of the major enantiomer increases as the reaction proceeds to completion. Using functionality located on both sides of the chiral products (**92**) and (**93**), the 1,3-polyol chain can be extended in two directions. Several stereoisomeric fragments involving eight hydroxyl functions at the 1,3-position were synthesized based on this strategy and was applied for the synthesis of mycoticin A and B, polyenemacrolide antibiotics, establishing their stereostructure unequivocally.



Scheme 21: Synthesis of *syn*-polyols

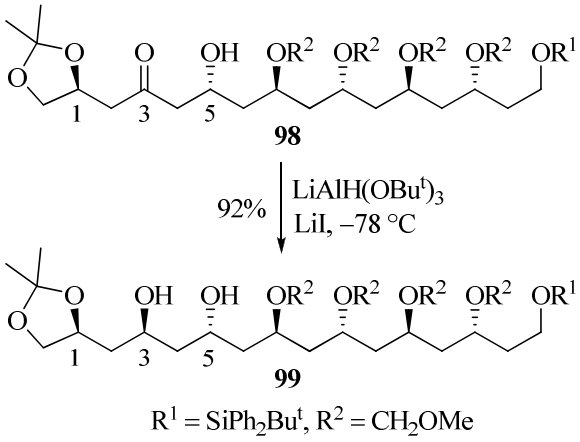
ii) Convergent synthesis of extended Polyol chain



Scheme 22: Synthesis of *syn*-polyol

When two stereochemically well-defined 1,3-polyol containing fragments are combined together, a higher member 1,3-polyol chain would be obtained. The crucial requirement is to achieve an effective coupling reaction, with both controlled and defined stereochemistry. Suzuki et al.[29] has been reported that opening of oxirane **95** with dithiane **94** followed by oxidation furnishes **96**, which upon reduction with LAH in the presence of LiI yields all-*syn*-pentaol derivative (**97**) (Scheme 22).

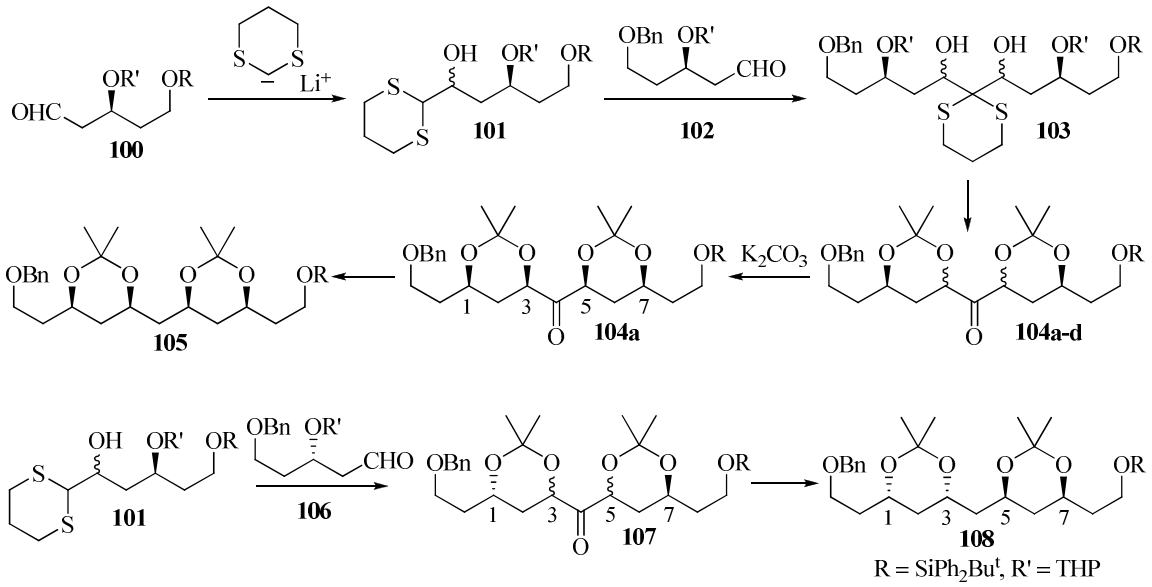
Whereas reduction of **98** with a *anti*-1,5-configuration with lithium tri-*tert*-butoxyaluminumhydride/lithium iodide produced *syn*-1,3-*anti*-3,5-triol derivative (**99**) containing other hydroxyl functions (Scheme 23) was studied by Suzuki et al.[29]



Scheme 23: Synthesis of polyol

ii-a) Coupling of two different aldehydes mediated by carbonyl dianion equivalents followed by Ancillary stereocontrol

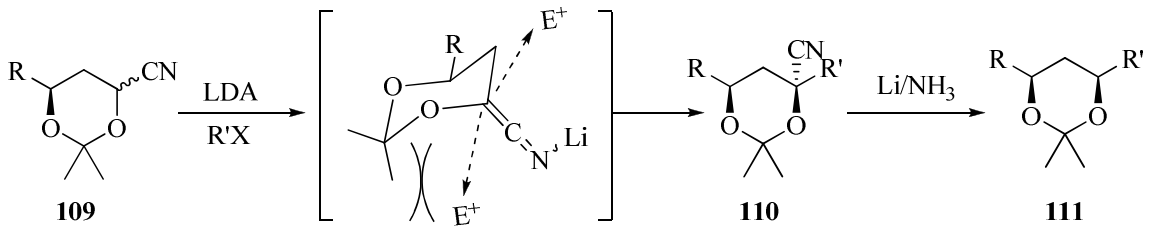
Aldehydes **100** and **102** are linked by 2-lithio-l,3-dithiane mediated coupling via **101** yielding tetraol derivative **103**, two additional hydroxyl groups are produced through these coupling reactions. It is not necessary to worry about the stereochemistry of these hydroxyl groups since a mixture of **104a-d** derived from **103** can be converted to the more stable isomer **104a** on potassium carbonate treatment. Reductive removal of the carbonyl group led to all-*syn*-tetraol (**105**) with virtually complete stereocontrol. In the same way, the *syn*-1,3-*anti*-3,5-*syn*-5,7-isomer (**108**) was synthesized from **106** and **101** (Scheme 24).



Scheme 24: Synthesis of polyol

9) Alkylation and reductive decyanation

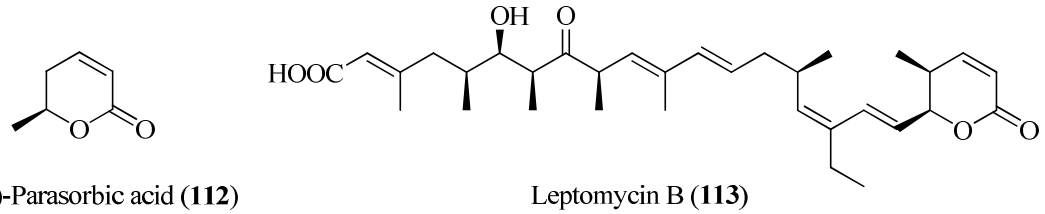
Alkylation of acetonide derivative **109** with alkyl halide in presence of base furnishes the *syn*-acetonide derivative **110**. The alkylation itself is highly selective, and are typically greater than 100:1 in favor of the axial nitrile. This selectivity can be rationalized by a chair-like intermediate for which equatorial alkylation is highly favored on steric grounds. Approach of the electrophile from an axial trajectory leads to a *syn*-pentane-like interaction, which upon reductive decyanation with Lithium/ammonia produces 1,3-*syn*-acetonide derivative (**111**) (Scheme 25). The decyanation simply proceeds with retention of configuration, and the diastereomer ratio reflects that of the alkylation. The selectivity arises from axial protonation.



Scheme 25: Synthesis of *syn*-1,3-diol

Introduction to δ-Lactones:[30]

Lactone rings are a structural feature of many natural products.[31] Of the naturally occurring lactones, which all display a wide range of pharmacological activities, those bearing a 5,6-dihydropyran-2-one moiety are relatively common in various types of natural sources.[32] Because of their manifold biological properties, these compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic. In addition, they inhibit HIV protease, induce apoptosis, and have even proven to be antileukemic, along with having many other relevant pharmacological properties. At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.[33] The structural features of this class of compounds vary widely. Indeed, molecules such as (+)-parasorbic acid (**112**), shown in Figure 3, barely display anything other than the dihydropyranone ring. In contrast, this moiety goes almost unnoticed within the complex molecular architecture of leptomycin B (**113**). For this reason, syntheses of naturally occurring dihydropyranones cannot be classified according to a general, unified criterion.



(+)-Parasorbic acid (**112**) Leptomycin B (**113**)

Figure 3: *Representatives for naturally occurring 5,6-dihydropyran-2-ones*

Synthetic methods for the construction of 5,6-dihydropyran-2-one

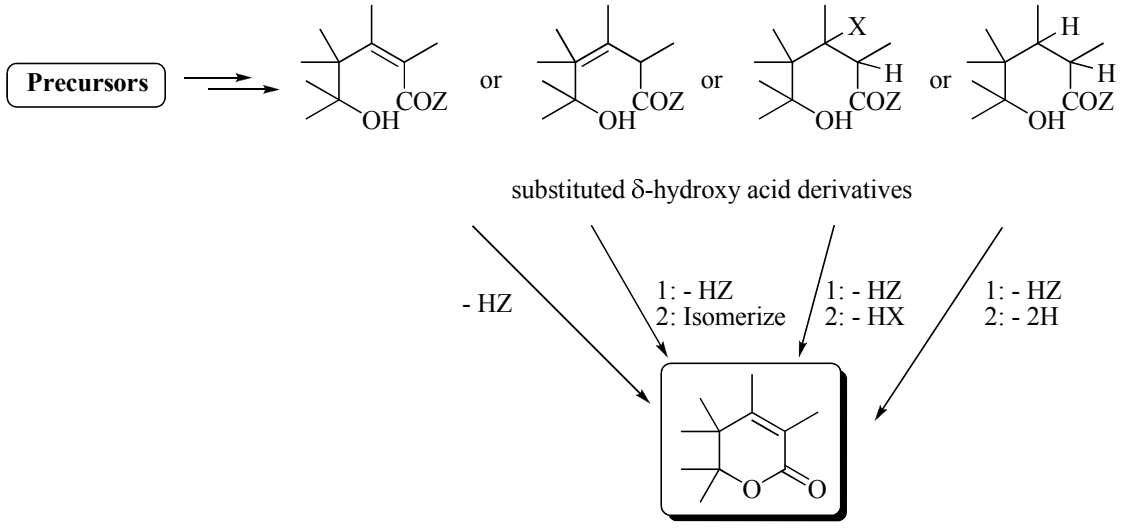
Many different synthetic methods for the creation of 5,6- dihydropyran-2-one rings have been reported. Emphasis has been placed almost exclusively on methods that have actually been employed for the synthesis of naturally occurring pyrones. These methods have been divided into four groups as follows:

- Lactonization of substituted δ-hydroxy acid derivatives

- ❖ Oxidation of substituted dihydropyran derivatives
- ❖ Ring closing metathesis
- ❖ Miscellaneous methods

(1) Lactonization of substituted δ-hydroxy acid derivatives

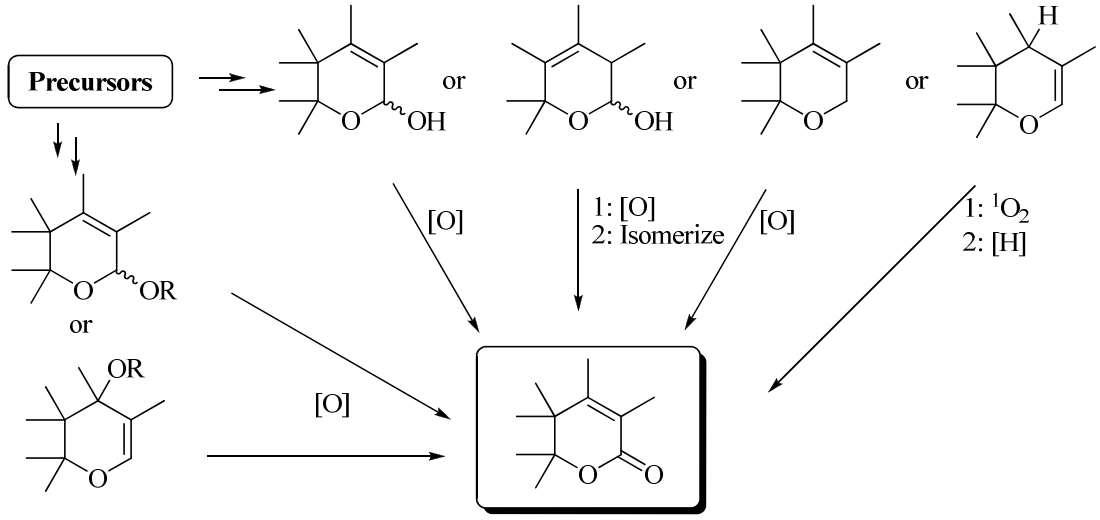
Methods that fall into this category include any reaction, which generates a δ-hydroxy acid or derivative thereof which later cyclizes to a δ-lactone, spontaneously in many cases. When the δ-hydroxy acid already carries a conjugated *Z* double bond, the final product will be the desired 5,6-dihydropyran-2-one. If the double bond is not present, but a suitable leaving group X is attached to the β-carbon (or, less often, the α-carbon), elimination of HX from the intermediate lactone can take place under mild conditions to yield the double bond. Often, these conditions may also cause double-bond migration from the β,γ-position to the conjugated α,β-position. In the absence of both the double bond and the leaving group, an additional dehydrogenation protocol is necessary (Scheme 26). This methodology for generating a 5,6-dihydropyran-2-one ring is widely represented in the literature.[34]



Scheme 26: Formation of 5,6-dihydropyran-2-ones via lactonization of a δ-hydroxy acid derivative

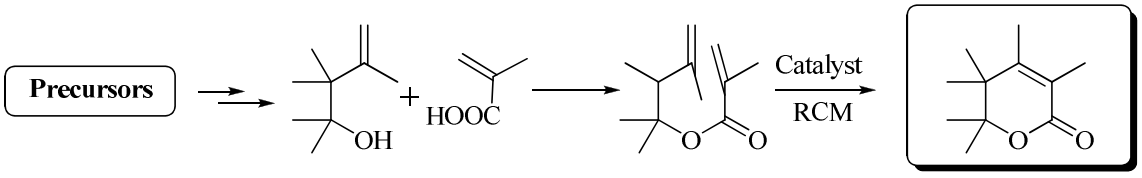
(2) Oxidation of substituted dihydropyran derivatives

Various synthetic methods begin by first generating a dihydropyran derivative. If this is a 2-hydroxy-5,6-dihydro-2H-pyran (a cyclic hemiacetal), a simple alcohol oxidation can be used to transform it into a 5,6-dihydropyran-2-one (Scheme 27). If the hydroxyl group is located at another position or is not present, the oxidation of a C–H bond contiguous to the oxygen atom is required. According to the position of the endocyclic C=C bond, this can be carried out either via direct C–H bond oxygenation or through a photochemical oxygenation with singlet oxygen, $^1O_2$. Other methods involve the treatment of pyranoid glycals or glycosides with specific oxidants.[35]



Scheme 27: Formation of 5,6-dihydropyran-2-ones via oxidation of dihydropyran intermediates

(3) Ring closing metathesis



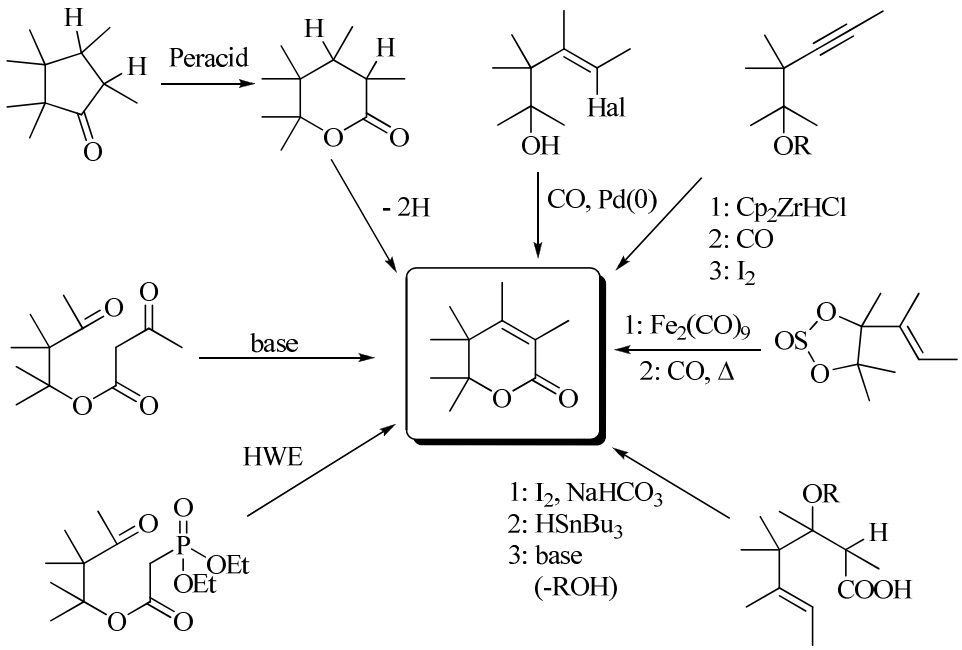
Scheme 28: Formation of 5,6-dihydropyran-2-ones via ring-closing metathesis

The transition-metal-catalyzed olefin metathesis is a very recent development, which has become an extremely useful synthetic tool in the last 15 years. The ring-closing variant of this reaction (RCM) has proven to be particularly useful in the preparation of carbo- and heterocycles of any ring size, except for those that are very strained. In the case of 5,6-dihydropyran-2-ones, RCM has been used for the direct creation of this heterocyclic system many times (Scheme 28).[36]

(4) Miscellaneous methods

In this last category, all those methods are grouped together, while not being intrinsically less valuable than those previously discussed, have been used in only a limited number of cases for the preparation of either tetrahydropyran-2-ones or 5,6-dihydropyran-2-ones. Scheme 29 illustrates these particular reactions.[37]

- Intramolecular HWE olefinations
- Baeyer–Villiger reactions
- Metal-mediated/catalyzed cyclocarbonylations
- Halo- and selenolactonizations
- Cycloadditions
- Intramolecular aldolizations



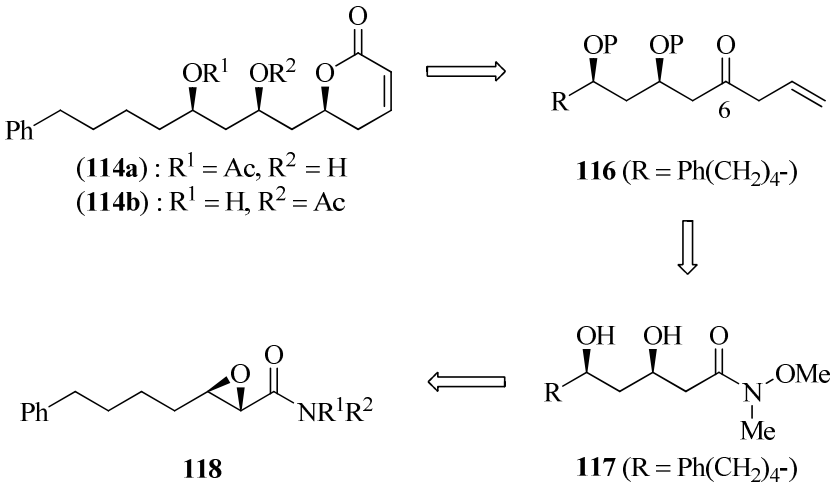
Scheme 29: Miscellaneous methods for the preparation of 5,6-dihydropyran-2-ones

As it can be seen in scheme 29, these methods require precursors of different structural types and afford different products. Thus, intramolecular HWE olefinations and metal-mediated carbonylations usually yield 5,6-dihydropyran-2-ones directly. The Baeyer–Villiger reaction, however, provides tetrahydropyran-2-ones, which must subsequently be dehydrogenated. The halolactonization method gives a halogenated lactone, which must then be subjected to both reductive dehalogenation and base-catalyzed elimination of ROH or a similar fragment. Similar considerations apply to the selenolactonization reaction.

PAST WORK:

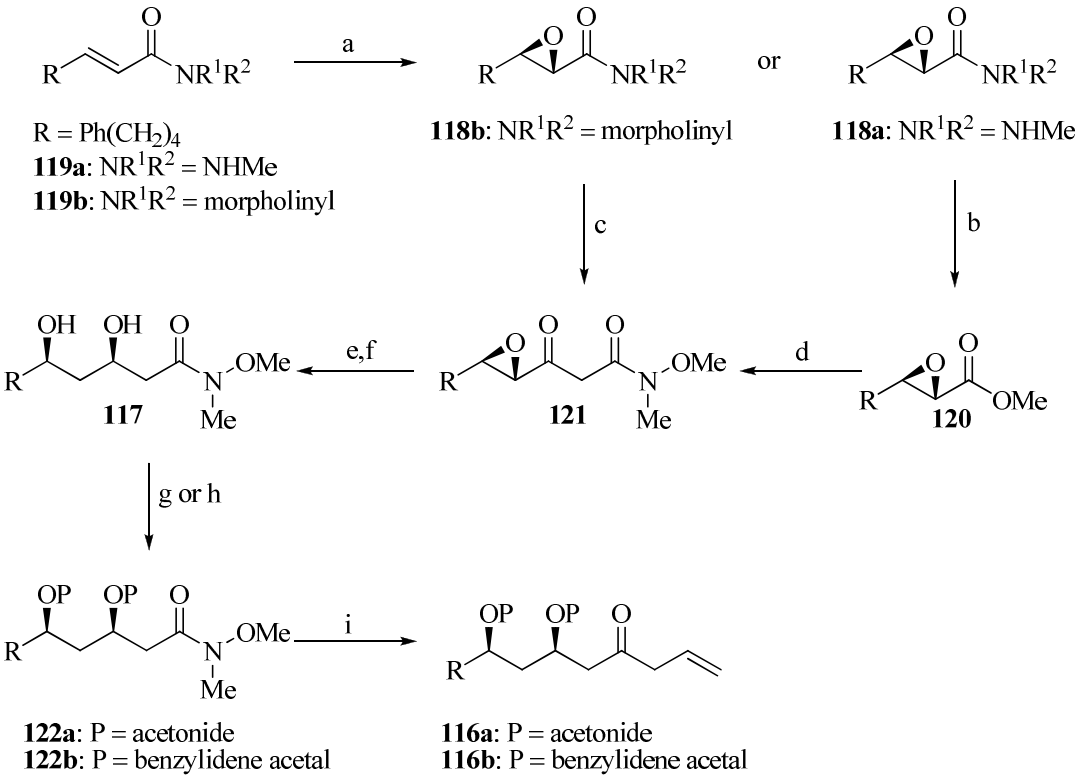
Synthesis of enantiomers of 1,3-polyol/α-pyrones: Shibasaki *et al*. (2003)

Shibasaki and coworkers developed the catalytic asymmetric synthesis of both *syn*- and *anti*-3,5-dihydroxy esters. The method relies upon catalytic asymmetric epoxidation of α,β-unsaturated imidazolides and amides, using lanthanide-BINOL (Ln-BINOL) complexes and diastereoselective reduction of ketones. This method was applied to the enantioselective synthesis of 1,3-polyol/α-pyrone natural products. The synthesis reported by Shibasaki *et al*. afforded the enantiomers of natural 1,3-polyol/α-pyrones.[38]



Scheme 30: Retrosynthetic strategy for the 1,3-polyol/α-pyrones

The retrosynthetic analysis of **114** is shown in Scheme 30. The C(6) stereocenter of **114** could be introduced by using a diastereoselective reduction of ketone **116**, which was expected to be obtained from *syn*-3,5-dihydroxy amide **117**, which in turn could be synthesized from α,β-epoxy amide **118**. The α,β-epoxy amide **118** could be secured from α,β-unsaturated amide **119a**/**119b** utilizing the key catalytic asymmetric epoxidation.

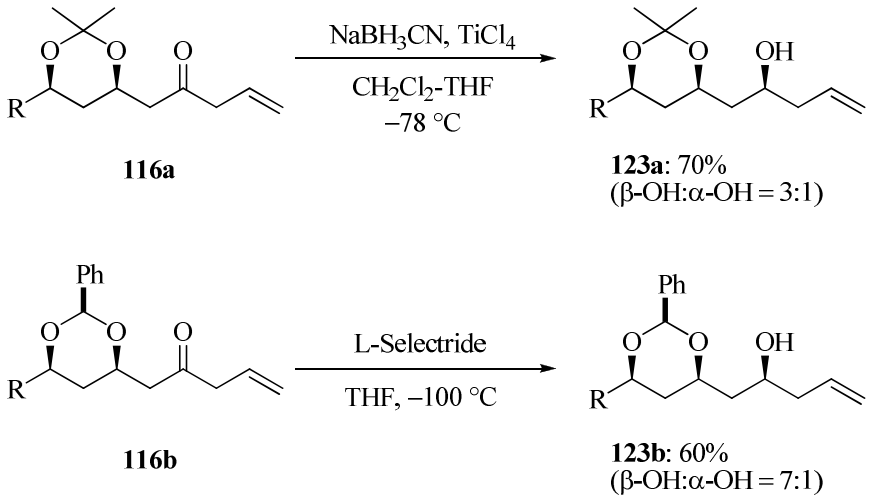


Scheme 31: Synthesis of *syn*-3,5 dihydroxy ketone

Reagents & Conditions: (a) (R)-Sm catalyst, TBHP, 4A° MS, THF, rt, 94%; (b) Martin Sulfuran, THF, rt, then NaOMe, 71% (conv. 97%); (c) MeCON(OMe)Me, LHMDS, THF, –78 to –50 °C, 60% (conv. 85%); (d) MeCON(OMe)Me, LHMDS, THF, –78 to –30 °C, 89%; (e) PhSeSePh, $NaBH_4$, EtOH, rt, 84%; (f) $BEt_2(OMe)$, $NaBH_4$, THF-MeOH, –78 °C; (g) 2,2-dimethoxypropane, TsOH (cat.), DMF, rt, 76% (2 steps); (h) $PhCH(OMe)_2$, PPTS (cat.), toluene, reflux, 74% (2 steps); (i) AllylMgBr, THF, 0 °C, **116a** 84%, **116b** 87%.

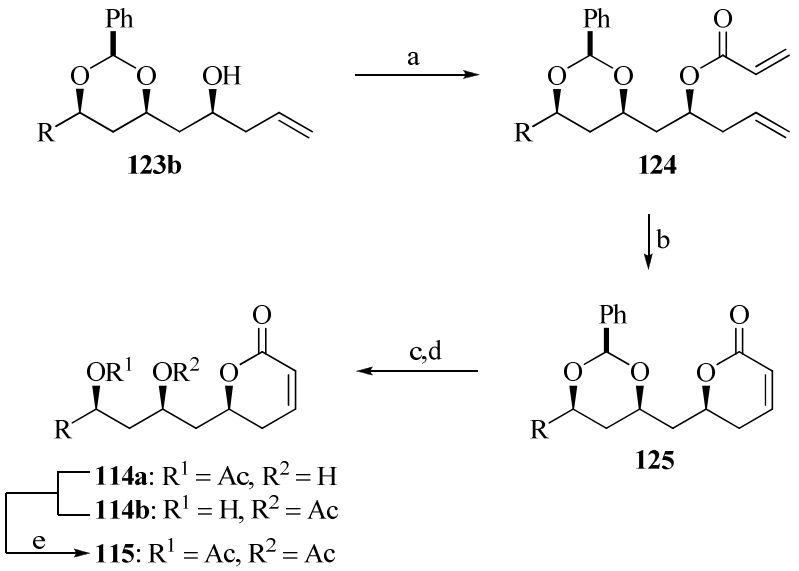
The synthesis started with catalytic asymmetric epoxidation of **119a** with 10 mol % of the (*R*)-Sm catalyst which proceeded smoothly, yielding α,β-epoxy amide **118a** in 87% yield and in 99% ee. **118a** was converted into the corresponding methyl ester **120** (71%, conv. 97%), which was subsequently treated with lithium enolate prepared from *N*-methoxy *N*-methyl acetoamide to give the desired γ,δ-epoxy β-keto amide **121** in 89% yield. Furthermore catalytic asymmetric epoxidation of morpholinyl amide **119b**, using 10 mol % of the (*R*)-Sm catalyst (92%, **>** 99% ee), followed by treatment with the corresponding lithium enolate, gave **121** in one fewer step (60%, conv. 85%). After a reductive epoxide opening reaction of **121** (84%), *syn*-selective reduction was performed to give the desired *syn*-3,5-dihydroxy amide **117** exclusively. The diol moiety was then converted into an acetonide or benzylidene acetal, to afford the protected amides **122a** (76% for 2 steps) and **122b** (74% for 2 steps), respectively. Treatment of **122a** and **122b** with allylmagnesium bromide resulted in successful conversion into the corresponding β,γ-unsaturated ketone (**116a**) (84%) and (**116b**) (87%), without double bond isomerization (Scheme 31).

The key diastereoselective reduction of **116a** gave the desired alcohol (**123a**) with modest selectivity using $NaBH_3CN$, $TiCl_4$ in dichloromethane. However the diastereoselective reduction of **116b** proceeded with higher selectivity to afford the desired alcohol (**123b**), with L-Selectride at –100 °C in THF (Scheme 32).



Scheme 32: Diastereoselective reduction of ketone

Acrylation of **123b**, afforded the acryloyl ester **124** (91%) in nearly quantitative yield. Now the stage was set for the construction of 5,6-dihydro-δ-pyrone ring, which was accomplished by employing ring-closing metathesis (Scheme 33).



Scheme 33: Synthesis of enantiomers of 1,3-polyol/α-pyrones

Reagents & Conditions: (a) acryloyl chloride, *i*-Pr_2NEt, CH_2Cl_2, rt, 91%; (b) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (4 mol %), CH_2Cl_2, reflux, 84%; (c) 80% aq. AcOH, 60 °C; (d) $MeC(OEt)_3$, PPTS (cat.), CH_2Cl_2, rt; then H_2O, 76% (2 steps); (e) Ac_2O, DMAP (cat.), pyridine, rt, 89%.

Diene **124** was subjected to RCM using 4 mol % of Grubbs' first generation catalyst to give lactone **125** in 84% yield. In this stage, two diastereomers of **125** were separated, and the major isomer was utilized for the final conversions. Finally, removal of the benzylidene group, followed by monoacetylation of the resulting crude diol *via* cyclic ortho ester formation yielded (**114a** and **114b**) in good yield (76% for 2 steps). Acetylation of **114a** and **114b** produced the diacetate derivative (**115**).

Present Work

The 1,3-skipped polyol systems with *anti*- or *syn*- configuration are the basic structural units of several important natural products including clinically valuable polyene macrolide antibiotics. The 5,6-dihydro-δ-pyrones integrated with 1,3-skipped polyol systems form a basic skeleton of several natural products with variation at the alkyl side chain. Cryptocarya diacetate (**126**),[39] passifloricin A (**127**),[40] the antifungal 1,3-polyol/α-pyrones (**128** and **129)**,[41] and strictifolione (**130**)[42] are some of the representative examples for this class of natural products (Figure 4). These natural products are isolated very recently, which show broad range of biological activities. The biological activities associated with these natural products were ascribed to their inherent ability to act as good Michael acceptors.[33] The regiomeric acetates (**128** and **129)**, were recently isolated by Kurt Hostettmann *et al*. from *Ravensara anisata* by activity guided fractionation and shown to inhibit *C. cucumerinum* fungal growth as efficiently as the commercial antifungal compounds miconazole and propiconazole.

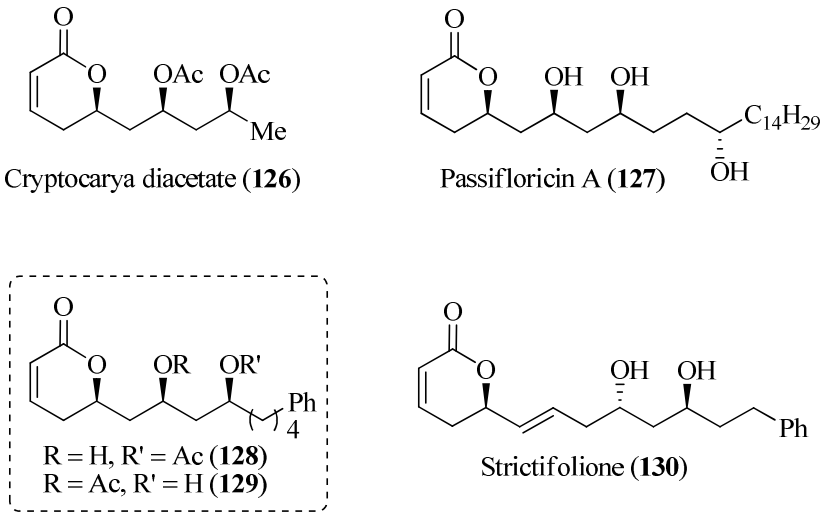
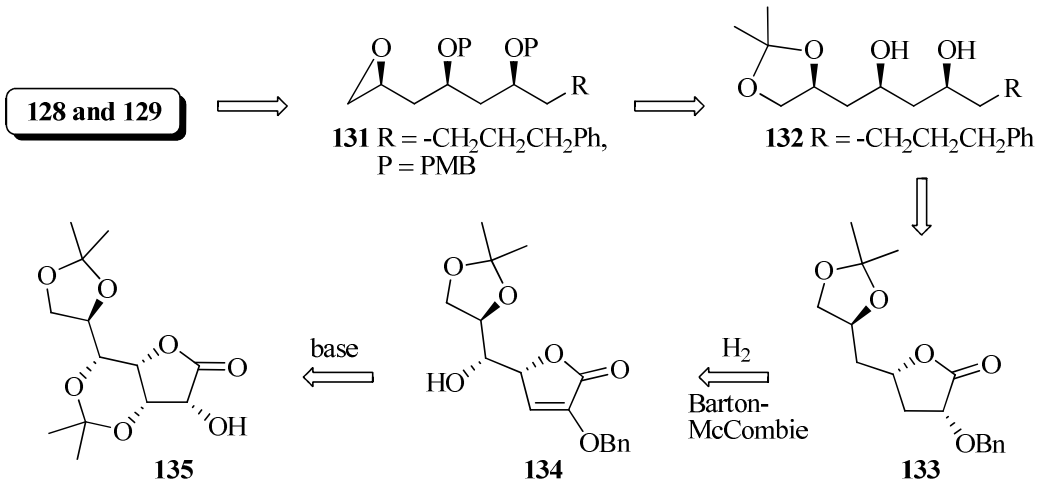


Figure 4: *Representative skipped polyol natural products with an integrated α-pyrone moiety*

Ravensara is considered as an endemic genus in Madagascar. Kostermans (1950) identified 27 *Ravensara* species in this genus including *R*. *anisata* Danguy. He also described *R*. *anisata* and *R*. *aromatica* Sonnerat as synonyms. However, studies on their essential oil composition discriminate between the two species: while methylchavicol is the major component of the bark essential oil of *R*. *anisata*, 1,8-cineol, sabinene and α-terpineol constitute more than 50% of the essential oil of *R*. *aromatica* (O'Tucker & Maciarello, 1995). Both species are used in traditional medicine. The essential oil has shown spasmolytic and neurosedative properties (Kostermans, 1950) and antimicrobial activity (de Medeci, Pieretti, Salvatore, Nicoletti & Rasoanaivo, 1992; aharivelomanana, 1989); spices are made from their fruits and leaves, and the bark is used to make perfume, local rum (Kostermans, 1950).

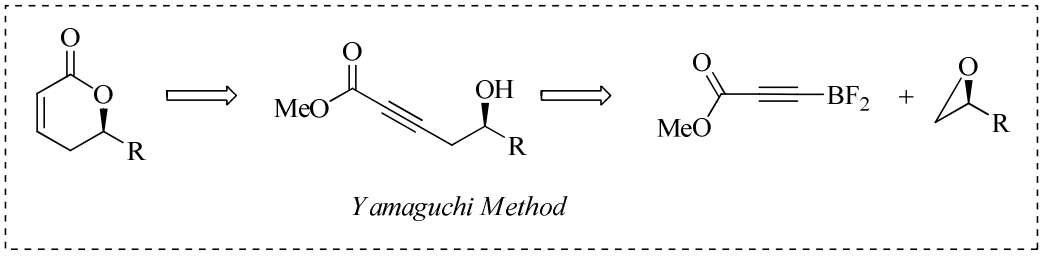
In a series of preliminary screenings, DCM extracts from the leaves and bark of *R*. *anisata* displayed interesting activities against the yeast *C*. *albicans* (Rahalison, Hamburger, Hostettmann, Monod, & Frenk, 1991) and the phytopathogenic fungus *C*. *cucumerinum* (Homans & Fuchs, 1970) in bioautographic TLC assays. Activity-guided isolation yielded two new α-pyrones (**128** and **129**). Their structure determination was achieved by 1D- and 2D-NMR spectroscopy [COSY, HSQC, HMBC and DEPT] experiments.

Our synthetic plan for the 1,3-polyol/α-pyrone natural products (**128** and **129**) is outlined in Scheme 34. After a careful analysis of the structures (**128** and **129**), we noticed that addressing the chiral pool synthesis of a suitably functionalized *syn*, *syn*-1,3,5-triol will be a key issue. As shown in the Scheme 34, after a careful stereochemistry comparison, isopropylidene derivative of α-D-glucoheptonic-γ-lactone **135**[43] having five contiguous stereocenters has been selected as a starting point. Synthesis of the advanced intermediate tetraol **132** was planned by a base mediated elimination and a stereo-controlled reduction[44] of enol **134** from the α-face resulting in a net deoxygenation of C-3. The Barton-McCombie deoxygenation[45] of the resulting hydroxylactone leads to a functionalized *anti*, *anti*-1,3,5-triol lactone **133**, which can be converted to the required *syn*, *syn*-1,3,5-triol system by Mitsunobu reaction[46] after appending the required side-chain.



Scheme 34: Retrosynthetic strategy for the key *syn*, *syn*-1,3,5-triol synthesis and 1,3-polyol/α-pyrone natural products

We envisioned that the lactone ring could be constructed by employing Yamaguchi method[47] of epoxide opening **131** (Scheme 35), subsequent partial hydrogenation followed by acid catalyzed lactonization should complete the total synthesis of the natural products **128** and **129**.

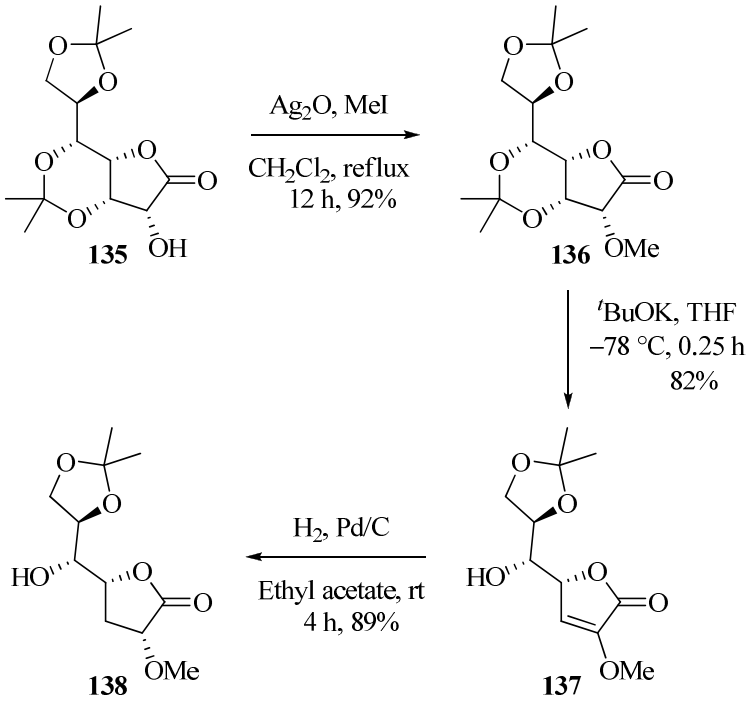


Scheme 35: Retrosynthetic strategy for the construction of δ-pyrone moiety

Synthesis was started with the known 3,5; 6,7 di-*O*-isopropylidene derivative of α-D-glucoheptonic-γ-lactone **135**.[43] This was synthesized from commercially available α-D-glucoheptonic-γ-lactone in a single step according to established procedure by using dimethoxypropane in acetone and conc. H_2SO_4 acid as a catalyst. This method was very

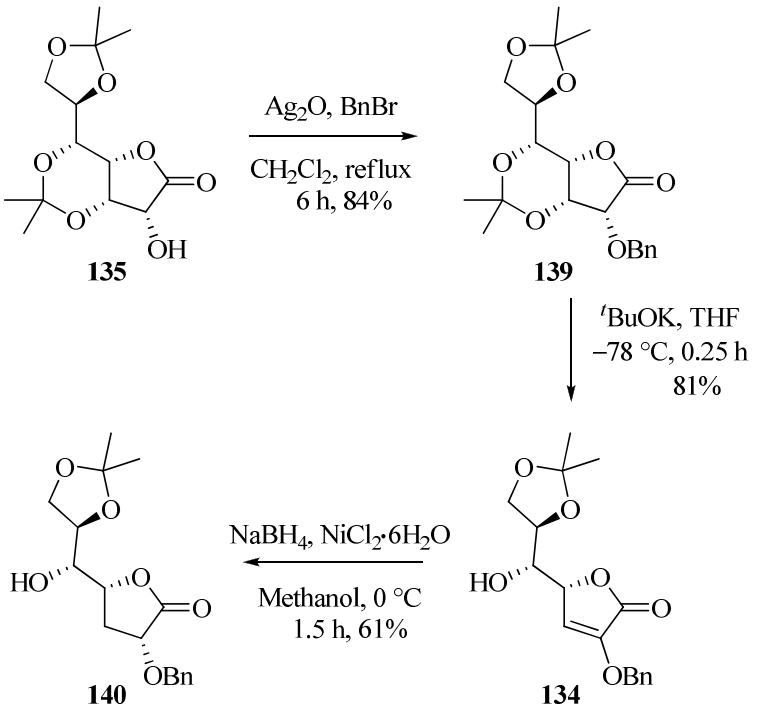
efficient as compared to the earlier methods as it affords regioselectivity, shorter reaction time and quality of isolated products.

Initially the synthesis was accompanied with the C-2 methyl ether for the establishment of reaction conditions. It was observed that compound **135** was sensitive towards acid and base. Therefore, protection of the hydroxyl group at C-2 was restricted to strongly acidic or basic conditions. So a much milder conditions like silver oxide and methyl iodide in refluxing dichloromethane was used to protect C-2 hydroxyl group as its methyl ether **136** (Scheme 36). The structure of methyl ether **136** was well supported by its ^{1}H, ^{13}C NMR spectrum and elemental analysis. In the ^{1}H NMR spectrum of **136** the isopropylidene groups resonated at δ 1.48, 1.42, 1.41 and 1.34 as singlets, methoxy group was observed at 3.64 ppm as a singlet. In the ^{13}C NMR spectrum, methoxy and lactone carbonyl resonated at δ 59.0, 172.3 as a quartet and singlet respectively. In the IR spectrum the C=O stretching was observed at 1801 cm^{-1}.



Scheme 36: Synthesis of hydroxy lactone **138**

After substantial experimentations, elimination reaction of **136** gave satisfactory results with potassium *tert*-butoxide in THF at –78 °C to afford α,β-unsaturated lactone **137**.[43d,44] The ^{1}H, ^{13}C NMR and IR spectrum of **137** revealed the presence of α,β-unsaturated lactone. The C-3 olefin proton appeared as a doublet at 6.14 ppm (J = 1.9 Hz) in the ^{1}H NMR spectrum of **137**. In the ^{13}C NMR spectrum C-2, C-3 carbons resonated at δ 147.2, 114.7 as a singlet and doublet respectively. In the IR spectrum the O–H stretching was observed at 3415 cm^{-1} and the conjugated C=O stretching at 1765 cm^{-1}. Conjugated lactone **137** was subjected to reduction of double bond under hydrogenation conditions using palladium on charcoal to furnish hydroxy lactone (**138**). Stereochemistry of **138** at C-2 was as expected since hydrogenation proceeds from the α-face resulting in a net retention of configuration at C-2 as *R* and deoxygenation at C-3. Spectral and analytical data of **138** were in agreement with the assigned structure. Signals corresponding to *endo* methylene protons located separately at 2.61–2.53, 2.31–2.25 ppm as multiplets in the ^{1}H NMR spectrum whereas C-3 carbon resonated at δ 31.1 as a triplet in the ^{13}C NMR spectrum.



Scheme 37: Synthesis of hydroxy lactone **140**

The protection of C-2 hydroxyl was now switched over to benzyl ether for easy and selective handling at the time of deprotection as the methyl ether requires harsh conditions. The C-2 hydroxyl of **135** was protected as its benzyl ether using silver oxide and benzyl bromide in dichloromethane at refluxing temperature to furnish the benzyl ether **139** (Scheme 37). The structure of benzyl ether **139** was well supported by ^{1}H, ^{13}C NMR spectrum and elemental analysis. In the ^{1}H NMR spectrum of **139** the isopropylidene groups resonated at δ 1.43, 1.39 and 1.33 as singlets, benzylic methylene protons resonated separately as doublets at 4.86, 4.79 ppm and the aromatic protons were observed at 7.39–7.36 ppm. In the ^{13}C NMR spectrum whereas benzylic CH_2 located at δ 72.3 as a triplet. In the IR spectrum the C=O stretching was observed at 1797 cm^{-1}.

As mentioned in above Scheme 37, the elimination of **139** was achieved with potassium *tert*-butoxide in THF at –78 °C affording α,β-unsaturated lactone **134**. The ^{1}H, ^{13}C NMR and IR spectrum of **134** revealed the presence of α,β-unsaturated lactone. The C-3 olefin proton appeared as a doublet at 6.17 ppm (J = 2.1 Hz) in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum C-2, C-3 resonated at δ 145.9, 115.9 as a singlet and doublet respectively. In the IR spectrum the O–H stretching was observed at 3420 cm^{-1} and the conjugated C=O stretching at 1760 cm^{-1}.

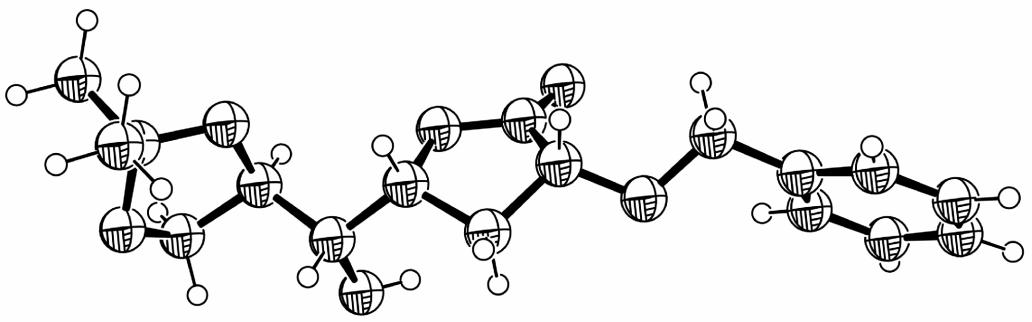
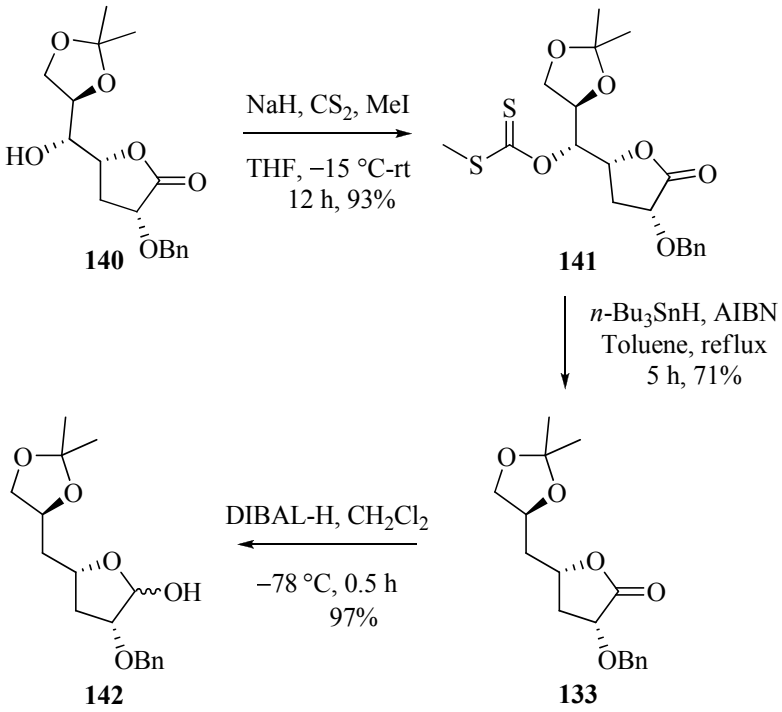


Figure 5: *ORTEP structure of compound* (**140**)

Attempted hydrogenation of **134** for the reduction of conjugated double bond ended up in an unidentified complex mixture of products using Pd/C. Selective stereo-controlled conjugate reduction of the lactone **134** with -OBn intact was achieved with

$NiCl_2$–$NaBH_4$[48] in methanol at 0 °C to furnish the hydroxy lactone (**140**).[44] Stereochemistry of C-2 was as expected, spectral and analytical data of **140** were in agreement with the assigned structure. Signals corresponding to *endo* methylene protons were observed separately at 2.51, 2.30 ppm as a doublet of doublet of doublet and a doublet of triplet in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum C-3 carbon resonated at δ 31.1 as a triplet. The assigned structure of **140** was further substantiated by single-crystal X-ray crystallography.[49]

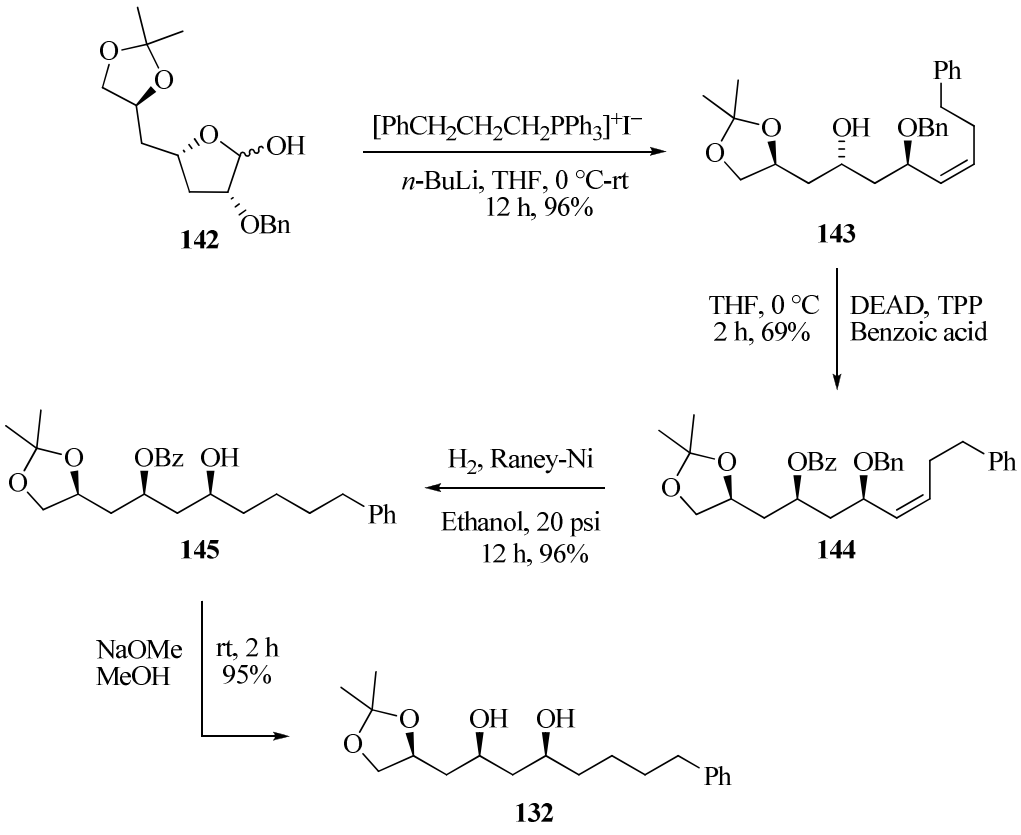


Scheme 38: Synthesis of lactol **142**

Deoxygenation at C-5 of hydroxylactone **140** was achieved by employing Barton-McCombie protocol[45] as shown in Scheme 38. Treatment of compound **140** with NaH, CS_2, followed by MeI in THF furnished xanthate ester **141** in nearly quantitative yield. The presence of xanthate ester was well supported by the spectral and analytical data of **141**. In the ^{1}H NMR spectrum of **141**, the H–C(5) resonated relatively down field at 5.99 ppm (J = 7.9, 1.7 Hz) as a doublet of doublet and a singlet for three protons at 2.54 ppm due to the S–CH_3. In the ^{13}C NMR spectrum thio carbonyl was located as a singlet at δ

216.8 and a quartet at δ 19.3 for S–CH_3 indicating the presence of xanthate ester. Treatment of compound **141** with *n*-Bu_3SnH and catalytic AIBN in refluxing toluene afforded functionalized *anti*, *anti*-1,3,5-triol lactone **133**. The signals corresponding to methylene protons appeared at 2.61 ppm as a ddd for one proton and at 2.03–1.81 ppm multiplet for three protons in the ^1H NMR spectrum. In the ^{13}C NMR spectrum the signals at δ 36.0, 40.2 resonated as triplets indicating the presence of two methylene units.

Having the functionalized *anti*, *anti*-1,3,5-triol lactone **133** in the hand our next object is to synthesize *syn*, *syn*-1,3,5-triol system with required side chain. As shown in Scheme 38, lactone **133** was subjected for controlled DIBAL-H reduction in dichloromethane at –78 °C to afford the lactol (**142**) in nearly quantitative yield.



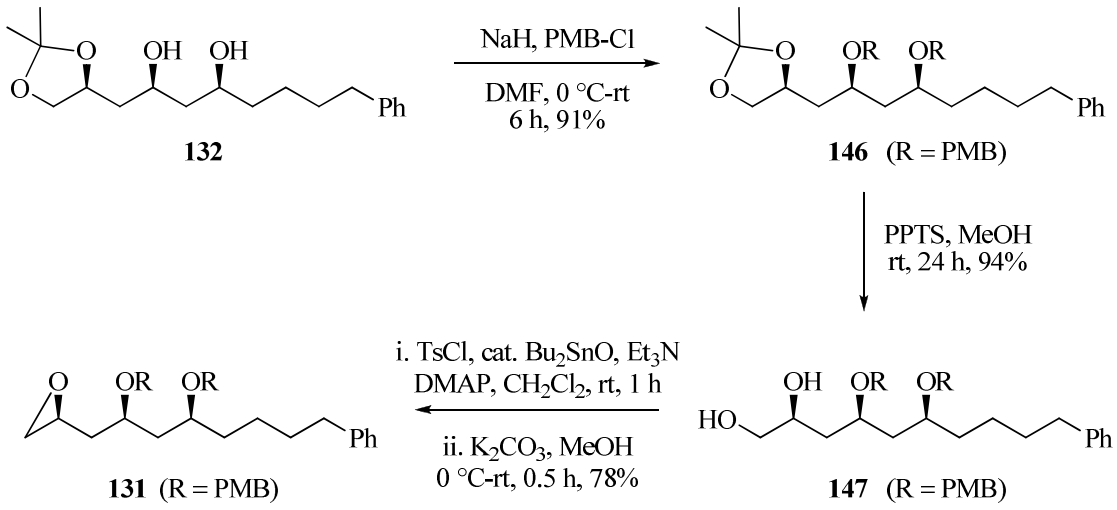
Scheme 39: Synthesis of *syn*, *syn*-1,3,5-triol

Wittig olefination of **142** with 3-phenylpropyltriphenylphosphorane in THF furnished *Z*-isomer **143** exclusively (Scheme 39). Results from ^{1}H, ^{13}C NMR, IR spectrum and elemental analysis were in accordance with the assigned structure **143**. In ^{1}H NMR spectrum the olefinic protons resonated at 5.66–5.60, 5.48–5.43 ppm as a dt and ddt with relatively lower coupling constant (J = 10.3 Hz) indicating the *Z*-configuration of **143**. In the ^{13}C NMR spectrum two doublets located at δ 127.6, 131.0 for the olefinic carbons.

Inversion of free hydroxyl group present in **143** by means of Mitsunobu reaction[46] using DEAD, TPP and benzoic acid in THF was facile to furnish the benzoate ester **144** as shown in Scheme 39. Presence of benzoate ester was evidenced by the appearance of additional signals in aromatic region, corresponding ester attached proton resonated at 5.37–5.18 ppm as a multiplet in ^{1}H NMR spectrum. In the ^{13}C NMR spectrum the ester carbonyl resonated at δ 165.7 as a singlet, in the IR spectrum, the C=O stretching was observed at 1715 cm^{-1}. Surprisingly, attempted hydrogenation for the double bond reduction of **144** by using Raney-Ni in ethanol afforded **145** with reduction of double bond and concomitant *O*-debenzylation. This unusual deprotection of benzyl ether may be due to the presence of activated allylic functionality. Saponification of **145** with catalytic NaOMe in methanol secured the required *syn*, *syn*-1,3,5-triol system (**132**). In the IR spectrum of the **132** the O–H stretching was observed at 3381 cm^{-1}.

The diol **132** was protected as its di-PMB ether by treating with NaH, *p*-methoxybenzyl chloride in DMF to secure di-PMB ether **146**. Subsequently, the 1,2-isopropylidene group was hydrolyzed in the presence of PPTS in methanol to obtain the terminal diol **147**. The assigned structure for **147** was well supported by spectral and analytical data, in the IR spectrum the O–H stretching was observed at 3429 cm^{-1}. The primary hydroxyl group of **147** was selectively tosylated by treating with TsCl, catalytic Bu_2SnO, and triethylamine in dichloromethane to obtain the tosylate, which was further used for next reaction without any chromatographic purification. Oxirane formation was facile with K_2CO_3 in methanol to furnish the epoxide (**131**) (Scheme 40). The formation of epoxide **131** was ascertained by its ^{1}H, ^{13}C NMR spectrum and elemental analysis. In the ^{1}H NMR spectrum of **131** all three oxirane protons were separately resonated relatively up field at 3.03–2.94 ppm as a multiplet for one proton and at 2.71–2.66, 2.36

ppm as a broad doublet of doublets for two protons. In the ^{13}C NMR spectrum, the oxirane carbons were observed at δ 46.6 as triplet and δ 49.3 as a doublet.

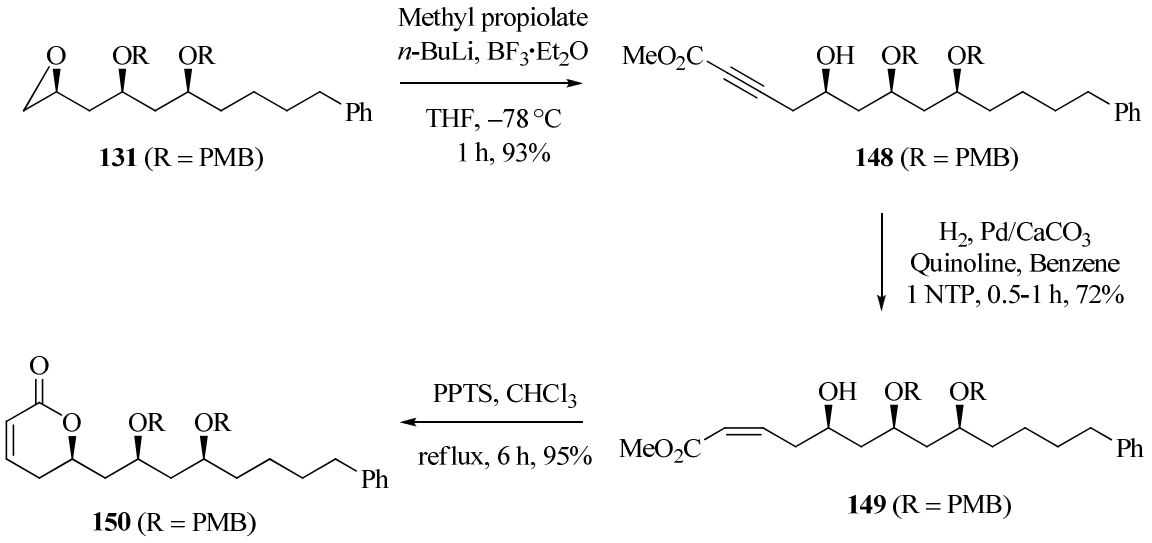


Scheme 40: Synthesis of epoxide **131**

The next concern was to construct the key pyrone ring as shown in Scheme 41. Epoxide **131** was subjected to Yamaguchi protocol[47] of epoxide opening using methyl propiolate, *n*-BuLi, $BF_3{\cdot}Et_2O$ in THF at –78 °C to furnish the β-hydroxy alkyne derivative **148**. In the ^1H NMR spectrum of **148** the propargylic protons resonated at 2.47–2.26 ppm as a multiplet and the ester methoxy was observed at 3.71 ppm as a singlet. In the ^{13}C NMR spectrum the alkyne carbons appeared at δ 74.5, 86.2 as singlets and the ester carbonyl appeared at δ 153.8 as a singlet. In the IR spectrum the O–H stretching was observed at 3457 cm^{-1} and the ester C=O stretching was observed at 1714 cm^{-1}.

Compound **148** was subjected to partial hydrogenation in presence Lindlar's catalyst $Pd/CaCO_3$ in benzene to provide the *Z*-acrylate **149**. The olefinic protons resonated at 6.34, 5.85 ppm with relatively lower coupling constant (J = 11.6 Hz) as a dt confirming the *Z* selectivity in the ^1H NMR spectrum of **149**. In the ^{13}C NMR spectrum the olefinic carbons were observed at δ 120.6, 146.8 as doublets and ester carbonyl resonated relatively down field at δ 166.8 as a singlet. Acid catalyzed lactonization of **149** with

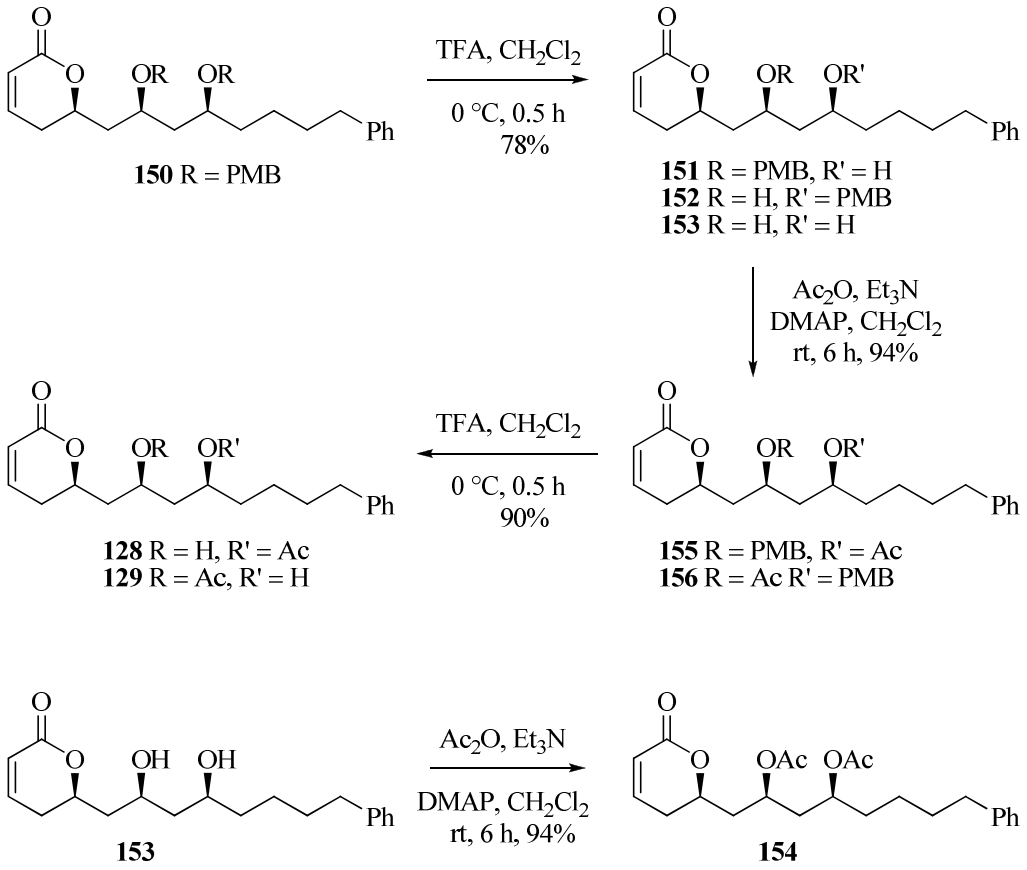
PPTS in refluxing chloroform resulted in the formation of the δ-pyrone (**150**). The structure of **150** was fully confirmed by ^{1}H and ^{13}C NMR analysis. In the ^{13}C NMR spectrum the characteristic lactone carbonyl resonated at δ 164.1 as a singlet and C=O absorption was observed at 1721 cm^{-1} in the IR spectrum.



Scheme 41: Synthesis of 5,6-dihydro-δ-pyrone ring **150**

Having complete skeleton in the hand, now the stage was set for the deprotection of PMB-ethers as shown in the Scheme 42. Attempted deprotection of PMB ethers of **150** by using trifluroacetic acid in dichloromethane at 0 °C afforded 1:1 regioisomeric mixture of mono PMB-ethers **151**/**152** (54%) along with the diol **153** (24%). Results from ^{1}H, ^{13}C NMR, IR spectrum and elemental analysis were in accordance with the assigned structures **151/152** and **153**. The compound **153** was acetylated by using Ac_2O, Et_3N, DMAP in dichloromethane furnishing diacetate (**154**) which showed the spectral data identical with the reported values.[41] In the ^{1}H NMR spectrum of (**154**), two methine protons attached to the acetate resonated relatively down field at 5.07–5.02, 4.95–4.90 as multiplets and acetate methyls resonated at 2.05, 2.03 ppm as singlets. In the ^{13}C spectrum, the methyls were located at δ 21.1, 21.1 as quartets, the acetate carbonyls resonated at δ 170.6, 170.8 as singlets and lactone carbonyl was observed relatively up

field at δ 163.7 as a singlet due to conjugation. In the IR spectrum of (**154**) the acetate C=O stretching was observed at 1730 cm^{-1}.



Scheme 42: Synthesis of Natural Products **128** and **129**

Without separation of **151** and **152**, the mixture was subjected for acetylation to afford the regiomeric mixture of mono-PMB-mono-acetate derivatives **155/156**. The assigned structure for **155/156** was well supported by spectral and analytical data. In the ^{1}H NMR spectrum of **155/156**, the acetate methyls resonated at 1.99, 1.98 ppm as two separate singlets for the two regiomers whereas the methyls were appeared at δ 21.1 as a quartet and the acetate carbonyl was observed at δ 170.5 as a singlet in the ^{13}C NMR spectrum.

Treatment of **155/156** with trifluroacetic acid in dichloromethane at 0 °C furnished equilibrium mixture of (**128** and **129**) in 3:1 ratio. A portion of (**128**/**129**)

mixture was subjected for preparative HPLC separation and the ^{1}H and ^{13}C NMR of the separated pure (**128** and **129**) were recorded. The spectral and analytical data of (**128** and **129**) were identical with the data reported for the natural products.[41] The optical rotation observed for natural products (**128**/**129**) is +33 (*c* 0.3, MeOH), and reported value for natural product is [lit +35 (*c* 0.05, MeOH)].[41]

In the ^{1}H NMR spectrum of major isomer (**128**), the conjugated olefinic protons resonated at 6.87 (dt, *J* = 9.8, 4.2 Hz), 6.01 (dt, *J* = 9.5, 1.7 Hz) ppm and the methine proton attached to acetate appeared at 4.97–4.92 ppm as a multiplet. In the ^{13}C NMR spectrum, lactone and acetate carbonyls resonated as singlets at δ 163.9, 171.3 respectively. In the IR spectrum the O–H stretching was observed at 3440 cm^{-1} and the lactone C=O stretching was observed at 1724 cm^{-1}.

In the ^{1}H NMR spectrum of minor isomer (**129**), the conjugated olefinic protons resonated at 6.87–6.84 (ddd, *J* = 9.7, 6.1, 2.4 Hz), 6.01 (ddd, *J* = 9.7, 2.6, 0.7 Hz) ppm and the methine proton attached to the acetate was observed at 5.24–5.19 ppm as a multiplet. In the ^{13}C NMR spectrum, lactone and acetate carbonyls resonated as singlets at δ 163.9, 170.9 respectively. In the IR spectrum the O–H stretching was observed at 3440 cm^{-1} and the lactone C=O stretching was observed at 1724 cm^{-1}.

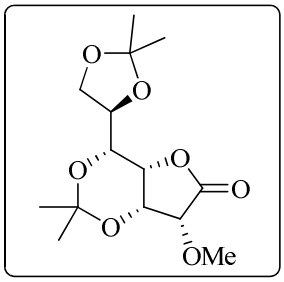
Notably, a periodic examination of ^{1}H NMR spectra of pure isomers **128** and **129** indicated the migratory aptitudes of acetyl groups in these compounds, however with different rate of migration. The inter conversion of **129** → **128** was substantially faster than **128** → **129**. In case of the minor isomer **129**, we found the equilibration is facile and the difference in the ratio of **129** : **128** changed from 1 : 0.14 (^{1}H NMR) to 1 : 0.75 (^{13}C NMR), the latter (^{13}C NMR) being recorded for overnight.

Conclusion:

In summary, we have developed a simple strategy for the synthesis of *anti*,*anti*- and *syn*,*syn*-1,3,5-polyol systems using a chiral pool approach. This study enabled us to carry out the first total synthesis of antifungal natural 1,3-polyol/α-pyrones **128** and **129**.

Experimental

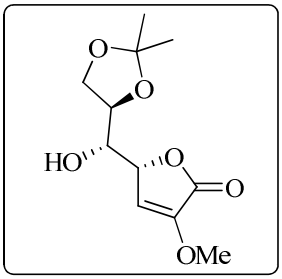
(4*R*,4a*S*,7*R*,7a*R*)-4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-7-methoxy-2,2-dimethyldihydro-4H-furo[3,2-d][1,3]-dioxin-6(4aH)-one (136)



To a solution of **135** (10 g, 34.68 mmol) in DCM (100 mL) was sequentially added methyl iodide (8.64 mL, 138.74 mmol), silver oxide (16.0 g, 69.37 mmol) and the mixture was refluxed for 12 h. The contents were filtered (*Celite*), concentrated and the resulting white solid was crystallized from ethyl acetate/hexane (1:3) to furnish **136** (9.645 g, 92%) as white needles.

Mol. Formula	: $C_{14}H_{22}O_7$
M. P.	: 144 °C.
$[\alpha]_D$	: −82.8 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2997, 1801, 1381, 1215, 1151, 1076, 832, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 4.67 (dd, *J* = 3.7, 1.8 Hz, 1H), 4.33–4.29 (ddd, *J* = 9.3, 6.2, 4.1 Hz, 1H), 4.22 (dd, *J* = 2.3, 0.5 Hz, 1H), 4.09–4.06 (m, 2H), 3.89 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.78 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.64 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.4 (q), 24.9 (q), 27.0 (q), 29.0 (q), 59.0 (q), 66.8 (t), 67.5 (d), 68.4 (d), 69.5 (d), 73.0 (d), 78.9 (d), 98.5 (s), 109.5 (s), 172.3 (s) ppm.
Elemental Analysis	Calcd.: C, 55.62; H, 7.33. Found: C, 55.58; H, 7.21.

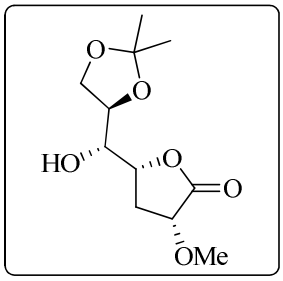
(*R*)-5-((*S*)-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-(hydroxy)methyl)-3-methoxyfuran-2(5H)-one (137)



At −78 °C, a suspension of KO^{t}Bu (1.86 g, 16.54 mmol) in anhydrous THF (50 mL) was treated with a solution of methyl ether **136** (5 g, 16.54 mmol) in anhydrous THF (60 mL) and stirred for 15 min. The reaction mixture was quenched with a solution of AcOH (0.95 mL, 16.54 mmol) in THF (5 mL) and allowed to warm to room temperature. The contents were filtered (*Celite*), concentrated and the crude product was purified by crystallization from ethyl acetate/hexane (1:3) to furnish **137** (3.325 g, 82%) as white solid.

Mol. Formula	: $C_{11}H_{16}O_6$
$[\alpha]_D$	: −22.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3415, 2998, 1765, 1383, 1217, 1059, 856, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 6.14 (d, *J* = 1.9 Hz, 1H), 5.09–5.08 (dd, *J* = 3.7, 1.9 Hz, 1H), 4.15–4.10 (m, 2H), 4.02–3.98 (m, 1H), 3.79 (s, 3H), 3.54 (dd, *J* = 6.7, 3.6 Hz, 1H), 2.77 (br.s, 1H), 1.40 (s, 3H), 1.34 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.1 (q), 26.8 (q), 58.0 (q), 67.3 (t), 72.8 (d), 75.3 (d), 79.5 (d), 109.6 (s), 114.7 (d), 147.2 (s), 167.8 (s) ppm.
Elemental Analysis	Calcd.: C, 54.09; H, 6.60. Found: C, 54.01; H, 6.53.

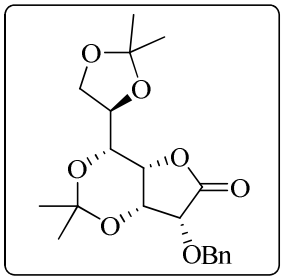
(3*R*,5*R*)-5-((*S*)-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl) (hydroxy)methyl)-3-methoxydihydrofuran-2(3H)-one (138)



To a solution of enol **137** (1 g, 4.09 mmol) in ethyl acetate (10 mL) was added 10% palladium on charcoal (50 mg) and the suspension was stirred at rt under balloon hydrogen pressure for 4 h. The reaction mixture was filtered through a pad of *Celite* and washed with ethyl acetate. The combined washings were concentrated to get a white solid. The crude product was purified by crystallization in dichloromethane/hexane to furnish **138** (900 mg, 89%) as white crystalline solid.

Mol. Formula	: $C_{11}H_{18}O_6$
$[\alpha]_D$	: –14.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2995, 1790, 1370, 1216, 848, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 4.64–4.61 (ddd, *J* = 8.7, 6.4, 2.3 Hz, 1H), 4.13–4.05 (m, 3H), 4.00 (dd, *J* = 8.1, 5.0 Hz, 1H), 3.59 (s, 3H), 3.45 (br d, *J* = 5.9 Hz, 1H), 2.61–2.53 (m, 2H), 2.31–2.25 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 25.2 (q), 26.9 (q), 31.1 (t), 58.4 (q), 67.3 (t), 73.3 (d), 75.4 (d), 75.6 (d), 76.4 (d), 109.7 (s), 173.7 (s) ppm.
Elemental Analysis	Calcd.: C, 53.65; H, 7.37. Found: C, 53.38; H, 7.24.

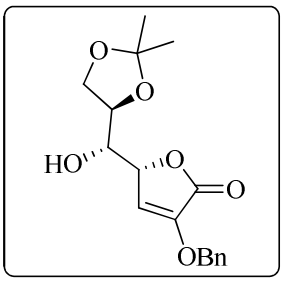
(4*R*,4a*S*,7*R*,7a*R*)-7-(Benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydro-4H-furo[3,2-d][1,3]-dioxin-6(4aH)-one (139)



To a solution of **135** (5.0 g, 17.3 mmol) in DCM (50 mL) was sequentially added benzyl bromide (2.47 mL, 20.8 mmol), silver oxide (6.02 g, 26 mmol) and the mixture was refluxed for 6 h. The contents were filtered (*Celite*), concentrated and the resulting white solid was crystallized from ethyl acetate/hexane (1:3) to furnish **139** (5.5 g, 84%) as colorless needles.

Mol. Formula	: $C_{20}H_{26}O_7$
M. P.	: 198 °C
$[\alpha]_D$	: −36.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3393, 3019, 1797, 1384, 1215, 1149, 1076, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.39–7.36 (m, 5H), 4.86 (d, *J* = 12.7 Hz, 1H), 4.79 (d, *J* = 12.7 Hz, 1H), 4.51–4.45 (m, 1H), 4.35–4.26 (m, 1H), 4.20–4.17 (m, 2H), 4.08 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.91 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.77 (br d, *J* = 8.8 Hz, 1H), 1.43 (s, 6H), 1.39 (s, 3H), 1.33 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.2 (q), 24.7 (q), 26.8 (q), 28.9 (q), 66.8 (t), 67.9 (d), 68.5 (d), 69.4 (d), 72.3 (t), 72.9 (d), 75.5 (d), 98.4 (s), 109.4 (s), 128.3 (d), 128.4 (d 4C), 136.3 (s), 172.8 (s) ppm.
Elemental Analysis	Calcd.: C, 63.48; H, 6.93. Found: C, 63.28; H, 7.21.

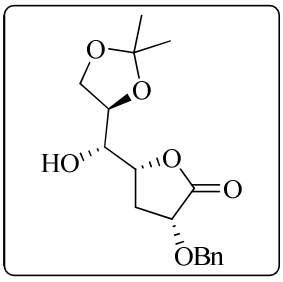
(*R*)-3-(Benzyloxy)-5-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)furan-2(5H)-one (134)



At −78 °C, a suspension of KO^{t}Bu (1.48 g, 13.2 mmol) in anhydrous THF (50 mL) was treated with a solution of benzyl ether **139** (5 g, 13.2 mmol) in anhydrous THF (80 mL) and stirred for 15 min. The reaction mixture was quenched with a solution of AcOH (0.8 mL, 13.2 mmol) in THF (5 mL) and allowed to warm to room temperature. The contents were filtered (*Celite*), concentrated and the crude product was purified by crystallization from ethyl acetate/hexane (1:3) to procure **134** (3.43 g, 81%) as colorless solid.

Mol. Formula	: $C_{17}H_{20}O_6$
M. P.	: 162 °C.
$[\alpha]_D$	: +31.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3420, 3020, 2400, 1760, 1652, 1381, 1215, 1059, 756, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.40–7.36 (m, 5H), 6.17 (d, *J* = 2.1 Hz, 1H), 5.09 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.02 (s, 2H), 4.16 (dd, *J* = 6.2, 4.1 Hz, 1H), 4.12 (dt, *J* = 6.2, 3.5 Hz, 1H), 3.99 (dd, *J* = 7.6, 3.5 Hz, 1H), 3.55 (dd, *J* = 7.6, 4.1 Hz, 1H), 2.40 (br.s, 1H), 1.37 (s, 3H), 1.35 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.1 (q), 26.7 (q), 67.1 (t), 72.8 (t), 73.1 (d), 75.3 (d), 79.5 (d), 109.7 (s), 115.9 (d), 127.6 (d 2C), 128.5 (d), 128.6 (d 2C), 134.7 (s), 145.9 (s), 167.8 (s) ppm.
Elemental Analysis	Calcd.: C, 63.74; H, 6.29. Found: C, 63.80; H, 6.03.

(3*R*,5*R*)-3-(Benzyloxy)-5-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)dihydrofuran-2(3H)-one (140)



At 0 °C, a solution of **134** (1 g, 3.1 mmol) in methanol (30 mL) was treated with $NiCl_2.6H_2O$ (220 mg, 0.9 mmol) and stirred for 30 min. To this $NaBH_4$ (342 mg, 9.1 mmol) and AcOH (to maintain pH = 7) were added in three portions with 10 minutes interval. After completing the addition, stirring was continued for another 30 min at 0 °C. The contents were filtered (*Celite*), concentrated, dissolved in ethyl acetate (25 mL), washed with water, brine, dried (Na_2SO_4) and concentrated to get a white solid. The crude product was purified by crystallization in dichloromethane/hexane to furnish **140** (615 mg, 61%) as white crystalline solid.

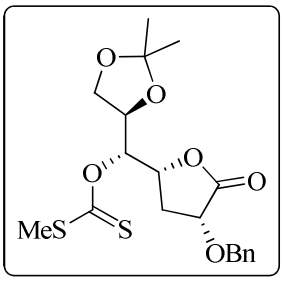
Mol. Formula	: $C_{17}H_{22}O_6$
M. P.	: 116 °C.
$[\alpha]_D$	: +32.4 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3442, 2992, 2881, 1787, 1455, 1370, 1216, 848, 755 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.38–7.32 (m, 5H), 4.96 (d, *J* = 11.8 Hz, 1H), 4.75 (d, *J* = 11.8 Hz, 1H), 4.59 (ddd, *J* = 8.9, 6.4, 2.9 Hz, 1H), 4.24 (dd, *J* = 9.2, 8.4 Hz, 1H), 4.19–3.96 (m, 3H), 3.45 (br.d, *J* = 4.4 Hz, 1H), 2.51 (ddd, *J* = 13.1, 8.3, 6.4 Hz, 1H), 2.30 (dt, *J* = 13.1, 9.1 Hz, 1H),1.38 (s, 3H), 1.33 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 25.1 (q), 26.7 (q), 31.1 (t), 67.2 (t), 72.1 (t), 72.9 (d), 73.2 (d), 75.3 (d), 76.4 (d), 109.4 (s), 127.9 (d), 128.0 (d 2C), 128.4 (d 2C), 136.9 (s), 174.5 (s) ppm.
Elemental Analysis	Calcd.: C, 63.34; H, 6.88. Found: C, 63.38; H, 7.14.

Crystal data for 140 ($C_{17}H_{22}O_6$):

Formula weight	322.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 9.195(1) Å b = 6.1777(8) Åbeta = 93.846(2)º c = 15.004(2) Å
Volume	850.38(18) $Å^{-3}$
Z, Calculated density	2, 1.259 Mg/m^{-3}
Absorption coefficient	0.095 mm^{-1}
F(000)	344
Crystal size	0.48 x 0.24 x 0.02 mm
Theta range for data collection	2.52 to 25.00°
Limiting indices	-9<=h<=10, -7<=k<=7, -17<=l<=16
Reflections collected / unique	4283 / 2795 [R_{int} = 0.0334]

Completeness to theta = 25.00°	99.2 %
Max. and min. transmission	0.9979 and 0.9556
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2795 / 25 / 211
Goodness-of-fit on F^2	1.017
Final R indices [I>2sigma(I)]	R_1 = 0.0594, wR_2 = 0.1375
R indices (all data)	R_1 = 0.0945, wR_2 = 0.1565
Absolute structure parameter	0.8(19)
Largest diff. peak and hole	0.188 and -0.172 e.Å^{-3}

_O_-(_S_)-((2_R_,4_R_)-4-(Benzyloxy)-5-oxotetrahydrofuran-2-yl)((_R_)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl S-methyl carbonodithioate (141)

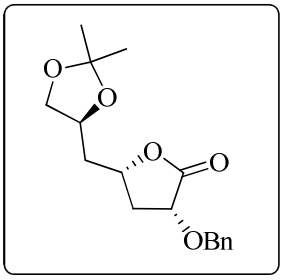


To a suspension of NaH (771 mg, 19.7 mmol) in anhydrous THF at −15 °C were added CS_2 (3.3 mL, 54 mmol), MeI (3.36 mL, 54 mmol) and stirred for 30 min. To this, a solution of **140** (5.8 g, 17.9 mmol) in anhydrous THF was added and allowed to stirr at rt for 12 h. The reaction mixture was poured in cold water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (15% ethyl acetate in petroleum ether) to afford xanthate **141** (6.89 g, 93%) as yellow solid.

Mol. Formula	: $C_{19}H_{24}O_6S_2$
M. P.	: 124 °C.
$[\alpha]_D$	: +50.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3393, 3019, 1788, 1454, 1374, 1215, 1069, 756, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.35–7.29 (m, 5H), 5.99 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 4.78–4.69 (m, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.49–4.39 (m, 1H), 4.20 (t, *J* = 9.0, Hz, 1H), 4.04 (dd, *J* = 8.8, 6.2 Hz, 1H), 3.88 (dd, *J* = 8.8, 5.2 Hz, 1H),

	2.54 (s, 3H), 2.48 (ddd, *J* = 13.1, 8.0, 6.2 Hz, 1H), 2.05 (ddd, *J* = 13.1, 9.8, 8.8 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.3 (q), 25.3 (q), 26.8 (q), 31.1 (t), 66.4 (t), 72.1 (t), 72.5 (d), 73.6 (d), 74.5 (d), 79.6 (d), 109.9 (s), 128.1 (d), 128.2 (d 2C), 128.5 (d 2C), 136.8 (s), 173.4 (s), 216.8 (s) ppm.
Elemental Analysis	Calcd.: C, 55.32; H, 5.86; S, 15.54. Found: C, 55.48; H, 5.62; S, 15.19.

(3*R*,5*S*)-3-(Benzyloxy)-5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)dihydrofuran-2(3H)-one (133)

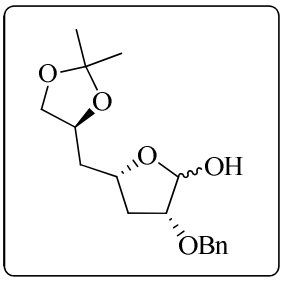


A degassed solution of xanthate **141** (6.89 g, 16.7 mmol) in 50 mL of dry toluene, AIBN (10 mg) and tri-*n*-butyltin hydride (6.64 mL, 25.1 mmol) was refluxed for 5 h. After the reaction was completed as monitored by TLC, the reaction mixture was concentrated and the resulting crude product was purified by column chromatography (20% ethyl acetate in petroleum ether) to furnish **133** (3.63 g, 71%) as colorless oil.

Mol. Formula	: $C_{17}H_{22}O_5$
$[\alpha]_D$	: +21.0 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3024, 2927, 1783, 1455, 1373, 1216, 757, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.39–7.30 (m, 5H), 4.99 (d, *J* = 11.8 Hz, 1H), 4.75 (d, *J* = 11.8 Hz, 1H), 4.60-4.46 (m, 1H), 4.34–4.21 (m, 1H), 4.22 (dd, *J* = 9.8, 8.1 Hz, 1H), 4.11 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.53 (dd, *J* = 8.1, 7.0 Hz, 1H), 2.61 (ddd, *J* = 12.9, 8.2, 5.7 Hz, 1H), 2.03–1.81 (m, 3H), 1.39 (s, 3H), 1.34 (s, 3H) ppm.
^{13}C NMR	: δ 25.6 (q), 26.9 (q), 36.0 (t), 40.2 (t), 69.3 (t), 72.1 (t),

($CDCl_3$, 50 MHz)	72.5 (d), 73.2 (d), 74.1 (d), 108.9 (s), 127.9 (d), 128.0 (d 2C), 128.4 (d 2C), 136.9 (s), 174.2 (s) ppm.
Elemental Analysis	Calcd.: C, 66.65; H, 7.24.
	Found: C, 66.79; H, 7.07.

(3*R*,5*S*)-3-(Benzyloxy)-5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)tetrahydrofuran-2-ol (142)

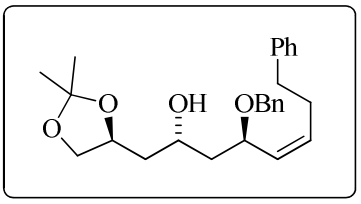


The lactone **133** (3.35 g, 10.95 mmol) was dissolved in dry DCM (20 mL), cooled to −78 °C, treated with DIBAL-H (9.71 mL, 19.71 mmol, 2.03 M solution in toluene) and stirred for 30 min at −78 °C. The reaction mixture was quenched by addition of saturated sodium potassium tartrate at −78 °C and the resulting mixture was warmed to room temp. The resulting suspension was filtered through *Celite* pad, dried (Na_2SO_4) and concentrated. Chromatographic purification of the crude product (25% ethyl acetate in petroleum ether) afforded lactol **142** (3.27 g, 97%) as colorless oil.

Mol. Formula	: $C_{17}H_{24}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 3404, 3019, 1731, 1660, 1215, 1067, 765, 669 cm^{-1}.
^{1}H NMR	: δ 7.35–7.28 (m, 5H), 5.43 (s, 0.8H), 5.23 (br d, J = 4.2
($CDCl_3$, 200 MHz)	Hz, 0.2H), 4.61–4.50 (m, 2H), 4.45–4.36 (m, 1H), 4.27–4.19 (m, 1H), 4.11–4.07 (m, 1H), 3.99–3.97 (m, 1H), 3.57–3.52 (m, 1H), 2.49–2.26 (m, 1H), 1.89–1.84 (m, 2H), 1.72–1.65 (m, 1H), 1.40, 1.32 (2s, 3H), 1.36, 1.28 (2s, 3H) ppm.
^{13}C NMR	: δ 25.8 (q), 27.0 (q), 35.3 (t), 36.6 (t), 40.8 (t), 69.9 (t),
($CDCl_3$, 75 MHz)	71.5 (t), 72.2 (t), 73.7 (d), 73.8 (d), 73.9 (d), 75.6 (d), 78.5 (d), 84.1 (d), 95.8 (d), 101.1 (d), 108.6 (s), 127.6 (d), 127.9 (d), 128.1 (d), 128.4 (d), 128.6 (d), 137.3 (s), 138.0 (s) ppm.

Elemental Analysis Calcd.: C, 66.21; H, 7.84.
Found: C, 66.05; H, 8.13.

(2*R*,4*R*,*Z*)-4-(Benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-8-phenyloct-5-en-2-ol (143)



A suspension of 3-phenylpropyl-triphenylphosphonium iodide (30.3 g, 59.67 mmol) in anhydrous THF (120 mL) was cooled to 0 °C, treated with *n*-BuLi (23 mL, 53.70 mmol, 2.34 M solution in hexane) and stirred at rt for 1 h. The resulting yellow solution was transferred drop wise to a solution of lactol **142** (3.68 g, 11.93 mmol) in 50 mL of anhydrous THF at 0 °C and the contents were stirred at rt for additional 12 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The crude product obtained was purified by column chromatography (15% ethyl acetate in petroleum ether) to furnish **143** (4.7 g, 96%) as colorless oil.

Mol. Formula : $C_{26}H_{34}O_4$

$[\alpha]_D$: +21.9 (*c* 1.0, $CHCl_3$).

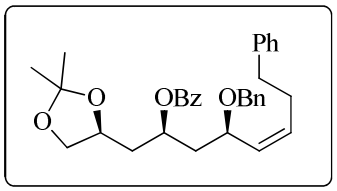
IR ($CHCl_3$) $\tilde{\nu}$: 3486, 2985, 2937, 1604, 1454, 1369, 1067, 1028, 736, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.32–7.29 (m, 2H), 7.26–7.22 (m, 5H), 7.17–7.12 (m, 3H), 5.66–5.60 (dt, *J* = 10.3, 7.5 Hz, 1H), 5.48–5.43 (ddt, *J* = 10.3, 9.2, 1.3 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.35 (br.dt, *J* = 8.5, 3.5 Hz, 1H), 4.25–4.20 (m, 1H), 4.15 (d, *J* = 11.8 Hz, 1H), 4.03 (dd, *J* = 8.2, 6.0 Hz, 1H), 4.01–3.97 (tt, *J* = 9.1, 3.1 Hz, 1H), 3.50–3.47 (t, *J* = 8.0 Hz, 1H), 2.75–2.64 (m, 2H), 2.42–2.32 (m, 2H), 1.65–1.53 (m, 3H), 1.46 (ddd, *J* = 12.3, 8.7, 3.5 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H) ppm.

^{13}C NMR : δ 25.7 (q), 26.9 (q), 29.6 (t), 35.7 (t), 40.7 (t), 42.6 (t),

($CDCl_3$, 75 MHz)	66.0 (d), 69.7 (t), 69.9 (t), 71.9 (d), 73.7 (d), 108.3 (s), 125.9 (d), 127.5 (d), 127.6 (d), 128.2 (d 6C), 128.5 (d), 131.0 (d), 132.1 (d), 138.3 (s), 141.2 (s) ppm.
Elemental Analysis	Calcd.: C, 76.06; H, 8.34.
	Found: C, 76.17; H, 8.53.

(2*S*,4*R*,*Z*)-4-(Benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-8-phenyloct-5-en-2-yl benzoate (144)



At 0 °C, a solution of **143** (1 g, 2.43 mmol) in THF (20 mL) was sequentially treated with TPP (830 mg, 3.16 mmol), DEAD (0.5 mL, 3.16 mmol) followed by benzoic acid (386 mg, 3.16 mmol) and stirring was continued for 2 h. The reaction mixture was concentrated and the resulting crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) to afford **144** (864 mg, 69%) as colorless oil.

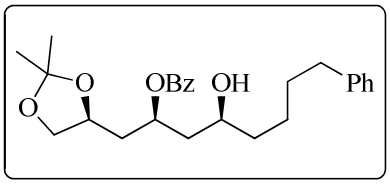
Mol. Formula	: $C_{33}H_{38}O_5$
$[\alpha]_D$	: +33.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3402, 3017, 1715, 1602, 1495, 1371, 1274, 1216, 1069, 1026, 756, 712, 699, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 7.96–7.92 (m, 2H), 7.58–7.51 (m, 1H), 7.45–7.35 (m, 2H), 7.24–7.11 (m, 8H), 7.00–6.96 (m, 2H), 5.69 (dt, *J* = 10.9, 7.3 Hz, 1H), 5.37–5.18 (m, 2H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.31–4.10 (m, 2H), 4.10 (d, *J* = 11.8 Hz, 1H), 4.04 (dd, *J* = 7.9, 5.8 Hz, 1H), 3.50 (dd, *J* = 7.8, 7.0 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.29–1.97 (m, 4H), 1.91–1.65 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.7 (q), 26.9 (q), 29.6 (t), 35.6 (t), 37.9 (t), 39.8 (t), 69.4 (t), 69.6 (t), 69.8 (d), 70.9 (d), 72.6 (d), 108.7 (s), 125.8 (d), 127.3 (d), 127.7 (d 2C), 128.2 (d 5C), 128.3 (d 3C), 129.5 (d 2C), 130.4 (d), 130.4 (s), 132.7 (d), 133.5

(d), 138.4 (s), 141.1 (s), 165.7 (s) ppm.

Elemental Analysis Calcd.: C, 77.01; H, 7.44.

Found: C, 76.86; H, 7.69.

(2*S*,4*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-8-phenyloctan-2-yl benzoate (145)



A suspension of **144** (1 g, 1.94 mmol), Raney-Ni (50 mg) in ethanol (20 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 12 h. The reaction mixture was filtered (*Celite*), concentrated and crude product obtained was purified by column chromatography (25% ethyl acetate in petroleum ether) to furnish the intermediate benzoate **145** (800 mg, 96%) as colorless oil.

Mol. Formula : $C_{26}H_{34}O_5$

$[\alpha]_D$: +1.5 (*c* 1.0, $CHCl_3$).

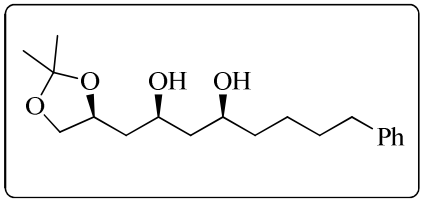
IR ($CHCl_3$) $\tilde{\nu}$: 3429, 3019, 2935, 1712, 1603, 1495, 1372, 1276, 1216, 1069, 756, 713, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 8.02 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.59–7.51 (m, 1H), 7.46–7.38 (m, 2H), 7.29–7.10 (m, 5H), 5.44–5.31 (ddd, *J* = 8.0, 5.9 Hz, 1H), 4.23 (dt, *J* = 13.1, 6.5 4.6 Hz, 1H), 4.12–4.00 (dd, *J* = 8.0, 5.9 Hz, 1H), 3.82–3.78 (m, 1H), 3.58 (dd, *J* = 8.0, 7.2 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.20–1.86 (m, 4H), 1.68–1.21 (m, 6H), 1.38 (s, 3H), 1.30 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.1 (t), 25.7 (q), 26.9 (q), 31.3 (t), 35.8 (t), 37.5 (t), 37.8 (t), 41.6 (t), 69.1 (d), 69.4 (t), 70.6 (d), 72.7 (d), 108.9 (s), 125.6 (d), 128.2 (d 2C), 128.3 (d 2C), 128.4 (d 2C), 129.6 (d 2C), 130.2 (s), 133.0 (d), 142.4 (s), 166.0 (s) ppm.

Elemental Analysis Calcd.: C, 73.21; H, 8.03.
Found: C, 73.06; H, 8.26.

(2*S*,4*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-8-phenyloctane-2,4-diol (132)



At 0 °C, a solution of benzoate **145** (0.5 g, 1.17 mmol) in dry methanol (15 mL) was treated with Na (40 mg, 1.76 mmol) and the resulting reaction mixture was stirred at rt being monitored by TLC. After 2 h, the reaction mixture was neutralized with AcOH at 0 °C, methanol was evaporated and crude product was purified by column chromatography (40% ethyl acetate in petroleum ether) to afford diol **132** (359 mg, 95%) as colorless oil.

Mol. Formula : $C_{19}H_{30}O_4$

$[\alpha]_D$: −2.9 (*c* 1.0, $CHCl_3$).

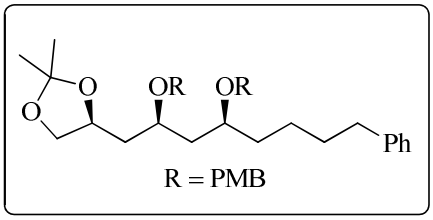
IR ($CHCl_3$) $\tilde{\nu}$: 3381, 2935, 1603, 1381, 1493, 1452, 1381, 1216, 1056, 756, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.28–7.12 (m, 5H), 4.31–4.18 (m, 1H), 4.12–3.98 (m, 2H), 3.91–3.76 (m, 2H), 3.58–3.49 (m, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.71–1.46 (m, 8H), 1.40–1.34 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.0 (t), 25.7 (q), 26.9 (q), 31.5 (t), 35.9 (t), 37.7 (t), 40.9 (t), 43.1 (t), 69.6 (t), 71.8 (d), 72.1 (d), 75.2 (d), 109.3 (s), 125.6 (d), 128.2 (d 2C), 128.3 (d 2C), 142.4 (s) ppm.

Elemental Analysis Calcd.: C, 70.77; H, 9.37.
Found: C, 70.59; H, 9.50.

(*S*)-4-((2*S*,4*S*)-2,4-Bis(4-methoxybenzyloxy)-8-phenyloctyl)-2,2-dimethyl-1,3-dioxolane (146)



To a solution of diol **132** (860 mg, 2.66 mmol) in dry DMF (3 mL) was added NaH (533 mg, 13.4 mmol) portion wise at 0 °C and stirred for 30 min. To this, *p*-methoxybenzyl chloride (1.7 mL, 12 mmol) was added at 0 °C and stirring was continued for 6 h at rt. The reaction mixture was quenched at 0 °C by adding sat. Na_2SO_4 solution, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (20% ethyl acetate in petroleum ether) furnished **146** (1.365 g, 91%) as colorless oil.

Mol. Formula : $C_{35}H_{46}O_6$

$[\alpha]_D$: +16.8 (*c* 1.0, $CHCl_3$).

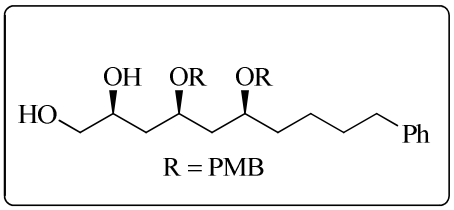
IR ($CHCl_3$) $\tilde{\nu}$: 3061, 2984, 2933, 2857, 1612, 1585, 1513, 1463, 1378, 1248, 1172, 1058, 821, 749, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.29–7.11 (m, 5H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.37 (s, 2H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.15 (br.ddd, *J* = 12.4, 7.4, 6.4 Hz, 1H), 3.87 (dd, *J* = 7.8, 5.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.55 (t, *J* = 5.8 Hz, 1H), 3.48–3.42 (m, 1H), 3.38 (t, *J* = 7.8 Hz, 1H), 2.62–2.54 (m, 2H), 1.99–1.82 (m, 2H), 1.73–1.47 (m, 6H), 1.43–1.26 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.9 (t), 25.8 (q), 27.1 (q), 31.6 (t), 33.9 (t), 36.0 (t), 37.7 (t), 38.5 (t), 55.2 (q 2C), 69.7 (t), 70.1 (t), 70.3 (t), 72.9 (d), 73.0 (d), 75.5 (d), 108.4 (s), 113.8 (d 4C), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 129.3 (d 2C), 129.4 (d 2C), 130.8 (s), 131.1 (s), 142.5 (s), 159.2 (s), 159.3 (s) ppm.

Elemental Analysis Calcd.: C, 74.70; H, 8.23.
Found: C, 74.83; H, 8.19.

(2*S*,4*R*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-10-phenyldecane-1,2-diol (147)



A solution of above compound **146**-diPMB (0.4 g, 0.7 mmol) and PPTS (267 mg, 1.07 mmol) in methanol (15 mL) was stirred 24 h at rt. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated, dissolved in DCM, washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product obtained was purified by column chromatography (50% ethyl acetate in petroleum ether) to afford diol **147** (350 mg, 94%) as colorless oil.

Mol. Formula : $C_{32}H_{42}O_6$

$[\alpha]_D$: +61.6 (*c* 1.0, $CHCl_3$).

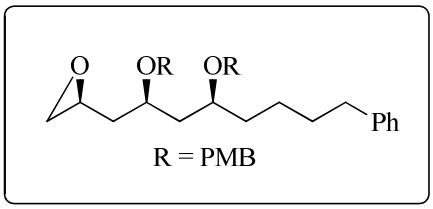
IR ($CHCl_3$) $\tilde{\nu}$: 3429, 3012, 2936, 1612, 1513, 1464, 1302, 1249, 1216, 1035, 755, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.29–7.11 (m, 9H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.26 (d, *J* = 11.5 Hz, 1H), 3.85–3.61 (m, 2H), 3.77 (2s, 2x 3H), 3.43 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.39–3.32 (m, 1H), 3.28 (dd, *J* = 11.2, 6.0 Hz, 1H), 2.97 (br.s, 2H), 2.64–2.57 (m, 2H), 1.95 (ddd, *J* = 13.2, 8.6, 3.6 Hz, 1H), 1.69–1.48 (m, 6H), 1.42–1.32 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.7 (t), 31.6 (t), 33.8 (t), 35.9 (t), 37.1 (t), 38.4 (t), 55.1 (q 2C), 66.6 (t), 70.0 (t), 70.1 (t), 71.5 (d), 74.5 (d), 76.1 (d), 113.7 (d 2C), 113.9 (d 2C), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 129.7 (d 4C), 129.8 (s), 130.5 (s), 142.3 (s), 159.2 (s), 159.3 (s) ppm.

Elemental Analysis Calcd.: C, 73.53; H, 8.09.
Found: C, 73.24; H, 8.04.

(*S*)-2-((2*S*,4*S*)-2,4-Bis(4-methoxybenzyloxy)-8-phenyloctyl)oxirane (131)



To a solution of diol **147** (0.5 g, 0.96 mmol) in dry DCM (10 mL) and Bu_2SnO (4 mg) were added *p*-TsCl (182 mg, 0.96 mmol) followed by triethylamine (0.266 mL, 1.9 mmol) and DMAP (20 mg). The resulting solution was stirred for 1 h at rt. The reaction mixture was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude tosylate (650 mg, 0.96 mmol) was dissolved in methanol (20 mL) and stirred with anhydrous K_2CO_3 (145 mg, 1.06 mmol) for 30 min. The reaction mixture was concentrated, the crude compound was dissolved in ethyl acetate and subjected for usual work up. Purification of the crude product by column chromatography (15% ethyl acetate in petroleum ether) furnished the epoxide **131** (375 mg, 78% for 2 steps) as colorless oil.

Mol. Formula : $C_{32}H_{40}O_5$

$[\alpha]_D$: −1.8 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3026, 2933, 2857, 1612, 1586, 1513, 1463, 1302, 1248, 1173, 1035, 821, 750, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.29–7.12 (m, 9H), 6.82 (br.d, *J* = 8.4 Hz, 4H), 4.41 (br.s, 2H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.33 (d, *J* = 11.3 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.69–3.58 (m, 1H), 3.50–3.39 (m, 1H), 3.03–2.94 (m, 1H), 2.71–2.66 (dd, *J* = 4.4, 5.1 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.36 (dd, *J* = 5.1, 2.8 Hz, 1H), 2.01–1.91 (m, 1H), 1.74–1.35 (m, 9H) ppm.

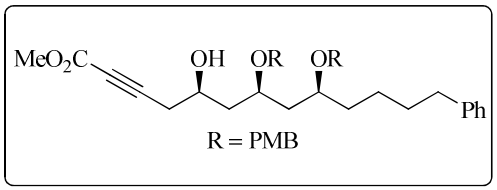
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.9 (t), 31.7 (t), 33.8 (t), 36.0 (t), 36.8 (t), 38.5 (t), 46.6 (t), 49.3 (d), 55.2 (q 2C), 70.2 (t 2C), 73.5 (d), 75.2 (d), 113.7 (d 4C), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 129.4 (d 4C), 130.6 (s), 130.9 (s), 142.5 (s), 159.1 (s), 159.2 (s)

ppm.

Elemental Analysis Calcd.: C, 76.16; H, 7.98.

Found: C, 76.00; H, 7.73.

(5*R*,7*R*,9*S*)-Methyl 5-hydroxy-7,9-bis(4-methoxybenzyloxy)-13-phenyltridec-2-ynoate (148)



Methyl propiolate (590 µl, 6.6 mmol) was taken in a flame dried two neck round bottom flask (50 mL) and dissolved in anhydrous THF (15 mL). The reaction mixture was cooled to −78 °C, treated with *n*-BuLi (4.2 mL, 6.64 mmol, 1.6 M in hexane) drop wise and stirred for 15 min, treated with $BF_3{\cdot}Et_2O$ (0.84 mL, 6.6 mmol) and continued stirring for an additional 15 minutes. Once the formation of dark black alkynyl borane was observed, a solution of epoxide **131** (335 mg, 0.66 mmol) in anhydrous THF (10 mL) was added and stirring was further continued for 30 min at −78 °C. The reaction was quenched at −78 °C by addition of sat. Na_2SO_4 (20 mL), taken in ethyl acetate water and the aqueous phase was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (20% ethyl acetate in petroleum ether) furnished **148** (365 mg, 93%) as colorless oil.

Mol. Formula : $C_{36}H_{44}O_7$

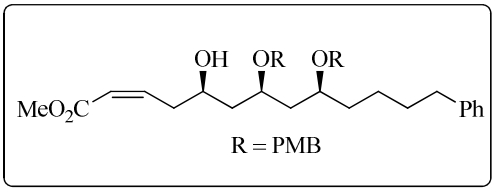
$[\alpha]_D$: +56.7 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3457, 3011, 2936, 2859, 2238, 1714, 1612, 1586, 1513, 1454, 1435, 1302, 1250, 1075, 1035, 822, 755, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.31–7.14 (m, 9H), 6.83 (br.d, *J* = 8.4 Hz, 4H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.90–3.73 (m, 2H), 3.71 (s, 3H), 3.44–3.33 (m, 1H), 2.66–2.58 (t, *J* = 7.5 Hz, 2H), 2.47–2.26 (m, 2H), 2.03–1.90 (m, 1H), 1.71–1.33 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.6 (t), 27.3 (t), 31.6 (t), 33.9 (t), 35.9 (t), 38.3 (t), 39.9 (t), 52.4 (q), 55.1 (q 2C), 69.3 (d), 70.0 (t), 70.5 (t), 74.5 (s), 74.8 (d), 76.4 (d), 86.2 (s), 113.7 (d 2C), 113.9 (d 2C), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 129.6 (d 2C), 129.6 (s), 129.7 (d 2C), 130.5 (s), 142.3 (s), 153.8 (s), 159.2 (s), 159.4 (s) ppm.
Elemental Analysis	Calcd.: C, 73.44; H, 7.53. Found: C, 73.14; H, 7.80.

(5*R*,7*R*,9*S*,*Z*)-Methyl 5-hydroxy-7,9-bis(4-methoxybenzyloxy)-13-phenyltridec-2-enoate (149)



A suspension of compound **148** (120 mg, 0.2 mmol), quinoline (50 µl) and $Pd/CaCO_3$ (50 mg) in benzene (15 mL) was flushed with hydrogen gas and stirred for 0.5 to 1 h under hydrogen atmosphere, the progress of reaction being monitored by TLC. After completion, the reaction mixture was filtered (*Celite*), concentrated and purified by column chromatography (20% ethyl acetate in petroleum ether) to furnish *Z*-acrylate **149** (87 mg, 72%) as an oil.

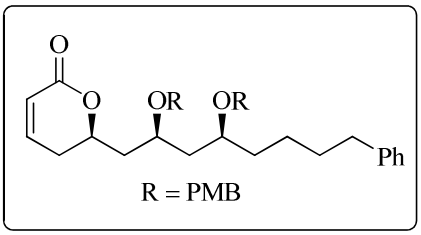
Mol. Formula	: $C_{36}H_{46}O_7$
$[\alpha]_D$	: +51.4 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 3019, 1717, 1647, 1612, 1514, 1440, 1249, 1215, 1035, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.30–7.14 (m, 9H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.34 (dt, *J* = 11.6, 7.3 Hz, 1H), 5.85 (dt, *J* = 11.6, 1.6 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 6H), 3.78–3.68 (m, 2H), 3.68 (s, 3H), 3.43–3.31 (m, 1H), 2.71 (dt, *J* = 8.9, 6.2, 1.6 Hz, 1H 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.95 (ddd, *J* = 13.8, 8.7, 3.7 Hz,

1H), 1.70–1.34 (m, 9H) ppm.

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 24.7 (t), 31.6 (t), 33.8 (t), 35.9 (t), 36.8 (t), 38.4 (t), 40.9 (t), 50.9 (q), 55.1 (q 2C), 70.0 (t), 70.3 (t), 70.7 (d), 74.7 (d), 76.8 (d), 113.7 (d 2C), 113.9 (d 2C), 120.6 (d), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 129.5 (d 2C), 129.6 (d 2C), 129.9 (s), 130.5 (s), 142.4 (s), 146.8 (d), 159.2 (s), 159.3 (s), 166.8 (s) ppm.

Elemental Analysis Calcd.: C, 73.19; H, 7.84.
Found: C, 72.96; H, 7.69.

(*R*)-6-((2*S*,4*S*)-2,4-Bis(4-methoxybenzyloxy)-8-phenyloctyl)-5,6-dihydro-2H-pyran-2-one (150)



A solution of above *Z*-acrylate **149** (100 mg, 0.17 mmol) and PPTS (85 mg, 0.34 mmol) in $CHCl_3$ (5 mL) was refluxed for 6 h and partitioned between $CHCl_3$ and water. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to afford the δ-pyrone **150** (90 mg, 95%) as yellow oil.

Mol. Formula : $C_{35}H_{42}O_6$

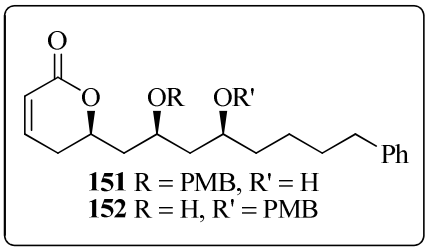
$[\alpha]_D$: +60.8 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3015, 2933, 2857, 1721, 1612, 1513, 1464, 1386, 1302, 1249, 1217, 1036, 818, 754, 666 cm^{-1}.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 7.30–7.13 (m, 9H), 6.86–6.79 (m, 4H), 6.74–6.65 (ddd, *J* = 9.8, 5.7, 2.9 Hz, 1H), 5.95 (ddd, *J* = 9.8, 2.4, 1.0 Hz, 1H), 4.55–4.45 (m, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 6H), 3.71–3.59 (m, 1H), 3.52–3.41 (m, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.01–1.86 (m, 3H), 1.81–1.51 (m, 7H), 1.44–1.32 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.6 (t), 29.0 (t), 31.6 (t), 33.7 (t), 35.9 (t), 37.9 (t), 38.9 (t), 55.1 (q 2C), 69.8 (t), 70.2 (t), 71.5 (d), 75.1 (d), 75.2 (d), 113.7 (d 4C), 121.3 (d), 125.6 (d), 128.2 (d 2C), 128.4 (d 2C), 129.4 (d 2C), 129.6 (d 2C), 130.4 (s), 130.8 (s), 142.4 (s), 144.8 (d), 159.1 (s), 159.2 (s), 164.1 (s) ppm.
Elemental Analysis	Calcd.: C, 75.24; H, 7.57. Found: C, 75.53; H, 7.49.

(*R*)-6-((2*S*,4*S*)-4-Hydroxy-2-(4-methoxy-benzyl-oxy)-8-phenyloctyl)-5,6-dihydro-2H-pyran-2-one (151) and (*R*)-6-((2*S*,4*S*)-2-Hydroxy-4-(4-methoxy-benzyloxy)-8-phenyl-octyl)-5,6-dihydro-2H-pyran-2-one (152)



151 R = PMB, R' = H
152 R = H, R' = PMB

A solution of compound **150** (145 mg, 0.26 mmol) in DCM (10 mL) at 0 °C, was treated with TFA (50 μl) and stirred for 30 min at 0 °C. The reaction was quenched by addition of saturated bicarbonate solution and the aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (40%→50% ethyl acetate in petroleum ether) to afford a 1:1 mixture of regioisomeric alcohols **151** and **152** (61 mg, 54%) and diol **153** (20 mg, 24%).

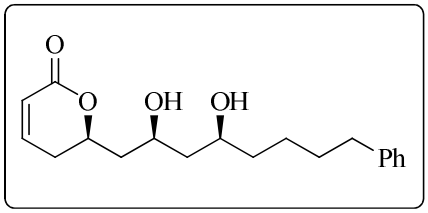
Mol. Formula	: $C_{27}H_{34}O_5$
$[\alpha]_D$	: +54.8 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3462, 3019, 2937, 2860, 1719, 1612, 1514, 1454, 1390, 1251, 1215, 1035, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.19–7.07 (m, 7H), 6.82–6.70 (m, 3H), 5.96–5.88 (m, 1H), 4.59–4.21 (m, 3H), 3.92–3.77 (m, 1H), 3.71 (s, 3H), 3.68–3.54 (m, 1H), 2.59–2.49 (m, 2H), 2.33–2.18 (m, 2H), 2.14–1.67 (m, 2H), 1.67–1.45 (m, 6H), 1.41–1.28 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.1 (t), 25.1 (t), 29.1 (t), 29.7 (t), 31.5 (t), 31.6 (t), 33.1 (t), 35.8 (t), 35.9 (t), 37.6 (t), 38.8 (t), 40.7 (t), 41.8 (t),

55.1 (q), 68.0 (d), 70.2 (t), 70.4 (t), 70.6 (d), 74.7 (d), 75.2 (d), 75.5 (d), 79.5 (d), 113.9 (d 2C), 121.2 (d), 121.4 (d), 125.6 (d), 125.7 (d), 128.2 (d), 128.3 (d 2C), 129.5 (d), 129.6 (d), 129.8 (s), 142.2 (s), 142.5 (s), 144.8 (d), 145.2 (d), 159.3 (s), 159.4 (s), 163.9 (s), 164.3 (s) ppm.

Elemental Analysis Calcd.: C, 73.94; H, 7.81.
Found: C, 74.05; H, 7.63.

Data of Diol 153:

(*R*)-6-((2*S*,4*S*)-2,4-Dihydroxy-8-phenyloctyl)-5,6-dihydro-2H-pyran-2-one (153)



Mol. Formula : $C_{19}H_{26}O_4$

$[\alpha]_D$: +62.1 (*c* 1.0, $CHCl_3$).

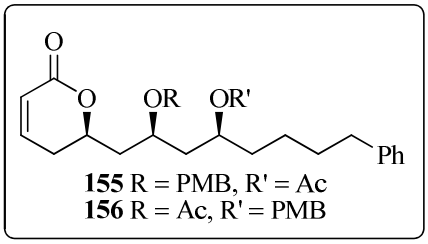
IR ($CHCl_3$) $\tilde{\nu}$: 3684, 3020, 2934, 1725, 1522, 1476, 1215, 1055, 759, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.30–7.11 (m, 5H), 6.89 (dt, *J* = 9.8, 3.8 Hz, 1H), 6.02 (dt, *J* = 9.8, 1.8 Hz, 1H), 4.72–4.57 (ddt, *J* = 8.9, 7.5, 5.5 Hz, 1H), 4.15–4.03 (m, 1H), 3.90–3.79 (m, 1H), 3.50 (b, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.45–2.39 (m, 2H), 2.08–1.94 (m, 1H), 1.81–1.32 (m, 9H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.9 (t), 29.4 (t), 31.4 (t), 35.8 (t), 38.1 (t), 42.3 (t), 42.7 (t), 69.5 (d), 72.7 (d), 76.2 (d), 121.2 (d), 125.7 (d), 128.2 (d 2C), 128.3 (d 2C), 142.4 (s), 145.4 (d), 164.2 (s) ppm.

Elemental Analysis Calcd.: C, 71.66; H, 8.23.
Found: C, 71.39; H, 8.81.

(2*S*,4*S*)-2-(4-Methoxybenzyloxy)-1-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-8-phenyl-octan-4-yl acetate (155) and (2*S*,4*S*)-4-(4-Methoxy-benzyloxy)-1-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-8-phenyloctan-2-yl acetate (156)



155 R = PMB, R' = Ac
156 R = Ac, R' = PMB

To a solution of regioisomeric mixture of alcohols **151** and **152** (54 mg, 0.12 mmol) in DCM (5 mL) was added sequentially acetic anhydride (60 µl, 0.62 mmol), triethylamine (85 µl, 0.61 mmol), DMAP (5 mg) and stirred for 6 h at rt. The reaction mixture was diluted with dichloromethane/water and the organic layer was separated, dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (30% ethyl acetate in petroleum ether) to afford 1:1 regioisomeric mixture of **155** and **156** (55 mg, 94%) as yellow oils.

Mol. Formula : $C_{29}H_{36}O_6$

$[\alpha]_D$: +48.9 (*c* 1.0, $CHCl_3$).

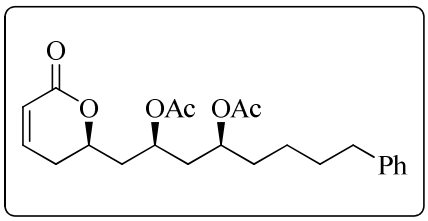
IR ($CHCl_3$) $\tilde{\nu}$: 3020, 2936, 2860, 1726, 1612, 1513, 1464, 1375, 1249, 1216, 1037, 757, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.30–7.11 (m, 7H), 6.88–6.81 (m, 2H), 6.80–6.71 (m, 1H), 6.00–5.94 (m, 1H), 5.21–4.89 (2m, 1H), 4.59–4.33 (m, 3H), 3.78 (2s, 3H), 3.59–3.37 (m, 1H), 2.64–2.54 (m, 2H), 2.39–2.03 (m, 3H), 1.99, 1.98 (2s, 3H), 1.92–1.51 (m, 7H), 1.45–1.29 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.1 (q), 24.5 (t), 24.8 (t), 29.1 (t), 29.1 (t), 31.1 (t), 31.5 (t), 33.3 (t), 34.4 (t), 35.7 (t), 35.8 (t), 38.1 (t), 38.4 (t), 38.6 (t), 39.3 (t), 55.2 (q), 68.3 (d), 69.8 (t), 69.9 (t), 71.2 (d), 71.3 (d), 74.9 (d), 74.9 (d), 75.1 (d), 113.7 (d 2C), 121.4 (d), 125.6 (d), 128.2 (d 2C), 128.3 (d 2C), 129.4 (d), 129.6 (d), 130.1 (s), 130.6 (s), 142.3 (s), 142.4 (s), 144.6 (d), 144.8 (d), 159.2 (s), 159.3 (s), 163.7 (s), 164.0 (s), 170.5 (s) ppm.

Elemental Analysis Calcd.: C, 72.47; H, 7.55.
Found: C, 72.39; H, 7.26.

(2*S*,4*S*)-1-((*R*)-6-Oxo-3,6-dihydro-2H-pyran-2-yl)-8-phenyloctane-2,4-diyl diacetate (154)



In a similar procedure that used in the preparation of **155**/**156**, treatment of **153** (29 mg, 0.09 mmol) in DCM (6 mL) with Ac_2O (85 µl, 0.91 mmol), triethylamine (126 µl, 0.91 mmol) and DMAP (5 mg) and usual work up after 6 h stirring followed by purification of the crude product by column chromatography (30% ethyl acetate in petroleum ether) afforded diacetate **154** (34 mg, 94%) as yellow oil.

Mol. Formula : $C_{23}H_{30}O_6$

$[\alpha]_D$: +48.6 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3020, 2936, 2861, 1730, 1496, 1374, 1242, 1216, 1152, 1038, 758, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.28–7.25 (m, 2H), 7.18–7.15 (m, 3H), 6.87–6.84 (m, 1H), 6.02–6.00 (dd, *J* = 9.7, 1.9 Hz, 1H), 5.07–5.02 (m, 1H), 4.95–4.90 (m, 1H), 4.50–4.45 (m, 1H), 2.61–2.58 (t, *J* = 7.5 Hz, 2H), 2.46–2.40 (m, 1H), 2.33–2.27 (m, 1H), 2.16–2.10 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99–1.89 (m, 2H), 1.84–1.79 (m, 1H), 1.66–1.57 (m, 4H), 1.39–1.28 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 21.1 (q 2C), 24.6 (t), 29.1 (t), 31.0 (t), 34.1 (t), 35.6 (t), 38.9 (t), 38.9 (t), 67.8 (d), 70.8 (d), 74.9 (d), 121.3 (d), 125.7 (d), 128.2 (d 2C), 128.4 (d 2C), 142.3 (s), 144.7 (d), 163.7 (s), 170.6 (s), 170.8 (s) ppm.

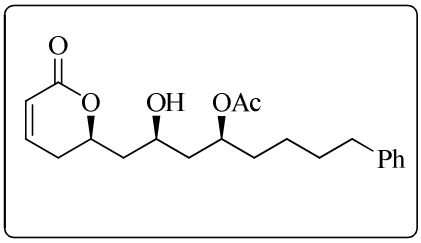
Elemental Analysis Calcd.: C, 68.64; H, 7.51.

Found: C, 68.89; H, 7.61.

MALDI-TOF (MS) Calcd.: $C_{23}H_{30}O_6Na$; 425.19

Found: $C_{23}H_{30}O_6Na$; 425.19

(2*S*,4*S*)-2-Hydroxy-1-((*R*)-6-oxo-3,6-dihydro-2-H-pyran-2-yl)-8-phenyloctan-4-yl acetate (128)



In a similar procedure that used in the deprotection of **150**, treatment of **155**/**156** (58 mg, 0.12 mmol) in DCM (6 mL) with TFA (20 μl) and stirring at 0 °C for 30 min, usual workup and purification of resulting crude product by column chromatography (40% ethyl acetate in petroleum ether) furnished an equilibrium mixture of natural regioisomers **128** and **129** (39 mg, 90%) as yellow color oils.

A portion of **128**/**129** mixture was subjected to preparative HPLC separation and the ^{1}H and ^{13}C NMR of the separated **128** and **129** were recorded.

Major Isomer 128:

Mol. Formula : $C_{21}H_{28}O_5$

$[\alpha]_D$: +33 (*c* 0.3, MeOH) [lit +35 (*c* 0.05, MeOH)][41].

IR ($CHCl_3$) $\tilde{\nu}$: 3440, 3019, 2934, 2859, 1724, 1513, 1496, 1384, 1250, 1216, 1043, 757, 668 cm^{-1}.

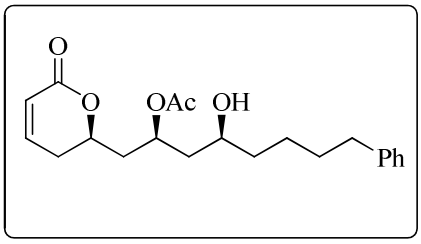
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.27-7.24 (m, 2H), 7.18-7.14 (m, 3H), 6.87 (dt, *J* = 9.8, 4.2 Hz, 1H), 6.01 (br.dt, *J* = 9.5, 1.7 Hz, 1H), 4.97–4.92 (m, 1H), 4.66–4.60 (m, 1H), 3.90–3.86 (m, 1H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.40–2.37 (m, 2H), 2.02 (s, 3H), 1.95–1.41 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 21.3 (q), 24.8 (t), 29.4 (t), 31.1 (t), 34.5 (t), 35.7 (t), 41.7 (t), 42.3 (t), 67.0 (d), 72.3 (d), 76.6 (d), 121.2 (d), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 142.3 (s), 145.2 (d), 163.9 (s), 171.3 (s) ppm.

Elemental Analysis	Calcd.: C, 69.98; H, 7.83.
	Found: C, 69.79; H, 7.96.
MALDI-TOF (MS)	Calcd.: $C_{21}H_{28}O_5Na$; 383.18
	Found: $C_{21}H_{28}O_5Na$; 383.17

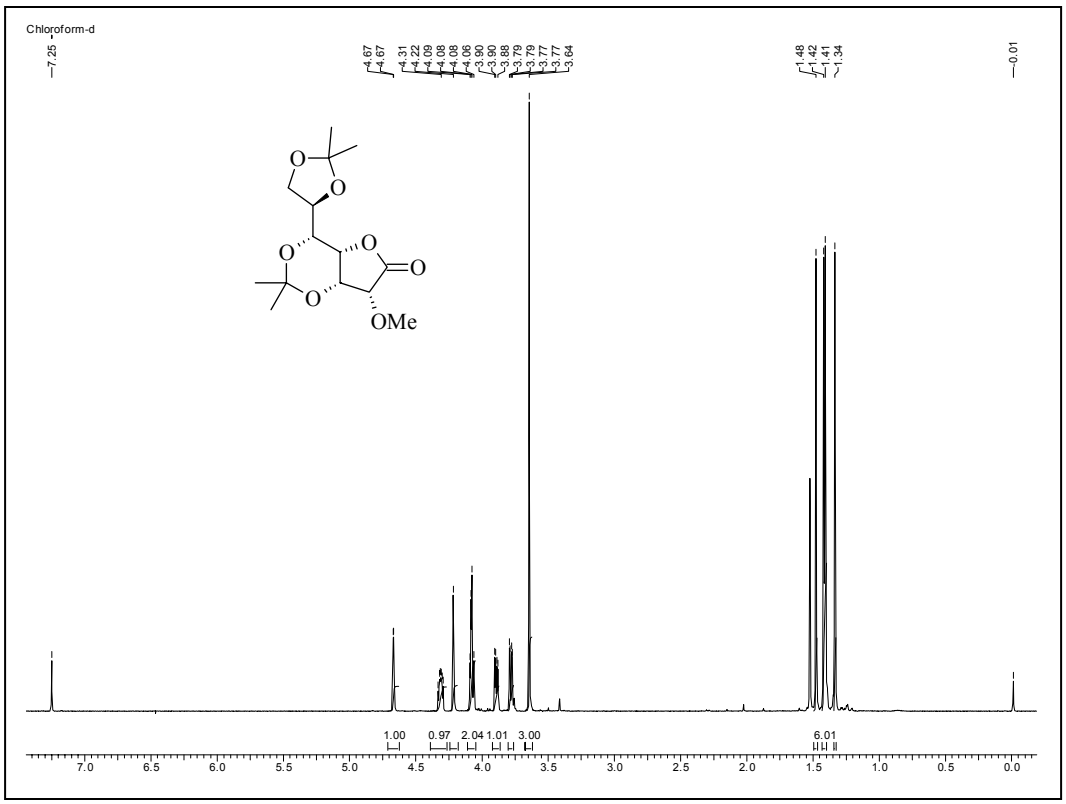
Minor Isomer 129:

(2*S*,4*S*)-4-Hydroxy-1-((*R*)-6-oxo-3,6-dihydro-2-H-pyran-2-yl)-8-phenyloctan-2-yl acetate (129)

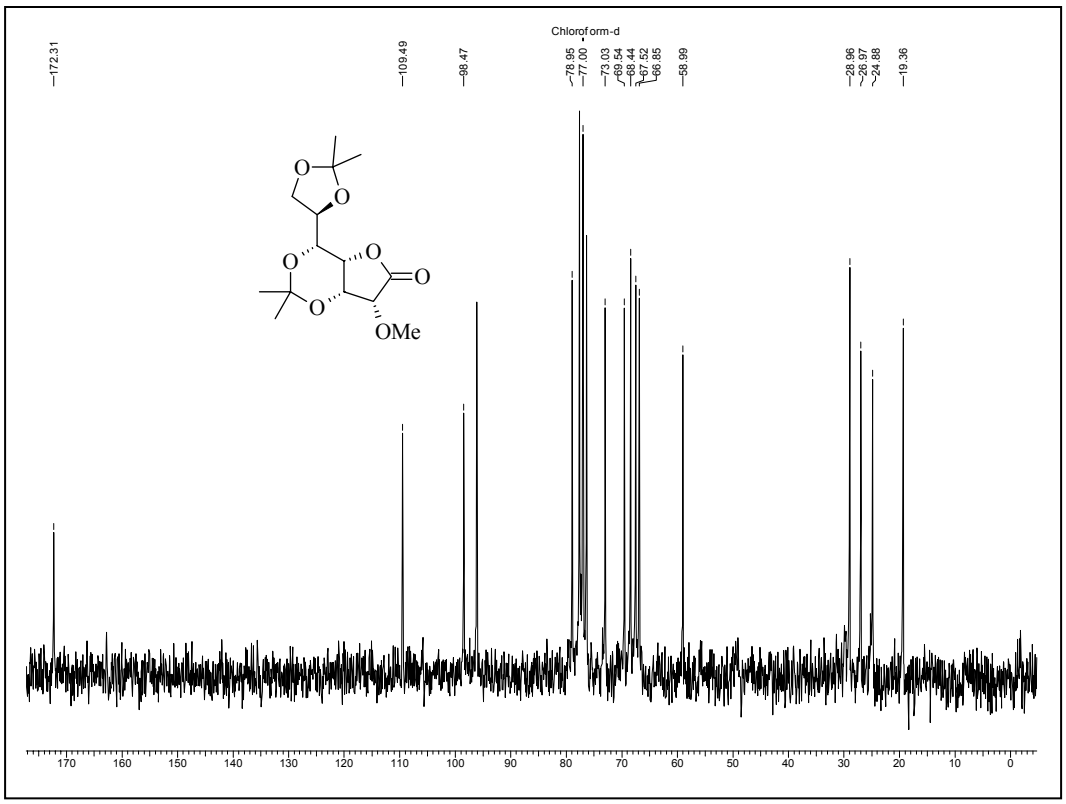


Mol. Formula	: $C_{21}H_{28}O_5$
$[\alpha]_D$	: +33 (*c* 0.3, MeOH) [lit +35 (*c* 0.05, MeOH)][41].
IR ($CHCl_3$) $\tilde{\nu}$	: 3440, 3019, 2934, 2859, 1724, 1513, 1496, 1384, 1250, 1216, 1043, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 7.27–7.24 (m, 2H), 7.18–7.14 (m, 3H), 6.87–6.84 (ddd, *J* = 9.7, 6.1, 2.4 Hz, 1H), 6.01 (ddd, *J* = 9.7, 2.6, 0.7 Hz, 1H), 5.24–5.19 (m, 1H), 4.54–4.48 (m, 1H), 3.72–3.67 (m, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.48–2.43 (m, 1H), 2.34–2.26 (m, 1H), 2.18 (ddd, *J* = 14.6, 8.4, 6.3 Hz, 1H), 2.05 (s, 3H), 1.95 (ddd, *J* = 14.6, 6.8, 4 Hz, 1H), 1.82–1.71 (m, 2H), 1.66–1.42 (m, 6H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 21.3 (q), 25.0 (t), 29.2 (t), 31.3 (t), 35.8 (t), 37.7 (t), 39.3 (t), 41.7 (t), 69.0 (d), 69.2 (d), 75.1 (d), 121.4 (d), 125.7 (d), 128.3 (d 2C), 128.4 (d 2C), 142.4 (s), 144.7 (d), 163.9 (s), 170.9 (s) ppm.
Elemental Analysis	Calcd.: C, 69.98; H, 7.83.
	Found: C, 69.79; H, 7.96.
MALDI-TOF (MS)	Calcd.: $C_{21}H_{28}O_5Na$; 383.18
	Found: $C_{21}H_{28}O_5Na$; 383.17

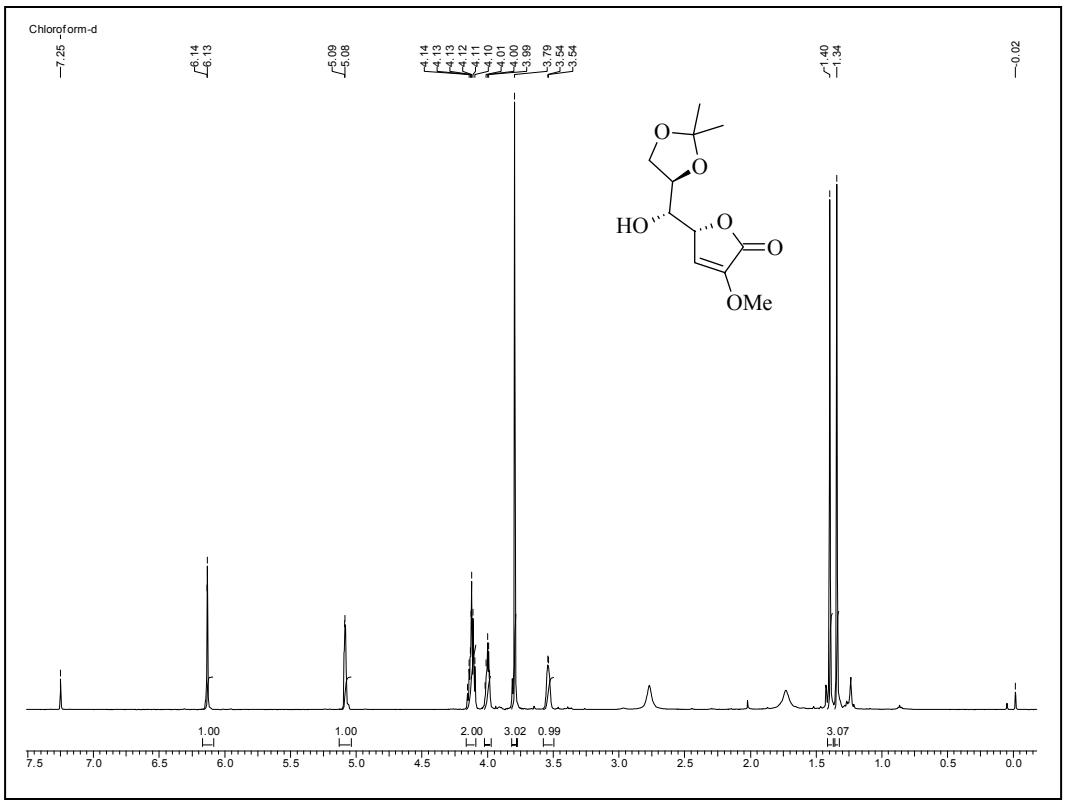
Spectroscopic Data



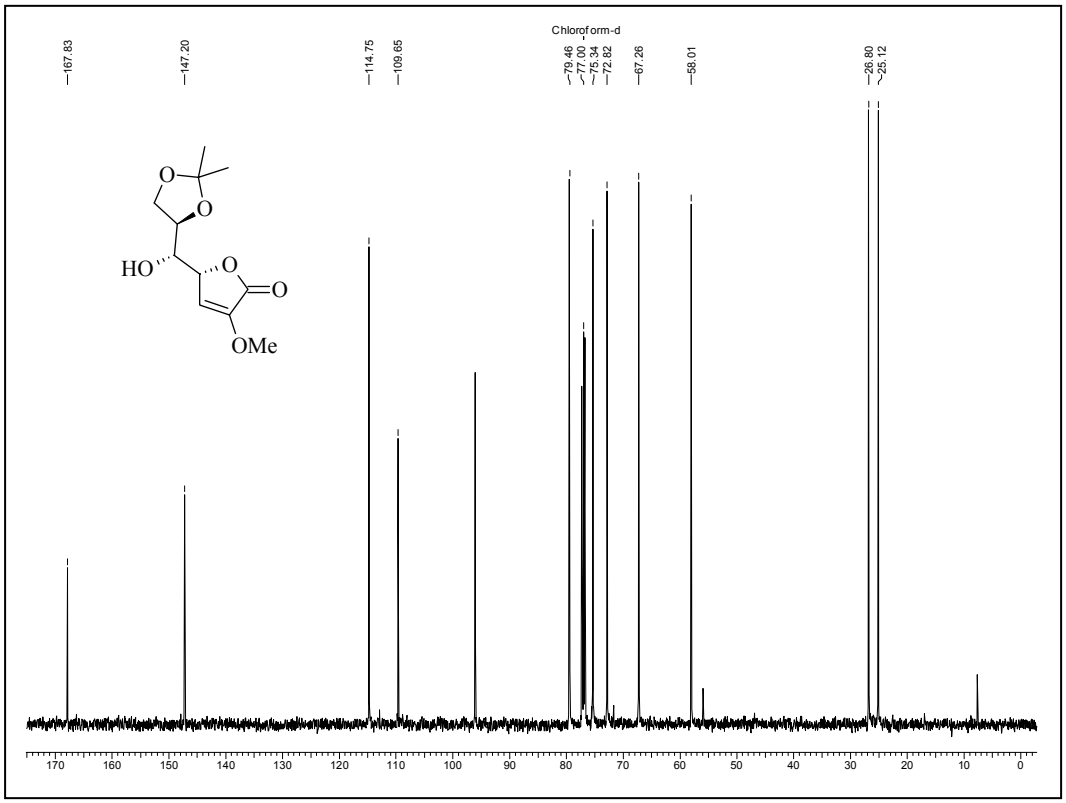
^{1}H NMR Spectrum of 136 in $CDCl_3$



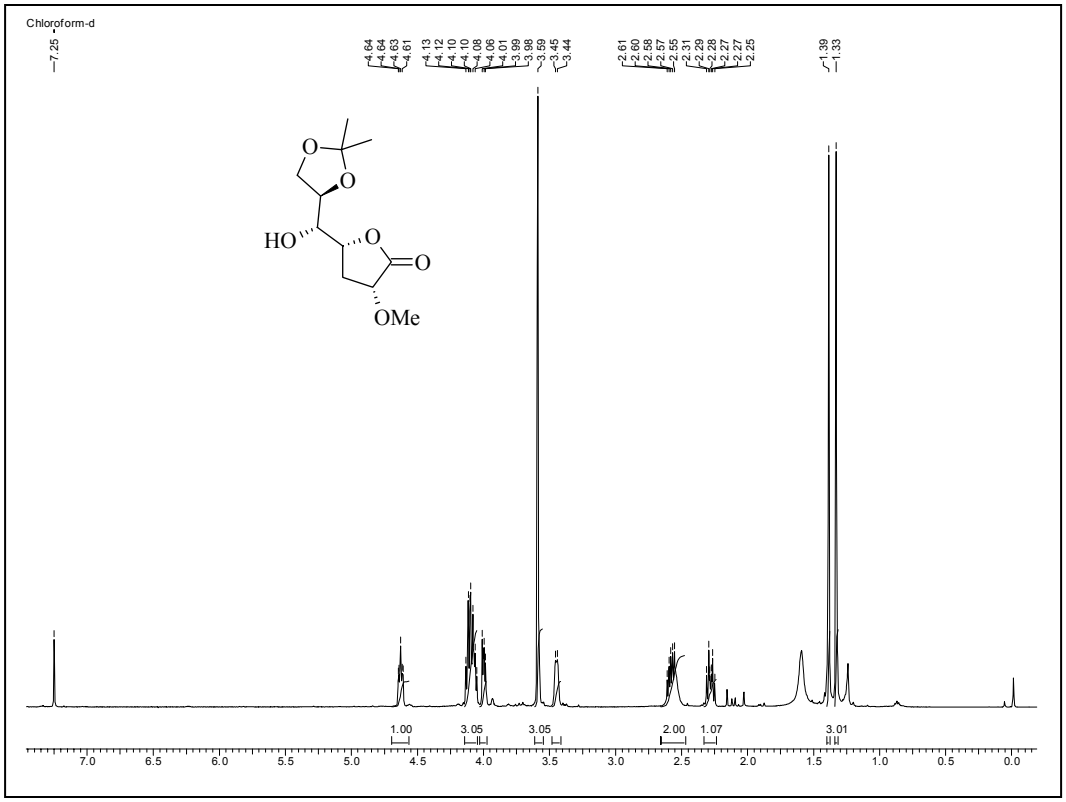
^{13}C NMR Spectrum of 136 in $CDCl_3$



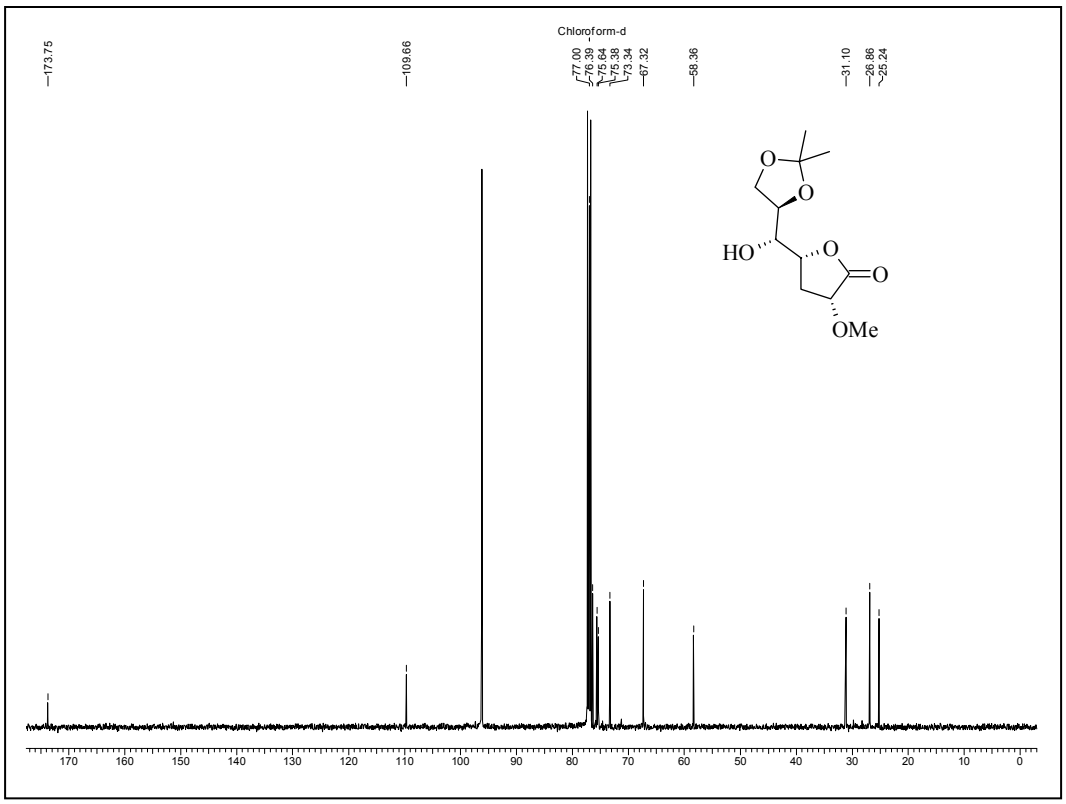
^{1}H NMR Spectrum of 137 in $CDCl_3$



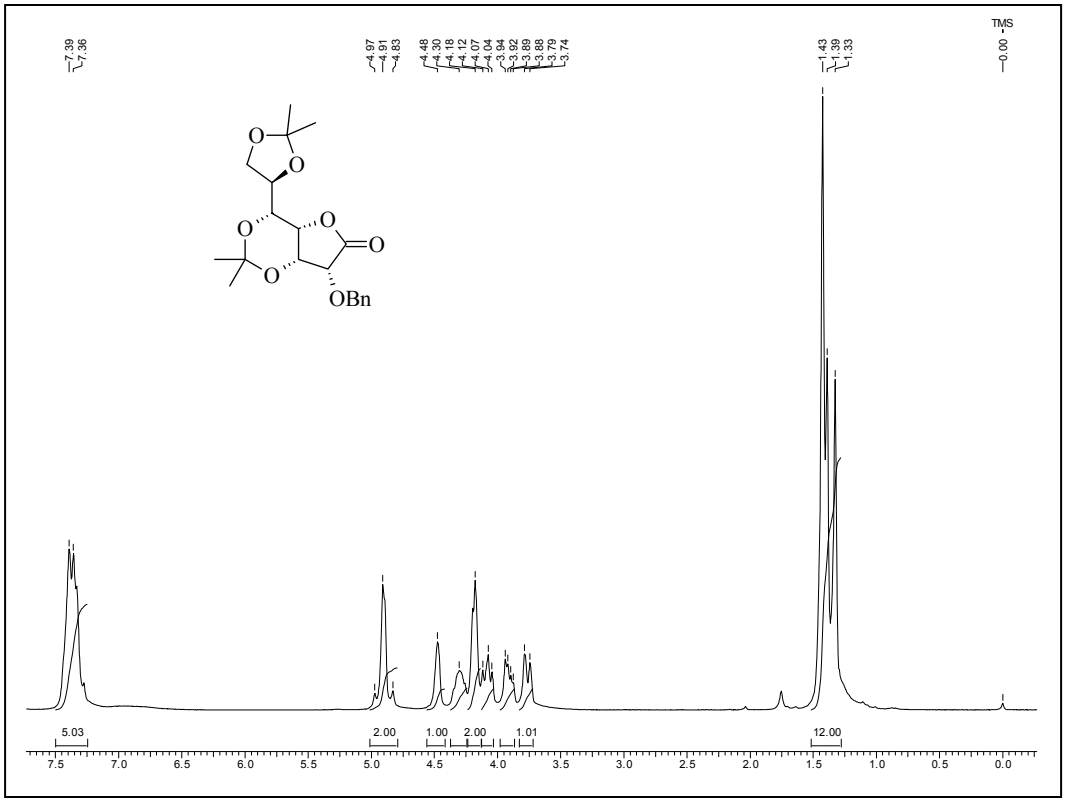
^{13}C NMR Spectrum of 137 in $CDCl_3$



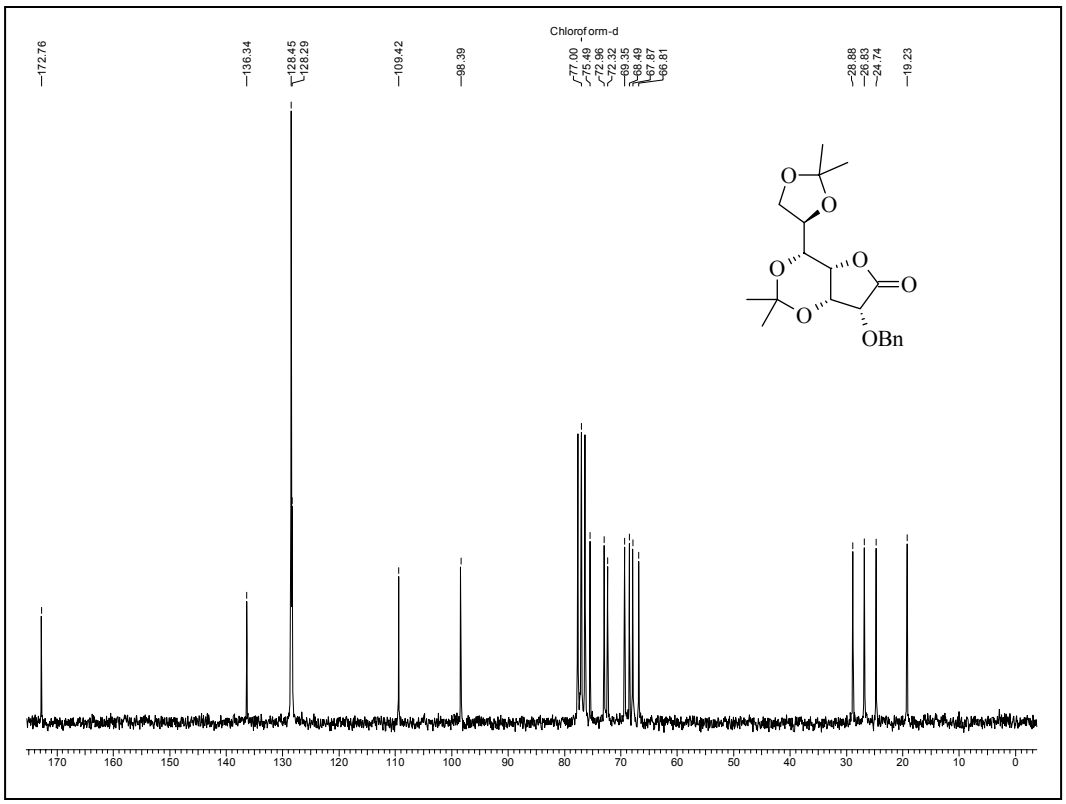
^{1}H NMR Spectrum of 138 in $CDCl_3$



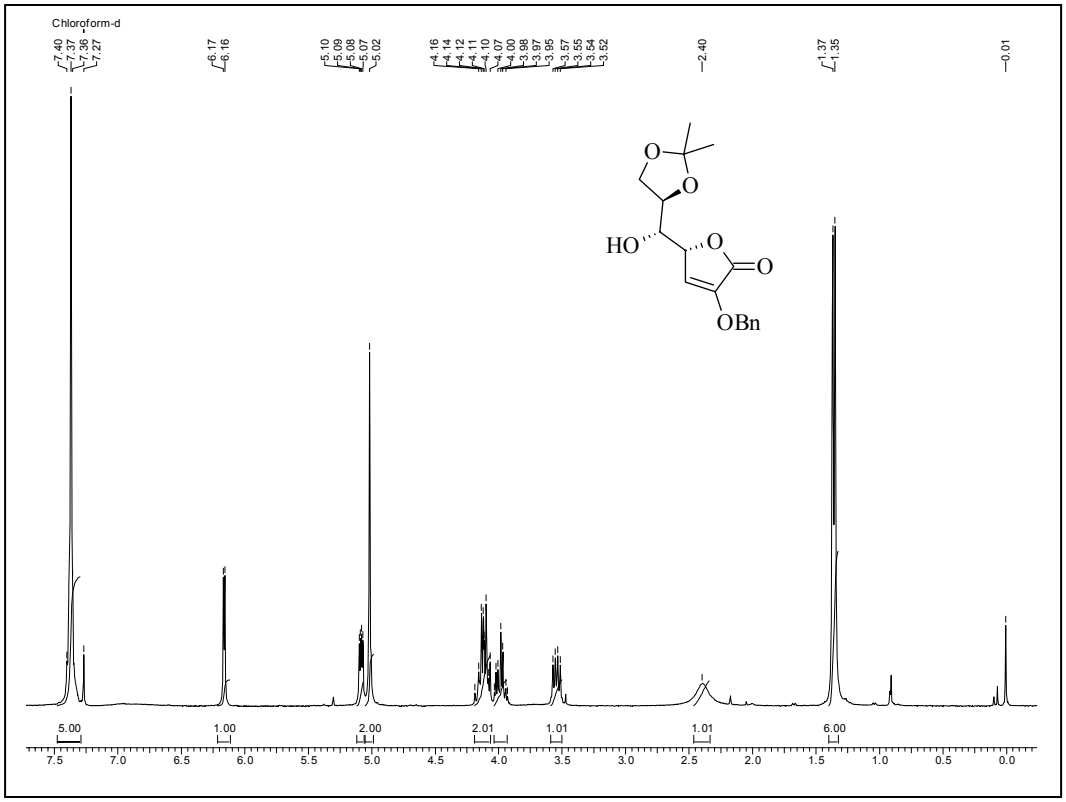
^{13}C NMR Spectrum of 138 in $CDCl_3$



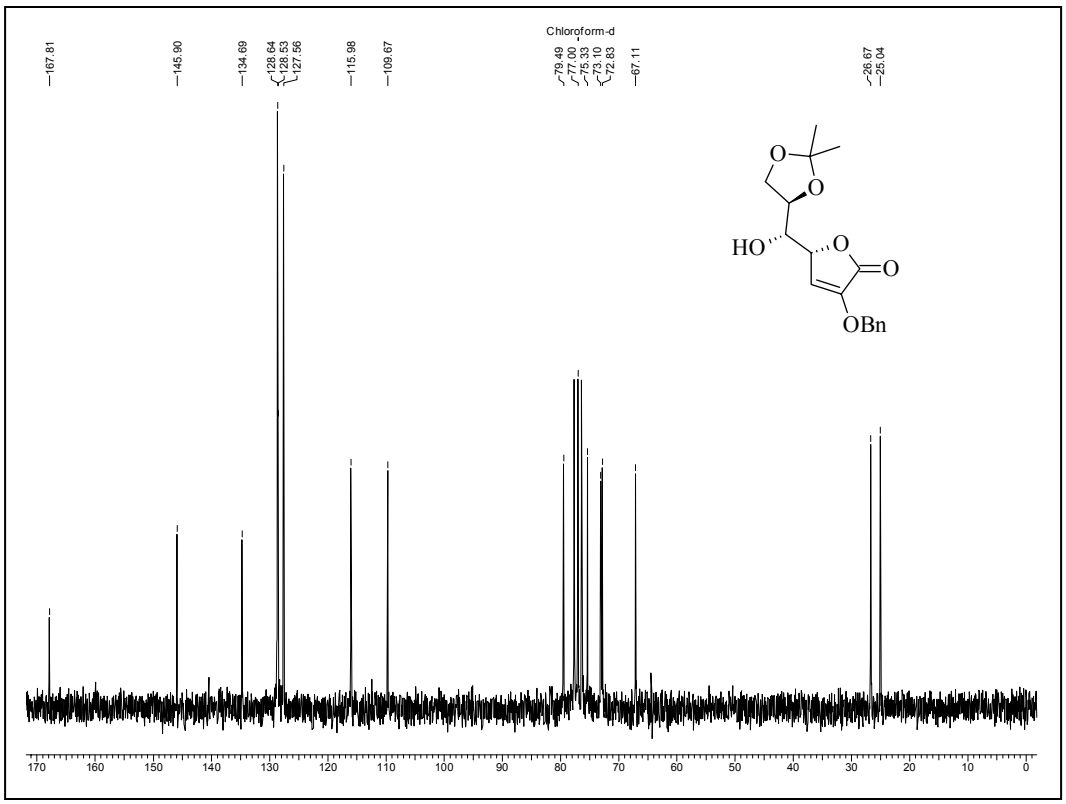
^{1}H NMR Spectrum of 139 in $CDCl_3$



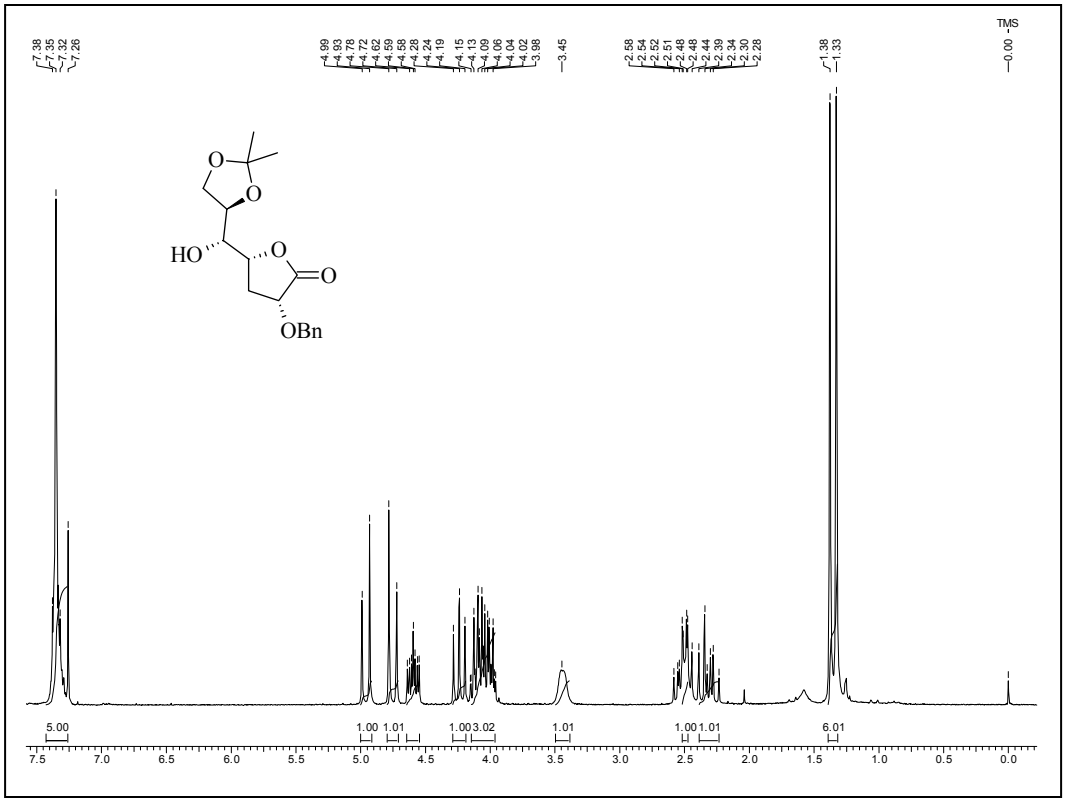
^{13}C NMR Spectrum of 139 in $CDCl_3$



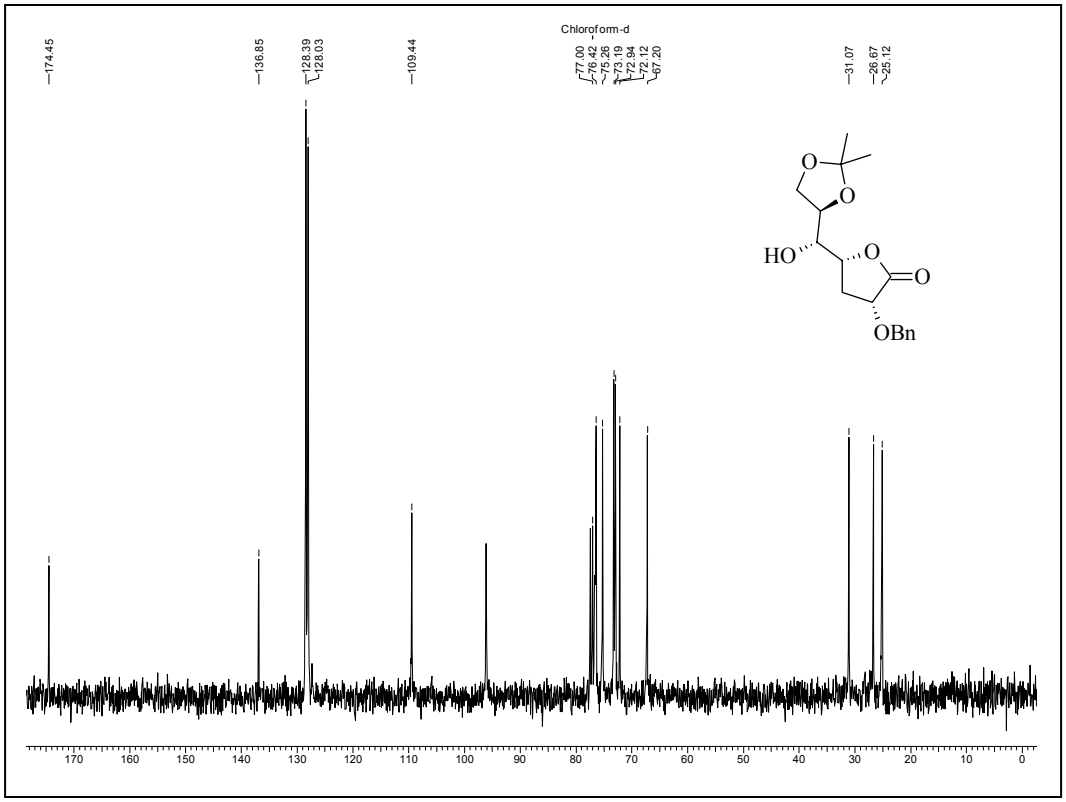
^{1}H NMR Spectrum of 134 in $CDCl_3$



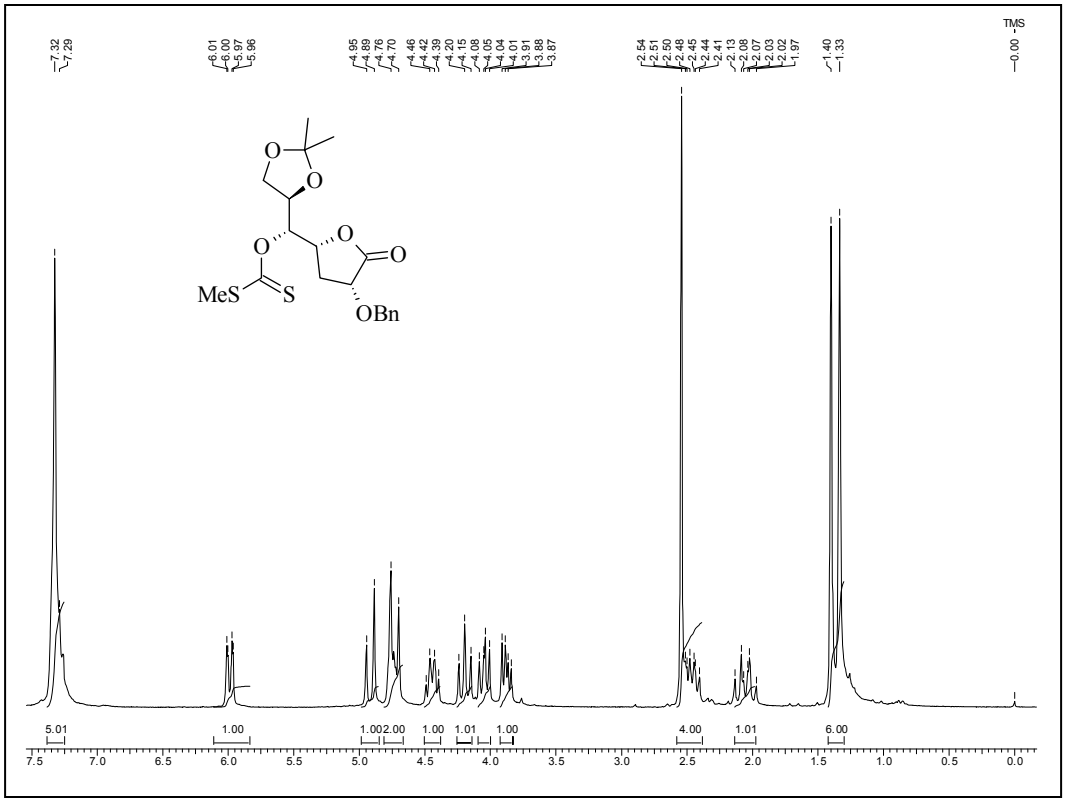
^{13}C NMR Spectrum of 134 in $CDCl_3$



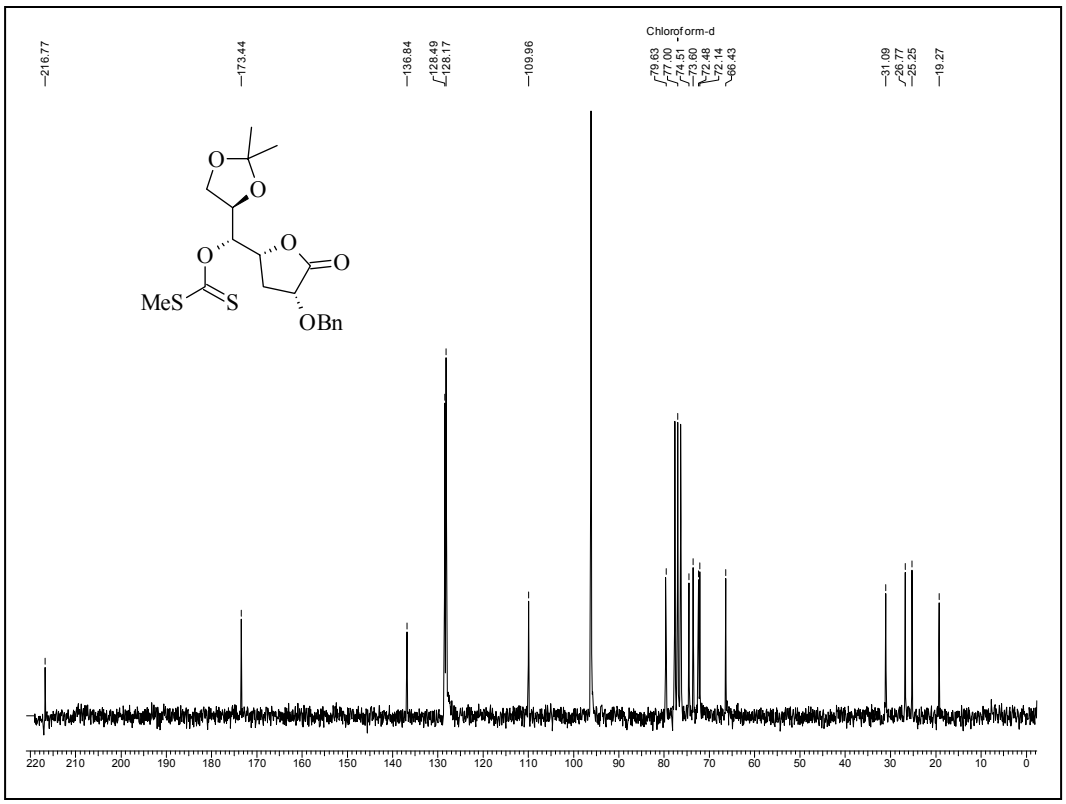
^{1}H NMR Spectrum of 140 in $CDCl_3$



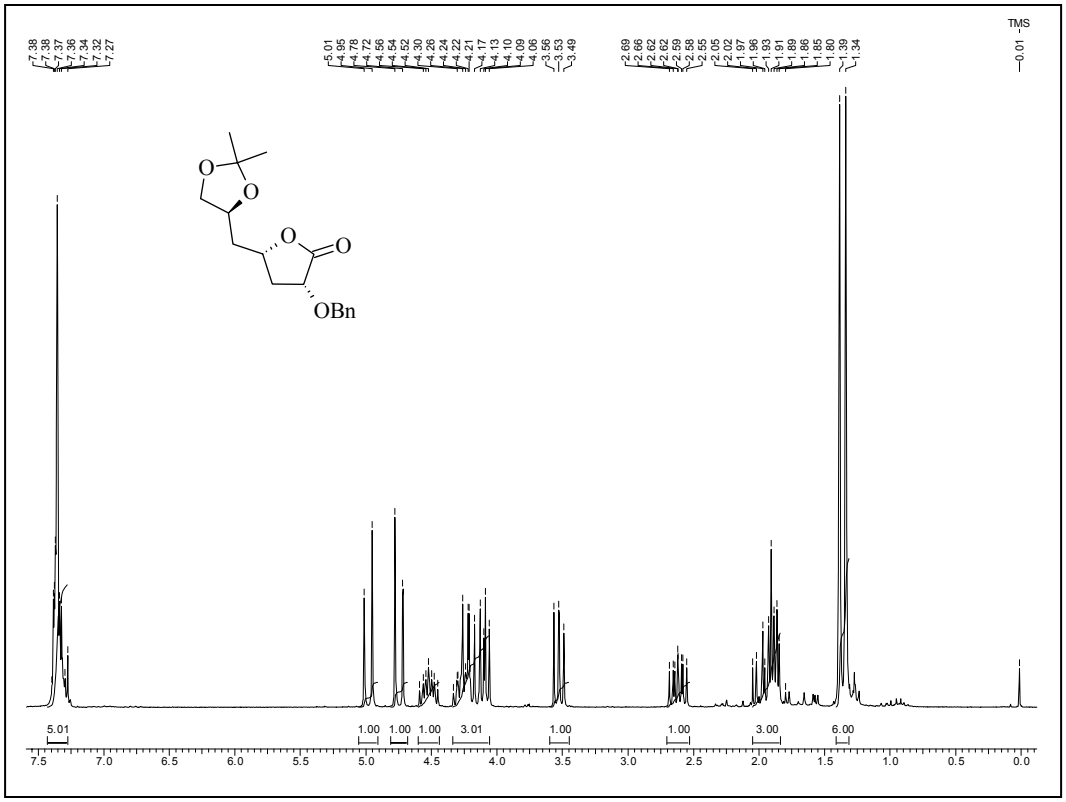
^{13}C NMR Spectrum of 140 in $CDCl_3$



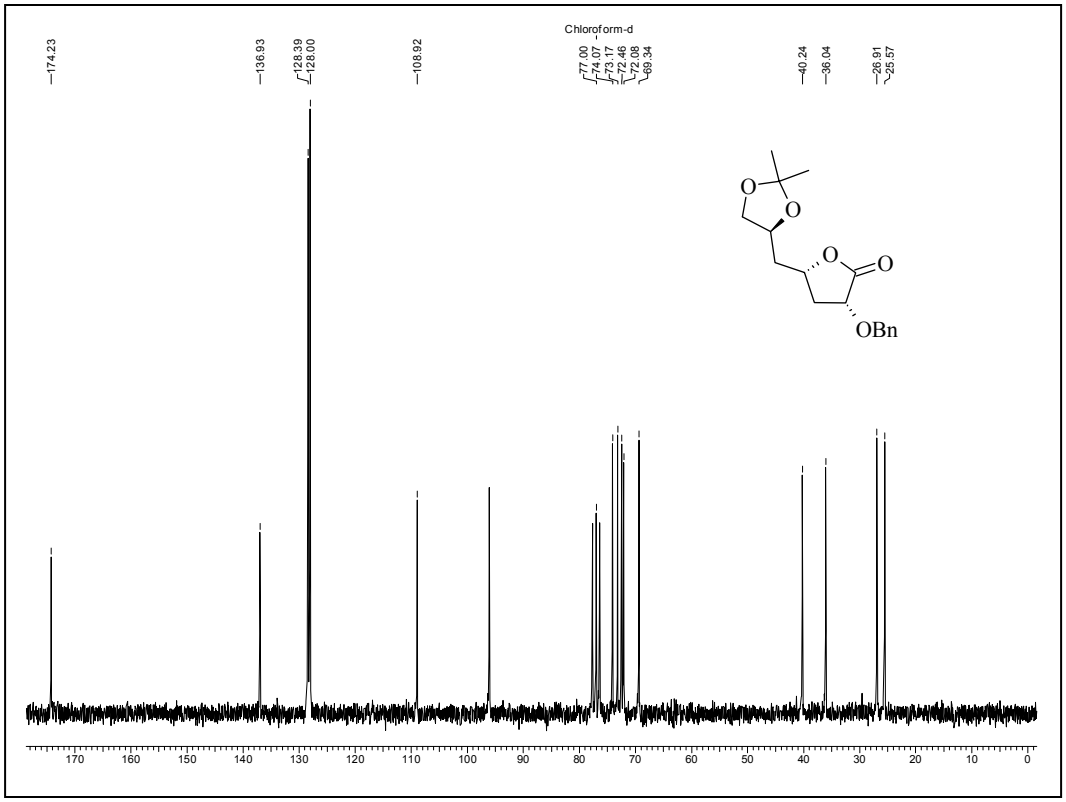
^{1}H NMR Spectrum of 141 in $CDCl_3$



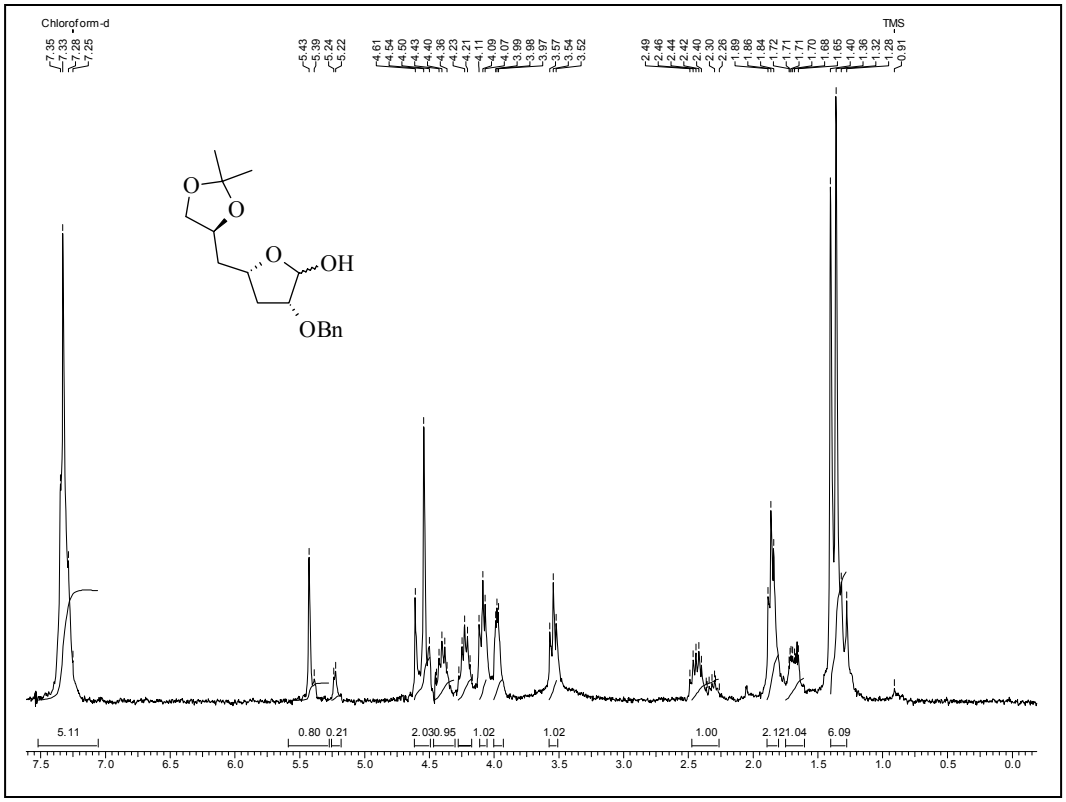
^{13}C NMR Spectrum of 141 in $CDCl_3$



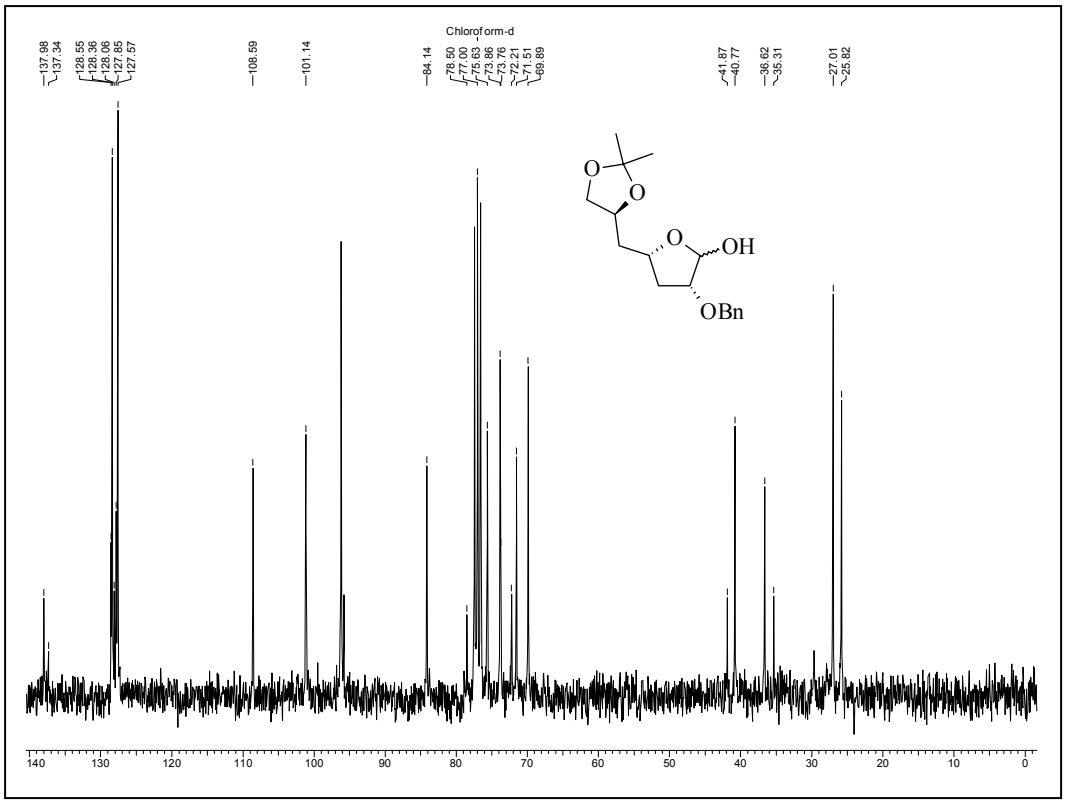
^{1}H NMR Spectrum of 133 in $CDCl_3$



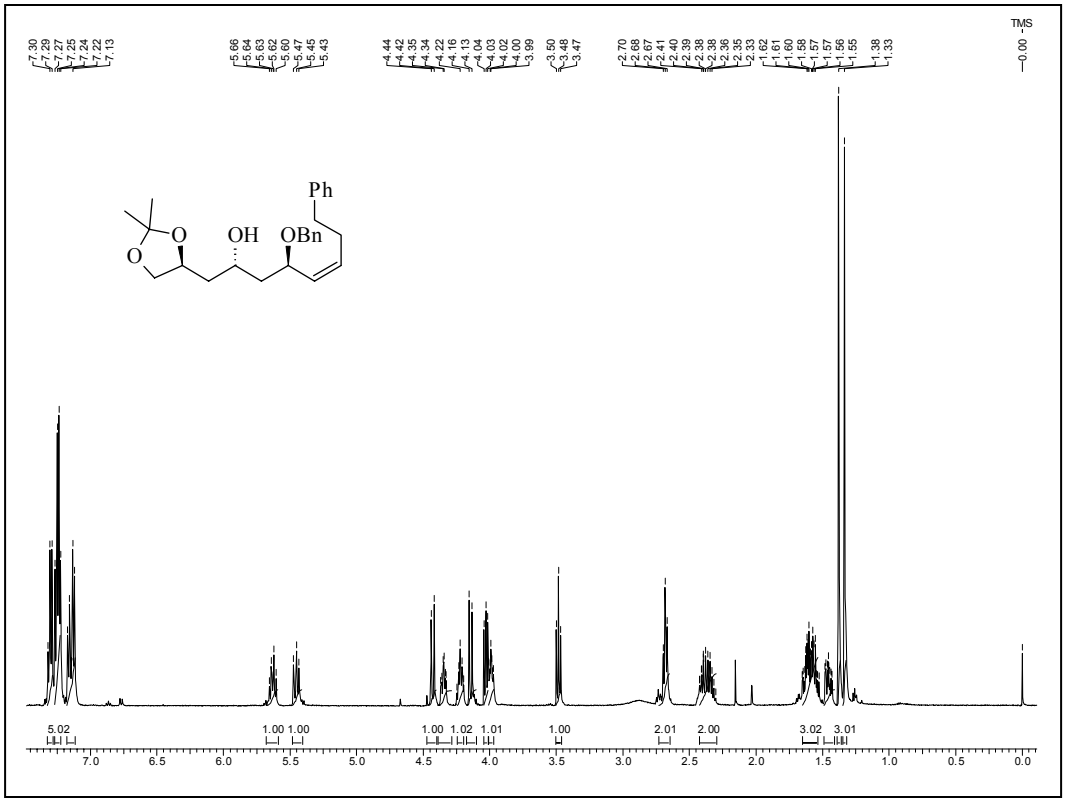
^{13}C NMR Spectrum of 133 in $CDCl_3$



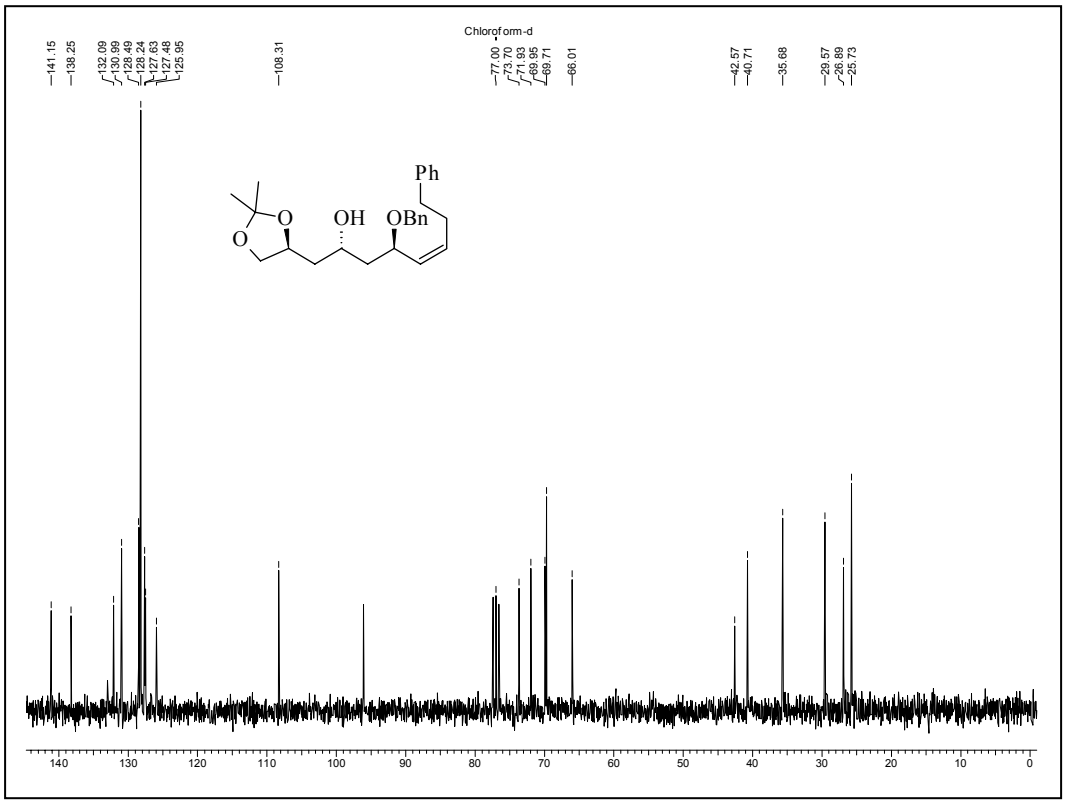
^{1}H NMR Spectrum of 142 in $CDCl_3$



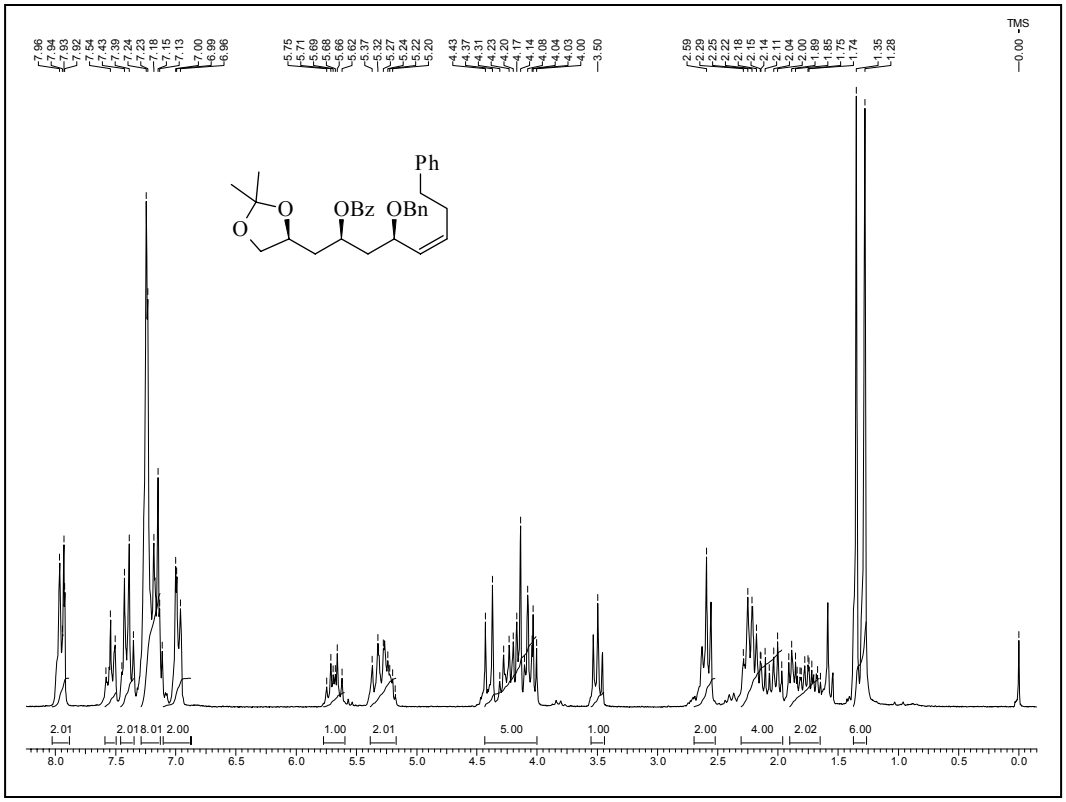
^{13}C NMR Spectrum of 142 in $CDCl_3$



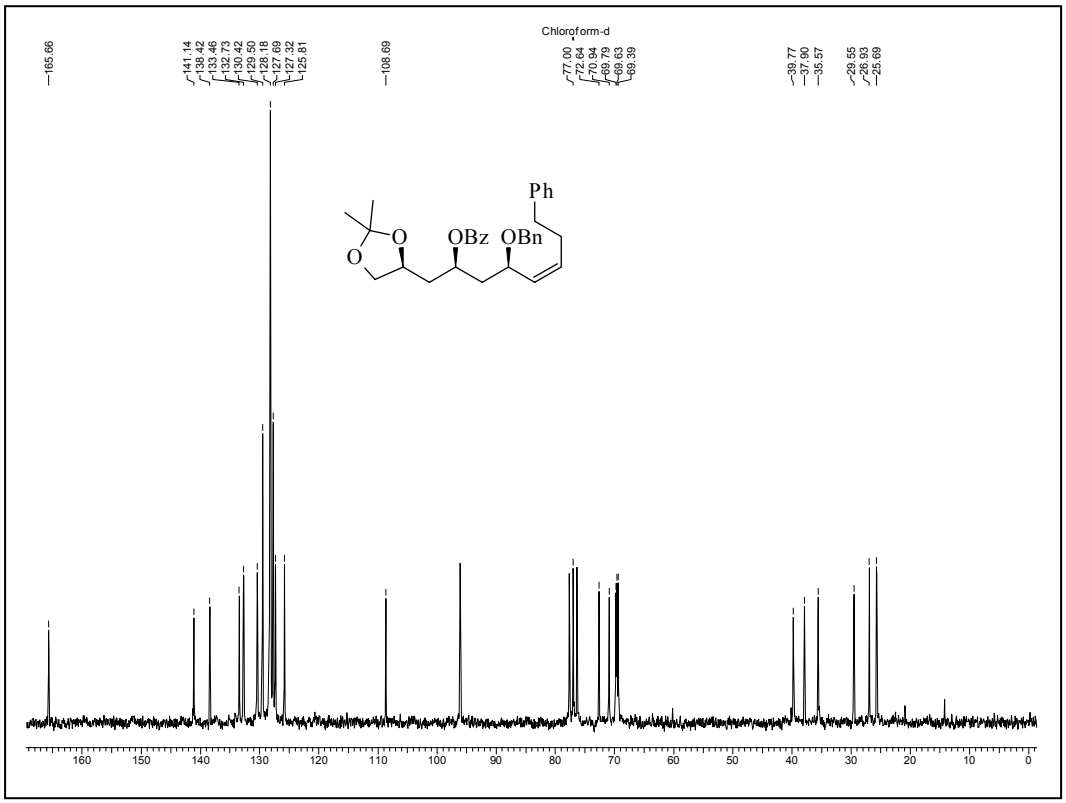
^{1}H NMR Spectrum of 143 in $CDCl_3$



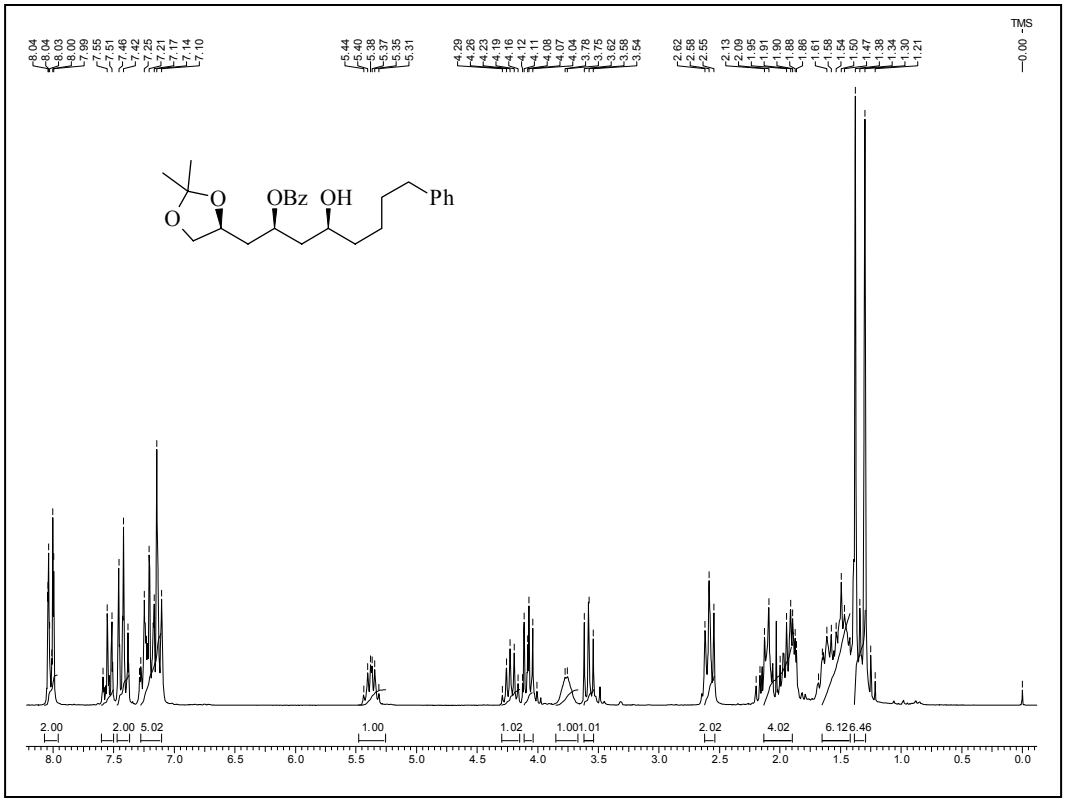
^{13}C NMR Spectrum of 143 in $CDCl_3$



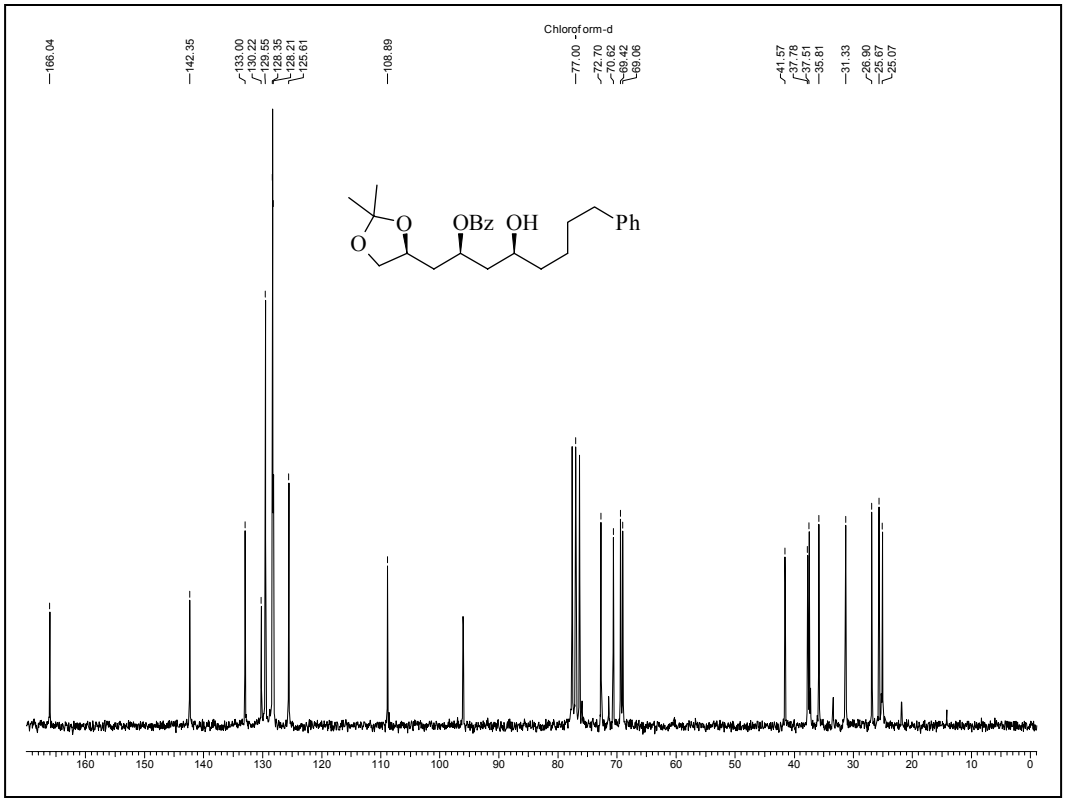
^{1}H NMR Spectrum of 144 in $CDCl_3$



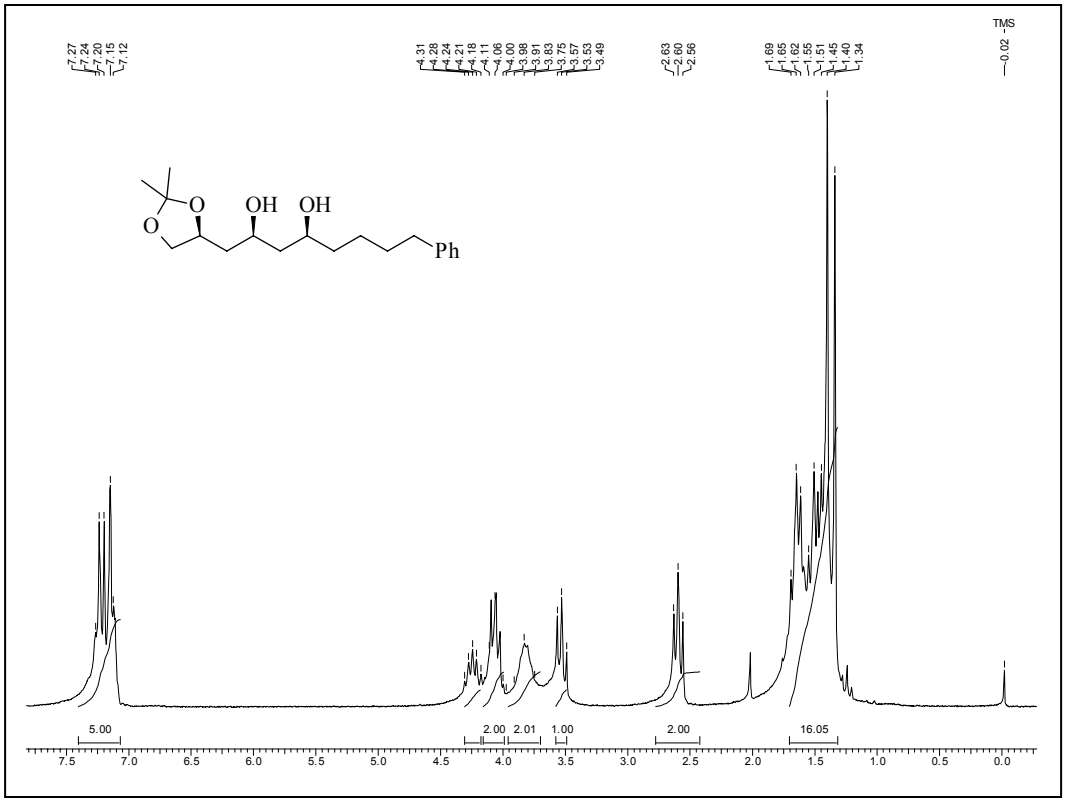
^{13}C NMR Spectrum of 144 in $CDCl_3$



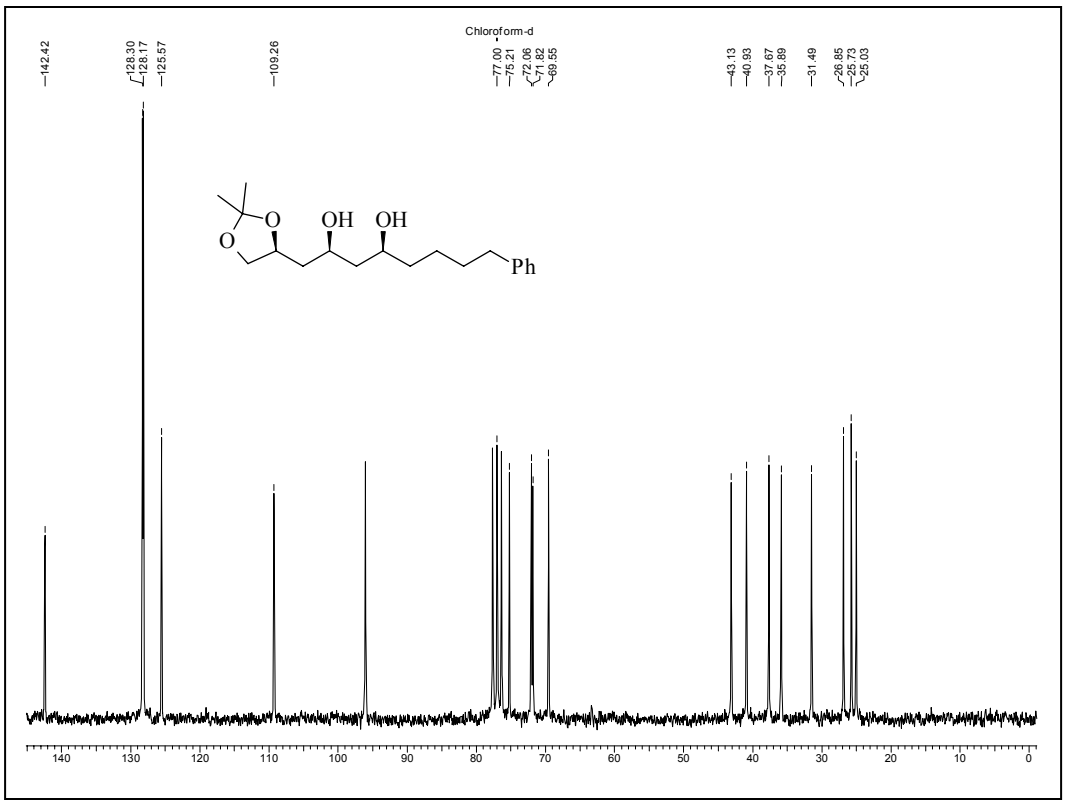
^{1}H NMR Spectrum of 145 in $CDCl_3$



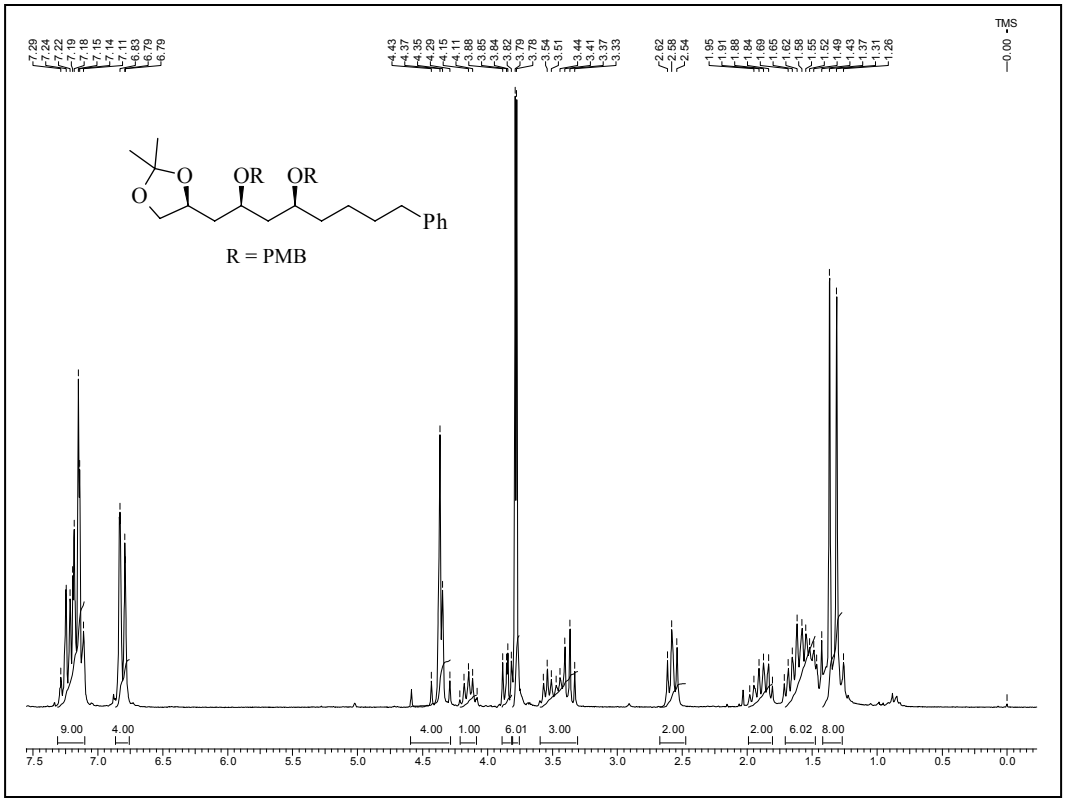
^{13}C NMR Spectrum of 145 in $CDCl_3$



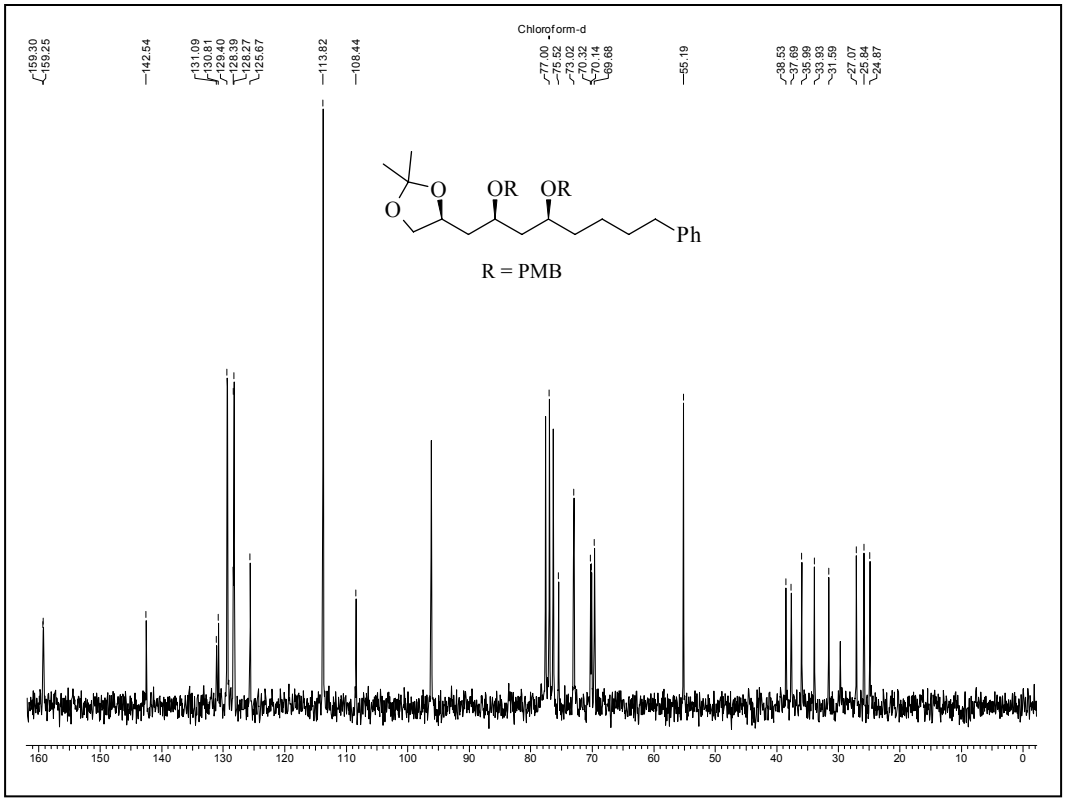
^{1}H NMR Spectrum of 132 in $CDCl_3$



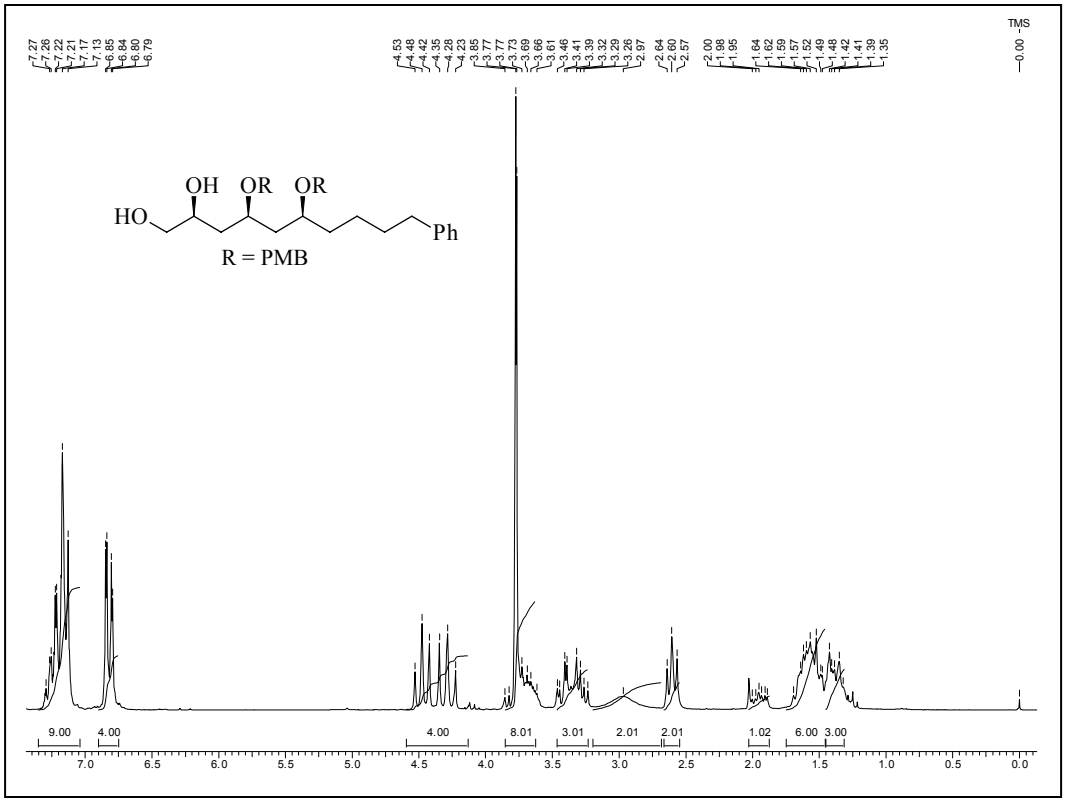
^{13}C NMR Spectrum of 132 in $CDCl_3$



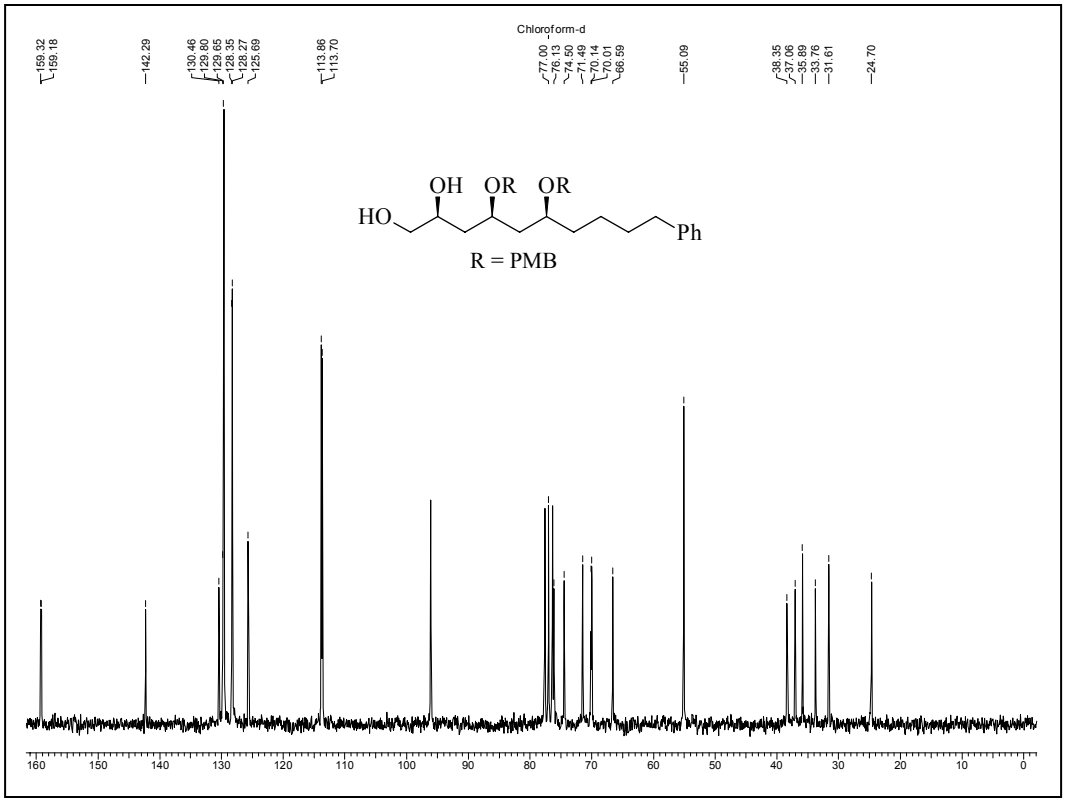
^{1}H NMR Spectrum of 146 in $CDCl_3$



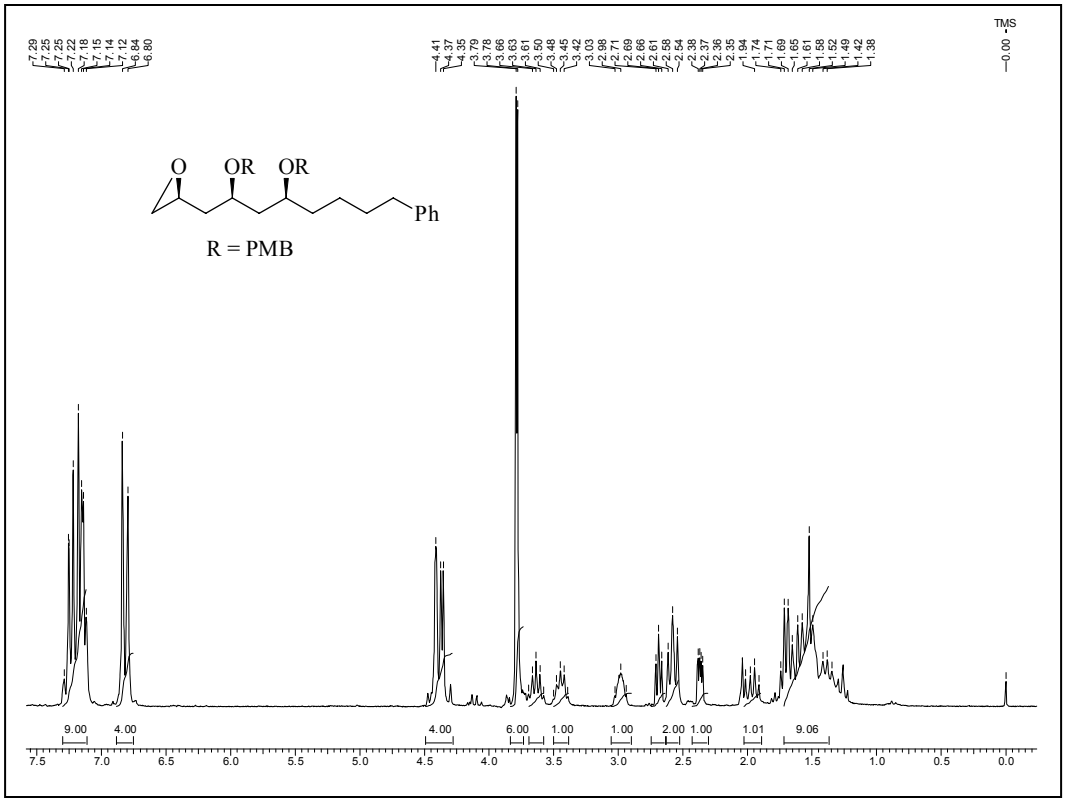
^{13}C NMR Spectrum of 146 in $CDCl_3$



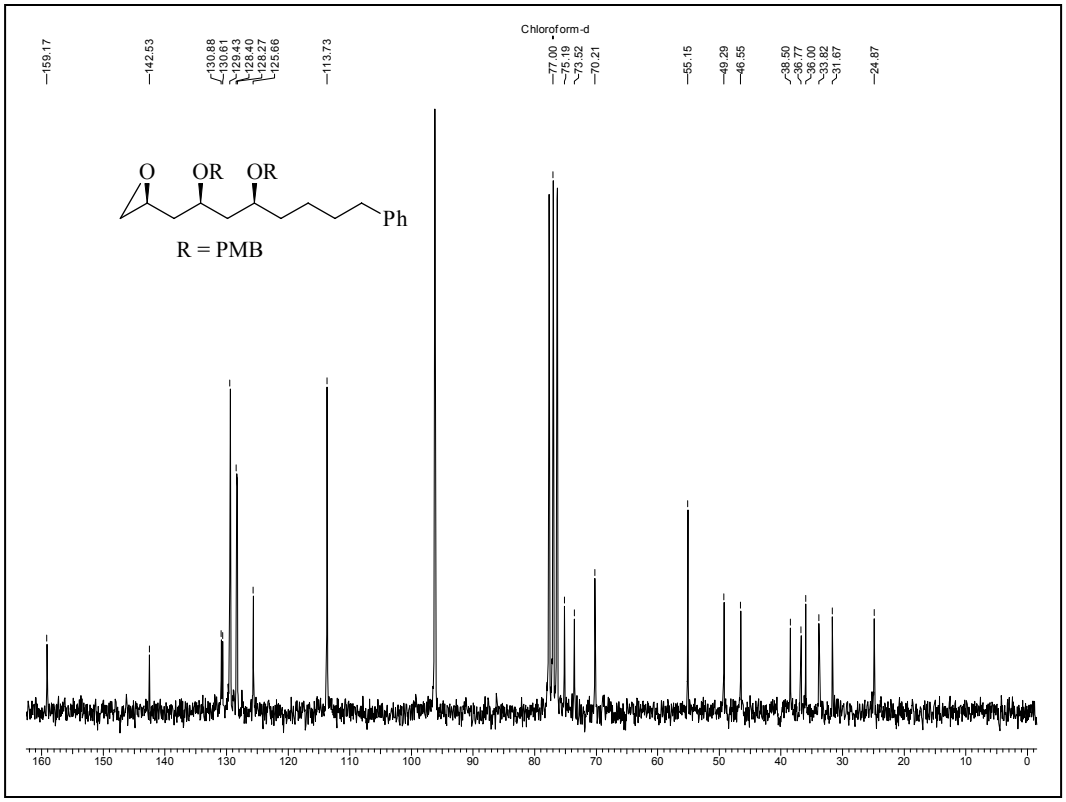
^{1}H NMR Spectrum of 147 in $CDCl_3$



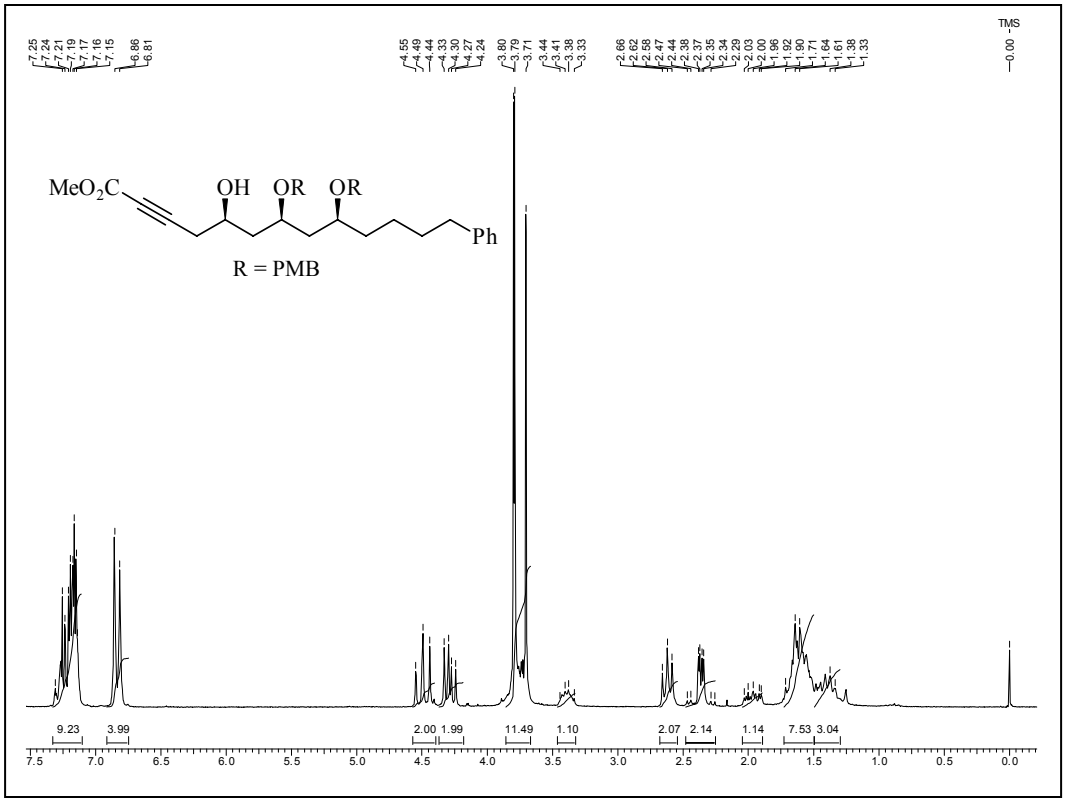
^{13}C NMR Spectrum of 147 in $CDCl_3$



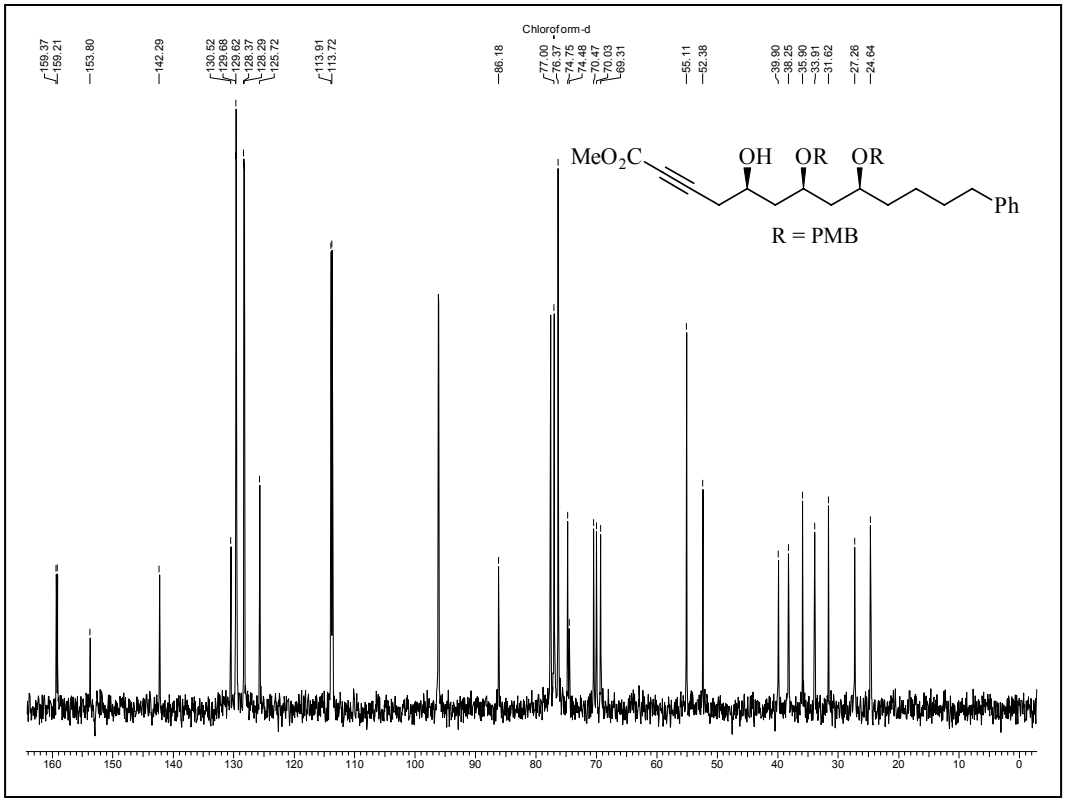
^{1}H NMR Spectrum of 131 in $CDCl_3$



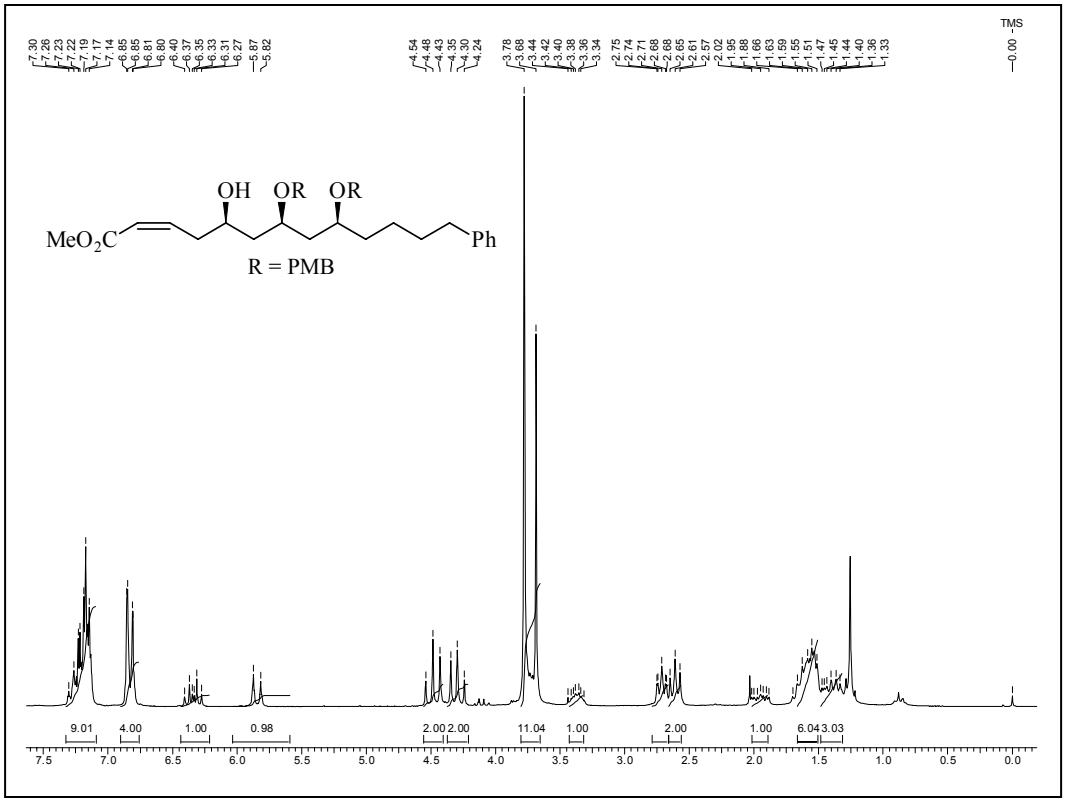
^{13}C NMR Spectrum of 131 in $CDCl_3$



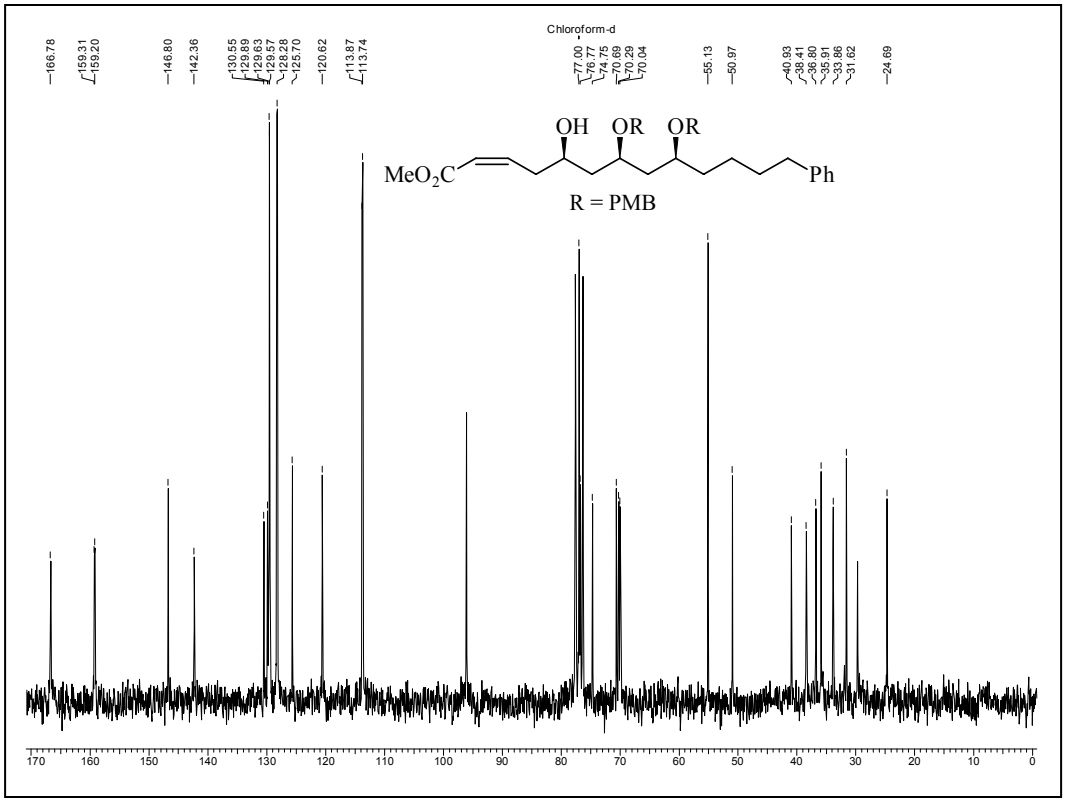
^{1}H NMR Spectrum of 148 in $CDCl_3$



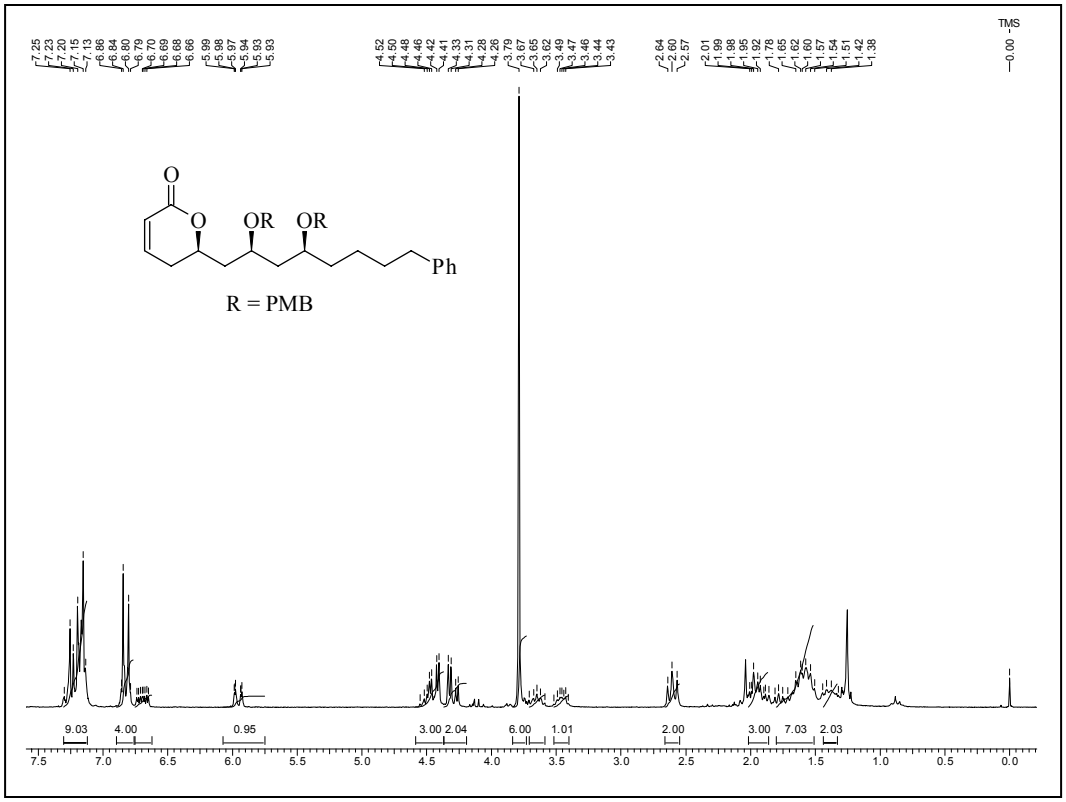
^{13}C NMR Spectrum of 148 in $CDCl_3$



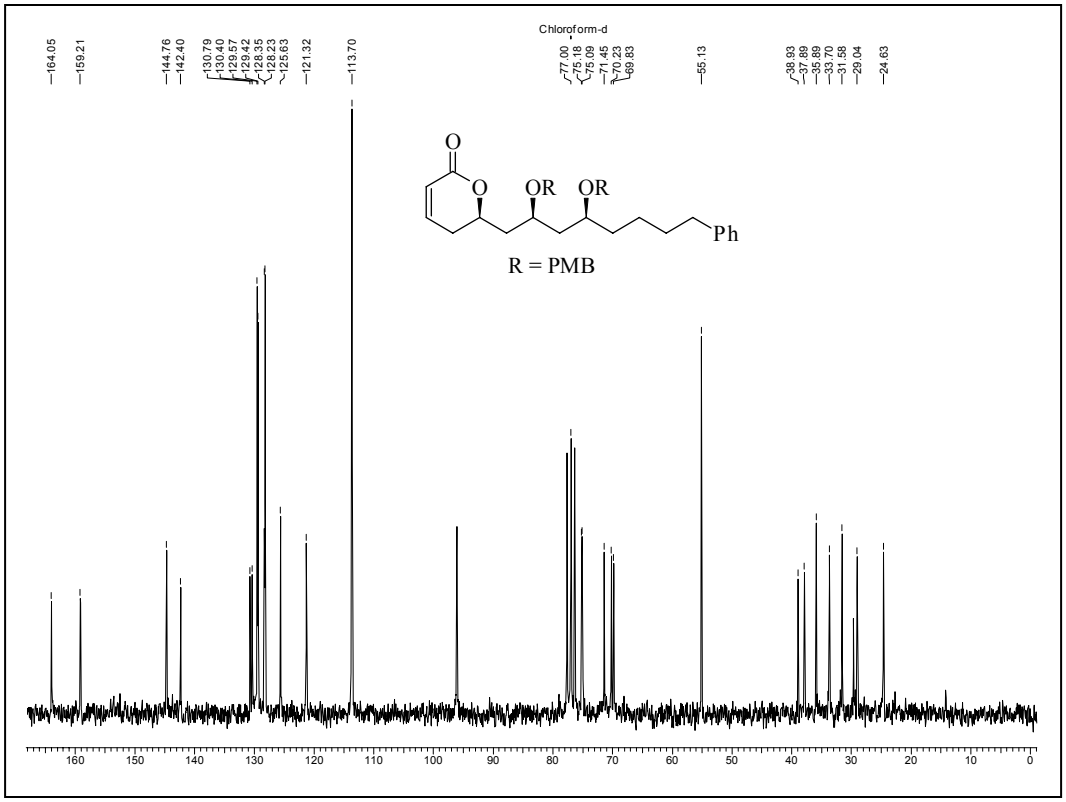
^{1}H NMR Spectrum of 149 in $CDCl_3$



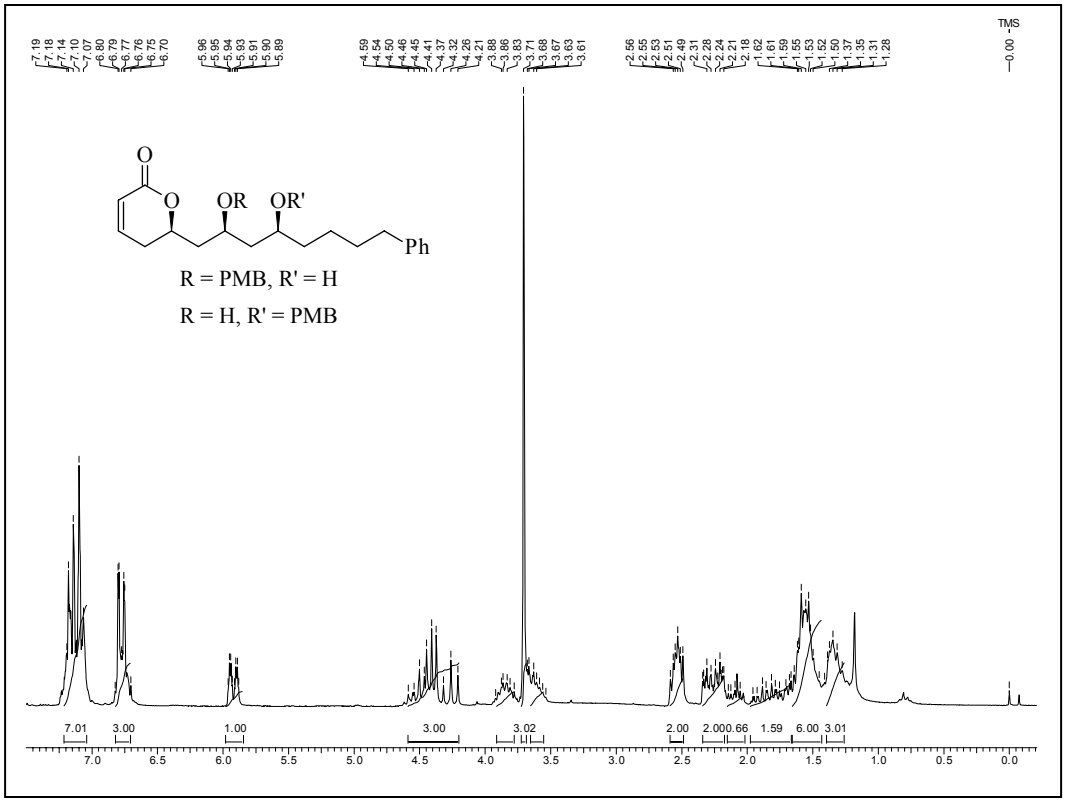
^{13}C NMR Spectrum of 149 in $CDCl_3$



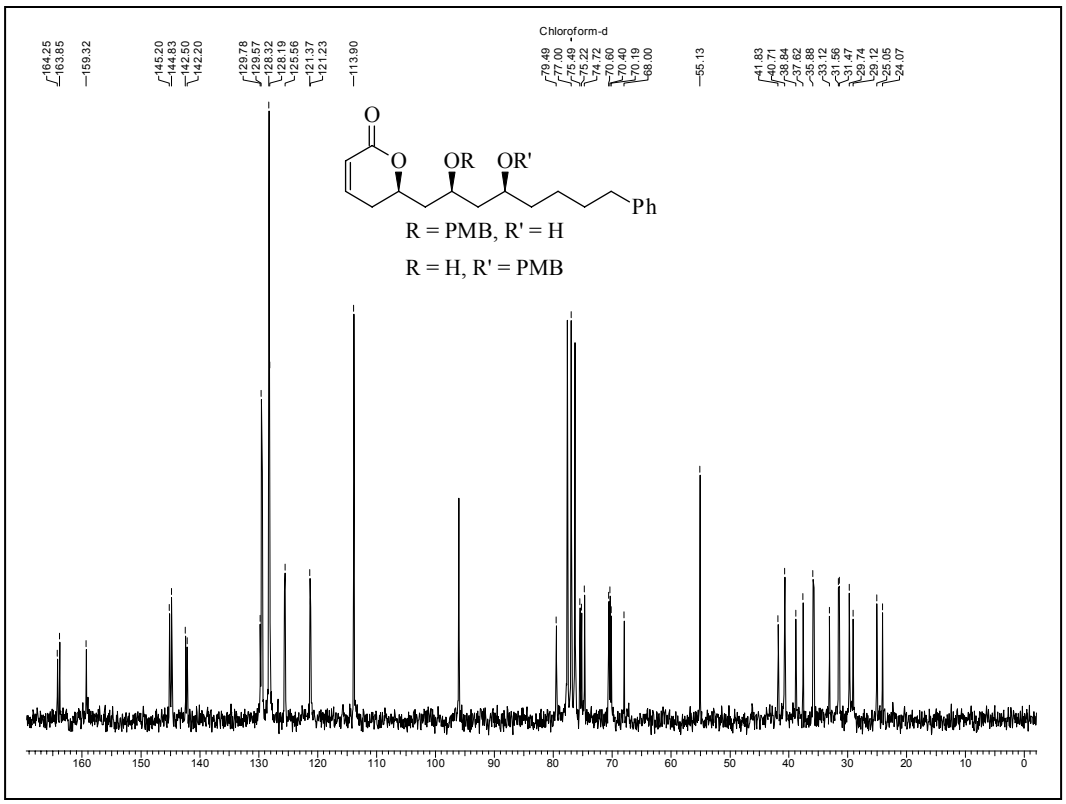
^{1}H NMR Spectrum of 150 in $CDCl_3$



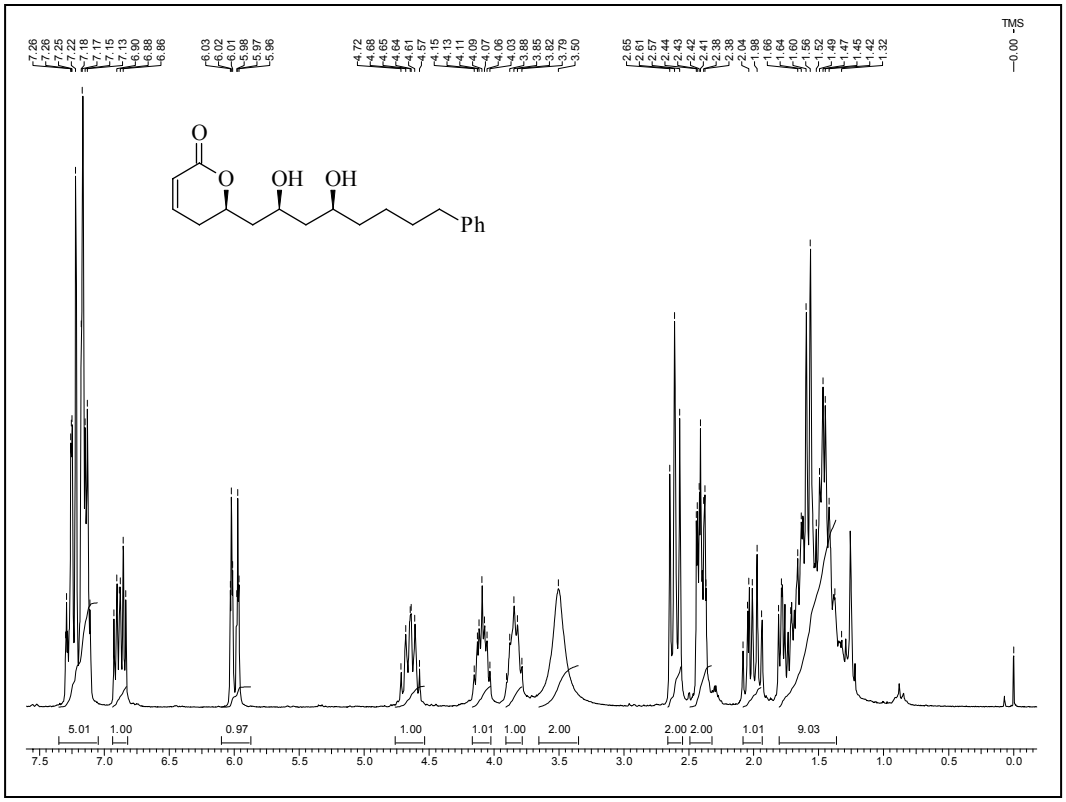
^{13}C NMR Spectrum of 150 in $CDCl_3$



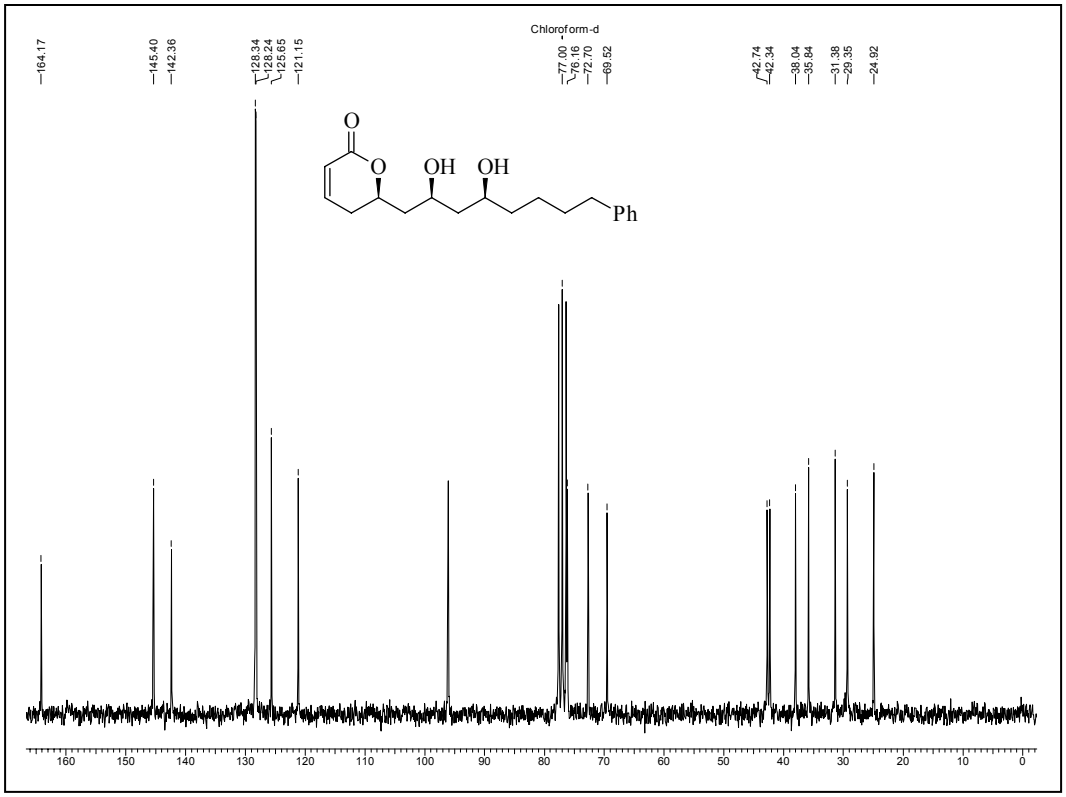
^{1}H NMR Spectrum of 151&152 in $CDCl_3$



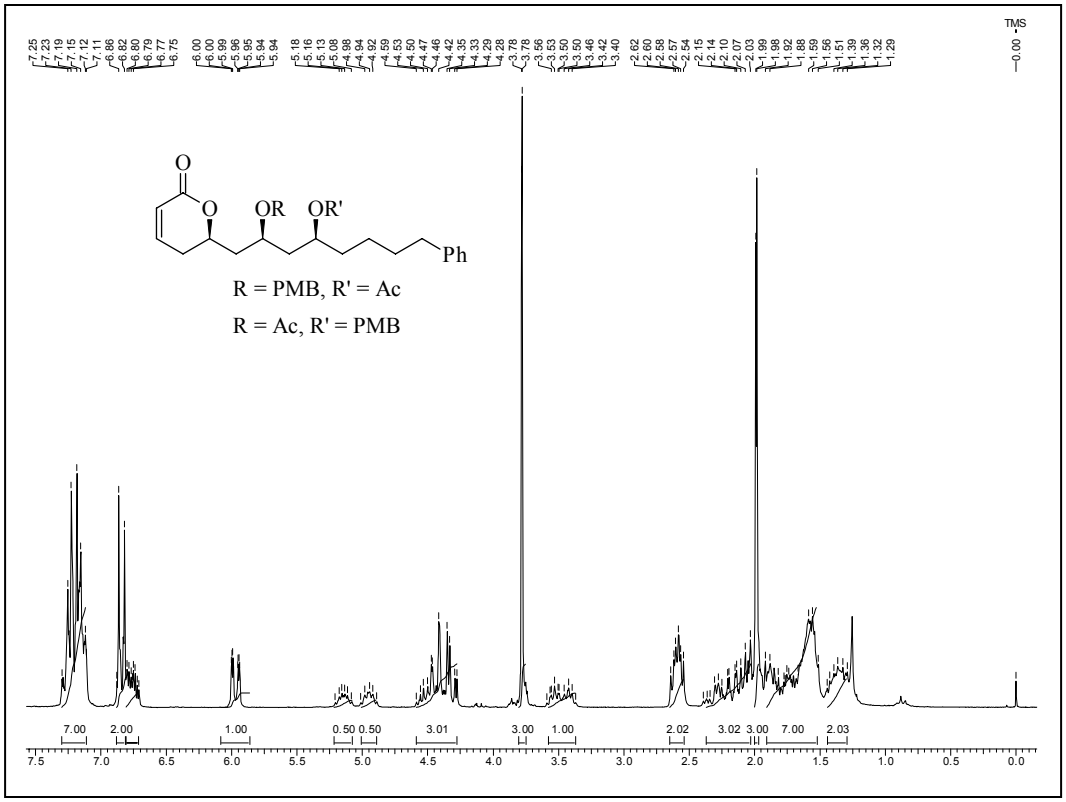
^{13}C NMR Spectrum of 151&152 in $CDCl_3$



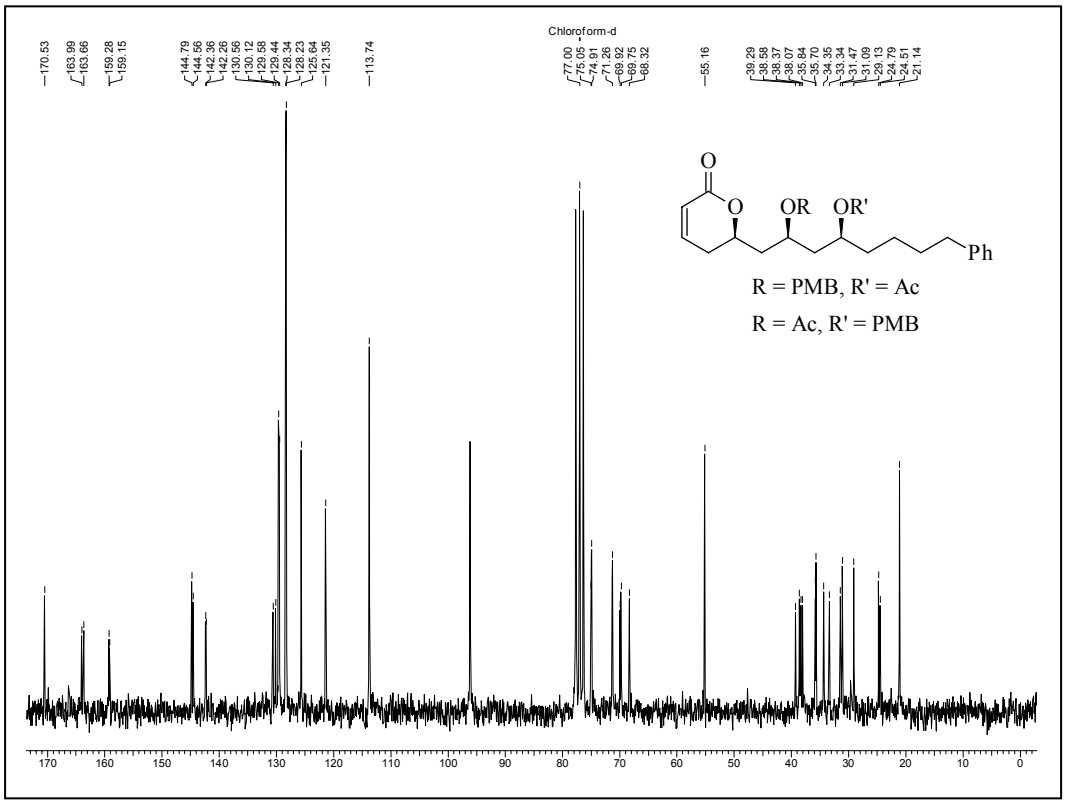
^{1}H NMR Spectrum of 153 in $CDCl_3$



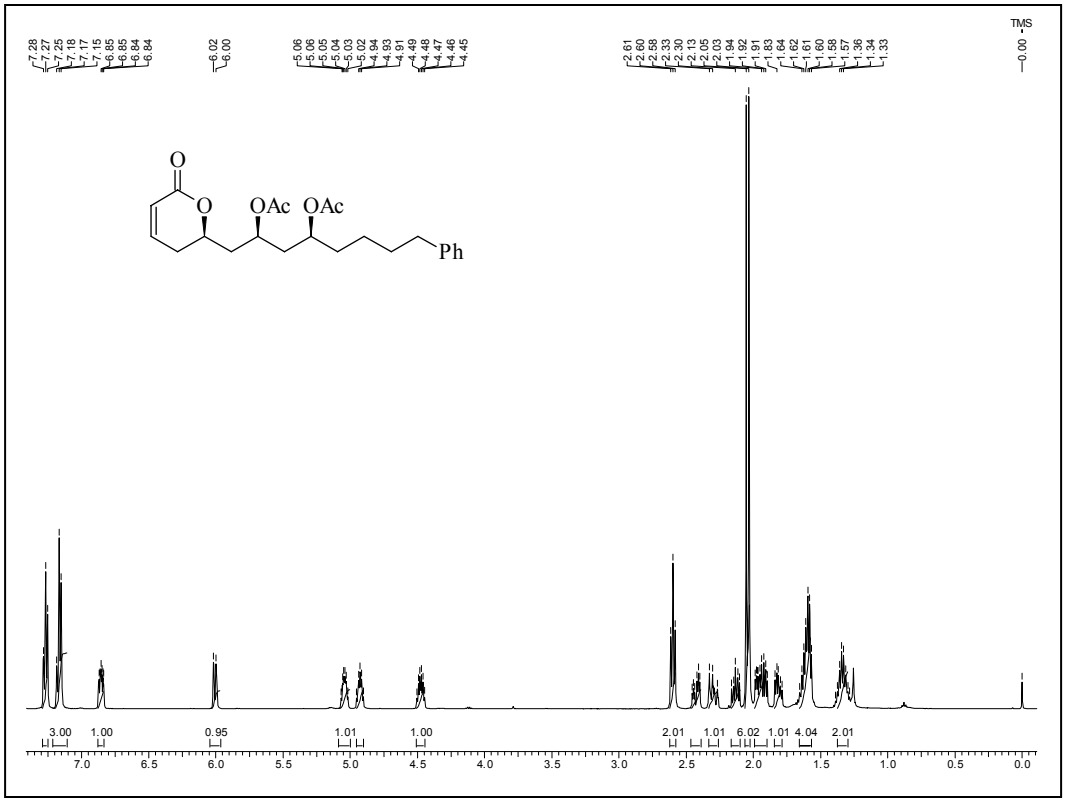
^{13}C NMR Spectrum of 153 in $CDCl_3$



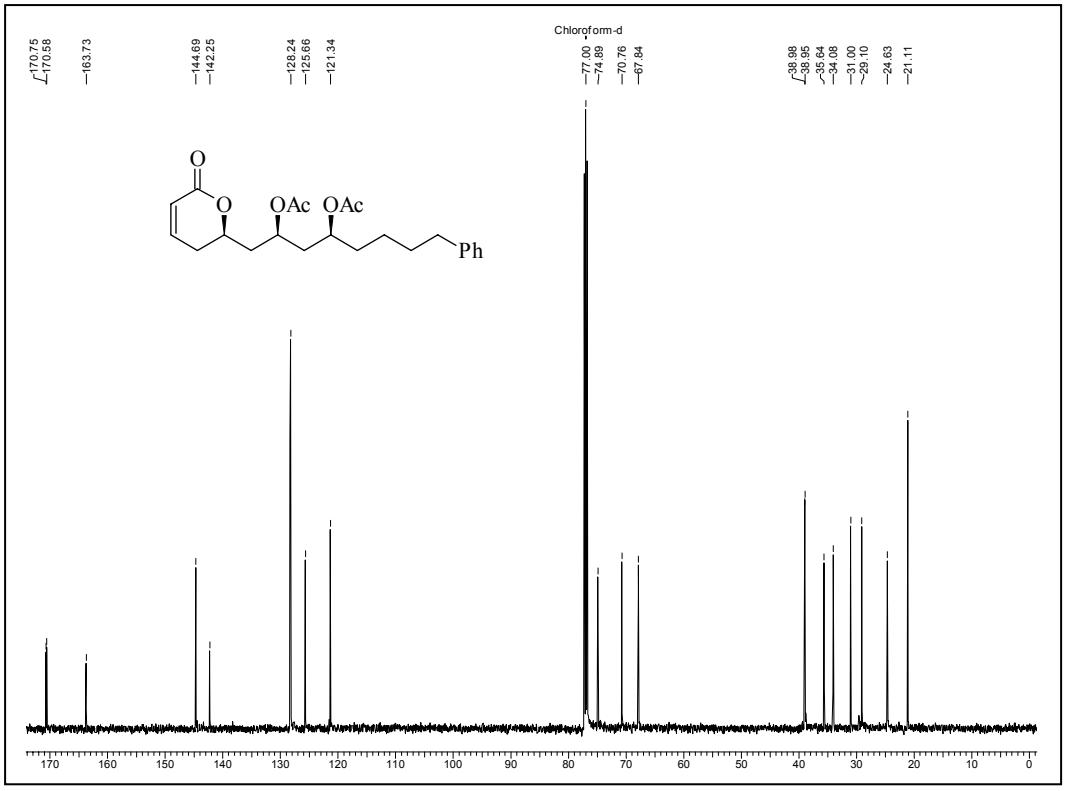
^{1}H NMR Spectrum of 155&156 in $CDCl_3$



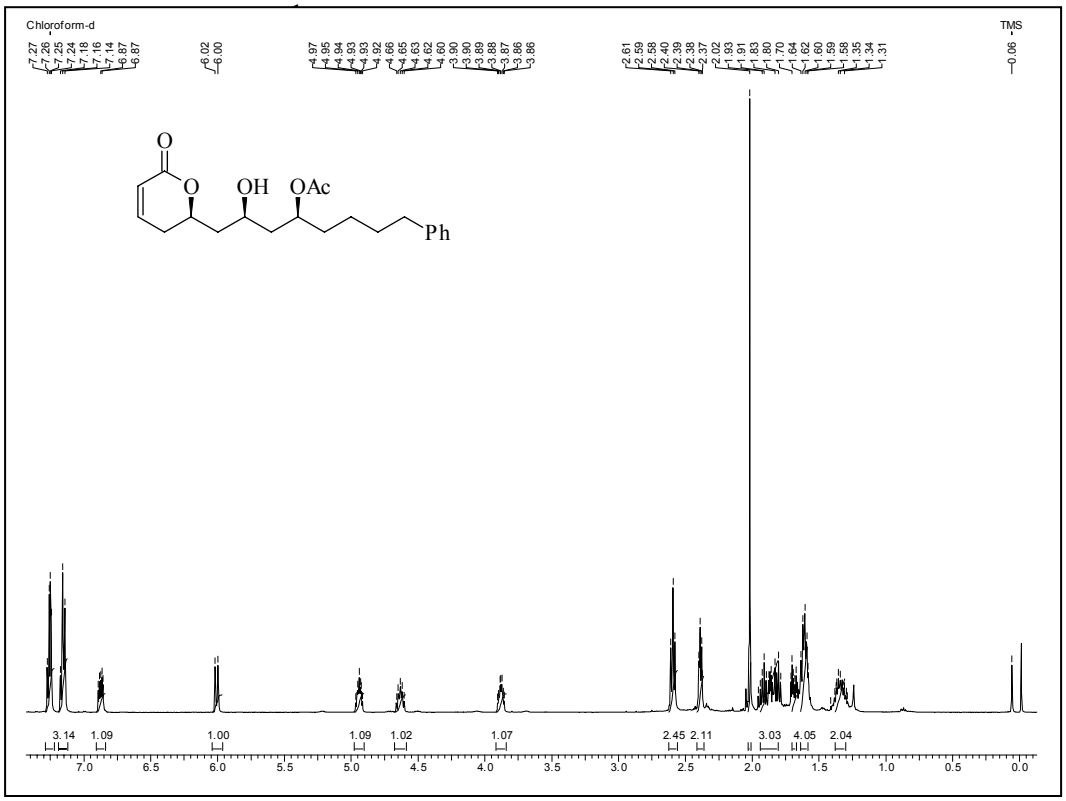
^{13}C NMR Spectrum of 155&156 in $CDCl_3$



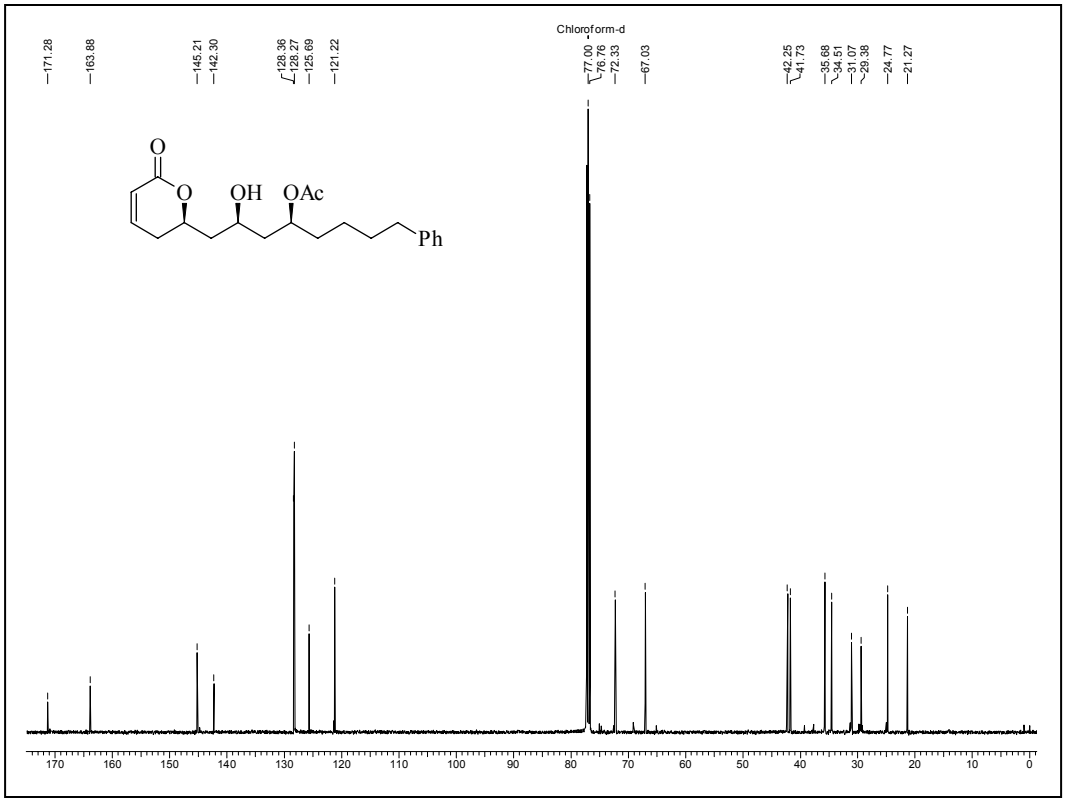
^{1}H NMR Spectrum of 154 in $CDCl_3$



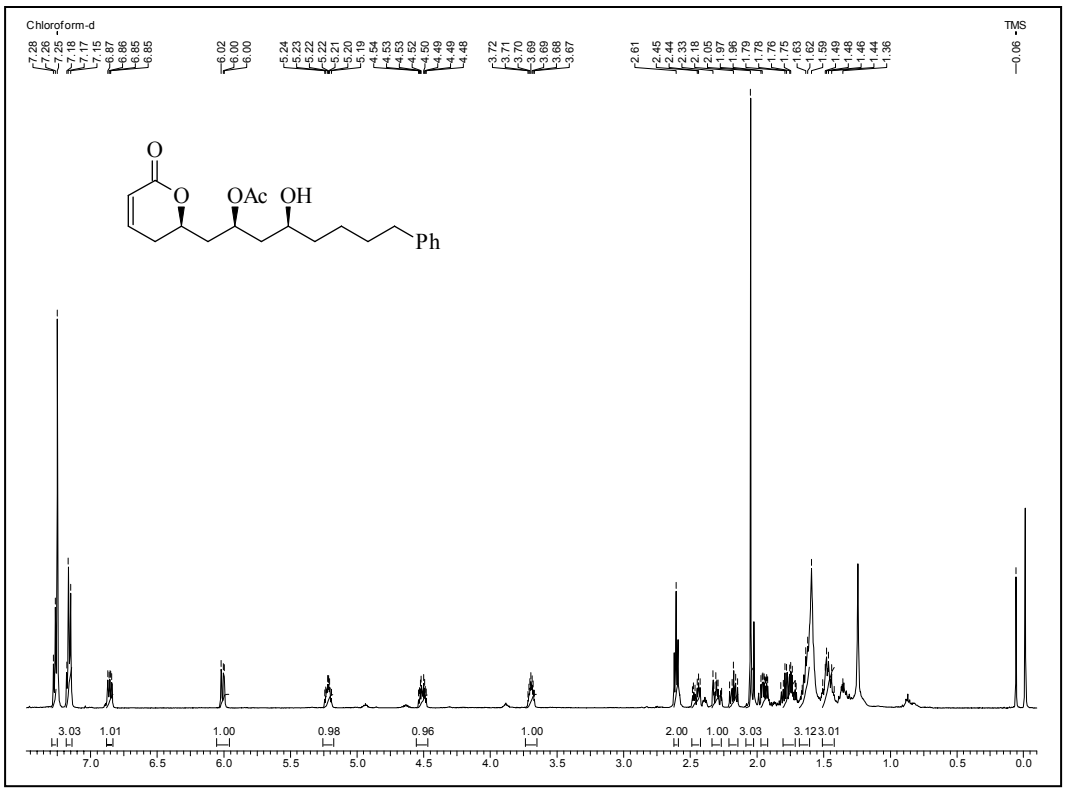
^{13}C NMR Spectrum of 154 in $CDCl_3$



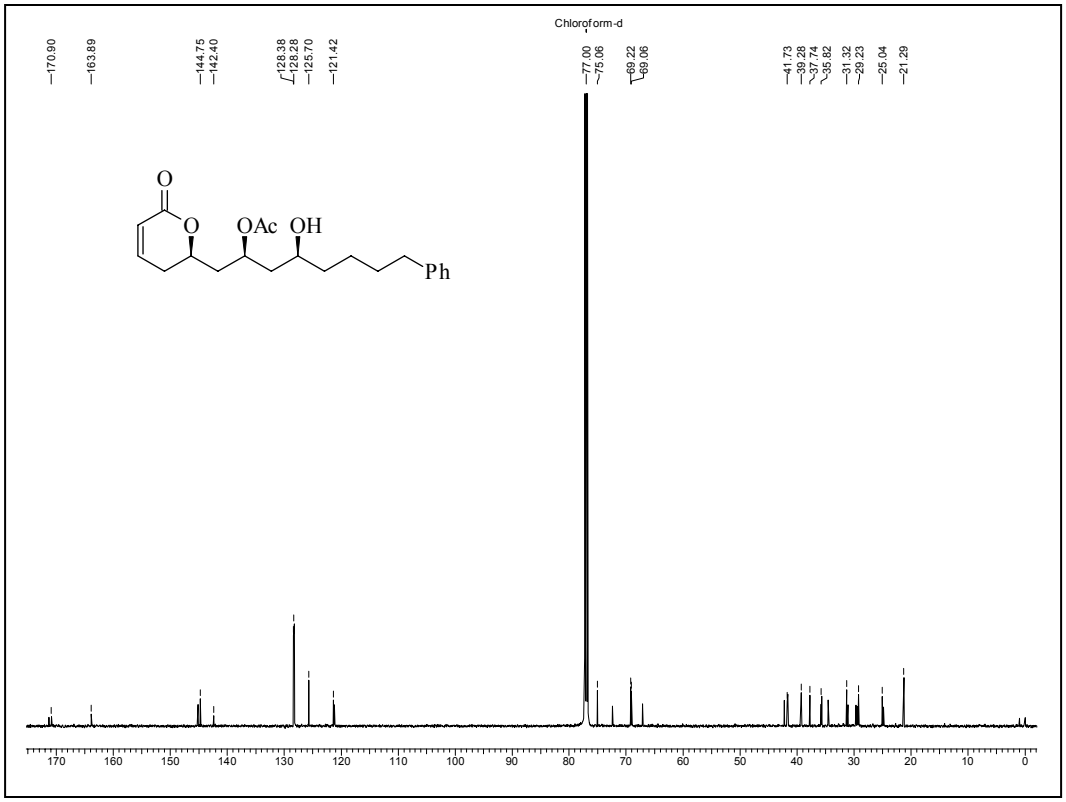
^{1}H NMR Spectrum of 128 in $CDCl_3$



^{13}C NMR Spectrum of 128 in $CDCl_3$



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



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

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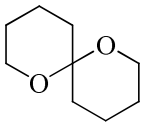
Chapter II

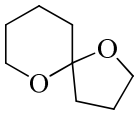
Total Synthesis of Aculeatin D and 6-*epi*-Aculeatin D

Introduction

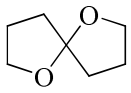
Spiroketals enjoy widespread occurrence as substructures of naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine organisms.[1] There is a wide range of structural complexity ranging from the relatively simple fly pheromones to the intricate frameworks of the polyether antibiotics and the spiroketal macrolides. Several of these have potent pharmacological activity. Three common spiroketal ring systems are known (Figure 1).[2]



1,7-Dioxaspiro[5.5]undecane



1,6-Dioxaspiro[4.5]decane



1,6-Dioxaspiro[4.4]nonane

Figure 1: *Representative spiroketal ring systems*

In several cases, the spiroketal structure itself is directly associated with the biological activity. Some representative biologically active natural products containing the spiroketal motif were given in Figure 2 where this empirically privileged substructure has been shown to bind to multiple classes of biological targets.[2a,3] Talaromycin (**1**) is a small spiroketal natural product that is a potent mycotoxin. In addition, spiroketals represent an important class of insect pheromones, demonstrating the ability of even simple spiroketals to bind to biological receptors. For example, both enantiomers of Olean are produced by the female olive fly, but their chemo-attractant activities are gender-specific, with the *R*-enantiomer (**2**) active on males, and the *S*-enantiomer (**3**) active on females (Figure 2). The exocyclic spiroketal in the avermectin (**4**) class of anti-parasitic compounds exhibits a pronounced, narrow structure-activity relationship profile, indicating that it is likely the spiroketal unit directly involved in target binding. Calcimycin (**6**) has been shown to be an ionophore antibiotic. It selectively transports divalent cations, and has been used for specific perturbation of transmembrane Ca^{2+} gradients in complex systems such as cells.

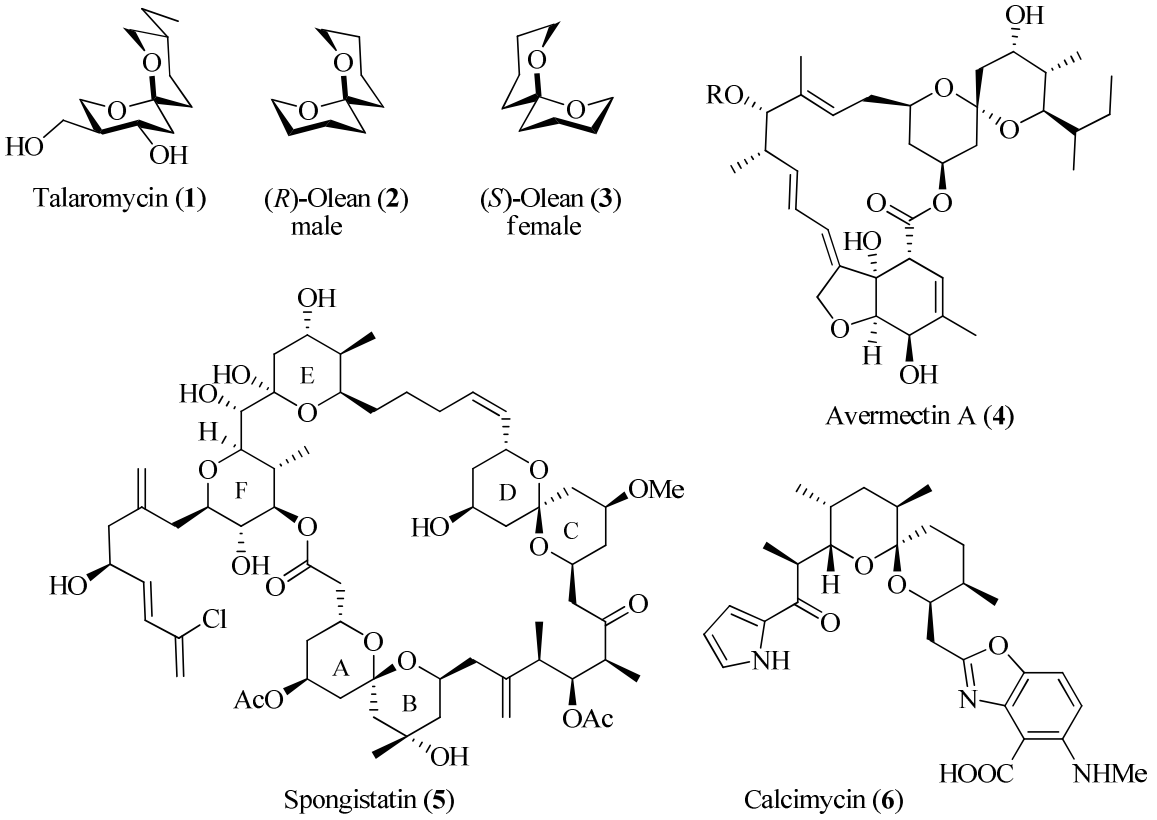


Figure 2: *Spiroketal-containing natural products*

There are several complex natural products that contain the spiroketal motif, where the role of spiroketal unit has been identified as rigid scaffolds that display substituents along various well-defined three-dimensional vectors.[4] For example, the spongistatins **5**, which inhibit tubulin protein-protein interactions. Although some reports indicate that simple spiroketal analogs of spongistatin exhibit activity of their own,[5] the main role of the spiroketal motif in these natural products is likely to act as a rigid scaffold to present complex sidechains along appropriate three-dimensional vectors.

The increasing pharmacological importance of compounds containing spiroketal assemblies has triggered intense interest in both their synthesis and chemical reactivity. This ascertained importance of spiroketals as valuable pharmacophore has attracted considerable attention in both target- and diversity-oriented synthesis.[6] In the latter context, spiroketals present an excellent opportunity to exploit stereochemical diversity,[7] wherein these rigid scaffolds can be used to display substituents along various well-

defined three-dimensional vectors. However, this concept has not been explored extensively, owing to the limitations of the existing synthetic approaches to spiroketals. In particular, there is still no general method to synthesize systematically stereodiversified spiroketals. Another important aspect in the chemistry of spiroketals is their stability and stereochemistry. These have been shown to be heavily influenced by the anomeric effect, which describes the preference of an electronegative substituent at C-1 of a tetrahydropyranal ring to adopt an axial orientation.

- **Conformational analyses of spiroketals**

The conformational analyses of spiroketals of 1,7-dioxaspiro[5.5]undecane system has been well documented in the literature, by virtue of its frequent occurrence. Studies by Deslongchamps[8] have determined that 1,7-dioxaspiro[5.5]undecane **7** exists exclusively in conformation $\mathbf{A_1}$ (Figure 3). This experimental observation has been explained by the fact that conformation $\mathbf{A_1}$ is stereoelectronically and sterically more stable than conformations $\mathbf{A_2}$ and $\mathbf{A_3}$ which were estimated to be less stable by a value of 2.4 and 4.8 Kcal/mol, respectively.

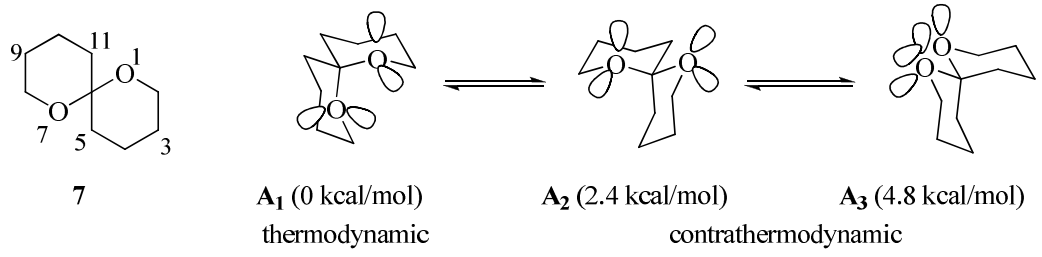


Figure 3: *Relative energies of the three possible chair-chair conformations of 7*

Spiroketals are readily formed by the acid-catalyzed convergence of two tethered alcohols onto a central ketone. During this process, only a single spiroacetal conformation is formed i.e conformer $\mathbf{A_1}$. Conformer $\mathbf{A_1}$ can be considered a *thermodynamic* spiroketal due to the existence of two anomeric stabilizing interactions wherein both acetal oxygen atoms have a set of lone pairs able to mutually donate into the C-O σ* of the other oxygen. Conformers $\mathbf{A_2}$ and $\mathbf{A_3}$, which are not formed under

these conditions, can be considered *contrathermodynamic* spiroketals because they lack atleast one anomeric stabilizing effect.

The formation of contrathermodynamic spiroacetals is generally disfavored on stereoelectronic and steric grounds.[8] Therefore; it is not surprising that there is no general method for forming contrathermodynamic spiroacetals. Hence, a method in which either desired spiroacetal could be generated selectively would constitute an important advance in this area.

More recently, the isolation and characterization of natural products possessing contrathermodynamic spiroketal motifs added new challenges for synthetic organic chemists. Representative examples are the ABCD subunit of azaspiracid 1 (**8**), spirofungin A (**14**), AB subunit of the pectenotoxins (**9**–**12**), aplysiatoxin (**13**), and the CD subunit of spongistatin 1 (**5**) (Figure 4).[9]

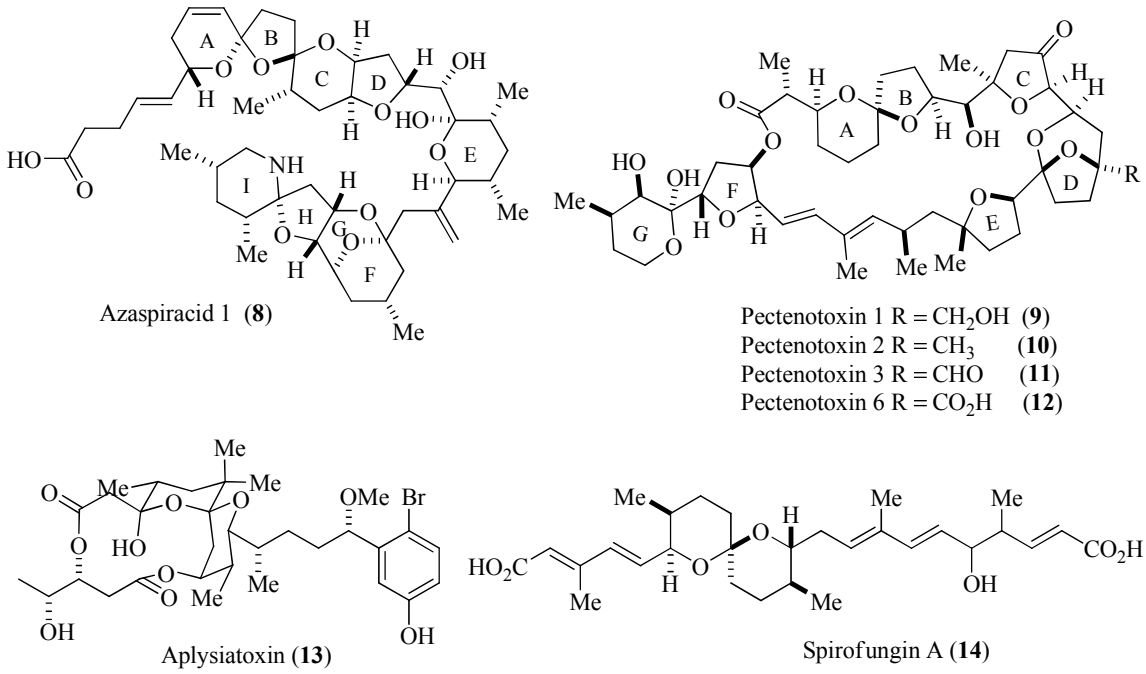


Figure 4: *Contrathermodynamic spiroketal motifs in natural products*

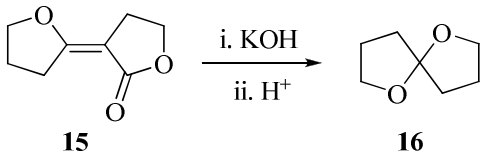
A unique feature of these natural products (Figure 4) is the presence of a partially anomerically stabilized spiroketal unit. To date, most synthetic methods rely on acid catalyzed cyclisation to access these motifs, leading to a thermodynamic mixture favoring

the undesired thermodynamic product. While lacking the energetically favorable double anomeric stabilization, the contrathermodynamic CD spiroketal fragment of spongistatin 1 (**5**) is presumed to be stabilized by an intramolecular hydrogen bond between the C-25 hydroxyl and the spiroketal oxygen atom. This postulated interaction has been the inspiration behind many attempts to synthesize this moiety with the desired contrathermodynamic configuration. The addition of divalent cations to the acid mediated epimerization was found to favor the desired spiroketal isomer over the fully anomerically stabilized spiroketal.[10]

Epimerization approaches have been demonstrated in a variety of systems allowing access to the contrathemodynamic configuration. However, without the stabilizing effects of a hydrogen bond, contrathermodynamic spiroketals such as the examples depicted in Figure 4, would be more difficult to access. The Rychnovsky group anticipates that the reductive cyclization approach would allow direct access to contrathermodynamic spiroketals under kinetically controlled conditions.

- **Spiroketal syntheses**

Spiroketals have been part of the synthetic literature for over a hundred years. The oldest reported spiroketal synthesis was performed by Rudolph Fittig in 1890.[11] Using a two step procedure, compound **15** was converted to racemic spiroketal **16** (Scheme 1).

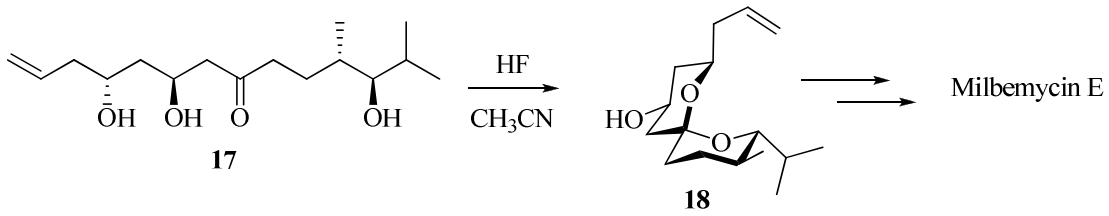


15 **16**

Scheme 1: Earliest reported spiroketal synthesis

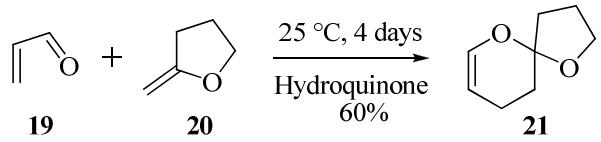
In a representative example of spiroketal synthesis, Merrifield and coworkers in 1987 utilized HF to induce spirocyclization followed by acid equilibration to form a thermodynamically favored spiroketal, which was then elaborated to milbemycin E (Scheme 2). This allowed them to synthesize the single spiroketal diastereomer that was found in the natural product, which was predicted to be the thermodynamically favored

diastereomer. This is a powerful approach when the target is significantly more stable than other potential diastereomers, however, this classical approach does not allow access to contrathermodynamic spiroketals, except through the separation of mixtures of spiroketals.

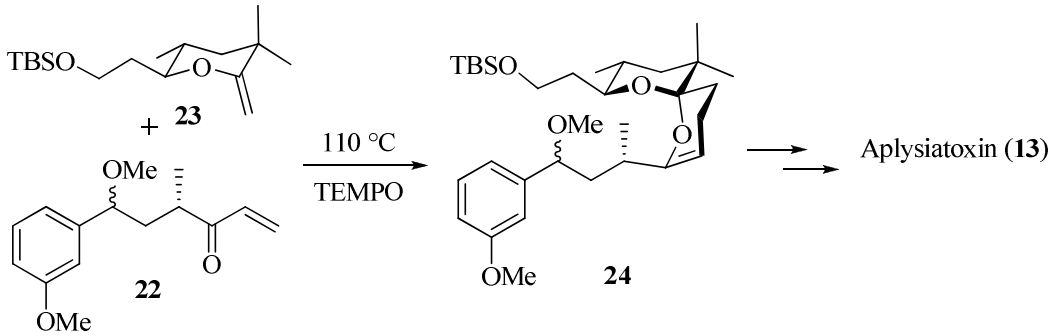


Scheme 2: Classic acid-catalyzed spirocyclization and equilibration

Another approach to synthesizing spiroketals involves the use of a hetero Diels-Alder cycloaddition strategy. This technique was first utilized in Paul and Tchelitcheff's synthesis of spiroketal (**21**), which was later repeated by Ireland, who improved the yield to 82% (Scheme 3).[12] This strategy was also used in other syntheses such as Ireland's synthesis of aplysiatoxin (**13**) (Scheme 4).[13]

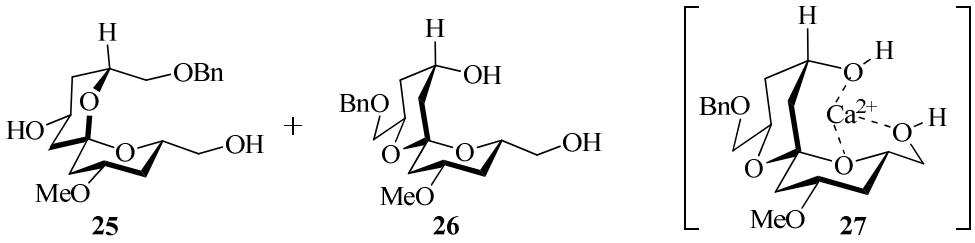


Scheme 3: Early hetero Diels-Alder spirocyclization



Scheme 4: Hetero Diels-Alder approach to aplysiatoxin **13**

There have been several routes that involved setting up an equilibrium with metal salts or protecting group motifs that shift the equilibrium in the desired direction, and then separating the two diastereomers. An effective example of this type of cyclization was in Smith's synthesis of spongistatin (**5**).[14] Treatment of a 2:1 mixture of spiroketals **25** and **26** with $HClO_4$ provided a 1:1 ratio of **25** to **26**. However, when $Ca(ClO_4)_2$ was included in the reaction, the equilibrium shifted to 1:9 of **25** to desired spiroketal **26**. They proposed that the calcium was chelated by the oxygens **27** as shown in Scheme 5, stabilizing that stereoisomer of spiroketal.

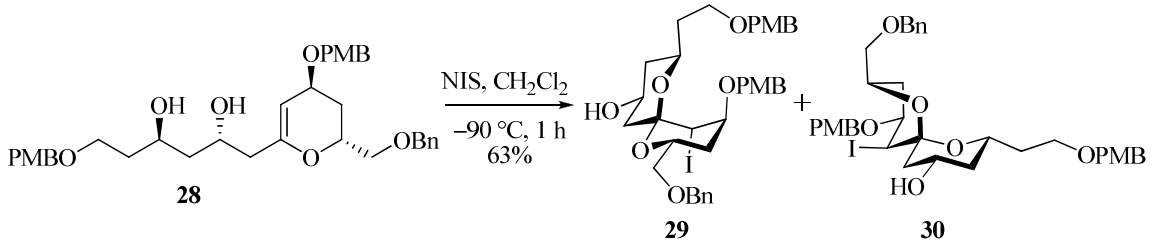


Scheme 5: Calcium chelation and equilibration leading to spiroketal **26**

- **Spirocyclization reactions to provide contrathermodynamic spiroketals**

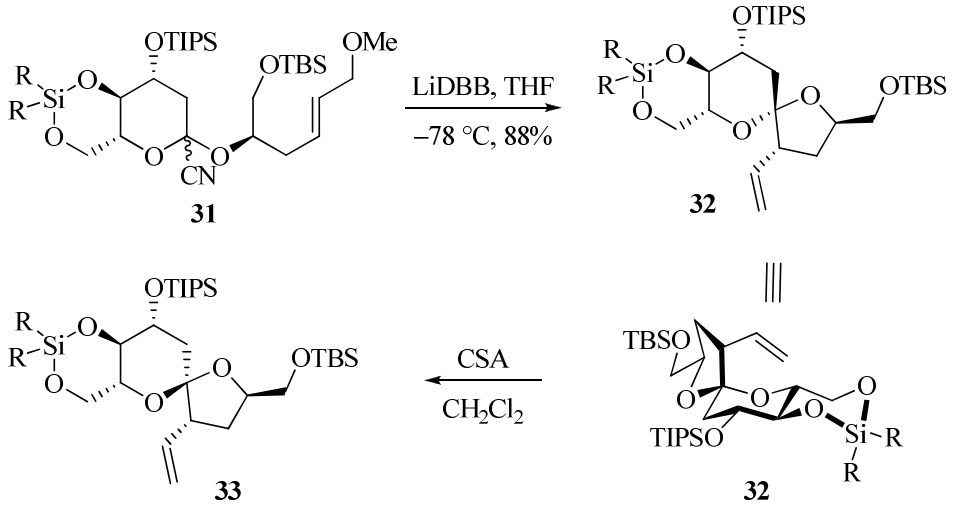
Several kinetic spirocyclization reactions have been developed to provide stereocontrolled access to contrathermodynamic spiroketals, particularly those stabilized by only one anomeric effect. However, these are usually limited by dependence upon spirocyclization of an oxygen nucleophile along an axial trajectory.[15,16] As a result, these thermodynamic and kinetic reactions are not fully stereocomplementary.

Roush and co-workers developed an iodo-spiroketalization reaction (Scheme 6),[16] where treatment of glycal **28** with *N*-iodosuccinamide forms the iodonium *anti* to the C3-OPMB. Subsequent spirocyclization with inversion of configuration at C1 provided the spiroketal (**29**) with only single anomeric stabilization as the major product (8:1; **29**:**30**). However, it was never demonstrated that this spiroketal was not, in fact, the more thermodynamically stable diastereomer. Indeed, it is possible that the reaction proceeds through an oxonium intermediate, forming a kinetic mixture of products, and the *N*-iodosuccinamide utilized in the reaction may be capable of inducing equilibration of the spiroketal.



Scheme 6: Roush iodo-spiroketalization

A flexible spirocyclization strategy which formed contrathermodynamic spiroketals came from the Rychnovsky group.[17] They used a reductive cyclization of 2-cyanotetrahydropyrans using lithium di-*tert*-butyl biphenyl to generate several contrathermodynamic spiroketals. As shown in Scheme 7, several spiroketals were generated, each possessing one equatorial oxygen at the anomeric center. Importantly, the authors treated a representative spiroketal **32** with camphor sulfonic acid, and showed that it was equilibrated to a spiroketal with two axial oxygens at the anomeric center (**33**). This demonstrated that their approach provides a kinetic spiroketalization, which has the potential to form contrathermodynamic stereoisomers. The only limitation of this approach is that it depends on a stereoelectronically favored axial attack of a side chain electrophile.

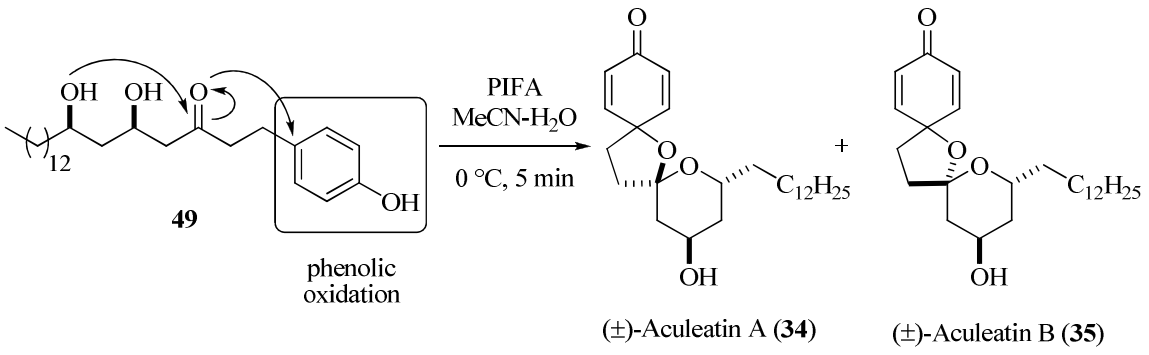


Scheme 7: Rychnovsky's route to contrathermodynamic spiroketals

- **Aculeatins: Natural products with unique 1,7-dioxa-dispiro[5.1.5.2]-9,12-dien-11-one tricyclic ring system:**

Aculeatins A – D (**34** – **37**, respectively) were isolated by Heilmann and co-workers from the petroleum ether extracts of the rhizomes of *Amomum aculeatum*.[18] Common to all four metabolites is the presence of a unique 1,7-dioxa-dispiro[5.1.5.2]-9,12-dien-11-one tricyclic ring system, which is without precedent in the literature. This structural novelty taken together with the promising biological activity, aculeatins A–D aroused substantial interest culminating in several total syntheses.[19–23]

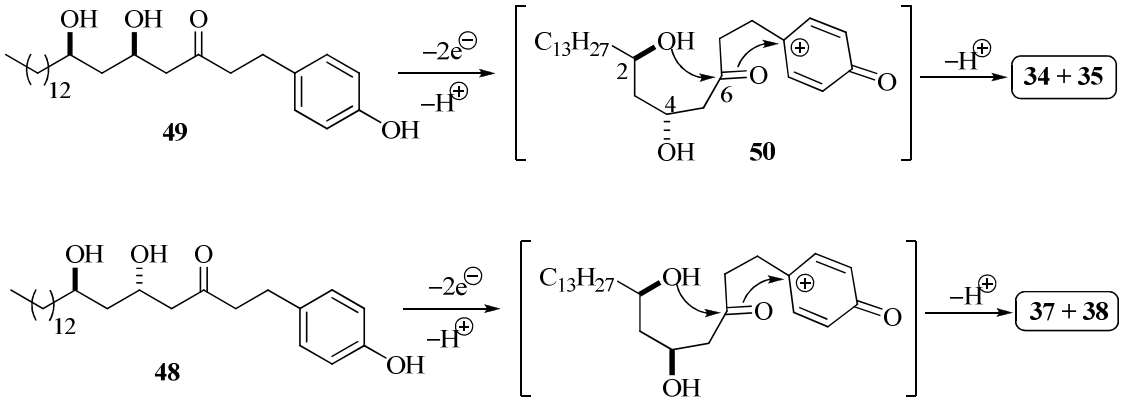
Considering the unique 1,7-dioxa-dispiro[5.1.5.2]-9,12-dien-11-one tricyclic ring system present in aculeatins, one of the key reaction that has been developed in designing synthesis of the generic aculeatin compound structure involves the biomimetic oxidative cyclisation cascade reaction to generate the tricyclic system of the natural product. Wong[19] has documented the first report in the area of aculeatins total synthesis by employing this as the key complexity transform and $PhI(O_2CCF_3)_2$ (PIFA) as the reagent of choice (Scheme 8). The initial success of this reaction has been accepted as the key disconnection approach in the syntheses of aculeatins reported later by several groups. The key retron used for this particular transform was a 1,3-diol-5-ketone and synthesis of which has been designated as the essence of various aculeatins total synthesis documented. In the context of objective of the present chapter, i.e the total synthesis of aculeatin D, the summary of available total synthesis of aculeatins was restricted for the aculeatin D.



Scheme 8: Spiroketalization to the aculeatin A and B

- **Biomimetic synthesis of (±)-aculeatin D (Baldwin et al. 2005)**

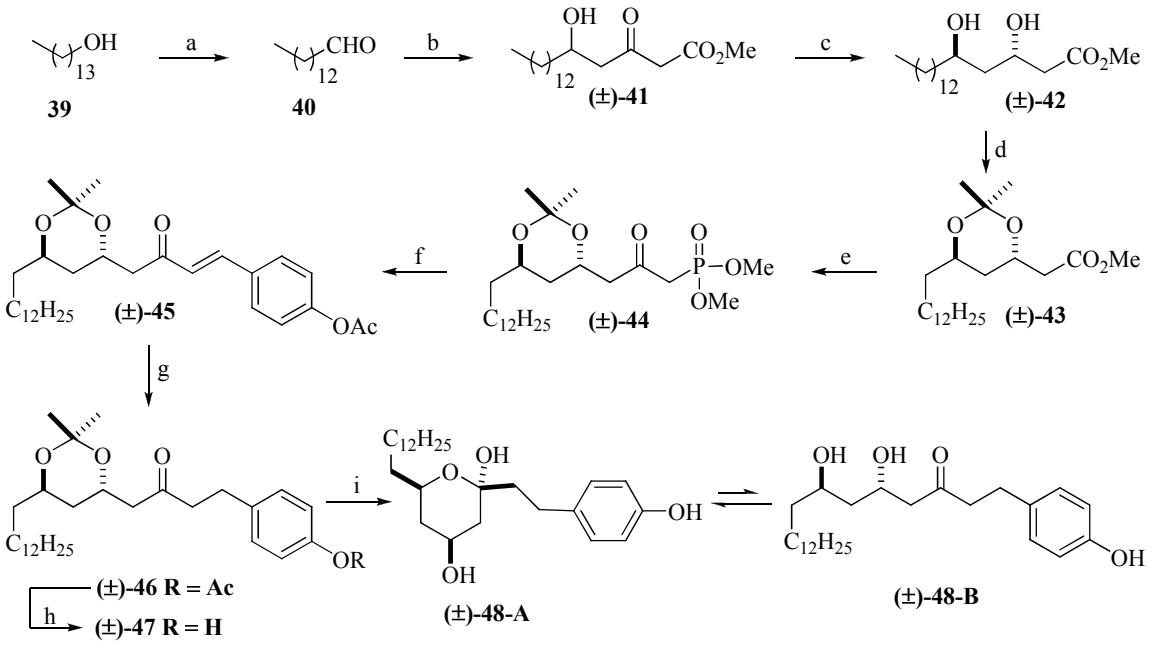
A practical, efficient and diastereoselective synthesis of the cytotoxic and antiprotozoal compound aculeatin D (**37**) is described by Baldwin et al.,[20] employing a biomimetic oxidative cyclisation cascade reaction to generate the tricyclic system of the natural product. A key consideration in designing a synthesis of the generic aculeatin compound structure involves a formal two-electron oxidation of the phenol ring in precursors **48** or **49** (Scheme 9) being followed by tandem cationic based intramolecular cyclisations, to generate the core tricyclic ring system in a single step from an open chain precursor. The oxidative double cyclisation of the *syn*-1,3-diol **49** would be expected to generate aculeatins A (**34**) and B (**35**), which would arise as the result of cyclisation of the C-2 hydroxyl group (aculeatin numbering) onto the *Re* and *Si* diastereotopic faces of the C-6 ketone group in intermediate **50** respectively. By analogy, the oxidative cyclisation of the *anti*-1,3-diol **48** would be expected to generate aculeatin D (**37**), as well as, potentially, the corresponding C-6 diastereoisomer (**38**).



Scheme 9: Biomimetic spiroketalization to the aculeatin class of compounds

Synthesis was started with the oxidation of commercially available 1-tetradecanol **39** using PCC to afford the corresponding aldehyde **40** (Scheme 10), then selective γ-alkylation of the dianion of methyl acetoacetate gave racemic alcohol (±)-**41** in good overall yield. Following the Evans' protocol, treatment of compound (±)-**41** with tetramethylammonium triacetoxyborohydride resulted in a chemo- and diastereoselective reduction of the ketone group resulting in formation of a 95:5 mixture of 1,3-*anti*-/1,3-

syn-diol products, and a single recrystallisation gave the pure 1,3-*anti* product (±)-**42** in excellent yield. Diol (±)-**42** was converted into the acetonide derivative (±)-**43**, followed by treatment with α-lithio methyl phosphonoacetate to give phosphonate (±)-**44**.



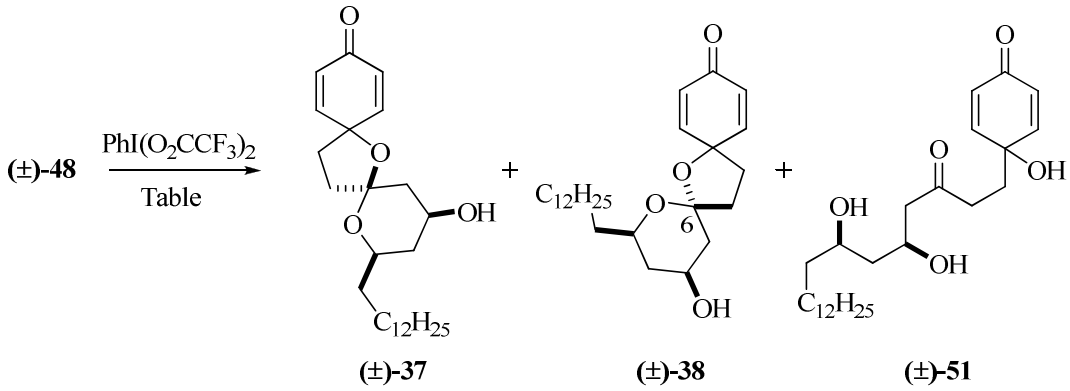
Scheme 10: Synthesis of anti-diol ketone

Reagents & Conditions: (a) PCC, DCM, rt, 2 h (85%); (b) methyl acetoacetate, NaH, THF, 0 °C, 10 min then *n*-BuLi, 0 °C, 10 min then **40**, 20 min (84%); (c) $Me_4NBH(OAc)_3$, MeCN/AcOH (1:1 v/v), –25 °C, 2 h then 0 °C, 3 h (89%); (d) 2,2-dimethoxypropane, CSA, 0 °C, 3 h (98%); (e) dimethyl methylphosphonate, *n*-BuLi, THF, –78 °C, 30 min then (±)-**43**, –78 °C, 20 min (65%); (f) NaH, THF, 0 °C→rt, 40 min then 4-acetoxybenzaldehyde, rt, 24 h (82%); (g) H_2 (1 atm), cat. Pd/C, EtOAc, rt, 16 h (76%); (h) K_2CO_3, MeOH, rt, 45 min (89%); (i) 0.5 M aq. HCl, THF, 0 °C→rt, 1 h (83%).

Wadsworth–Emmons olefination of phosphonate (±)-**44** with commercially available 4-acetoxybenzaldehyde proceeded efficiently at room temperature to afford alkene (±)-**45** in good yield (Scheme 10), and exclusively as the (*E*)-isomer. The palladium-catalysed hydrogenation of alkene (±)-**45** then afforded ketone (±)-**46**, and subsequent basic cleavage of the acetate group gave phenol (±)-**47**. The acetonide protecting group was then cleanly removed from ketone (±)-**47** under aqueous acidic

conditions. The product was formed as a white solid in good yield, and was shown to be the cyclic compound (±)-**48-A**. However, in solution this material was found to equilibrate to a mixture of cyclic compound (±)-**48-A** and the open chain derivative (±)-**48-B**; in deuterated acetone a 2:1 equilibrium mixture of compounds (±)-**48-A**:(±)-**48-B** was formed within 3 h at room temperature.

Treatment of ketone (±)-**48** with $PhI(O_2CCF_3)_2$ in MeCN at 0 °C led to the rapid consumption of the starting material, and the formation of two new products in moderate yield (Scheme 11), spectroscopic analysis revealed that these two compounds were tricyclic compounds (±)-**38** and ketone (±)-**51**. The next conditions attempted were the use of aqueous acetonitrile as the solvent for the oxidation of phenol (±)-**48**, however it did not produce any of the desired aculeatin D (±)-**37**, but instead merely increased the yield of ketone (±)-**51** (Table).



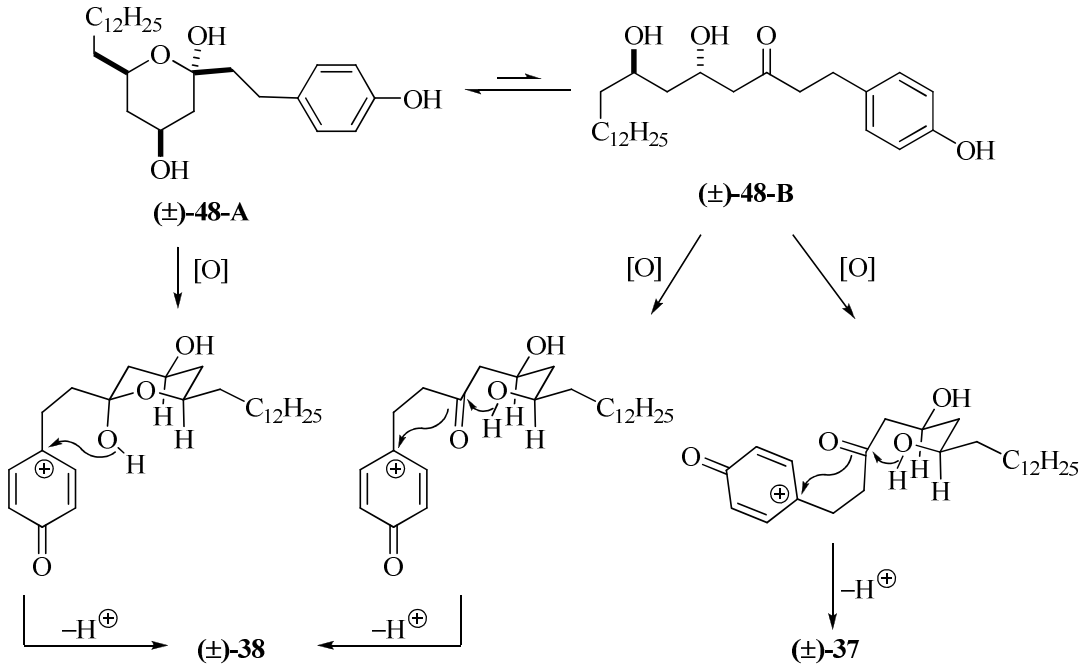
(±)-37 (±)-38 (±)-51

Conditions	Yield of (±)-37 (%)	Yield of (±)-38 (%)	Yield of (±)-51 (%)
MeCN, 0 °C, 1 h	0	33	15
MeCN/H_2O (6:1 v/v), 0 °C, 1 h	0	29	44
Acetone, rt, 20 min	11	40	20
Acetone/H_2O (9:1 v/v), rt, 20 min	19	43	27

Scheme 11: *Synthesis of* (±)*-aculeatin and 6-epimer*

After extensive variation of the reaction conditions, it was found that performing the oxidation in acetone resulted in the formation of an additional third product, isolated

in 11% yield, found to be the desired racemic aculeatin D (±)-**37** (Table). The relative stereochemistry of the spiroacetal ring system in (±)-**37** were confirmed by NOE analysis. Further optimization of reaction condition, it was found that using an acetone/water (9:1 v/v) solvent system for the reaction maximised the yield of aculeatin D (±)-**37** (18%), the proportion of the desired product (±)-**37** is ((±)-**37**:(±)-**38**:(±)-**51** 1.0:2.4:1.5) and also the overall yield of the reaction (88%).



Scheme 12: Mechanism of oxidative cyclisation

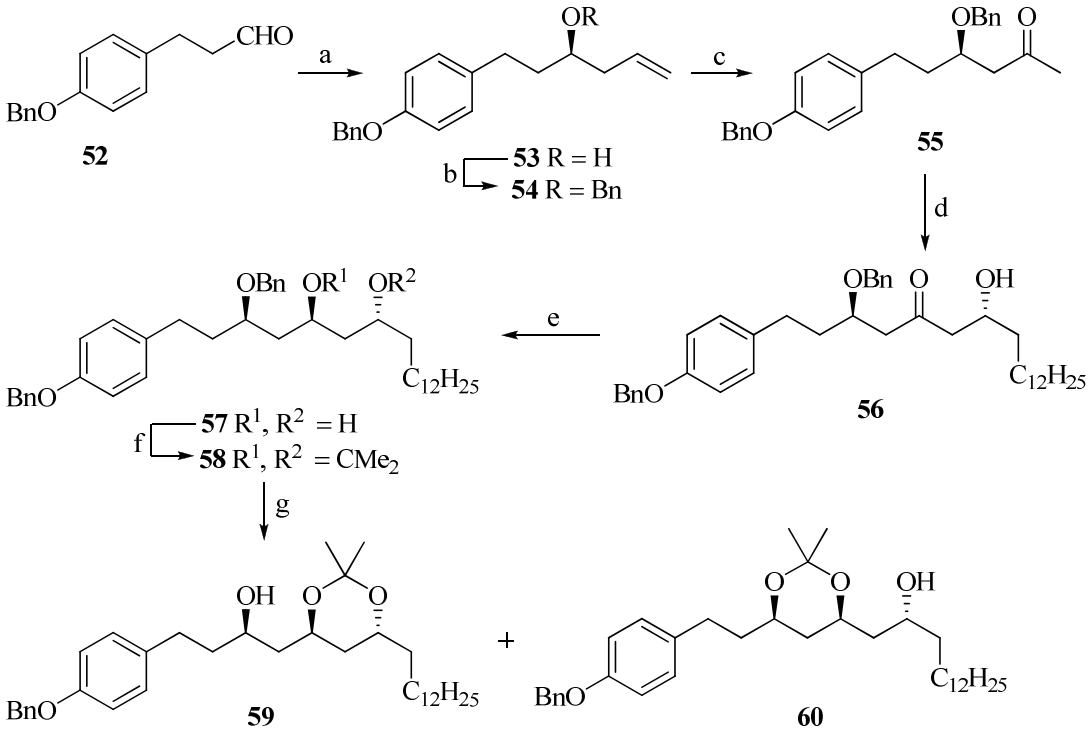
Baldwin et al. proposed a mechanistic rationale for the dramatic influence of the nature of the solvent on the product distribution on the oxidative cyclisation (Scheme 12). The cyclisation precursor was found to exist as an equilibrium mixture of the cyclic compound (±)-**48-A** and the open-chain compound (±)-**48-B** in solution (*vide supra*). In deuterated acetone the equilibrium ratio of (±)-**48-A**: (±)-**48-B** was shown to be 2:1 (by 500 MHz NMR analysis), whereas in deuterated acetonitrile compound (±)-**48-A** was present almost exclusively [(±)-**48-A**: (±)-**48-B** > 95:5]; this suggests that the partitioning between (±)-**48-A** and (±)-**48-B** is likely to be due to hydrogen-bonding effects, since acetone would be expected to stabilize intermolecular hydrogen bonds [and thus favour

the open-chain compound (±)-**48-B**] to a greater extent than would acetonitrile. Greater solvent polarity would thus be expected to increase the proportion of (±)-**37** formed in the reaction, as is observed experimentally. It is possible to speculate that metal ion coordination could favour the open-chain structure (±)-**48-B** (required for formation of aculeatin D (±)-**37**) over the cyclic compound (±)-**48-A**, thus increasing the proportion of (±)-**37** formed during the oxidative cyclisation.

- **Enantioselective synthesis of aculeatins (Falomir et al. 2006)**

The three naturally occurring, bioactive spiroacetals aculeatins A, B, and D, as well as the non-natural 6-*epi*-aculeatin D have been synthesized by Falomir et al.[21] for the first time in enantiopure form using an asymmetric allylation as the only chirality source. A further key step was a stereoselective aldol reaction with remote induction. The absolute configurations of the natural products have been established and an erroneous structural assignment has been corrected.

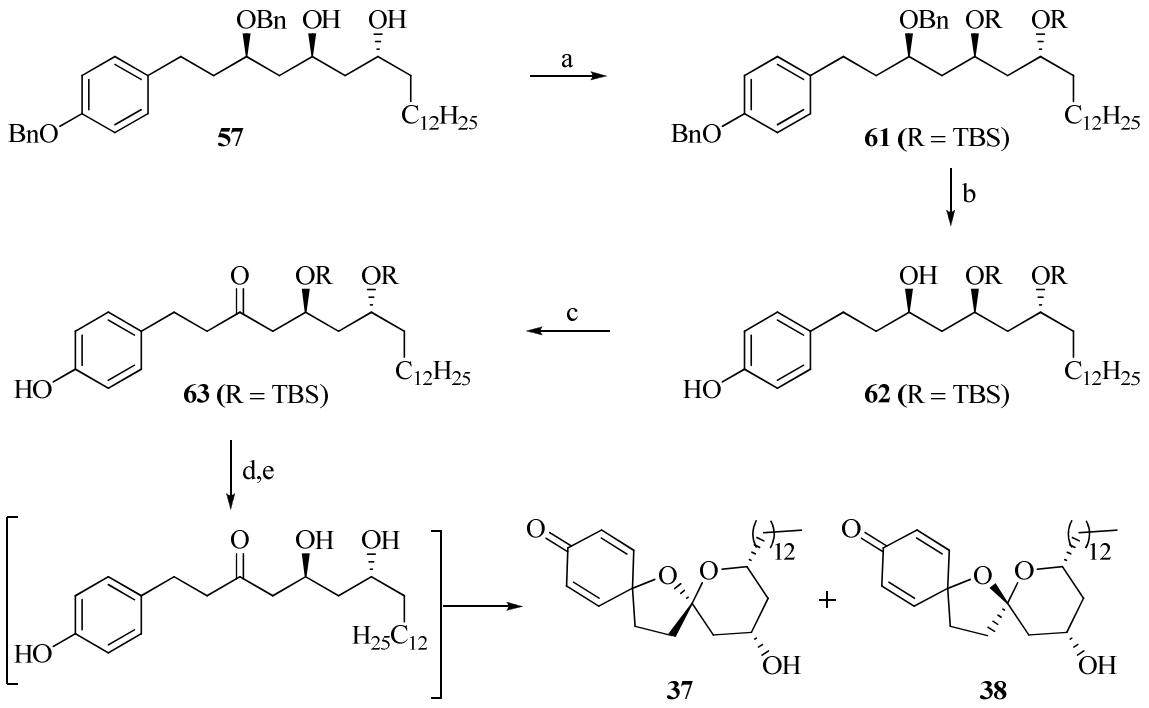
The synthesis was started with the known 3-(*p*-benzyloxyphenyl)propanal **52** which was subjected to asymmetric allylation using the chiral allylborane prepared from allylmagnesium bromide and (–)-DIPCl [(–)-diisopinocamphenylchloroborane]. In this way, homoallyl alcohol **53** was obtained in over 96% *ee* as judged by NMR examination of the Mosher ester. Benzylation of the hydroxyl group present in **53** followed by Wacker oxidation provided methyl ketone **55**. Boron aldol reaction of ketone **55** with *n*-tetradecanal afforded the desired aldol **56** in 70% yield as a single diastereomer. The aldol **56** was reduced with TABH to stereoselectively afford the expected *anti*-1,3- diol **57**, which was subsequently transformed into its acetonide **58** (Scheme 13). Problems arose, however, during hydrogenolytic cleavage of the two benzyl groups. Under all attempted conditions, partial migration (transacetalization) of the acetonide group took place with formation of two isomeric acetonides in low yield, the undesired **60** being the major compound.



Scheme 13: Synthesis of **57**

Reagents & Conditions: (a) allylBIpc$_2$ from (–)-Ipc$_2$BCl and allylmagnesium bromide, Et$_2$O, 3 h, –90 °C; (b) NaH, THF, then BnBr, rt, overnight, 85% overall from **52**; (c) PdCl$_2$, CuCl$_2$, aq DMF, O$_2$, 2 d, 75%; (d) Bu$_2$BOTf, EtN^{i}Pr$_2$, CH$_2$Cl$_2$, –78 °C, 1 h, followed by addition of *n*-tetradecanal, 3 h, –78 °C, 70%; (e) TABH, AcOH–MeCN, –30 °C, 12 h, 86%; (f) 2,2-dimethoxypropane, CSA (cat.), Me$_2$CO, rt, 12 h, 89%; (g) H$_2$ (1 atm), 10% Pd–C, EtOAc, rt, 6 h, 40%.

The acetonide moiety was then replaced by other protecting groups such as MOM, MEM or TES (triethylsilyl), all cleavable under mild conditions. However, no success was achieved with these groups, either. The acetal-like MOM or MEM groups were introduced with unsatisfactory yields and showed a marked tendency to form six-membered formaldehyde acetals with the proximal hydroxy group. The TES group behaved better in this aspect but was partially cleaved under hydrogenolytic conditions. Eventually, the TBS group proved appropriate.



Scheme 14: Synthesis of aculeatin D and its 6-epimer

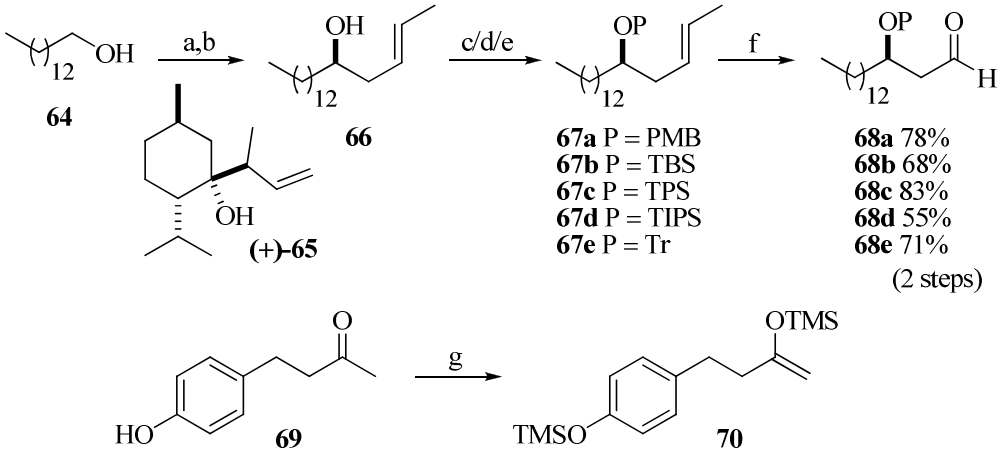
Reagents & Conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, Δ, 91%; (b) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 15 min, 74%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, –78 °C →0 °C, 81%; (d) TASF, DMF, 0 °C, 90 min, then rt, 4 h and (e) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 30 min, 77% overall for the two steps.

Double silylation of diol **57** worked well, as did the subsequent hydrogenolysis and oxidation steps, which finally yielded ketone **63** (Scheme 14). The latter was desilylated under mild conditions with TASF. Without purification, the intermediate diol was subjected to oxidative spiroacetalization with $PhI(OCOCF_3)_2$ to yield a 2.7:1 mixture of compounds (**37** minor) and (**38** major), with no 4-hydroxycyclohexa-2,5-dienone being isolated. Compounds (**37**) and (**38**) displayed physical and spectral features identical to those reported for natural aculeatin D and synthetic 6-*epi*-aculeatin D, respectively.

- **Diastereodivergent synthesis of aculeatins (Wong et al. 2007)**

Wong et al.[22] reported a concise and stereocontrolled syntheses of aculeatins (–)-A, (+)-B, (+)-D, and (+)-6-*epi*-D. Diastereodivergent 1,3-inductions in Mukaiyama aldol coupling contribute to reduce steps and to increase flexibility with reactants having sterically restricted proximal substituents (-CH_2), involving either a good *anti* or a

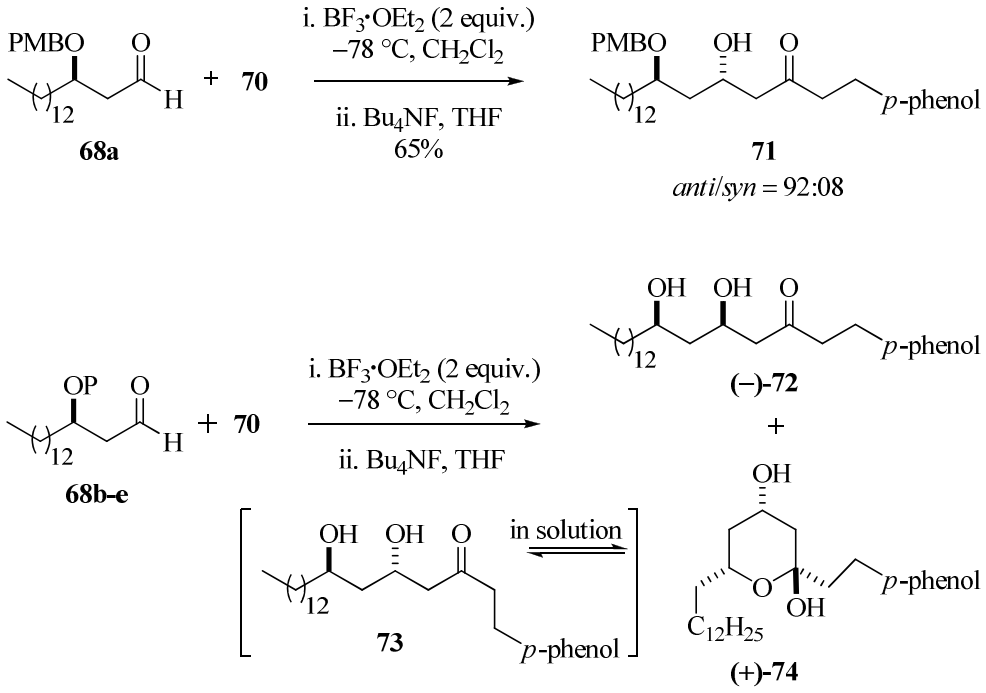
moderate *syn* 1,3-induction, depending on the nature of protecting group (P). In addition, the 3,5-*syn*-diol-ketone resulting from concomitant deprotection of the β-alkoxy (Tr = trityl) group proves to be remarkably stable whereas the 3,5-*anti* diastereoisomer cyclizes spontaneously to the corresponding tetrahydropyran hemiketal, thus enabling a useful and facile separation. The second part of study is devoted to improving the yield and the diastereoselectivity of the final phenolic oxidation reaction leading to aculeatins.



Scheme 15: Syntheses of **68a–e** and **70**

Reagents & Conditions: (a) PCC; (b) Nokami's reagent **(+)-65**, *p*-TsOH, CH_2Cl_2, 62%; (c) 4-(OMe)-benzyltrichloroacetimidate, CSA, CH_2Cl_2; (d) R_3SiCl, imidazole; (e) Tr-Cl, DMAP, NEt_3, CH_2Cl_2; (f) NMO, OsO_4, $NaIO_4$; (g) LDA, THF, –78 ^oC, then TMSCl, 62%.

The synthesis was started with the oxidation of 1-tetradecanol **64** with PCC followed by treatment of the corresponding aldehyde with the Nokami's reagent **(+)-65** to give the alcohol **66** in 62% overall yield with an excellent enantioselectivity (*er* > 95:5). A two-step sequence, i.e., protection of alcohol group yielding PMB, TBS, *tert*-butyldiphenylsilyl (TPS), triisopropylsilyl (TIPS), or trityl (Tr) ethers, and an oxidative cleavage of the double bond, gave the desired protected β-alkoxy aldehydes **68a-e**. The enolsilane nucleophile **70** was readily prepared in one step (62%) from the commercially available 4-hydroxyphenyl-2-butanone **69** (Scheme 15).

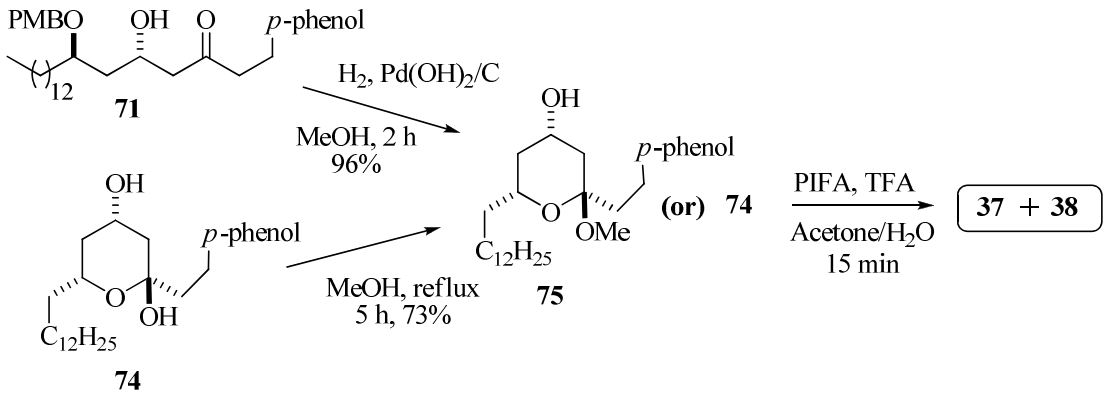


Scheme 16: Syntheses of keto-diol

The aldol addition of enolsilane **70** to aldehyde **68a** at –78 °C in CH_2Cl_2 by slow addition of $BF_3{\cdot}OEt_2$ (Scheme 16), followed by hydrolysis and TMS group deprotection with Bu_4NF in THF, proceeded with a good 1,3-*anti* induction (*dr* = 92:08) to give the 3,5-*anti* product **71** (65%). The addition of less than 2 equiv of $BF_3{\cdot}OEt_2$ gave lower yields, presumably because of the sensitive TMS group carried by the enolsilane **70**. In contrast, the 1,3-*anti* induction of aldol coupling dramatically dropped with β-alkoxy aldehydes protected by bulky silyl ethers (**68b**–**d**). With the TBS ether, the *anti*/*syn* ratio was only 60:40, and almost no 1,3-induction was observed with TPS and TIPS ethers.

To evaluate a new protecting group, trityl ether was tested in the Mukaiyama coupling/deprotection/demixing step. This acid-labile protecting group, which can be compared to bulky PMB ether, offers the opportunity to undergo simultaneous deprotection with $BF_3{\cdot}OEt_2$. Thus, using the same experimental conditions, 2 equiv of $BF_3{\cdot}OEt_2$ was added to a mixture of β-alkoxy aldehyde **68e** and enolsilane **70** at –78 °C. Unexpectedly, after treatment with Bu_4NF/THF, a weak *syn* 1,3-induction was observed, giving **72** (41%) and **74** (27%) in a *syn*/*anti* ratio of 60:40. When $BF_3{\cdot}OEt_2$ was added to

the aldehyde **68e**, prior to the addition of the enolsilane **70**, an improved 1,3-*syn* induction was obtained yielding **72** (51%) and **74** (21%) in a *syn*/*anti* ratio of 71:29.



Scheme 17: Syntheses of aculeatin D and its 6-epimer

The investigation of the key oxidative spiro-annulation by using a mixture of precursors **73** and **74** makes it difficult to clearly analyze effects involved in the diastereoselectivity. They anticipated that the tetrahydropyran methoxy ketals **75** would be more stable precursor. To obtain cyclic analogues **75**, simply refluxing the tetrahydropyran hemiketal **74** in methanol (Scheme 17) generated the **75** (73%). An alternative way to obtain **75** was the PMB deprotection of the 3,5-*anti* adduct **71** with $Pd(OH)_2/C$ in MeOH for 2 h. This approach directly afforded the crude product **75** (96%), which was pure enough to be used for the next step without any chromatography.

Starting from these structurally distinct precursors (**74**, **75**), investigated their effects on the stereochemistry during the oxidative phenolic spiro-annulation using conditions that ensured good yields of products. For instance, presence of water in the medium was necessary to get high yield of aculeatins. In addition, they have found that running the reaction at higher concentration (0.04 M) using PIFA in acetone/H_2O (10:1) at room temperature in darkness for only 15 min allows the corresponding aculeatins to be isolated in good yields. The yield was improved by adding additional TFA (CF_3-CO_2H, optimized at 0.4 equiv) beyond that generated in situ from the PIFA reagent.

Present Work

Isolation:-

During the course of research on novel cytotoxic and antiprotozoal comounds derived from plants, three novel compounds, named aculeatins A (**34**), B (**35**) and C (**36**) (Figure 5) were isolated by Heilmann and co-workers from the petroleum ether extracts of the rhizomes of *Amomum aculeatum*.[18a] Further investigation of these extracts led to the isolation of a fourth member, named aculeatin D (**37**), of this small class of natural products.[18b] Common to all four metabolites is the presence of a unique 1,7-dioxa-dispiro[5.1.5.2]-9,12-dien-11-one tricyclic ring system, which is without precedent in the literature, while aculeatin C (**36**) also contains an additional cyclohexadienone unit. All four compounds were found to display optical activity.

Biological activity:-

The plant from which the aculeatin class of compounds have been isolated, A. *aculeatum*, has traditionally been used by the indigenous people of Papau New Guinea as a folk medicine against fever and malaria.[24] Initial studies have shown the aculeatin compounds to display an impressive range of biological effects, including antibacterial activity against *Bacillus cereus* and *Escherichia coli*, and potent antiprotozoal activity against both the NF54 and the chloroquine-resistant K1 strains of the malarial parasite *Plasmodium falciparum* and *Trypanosoma* Species. Most intriguingly, all four compounds were found to display potent cytotoxicity against a KB carcinoma cell line (ATCC CCL 17). The relative stereochemistry of the C-2, C-4 and C-6 tetrahydropyran ring substituents was found to be important in determining the relative potency of the compounds; aculeatin D (**37**) was found to be the most active in the cytotoxicity assay, with an IC_{50} value of 0.38 μg/mL.[18b] The structural novelty of these compounds potentially indicates a hitherto unknown mode of cytotoxicity.

Aculeatin D (**37**) was evaluated for its cytotoxicity and antiprotozoal activity. Compared to aculeatin B (**35**), inversion of stereochemistry at C-4 led to a doubled cytotoxicity against the KB cell line (IC_{50} = 0.38 μg/mL versus 0.82 μg/mL (aculeatin

B)). In contrast, activity against the *Plasmodium falciparum* strains K1 and NF54 decreased significantly from aculeatin B (**35**) to aculeatin D (**37**) (0.18 versus 0.42 µg/mL for P. *falciparum* strain K1 and 0.26 versus 0.47 µg/mL for P. *falciparum* strain NF54). Ongoing studies focus now on the discovery of the hitherto unknown mechanisms of cytotoxicity and anti- plasmodial activity to find analogous structures with more specific biological effects.

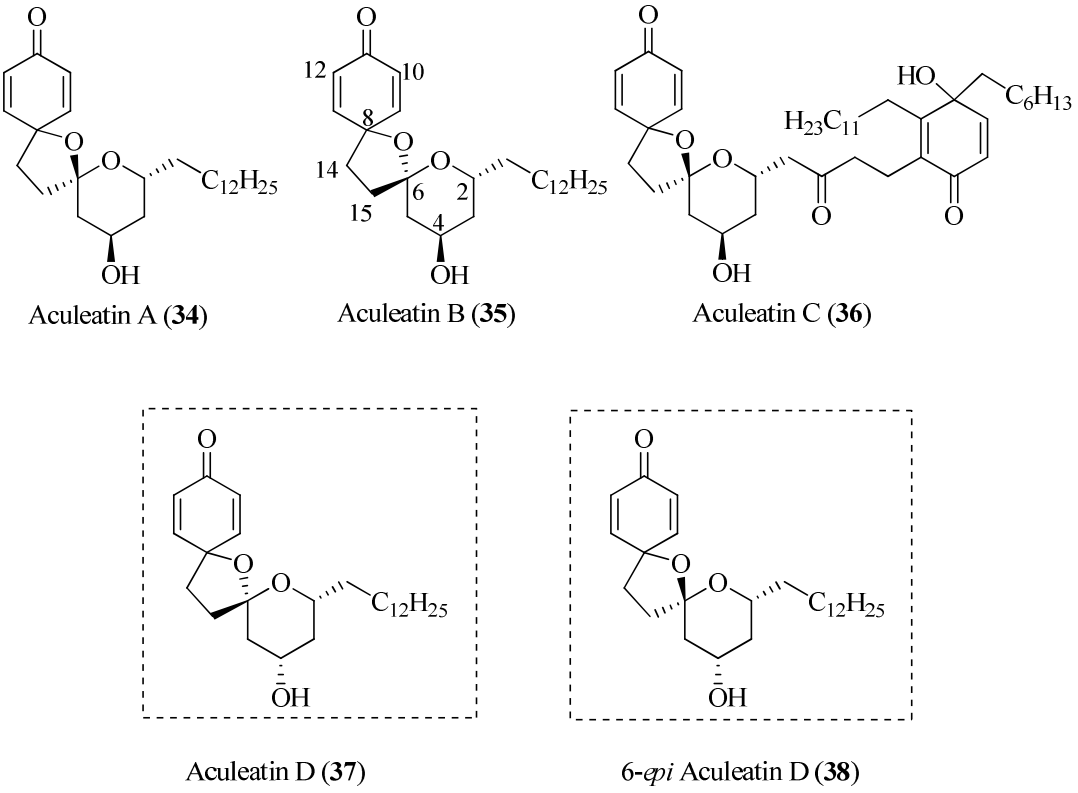
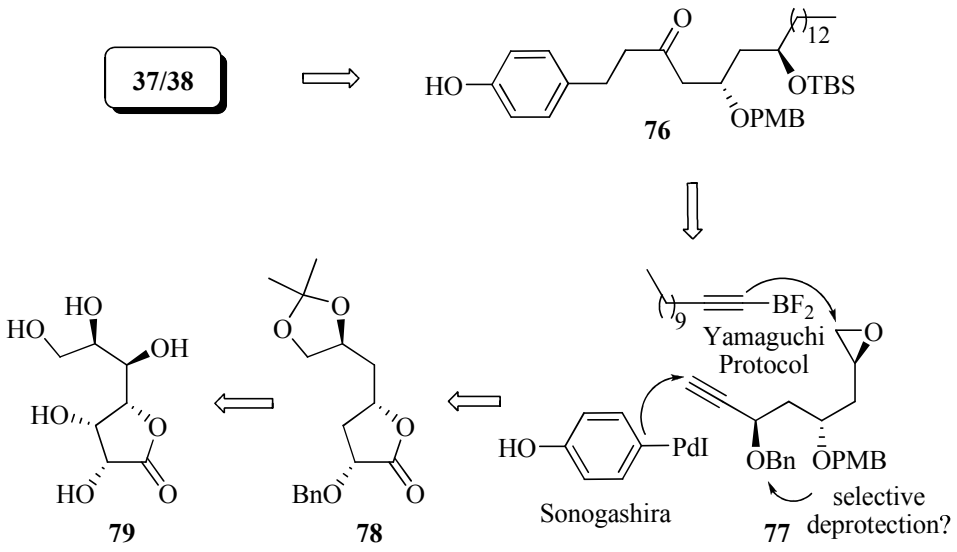


Figure 5: *Aculeatins A–D and 6-epi-Aculeatin D*

Their promising biological activity taken together with the presence of structurally fascinating 1,7-dioxadispiro[5.1.5.2]-pentadecane spirocyclic architecture, aculeatins A–D aroused substantial interest culminating in several total syntheses.[19–23] As described in the introduction the reported syntheses for aculeatins in general are linear in nature and involve a stepwise construction of each chiral center present by either asymmetric aldol or chiral allylation protocols and finally phenolic oxidation of a 3,5-

syn- or *anti*-diol ketone. A flexible total synthesis that would allow access to modified aculeatins like functional group addition to cyclohexadienone unit and/or the alterations on the aliphatic side chain should give access to various synthetic analogues for structure-activity studies. It was reasoned that addition of these units at a late stage in the synthesis would suffice this criteria. Here we opted a concise and flexible approach by selecting aculeatin D (**37**) as a target considering its documented superior cytotoxicity (IC_{50} = 0.38 µg/mL).

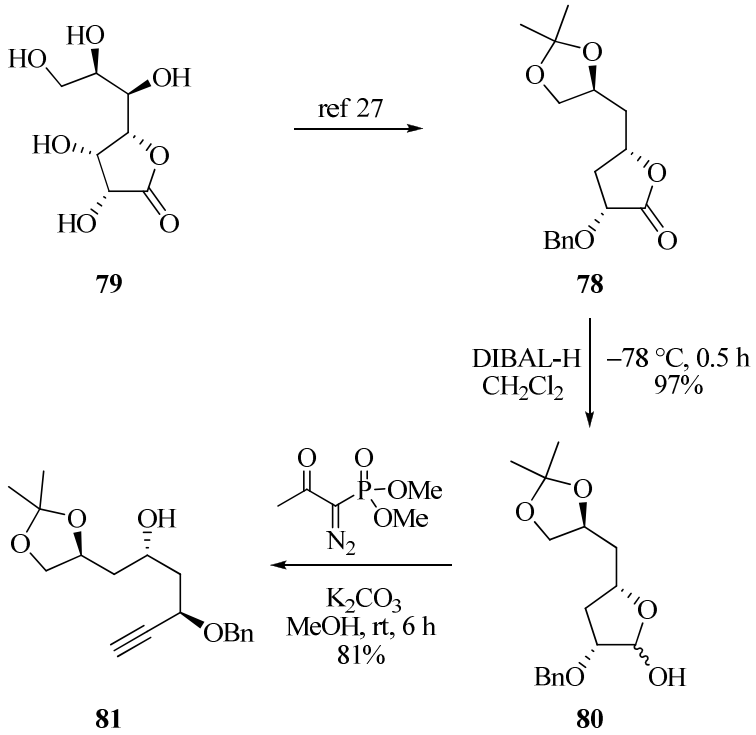


Scheme 18: Retrosynthetic strategy for the aculeatin D and 6-*epi*-aculeatin D

As outlined in Scheme 18, the retrosynthetic disconnection identified an epoxy alkyne **77** as the key intermediate which can be extended to the advanced keto 3,5-diol unit **76** by Yamaguchi protocol[25] at one end and the Sonogashira coupling[26] on the alkyne end thus keeping flexibility at both sides. Keeping our previous observation, we hypothesized a selective propargylic–OBn cleavage during the Raney Ni hydrogenation of the alkyne units.[27,28] Oxidation of the released free C6-OH and subsequent global deprotection and phenolic oxidation should complete the total synthesis of aculeatin D (**37**) and its 6-epimer (**38**). The epoxy alkyne **77** could be obtained from the intermediate lactone **78**, upon successive controlled reduction, Ohira-Bestmann alkynylation[29] and

oxirane formation. The intermediate lactone **78** in turn could be secured following our established procedure[27] from commercially available glucoheptono-1,4-lactone **79**.

To explore in this direction, commercially available glucoheptono-1,4-lactone (**79**) was advanced to the key intermediate lactone **78** following our established procedure (as described in chapter 1).[27] Controlled reduction of lactone **78** with DIBAL-H in dichloromethane at –78 °C yielded the lactol **80** in nearly quantitative yield. Subsequent Ohira-Bestmann alkynylation of intermediate lactol **80** with dimethyl-1-diazo-2-oxopropyl phosphonate and K_2CO_3 in methanol at rt afforded the alkyne (**81**) (Scheme 19).[29]

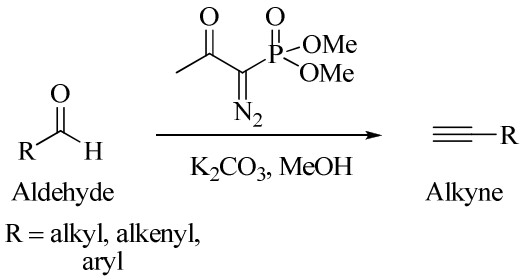


Scheme 19: Synthesis of alkyne **81**

The structure of alkyne **81** was well supported by its ^{1}H, ^{13}C NMR spectra and elemental analysis. In the ^{1}H NMR spectrum of **81** the isopropylidene groups resonated at δ 1.34, 1.39 as singlets, alkyne C–H located at 2.53 ppm as a doublet (J = 2.1 Hz) and aromatic protons were observed at 7.28–7.36 ppm as a multiplet. In the ^{13}C NMR

spectrum, alkyne carbons resonated at δ 74.7, 82.0 as a doublet and singlet respectively. In the IR spectrum of **81** the O–H stretching was observed at 3486 cm^{-1} and C≡C stretching was observed at 2126 cm^{-1}.

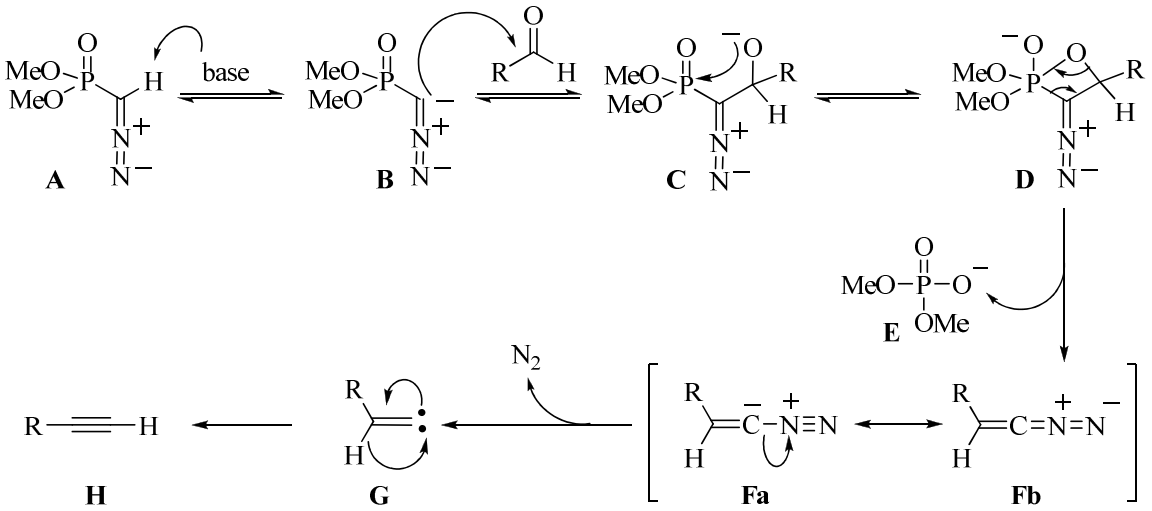
***Ohira-Bestmann homologation of aldehydes*:**



Scheme 20

*An extremely mild and efficient method, utilizing dimethyldiazomethylphosphonate as a reagent for the homologation of aldehydes into alkynes. This is a widely used alternative to the longer known Corey-Fuchs method. The phosphonate is some times referred to as the Seyferth-Gilbert reagent though the corresponding diethyl ester was first synthesized by Regitz et al. and the reagent was first used for the synthesis of alkynes by Colvin et al. The modified Bestmann reagent, dimethyl-1-diazo-2-oxopropylphosphonate makes the method more convenient for the synthesis of terminal alkynes. The procedure utilizes in situ preparation of dimethyldiazomethylphophonate (Seyferth-Gilbert reagent). The easy one-pot procedure avoids the use of strong bases, low temperatures and inert gas techniques. The use of the milder potassium carbonate makes this procedure much more compatible with a wide variety of functional groups. The proposed mechanism (Scheme 21) of the transformation includes a Horner-Wadsworth-Emmons-type reaction, followed by loss of nitrogen and rearrangement of the resulting alkenylidenecarbene into the alkyne. Deprotonation of the Seyferth-Gilbert reagent **A** gives an anion **B** which reacts with the aldehyde to form the oxaphosphatane **D**. Elimination of dimethylphosphate **E** gives the vinyl diazo-intermediate **Fa** and **Fb**.*

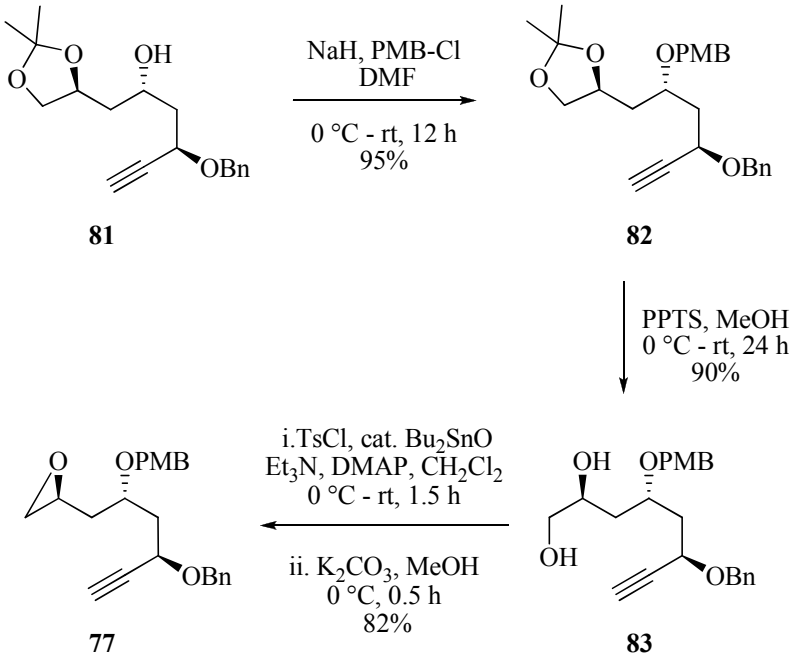
*The generation of nitrogen gas gives a vinyl carbine **G** which via a 1,2-migration forms the desired alkyne **H**.*



Scheme 21: *Mechanism of alkynylation*

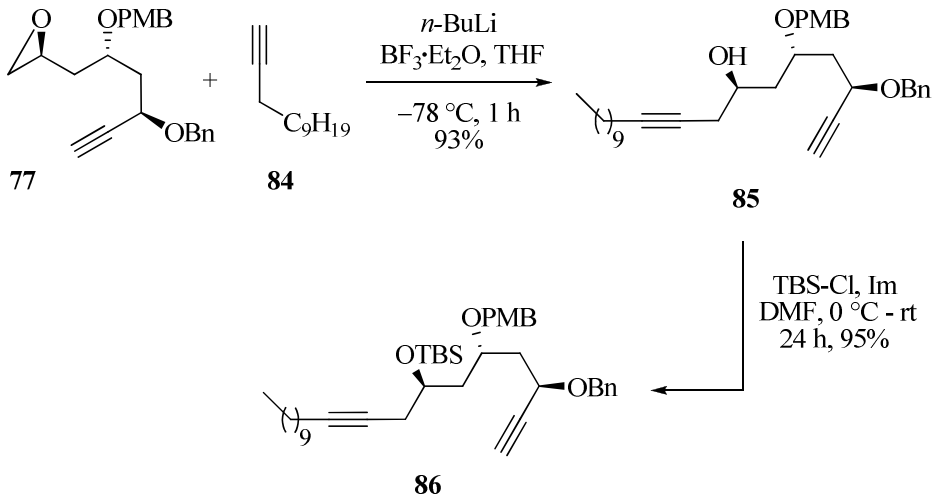
Treatment of **81** with *p*-methoxybenzyl chloride in the presence of NaH in DMF at 0 °C–rt furnished the PMB-ether **82**. Subsequently, the 1,2-isopropylidene group was hydrolyzed in the presence of PPTS in methanol at 0 °C–rt to afford the terminal diol **83** (Scheme 22). The assigned structure for **83** was well supported by spectral and analytical data. In the IR spectrum of **83**, O–H stretching was observed at 3411 cm^{-1} and C≡C stretching was observed at 2110 cm^{-1}. The primary hydroxyl group of **83** was selectively tosylated by treating with TsCl, catalytic Bu_2SnO, and triethylamine in dichloromethane to obtain the primary tosylate, which was further used for next reaction without any chromatographic purification. Oxirane formation was facile with K_2CO_3 in methanol to furnish the epoxide (**77**) (82% over two steps). The formation of epoxide **77** was ascertained from its ^1H, ^{13}C NMR spectrum and elemental analysis. In the ^1H NMR spectrum of **77** all three oxirane protons separately resonated relatively upfield at 3.03 (ddt, J = 5.8, 3.9, 2.7 Hz), 2.78 (dd, J = 5.0, 4.0 Hz) and 2.49 (dd, J = 5.0, 2.7 Hz) ppm

and alkyne C–H resonated at 2.47 (d, J = 2.1 Hz) ppm. In the ^{13}C NMR spectrum of **77** the oxirane carbons were observed at δ 47.3 a triplet and δ 49.2 a doublet.



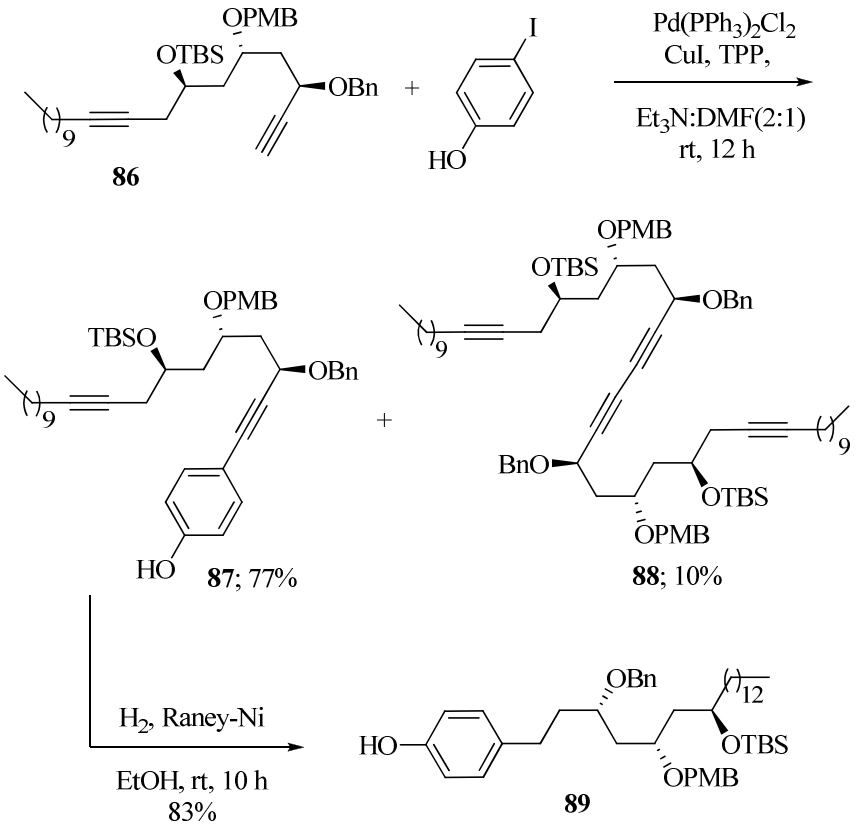
Scheme 22: Synthesis of epoxide **77**

After having the epoxide **77**, we next focused our efforts on the synthesis of the keto-3,5-diol unit **76**. Thus the projected opening of epoxide **77** following Yamaguchi protocol with dodec-1-yne **84** (prepared from Swern oxidation of undecanol followed by Ohira-Bestmann alkynylation of resulting aldehyde) in the presence of *n*-BuLi, $BF_3{\cdot}Et_2O$ in THF at –78 °C furnished the diyne **85** in near quantitative yields (Scheme 23).[25] In the ^{1}H NMR spectrum of **85** the propargylic CH_2 protons resonated at 2.34–2.29, 2.16–2.07 ppm as two multiplets and the terminal methyl was observed at 0.86 (t, J = 6.2 Hz) ppm. In the ^{13}C NMR spectrum of **85** alkyne carbons appeared at δ 74.0 doublet, δ 75.9, 82.7, 82.9 as singlets, propargylic carbons appeared at δ 39.2, 41.0 as triplets and the terminal methyl resonated at δ 14.1 quartet. The free hydroxyl group present in **85** was protected as its TBS ether with TBS-Cl, imidazole in DMF to afford the TBS-ether derivative (**86**) in excellent yields.



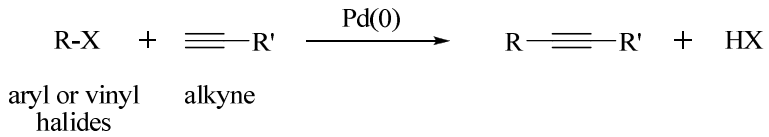
Scheme 23: Yamaguchi protocol

Having complete aliphatic skeleton in hand, now the stage was set for the coupling of phenolic moiety. Thus the terminal alkyne **86** was subjected to Sonogashira coupling with *p*-iodophenol, in presence of $Pd(PPh_3)_2Cl_2$, CuI in triethylamine/DMF at rt to furnish the required coupling product **87** (77%) along with small amounts of self dimerized product **88** (10%).[26] The presence of phenolic moiety in **87** is evidenced from the appearance of additional signals in the aromatic region. Results from ^{1}H, ^{13}C NMR, IR spectrum and elemental analysis were in accordance with the assigned structures **87** and **88**. Our next concern was the hydrogenation of diyne **87** along with the desired selective propargyl-*O*-debenzylation.[27] To our surprise, hydrogenation of **87** was facile with Raney-Ni in ethanol, at rt or higher temperatures, but resulted exclusively in diyne reduction to afford product (**89**) with *O*-benzyl intact (Scheme 24)**.**



Scheme 24: Sonogashira coupling, hydrogenation

Sonogashira coupling



Scheme 25: *General Sonogashira coupling*

In 1975, K. Sonogashira and co-workers reported that symmetrically substituted alkynes could be prepared under mild conditions by reacting acetylene gas with aryl

iodides or vinyl bromides in the presence of catalytic amounts of $Pd(PPh_3)Cl_2$ and cuprous iodide (CuI). During the same year both the research groups R. F. Heck and L. Cassar independently disclosed similar Pd-catalysed processes, but these were not using copper co-catalysis, and the reaction conditions were harsh. The copper-palladium catalysed coupling of terminal alkynes with aryl and vinyl halides to give enynes is known as the 'Sonogashira coupling' and can be considered as catalytic version of the Castro- Stephens coupling. The general features of the reaction are:

1) the coupling can usually be conducted at or slightly above room temperature, and this is the major advantage over the forcing conditions required for the alternative Castro-Stephenes coupling; 2) the handling of the shock-sensitive/explosive copper acetylides is avoided by the use of a catalytic amounts of copper(I)salt; 3) the copper(I) salt can be commercially available CuI or CuBr and usually applied in 0.5 -5 mol % with respect to the halide or alkyne; 4) the best palladium catalyst are $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$; 5) the solvents and the reagents do not need to be rigorously dried. However, a thorough deoxygenation is essential to maintain the activity of the Pd-catalyst; 6) often the base serves as the solvent but occasionally a co-solvent is used; 7) the reaction works well on both very small and large scale (>100 g); 8) the coupling is stereospecific; the stereochemical information of the substrates is preserved in the products; 9) the order of the reactivity for the aryl and vinyl halides is I ~ OTf > Br >> Cl; 10) the difference between the reaction rates of iodides and bromides allows selective coupling with the iodides in the presence of bromides; 11) almost all functional groups are tolerated on the aromatic and vinyl halide substrates. However, alkynes with conjugated electron-withdrawing groups ($(R^2$= COOMe) give Michael addition products and propargylic substrates with electron-withdrawing groups ($(R^2$= COOMe or NH_2) tend to rearrange to allenes under the reaction conditions; 12) the exceptional functional group tolerance of the process makes it feasible to use this coupling for complex substrates in the late stages of a total synthesis.

The coupling of sp^2-C halides with sp-C metal derivatives is also possible by using other reactions such as the Negishi-, Stille-, Suzuki-, and Kumada cross-couplings. In terms of functional group tolerance, the Negishi cross-coupling is the best alternative to the Sonogashira reaction. There are certain limitations on the Sonogashira coupling:

1) aryl halides and bulky substrates that are not very reactive require higher reaction temperature; and 2) at higher temperatures terminal alkynes undergo side reactions.

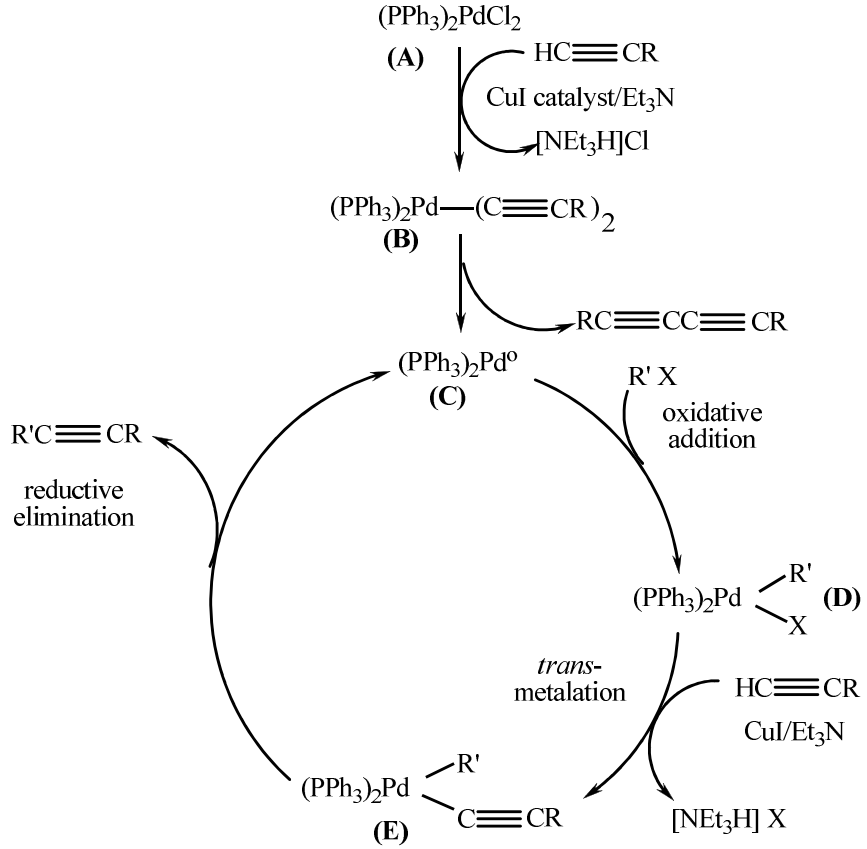
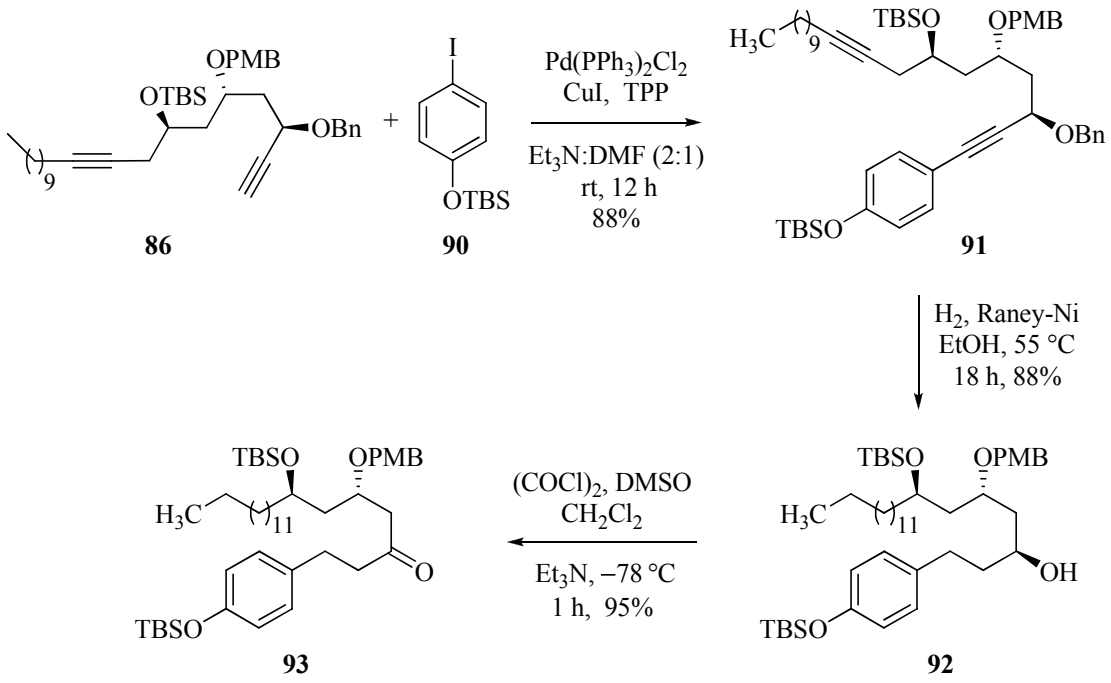


Figure 6: *Sonogashira catalytic cycle*

Mechanism

*Although the detailed mechanism of the reaction is yet to be clarified, it seems likely that the substitution occurs through an initial formation of bis-(triphenylphosphine)dialkynylpalladium (II) (**B**), which gives a catalytic species, bis-(triphenylphosphine)palladium (0) (**C**), through a reductive elimination of 1,4-diphenylbutadiyne. Subsequent oxidative addition of vinyl halide to (**C**), followed by an alkynylation of the adduct (**D**), gives vinyl-alkynyl derivative of palladium (**E**), which easily regenerates the original bis-(triphenylphosphine)palladium (0) (**C**) through the reductive elimination of the substitution products. The alkynylation of the starting*

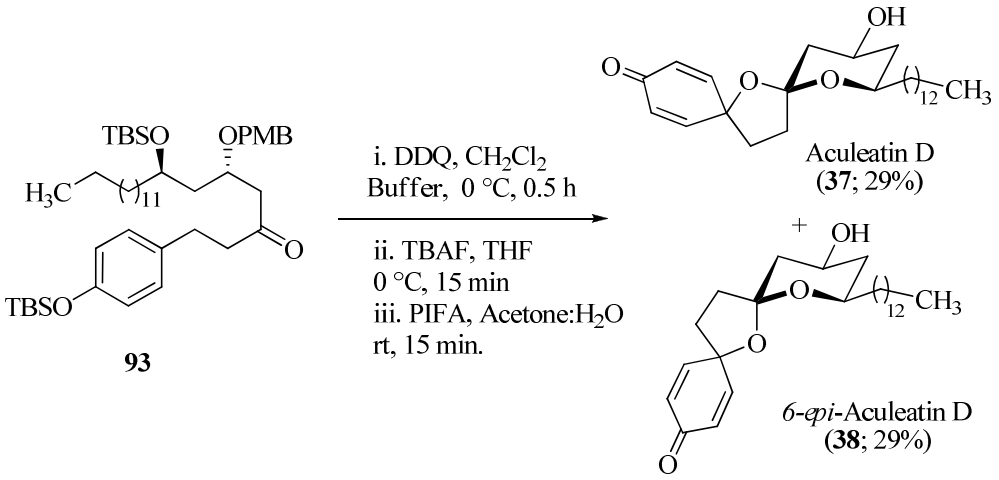
*catalyst (**A**) or an oxidative adduct (**D**) in the catalytic cycle in Figure 6 is catalysed by cuprous iodide in the presence of triethylamine.*



Scheme 26: Sonogashira coupling, hydrogenation, oxidation

After careful experimentation by employing protected *p*-iodophenol derivatives for Sonogashira coupling and subsequent Raney Ni hydrogenation, we concluded that TBS was the optimal protecting group that improved the yield in Sonogashira coupling and, to our delight; the anticipated *O*-debenzylation was achieved during the hydrogenation of respective intermediate **91** affording **92**. Thus the diyne **86** was subjected to Sonogashira coupling with TBS protected *p*-iodophenol derivative **90** (prepared from *p*-iodophenol in presence of TBS-Cl, imidazole in DMF) in presence of $Pd(PPh_3)_2Cl_2$, CuI in triethylamine/DMF at rt to furnish the required coupling product **91** (88%) (Scheme 26). Coupling was evidenced from the appearing of additional signals in the aromatic region.

Diyne **91** was subjected to hydrogenation with Raney Ni in ethanol at 55 °C, to yield **92** with the anticipated *O*-debenzylation (Scheme 26). The assigned structure for **92** was well supported by spectral and analytical data. In the IR spectrum of **92**, O–H stretching was observed at 3480 cm^{-1}. Oxidation of **92** under Swern conditions in presence of $(COCl)_2$, DMSO, Et_3N in dichloromethane at −78 °C afforded the keto-3,5-diol unit (**93**). The structure of **93** was well supported by spectral and analytical data. In the ^{13}C NMR spectrum of **93**, keto carbonyl resonated at 208.6 ppm as a singlet, in the IR spectrum C=O stretching was observed at 1715 cm^{-1}.



Scheme 27: Synthesis of aculeatin D and 6-*epi*-aculeatin D

Having the keto-3,5-*anti*-diol **93**, the stage was set for the global deprotection and subsequent phenol oxidation.[30] Attempted global deprotection of PMB, TBS-ethers under acidic conditions with TFA, PTSA or PPTS in solvents like methanol or dichloromethane yielded an unidentified complex mixture. Sequential deprotection of PMB-ether by using DDQ in dichloromethane under buffered conditions at 0 °C followed by, TBS-ether deprotection in presence of TBAF in THF at 0 °C produced the free diol. The free diol obtained was further used for next transformation without any chromatographic purification. Oxidative spiroacetalization of intermediate ketodiol by using phenyliodine(III) bis(trifluroacetate) (PIFA) in acetone/water (10:1, v/v solution) at darkness completed the synthesis of epimeric aculeatins, furnishing (**37**) and (**38**) (58%

for three steps) as a 1:1 mixture, which were separated by flash column chromatography (Scheme 27). Physical and spectral data of these compounds were in agreement with the data reported for natural aculeatin D (**37**) and synthetic 6-*epi*-aculeatin D (**38**), respectively.[21]

Aculeatin D (**37**)**:** In the ^{1}H NMR spectrum of (**37**), conjugated olefinic protons resonated at δ 6.98 (dd, *J* = 10.5, 3.2 Hz), 6.77 (dd, *J* = 10.5, 3.2 Hz), 6.13 (dd, *J* = 10.3, 1.9 Hz) and 6.12 (dd, *J* = 10.3, 1.9 Hz). In the ^{13}C NMR spectrum, conjugated keto carbonyl was observed at δ 185.5 as a singlet. In the IR spectrum O–H stretching was observed at 3410 cm^{-1} and C=O stretching was observed at 1665 cm^{-1}. The optical rotation observed for synthetic aculeatin D is +47.7 (*c* 0.2, $CHCl_3$), and reported value for natural aculeatin D is [lit +46.5 (*c* 1.0, $CHCl_3$)].

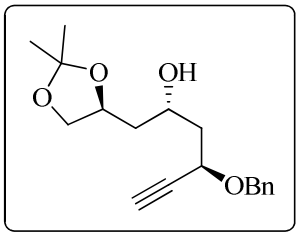
6-*epi*-Aculeatin D (**38**)**:** In the ^{1}H NMR spectrum of (**38**), conjugated olefinic protons resonated at δ 6.81 (dd, *J* = 10.4, 3.2 Hz), 6.76 (dd, *J* = 10.4, 3.2 Hz), 6.11 (dd, *J* = 10.1, 1.9 Hz) and 6.10 (dd, *J* = 10.1, 1.9 Hz). In the ^{13}C NMR spectrum, conjugated keto carbonyl was observed at δ 185.5 as a singlet. In the IR spectrum O–H stretching was observed at 3410 cm^{-1} and C=O stretching was observed at 1664 cm^{-1}. The optical rotation observed for synthetic 6-*epi*-aculeatin D is +14.6 (*c* 0.2, $CHCl_3$), and reported value for synthetic 6-*epi*-aculeatin D is [lit +15.0 (*c* 1.0, $CHCl_3$)].

Conclusion:

In summary, a chiral pool approach employing an easily accessible differentially protected *anti*,*anti*-1,3-polyol unit for the total synthesis of naturally occurring aculeatin D and its 6-epimer was documented. As such, this route employs the addition of both the terminal units (phenol and side chain) at the late stage of the synthesis thus providing sufficient flexibility for related analogues synthesis.[31]

Experimental

(2*R*,4*R*)-4-(Benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-5-yn-2-ol (81)

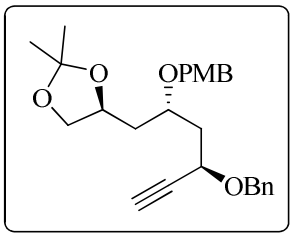


Lactol **80** (2 g, 6.48 mmol) was dissolved in dry methanol (20 mL), treated with anhydrous K_2CO_3 (1.79 g, 12.97 mmol) followed by dimethyl-1-diazo-2-oxopropyl phosphonate (2.49 g, 12.97 mmol) at 0 °C. After stirring under nitrogen atmosphere at rt for 6 h, methanol was evaporated under reduced pressure, partitioned between ethyl acetate and water. Organic layer was separated and the aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuum, and the residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford the terminal alkyne **81** (1.6 g, 81%) as colorless oil.

Mol. Formula	: $C_{18}H_{24}O_4$
$[\alpha]_D$	: +129.8 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3486, 3305, 2935, 2126, 1380, 1217, 1072, 756, 698, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.36–7.28 (m, 5H), 4.82 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.38 (ddd, *J* = 5.8, 5.2, 2.1 Hz, 1H), 4.32–4.12 (m, 2H), 4.06 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.53 (t, *J* = 7.8 Hz, 1H), 2.96 (d, *J* = 3.9 Hz, 1H), 2.53 (d, *J* = 2.1 Hz, 1H), 1.92 (dd, *J* = 6.0, 5.4 Hz, 2H), 1.79–1.56 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.7 (q), 26.9 (q), 40.4 (t), 42.5 (t), 65.7 (d), 66.2 (d), 69.6 (t), 70.8 (t), 73.5 (d), 74.7 (d), 82.0 (s), 108.4 (s), 127.8 (d), 128.0 (d, 2C), 128.4 (d, 2C), 137.2 (s) ppm.
ESI-MS (*m/z*)	: 327.4 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.03; H, 7.95.
Found: C, 70.85; H, 7.94.

(*S*)-4-((2*R*,4*R*)-4-(Benzyloxy)-2-(4-methoxybenzyl-oxy)hex-5-ynyl)-2,2-dimethyl-1,3-dioxolane (82)



To a solution of alcohol **81** (0.5 g, 1.64 mmol) in dry DMF (2 mL), NaH (78 mg, 1.97 mmol) was added portion wise at 0 °C and stirred for 30 min, followed by *p*-methoxybenzyl chloride (0.280 mL, 1.97 mmol). After stirring for additional 12 h at rt, the reaction mixture was quenched at 0 °C by adding sat. Na_2SO_4, poured into water and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (15% ethyl acetate in petroleum ether) yielded the PMB derivative **82** (0.662 g, 95%) as colorless oil.

Mol. Formula : $C_{26}H_{32}O_5$

$[\alpha]_D$: +53.5 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3305, 3014, 2401, 1612, 1514, 1216, 822, 759, 668 cm^{-1}.

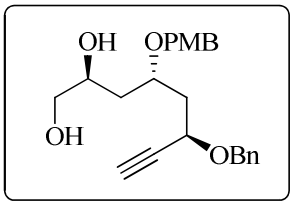
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.38–7.27 (m, 5H), 7.14 (dt, *J* = 8.6, 2.8 Hz, 2H), 6.82 (dt, *J* = 8.6, 2.7 Hz, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.31–4.12 (m, 2H), 4.02 (dd, *J* = 7.9, 5.8 Hz, 1H), 3.89–3.77 (m, 1H), 3.77 (s, 3H), 3.48 (t, *J* = 7.8 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.04–1.95 (m, 2H), 1.82–1.70 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.7 (q), 26.9 (q), 39.2 (t), 41.8 (t), 55.1 (q), 65.0 (d), 69.8 (t), 70.5 (t), 71.7 (t), 72.5 (d), 73.0 (d), 74.1 (d), 82.7 (s), 108.4 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.3 (d, 2C), 129.4 (d, 2C), 130.4 (s), 137.5 (s), 159.1 (s) ppm.

ESI-MS (*m/z*) : 447.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.56; H, 7.60.
Found: C, 73.45; H, 7.55.

(2*S*,4*S*,6*R*)-6-(Benzyloxy)-4-(4-methoxybenzyloxy)oct-7-yne-1,2-diol (83)



A solution of PMB-derivative **82** (0.5 g, 1.17 mmol) in methanol (20 mL) was cooled to 0 °C, PPTS (0.443 g, 1.76 mmol) was added in portions at 0 °C, and the reaction mixture was warmed to rt, stirred for 24 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue obtained was purified by column chromatography (50% ethyl acetate in petroleum ether) to afford the diol **83** (0.407 g, 90%) as colorless oil.

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

$[\alpha]_D$: +73.4 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3411, 2934, 2110, 1613, 1514, 1248, 1068, 752, 699 cm^{-1}.

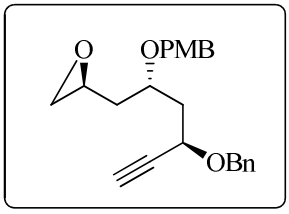
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.35–7.27 (m, 5H), 7.13 (dt, *J* = 8.7, 2.8 Hz, 2H), 6.82 (dt, *J* = 8.7, 2.8 Hz, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 10.9 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 10.9 Hz, 1H), 4.29–4.21 (m, 1H), 4.01–3.88 (m, 2H), 3.76 (s, 3H), 3.57 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.39 (dd, *J* = 11.1, 6.4 Hz, 1H), 2.50 (d, *J* = 2.0 Hz, 1H), 2.21–1.96 (m, 2H), 1.94–1.78 (m, 1H), 1.48 (ddd, *J* = 14.7, 5.9, 2.8 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 36.1 (t), 40.9 (t), 55.2 (q), 65.0 (d), 66.7 (t), 69.0 (d), 70.6 (t), 71.4 (t), 72.9 (d), 74.2 (d), 82.6 (s), 113.8 (d, 2C), 127.8 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 129.9 (s), 137.4 (s), 159.3 (s) ppm.

ESI-MS (*m/z*) : 407.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.85; H, 7.34.
Found: C, 71.75; H, 7.26.

(*S*)-2-((2*R*,4*R*)-4-(Benzyloxy)-2-(4-methoxybenzyloxy)-hex-5-ynyl)oxirane (77)



To a solution of diol **83** (600 mg, 1.56 mmol) in dry DCM (15 mL) were added Bu_2SnO (7 mg), *p*-TsCl (327 mg, 1.71 mmol) followed by triethylamine (435 µL, 3.12 mmol) and DMAP (20 mg) at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 1.5 h. Reaction mixture was diluted with DCM, and extracted. Combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude tosylate (840 mg, 1.56 mmol) was dissolved in methanol (20 mL) and stirred with anhydrous K_2CO_3 (270 mg, 1.94 mmol) for 30 min at 0 °C and concentrated. The crude product was dissolved in ethyl acetate and washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (15% ethyl acetate in petroleum ether) gave epoxide **77** (470 mg, 82% for two steps) as colorless oil.

Mol. Formula : $C_{23}H_{26}O_4$

$[\alpha]_D$: +86.9 (*c* 1.0, $CHCl_3$).

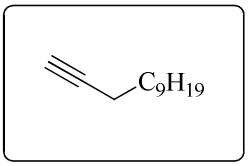
IR ($CHCl_3$) $\tilde{\nu}$: 3432, 3289, 2927, 2110, 1612, 1513, 1248, 1069, 753, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.36–7.27 (m, 5H), 7.14 (dt, *J* = 8.7, 2.8 Hz, 2H), 6.82 (dt, *J* = 8.7, 2.8 Hz, 2H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 4.34–4.25 (m, 1H), 3.86 (ddd, *J* = 12.7, 11.9, 5.9 Hz, 1H), 3.76 (s, 3H), 3.03 (ddt, *J* = 5.8, 3.9, 2.7 Hz, 1H), 2.78 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.49 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.47 (d, *J* = 2.1 Hz, 1H), 2.01 (dd, *J* = 7.0, 5.9 Hz, 2H), 1.74 (t, *J* = 5.8 Hz, 2H) ppm.

^{13}C NMR : δ 37.6 (t), 41.7 (t), 47.3 (t), 49.2 (d), 55.1 (q), 64.8 (d),

($CDCl_3$, 50 MHz)	70.5 (t), 71.4 (t), 72.6 (d), 73.9 (d), 82.7 (s), 113.6 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.3 (d, 2C), 129.4 (d, 2C), 130.3 (s), 137.5 (s), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 389.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 75.38; H, 7.15.
	Found: C, 75.30; H, 7.08.

Dodec-1-yne (84)

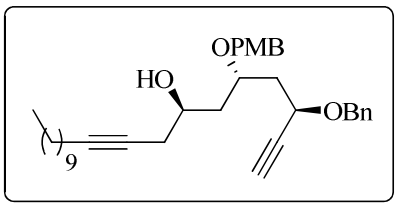


In a flame dried two necked round bottom flask (100 mL), Oxalyl chloride (2 mL, 23.21 mmol) was added dropwise to a solution of dry DMSO (2.47 mL, 34.82 mmol) in dry DCM (20 mL) at –78 °C. After stirring for 15 min, a solution of undecanol (2 g, 11.60 mmol) in dry DCM (20 mL) was then introduced drop wise with an additional stirring for 45 min, before it was treated with Et_3N (8 mL, 58.03 mmol) and allowed to ambient temperature. After stirring for an additional 15 min, the reaction was quenched with brine (20 mL) and the organic layer was successively washed with sat. $NaHCO_3$, water, brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification of crude by column chromatography (5% ethyl acetate in petroleum ether) afforded aldehyde (1.8 g, 91%) as colorless oil.

Aldehyde (1.8 g, 10.56 mmol) was dissolved in dry methanol (25 mL), treated with anhydrous K_2CO_3 (2.2 g, 15.85 mmol), followed by dimethyl-1-diazo-2-oxopropyl phosphonate (3 g, 15.85 mmol) at 0 °C. After stirring under nitrogen atmosphere at rt for 6 h, methanol was evaporated under reduced pressure, partitioned between ethyl acetate and water, organic layer was separated and aqueous layer extracted with ethyl acetate. Combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuum and the residue obtained was purified by column chromatography (5% ethyl acetate in petroleum ether) to afford dodecyne **84** (1.4 g, 80%) as colorless oil

Mol. Formula	: $C_{12}H_{22}$
IR ($CHCl_3$) $\tilde{\nu}$	: 2927, 2119, 1667, 1556, 1366, 1214, 861 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.17 (dt, *J* = 6.9, 2.6 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.59–1.25 (m, 16H), 0.87 (t, *J* = 6.2 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.0 (q), 18.4 (t), 22.7 (t), 28.5 (t), 28.8 (t), 29.1 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 70.0 (d), 84.5 (s) ppm.
ESI-MS (*m/z*)	: 189.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 86.67; H, 13.33.
	Found: C, 86.61; H, 13.40.

(3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)icosa-1,9-diyn-7-ol (85)

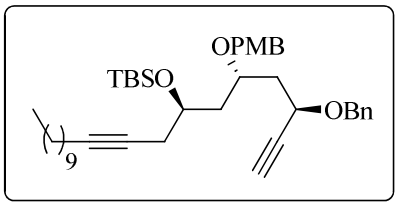


Dodec-1-yne **84** (0.816 g, 4.91 mmol) was taken in a flame dried two-necked round bottom flask (50 mL) and dissolved in anhydrous THF (15 mL). The reaction mixture was cooled to −78 °C, treated with *n*-BuLi (2.1 mL, 4.91 mmol, 2.34 M in hexane) drop wise and stirred for 15 min, treated with $BF_3{\cdot}Et_2O$ (0.553 mL, 4.36 mmol) and stirring was continued for an additional 15 minutes. A solution of epoxide **77** (0.4 g, 1.09 mmol) in anhydrous THF (10 mL) was added and stirred for 30 min at −78 °C. The reaction was quenched at −78 °C by addition of sat. Na_2SO_4 (20 mL), diluted with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude residue by column chromatography (20% ethyl acetate in petroleum ether) afforded **85** (0.54 g, 93%) as colorless oil.

Mol. Formula	: $C_{35}H_{48}O_4$
$[\alpha]_D$	: +54.3 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3469, 3306, 2926, 2111, 1612, 1514, 1248, 1070, 821, 746, 698 cm^{-1}.
^{1}H NMR	: δ 7.35–7.27 (m, 5H), 7.13 (dt, *J* = 8.7, 2.8 Hz, 2H), 6.81

($CDCl_3$, 200 MHz)	(dt, *J* = 8.7, 2.8 Hz, 2H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.26 (d, *J* = 10.6 Hz, 1H), 4.29–4.22 (m, 1H), 4.02–3.91 (m, 2H), 3.76 (s, 3H), 2.95 (d, *J* = 3.3 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.34–2.29 (m, 2H), 2.16–2.07 (m, 2H), 2.05–1.63 (m, 4H), 1.50–1.25 (m, 16H), 0.86 (t, *J* = 6.2 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.1 (q), 18.7 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.3 (t), 29.5 (t), 29.5 (t), 31.8 (t), 39.2 (t), 41.0 (t), 55.2 (q), 65.0 (d), 67.3 (d), 70.6 (t), 71.5 (t), 73.0 (d), 74.0 (d), 75.9 (s), 82.7 (s), 82.9 (s), 113.8 (d, 2C), 127.8 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 130.0 (s), 137.5 (s), 159.2 (s) ppm.
ESI-MS (*m/z*)	: 555.6 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 78.91; H, 9.08.
	Found: C, 78.80; H, 9.01.

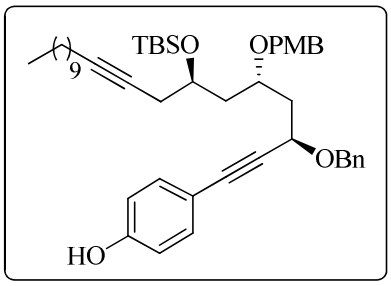
((3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)icosa-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethyl-silane (86)



A solution of alcohol **85** (1 g, 1.87 mmol) in dry DMF (4 mL) was cooled to 0 °C, imidazole (766 mg, 11.26 mmol) was added followed by TBS-Cl (0.848 g, 5.63 mmol) and stirring was continued at rt for 24 h. The reaction mixture was partitioned between ethyl acetate and water, organic layer was separated and aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuum. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded TBS-derivative **86** (1.15 g, 95%) as colorless oil.

Mol. Formula	: $C_{41}H_{62}O_4Si$
$[\alpha]_D$	: +49.2 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3308, 2927, 2110, 1613, 1514, 1249, 1095, 836, 775, 697 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.36–7.28 (m, 5H), 7.14 (dt, *J* = 8.7, 2.8 Hz, 2H), 6.81 (dt, *J* = 8.7, 2.8 Hz, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 10.7 Hz, 1H), 4.30–4.22 (m, 1H), 4.00–3.82 (m, 2H), 3.76 (s, 3H), 2.45 (d, *J* = 2.1 Hz, 1H), 2.32–2.29 (m, 2H), 2.16–2.08 (m, 2H), 2.05–1.93 (m, 3H), 1.68–1.59 (m, 1H), 1.49–1.24 (m, 16H), 0.88 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –4.6 (q), –4.1 (q), 14.1 (q), 18.0 (s), 18.8 (t), 22.7 (t), 25.9 (q, 3C), 28.2 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 41.8 (t), 42.2 (t), 55.2 (q), 65.3 (d), 68.6 (d), 70.3 (t), 70.6 (t), 72.1 (d), 73.8 (d), 76.6 (s), 82.4 (s), 83.0 (s), 113.7 (d, 2C), 127.6 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 130.8 (s), 137.8 (s), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 669.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 76.11; H, 9.66. Found: C, 76.02; H, 9.61.

4-((3*R*,5*R*,7*R*)-3-(Benzyloxy)-7-(*tert*-butyl-dimethylsilyloxy)-5-(4-methoxybenzyloxy)-icosa-1,9-diynyl)phenol (87)



To a solution of alkyne **86** (0.8 g, 1.23 mmol), iodophenol (0.408 g, 1.85 mmol), in Et_3N (8 mL) and DMF (4 mL), TPP (32 mg, 0.12 mmol) and $Pd(PPh_3)_2Cl_2$ (86 mg,

0.12 mmol) were added and degassed with argon for 30 min. CuI (23 mg, 0.12 mmol) was added and degassed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried (Na_2SO_4), concentrated and the residue obtained was purified by column chromatography (5% and 10% ethyl acetate in petroleum ether) to afford dimer **88** (10%) and the Sonogashira product **87** (700 mg, 77%) as colorless oils.

Mol. Formula : $C_{47}H_{66}O_5Si$

$[\alpha]_D$: +27.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3378, 2927, 2224, 1609, 1512, 1251, 1098, 834, 776, 698 cm^{-1}.

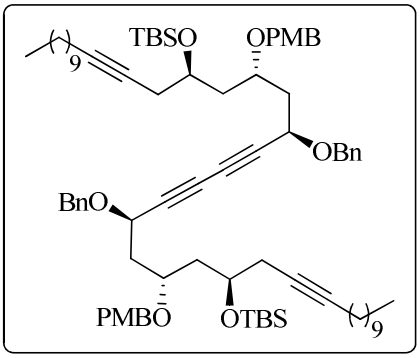
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.38–7.27 (m, 5H), 7.30 (dt, *J* = 8.6, 2.6 Hz, 2H), 7.17 (dt, *J* = 8.6, 2.6 Hz, 2H), 6.81 (dt, *J* = 8.6, 2.6 Hz, 2H), 6.74 (dt, *J* = 8.6, 2.6 Hz, 2H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.49–4.46 (m, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 3.99–3.89 (m, 2H), 3.76 (s, 3H), 2.33–2.32 (m, 2H), 2.13–2.00 (m, 4H), 1.72–1.65 (m, 1H), 1.49–1.42 (m, 2H), 1.34–1.24 (m, 15H), 0.87 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ –4.6 (q), –4.1 (q), 14.1 (q), 18.1 (s), 18.8 (t), 22.7 (t), 25.9 (q, 3C), 28.2 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 41.9 (t), 42.3 (t), 55.3 (q), 66.1 (d), 68.6 (d), 70.4 (t), 70.6 (t), 72.5 (d), 82.3 (s), 82.6 (s), 85.9 (s), 86.7 (s), 113.8 (d, 2C), 114.8 (s), 115.4 (d, 2C), 127.6 (d), 128.1 (d, 2C), 128.3 (d, 2C), 129.4 (d, 2C), 130.7 (s), 133.4 (d, 2C), 137.9 (s), 155.9 (s), 159.0 (s) ppm.

ESI-MS (*m/z*) : 761.2 $[M+Na]^+$.

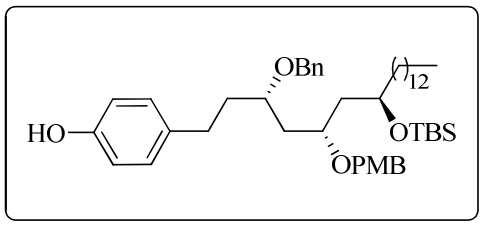
Elemental Analysis Calcd.: C, 76.38; H, 9.00.
Found: C, 76.32; H, 9.08.

(5*R*,7*R*,9*R*,14*R*,16*R*,18*R*)-9,14-Bis(benzyloxy)-7,16-bis(4-methoxybenzyloxy)-2,2,3,3,20,20,21,21-octamethyl-5,18-di(tridec-2-ynyl)-4,19-dioxa-3,20-disiladocosa-10,12-diyne (88)



Mol. Formula	: $C_{82}H_{122}O_8Si_2$
$[\alpha]_D$	: +45.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3368, 3019, 2400, 1612, 1514, 1215, 1035, 836, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.34–7.28 (m, 5H), 7.13 (dt, *J* = 8.7, 2.7 Hz, 2H), 6.81 (dt, *J* = 8.7, 2.7 Hz, 2H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.37–4.30 (m, 1H), 4.26 (d, *J* = 10.9 Hz, 1H), 3.95–3.79 (m, 2H), 3.75 (s, 3H), 2.32–2.28 (m, 2H), 2.15–2.08 (m, 2H), 2.04–1.94 (m, 3H), 1.66–1.60 (m, 1H), 1.53–1.24 (m, 16H), 0.88 (s, 9H), 0.85 (t, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –4.6 (q), –4.2 (q), 14.1 (q), 18.0 (s), 18.8 (t), 22.6 (t), 25.9 (q, 3C), 28.2 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 41.6 (t), 42.1 (t), 55.2 (q), 65.8 (d), 68.6 (d), 69.9 (s), 70.3 (t), 70.9 (t), 72.0 (d), 76.5 (s), 78.6 (s), 82.5 (s), 113.7 (d, 2C), 127.7 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 130.7 (s), 137.5 (s), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 1313.9 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 76.23; H, 9.52. Found: C, 76.12; H, 9.41.

4-((3*S*,5*R*,7*R*)-3-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-5-(4-methoxy-benzyloxy)icosyl)phenol (89)



A suspension of dialkyne **87** (200 mg, 0.27 mmol) and Raney-Ni (20 mg) in ethanol (10 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 10 h at rt. The reaction mixture was filtered through a plug of filter aid, washed with methanol thoroughly (5 x 10 mL), concentrated. Purification of crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **89** (168 mg, 83%) as colorless oil.

Mol. Formula : $C_{47}H_{74}O_5Si$

$[\alpha]_D$: +14.9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3368, 2854, 1613, 1514, 1216, 1039, 834, 758, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.34–7.24 (m, 5H), 7.17 (dt, *J* = 8.6, 2.8 Hz, 2H), 7.01 (dt, *J* = 8.4, 3.0 Hz, 2H), 6.83 (dt, *J* = 8.6, 2.8 Hz, 2H), 6.72 (dt, *J* = 8.4, 2.9 Hz, 2H), 5.00 (br s, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.27 (d, *J* = 10.9 Hz, 1H), 3.83 (dt, *J* = 12.2, 5.5 Hz, 1H), 3.77 (s, 3H), 3.70 (dt, *J* = 12.2, 6.3 Hz, 1H), 3.60 (dt, *J* = 11.7, 5.8 Hz, 1H), 2.61 (t, *J* = 8.0 Hz, 2H), 1.90–1.76 (m, 3H), 1.74 (t, *J* = 6.2 Hz, 2H), 1.55 (ddd, *J* = 13.4, 6.8, 6.0 Hz, 1H), 1.46–1.39 (m, 2H), 1.31–1.25 (m, 22H), 0.88 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ –4.3 (q), –4.1 (q), 14.1 (q), 18.1 (s), 22.7 (t), 24.7 (t), 26.0 (q, 3C), 29.3 (t), 29.6 (t, 2C), 29.7 (t, 2C), 29.7 (t, 2C), 29.9 (t), 30.4 (t), 31.9 (t), 36.1 (t), 37.6 (t), 40.4 (t), 42.6 (t), 55.2 (q), 69.5 (d), 70.3 (t), 70.8 (t), 73.3 (d), 75.3 (d), 113.7 (d, 2C), 115.2 (d, 2C), 127.4 (d), 127.8 (d, 2C), 128.3 (d, 2C), 129.3 (d, 2C), 129.4 (d, 2C), 130.9 (s), 134.3

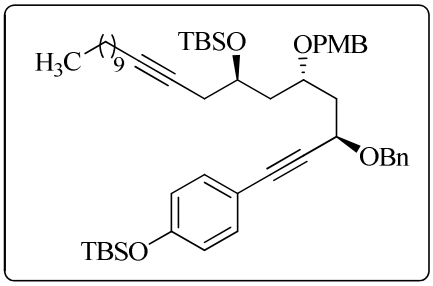
(s), 138.8 (s), 153.6 (s), 159.0 (s) ppm.

ESI-MS (*m/z*) : 770.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 75.55; H, 9.98.

Found: C, 75.48; H, 9.90.

((3*R*,5*R*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethylsilyloxy)phenyl)-5-(4-methoxy-benzyloxy)icosa-1,9-diyn-7-yloxy)(tert-butyl)dimethylsilane (91)



To a solution of alkyne **86** (0.8 g, 1.23 mmol), TBS-iodophenol **90** (0.619 g, 1.85 mmol), in Et_3N (8 mL) and DMF (4 mL), TPP (32 mg, 0.12 mmol) and $Pd(PPh_3)_2Cl_2$ (86 mg, 0.12 mmol), were added and degassed with argon for 30 min. CuI (23 mg, 0.12 mmol) was added and degassed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried (Na_2SO_4), concentrated and the residue obtained was purified by column chromatography (5% and 10% ethyl acetate in petroleum ether) to afford Sonogashira product **91** (928 mg, 88%) as colorless oil.

Mol. Formula : $C_{53}H_{80}O_5Si_2$

$[\alpha]_D$: +26.1 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3351, 2929, 2224, 1603, 1507, 1217, 1094, 838, 759, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.40–7.28 (m, 5H), 7.32 (dt, *J* = 8.7, 2.7 Hz, 2H), 7.17 (dt, *J* = 8.7, 2.8 Hz, 2H), 6.82 (dt, *J* = 8.8, 2.8 Hz, 2H), 6.77 (dt, *J* = 8.7, 2.7 Hz, 2H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.47–4.42 (m, 1H), 4.45 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 4.02–3.84 (m, 2H), 3.76 (s, 3H), 2.34–2.31 (m, 2H), 2.16–1.95 (m, 5H), 1.74–1.61 (m, 1H), 1.48–1.24 (m, 16H), 0.97 (s, 9H), 0.87 (s, 9H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.19 (s, 6H), 0.07 (s, 3H),

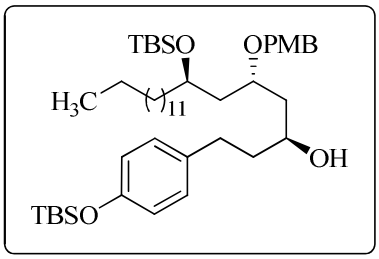
0.06 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ –4.6 (q), –4.5 (q, 2C), –4.1 (q), 14.1 (q), 18.0 (s), 18.2 (s), 18.8 (t), 22.6 (t), 25.6 (q, 3C), 25.9 (q, 3C), 28.2 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 41.9 (t), 42.3 (t), 55.2 (q), 66.1 (d), 68.6 (d), 70.3 (t), 70.5 (t), 72.3 (d), 76.7 (s), 82.4 (s), 85.8 (s), 87.0 (s), 113.7 (d, 2C), 115.5 (s), 120.1 (d, 2C), 127.5 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 130.9 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.0 (s) ppm.

ESI-MS (*m/z*) : 875.9 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 74.59; H, 9.45.
Found: C, 74.48; H, 9.40.

(3*S*,5*R*,7*R*)-7-(*Tert*-butyldimethylsilyloxy)-1-(4-(tert-butyldimethylsilyloxy)phenyl)-5-(4-methoxybenzyloxy)icosan-3-ol (92)



A suspension of di-TBS derivative **91** (1 g, 1.17 mmol), Raney-Ni (100 mg) in ethanol (30 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere at 55 °C for 18 h. The reaction mixture was filtered through a plug of filter aid, washed with methanol thoroughly (5 x 20 mL), concentrated. Purification of crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **92** (800 mg, 88%) as colorless oil.

Mol. Formula : $C_{46}H_{82}O_5Si_2$

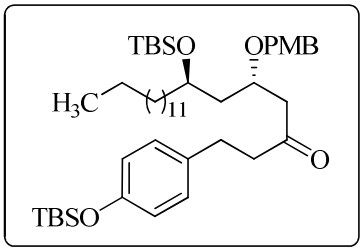
$[\alpha]_D$: –5.1 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.23 (dt, *J* = 8.6, 2.9 Hz, 2H), 7.03 (dt, *J* = 8.4, 2.9 Hz, 2H), 6.86 (dt, *J* = 8.6, 2.9 Hz, 2H), 6.73 (dt, *J* = 8.4, 2.9 Hz, 2H), 4.51 (d, *J* = 10.9 Hz, 1H), 4.42 (d, *J* = 10.9 Hz, 1H), 3.93–3.90 (m, 1H), 3.84–3.79 (m, 1H), 3.79 (s, 3H),

	3.77–3.71 (m, 1H), 3.11 (br s, 1H), 2.73–2.67 (m, 1H), 2.60–2.54 (m, 1H), 1.90–1.83 (m, 2H), 1.78–1.71 (m, 1H), 1.68–1.59 (m, 3H), 1.56–1.51 (m, 2H), 1.44–1.40 (m, 2H), 1.28–1.25 (m, 20H), 0.97 (s, 9H), 0.87 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H), 0.17 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ –4.4 (q, 2C), –4.4 (q), –4.0 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t), 24.7 (t), 25.7 (q, 3C), 25.9 (q, 3C), 29.3 (t), 29.7 (t, 2C), 29.7 (t, 2C), 29.7 (t, 2C), 29.9 (t), 31.1 (t), 31.9 (t), 37.7 (t), 39.5 (t), 39.8 (t), 41.5 (t), 55.3 (q), 68.1 (d), 69.8 (d), 70.6 (t), 74.9 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.4 (d, 2C), 130.2 (s), 134.9 (s), 153.6 (s), 159.3 (s) ppm.
ESI-MS (*m/z*)	: 794.0 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 71.63; H, 10.72.
	Found: C, 71.58; H, 10.60.

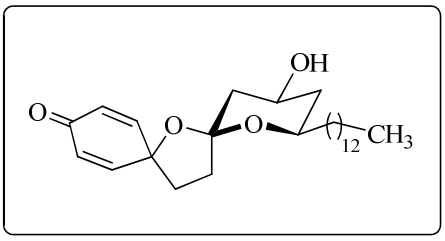
(5*S*,7*R*)-7-(*Tert*-butyldimethylsilyloxy)-1-(4-(tert-butyldimethylsilyloxy)phenyl)-5-(4-methoxy-benzyloxy)icosan-3-one (93)



In a flame dried two necked round bottom flask (25 mL), oxalyl chloride (67 µL, 0.77 mmol) was dissolved under N_2 in dry DCM (5 mL). After cooling the solution to –78 °C, dry DMSO (100 µL, 1.42 mmol) was added dropwise with stirring for 15 min. A solution of alcohol **92** (200 mg, 0.25 mmol) in dry DCM (5 mL) was added dropwise and stirred for 30 min. To this Et_3N (216 µL, 1.55 mmol) was added stirring continued for 15 min at –78 °C. The reaction mixture was partitioned between DCM and water, organic phase was separated and aqueous phase was extracted with DCM. Combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (5% ethyl acetate in petroleum ether) afforded ketone **93** (190 mg, 95%) as a colorless oil.

Mol. Formula	: $C_{46}H_{80}O_5Si_2$
$[\alpha]_D$	: –4.5 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3415, 2927, 1715, 1612, 1511, 1252, 1040, 836, 759, 686 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 7.19 (dt, *J* = 8.6, 2.9 Hz, 2H), 6.99 (dt, *J* = 8.4, 2.9 Hz, 2H), 6.85 (dt, *J* = 8.6, 2.9 Hz, 2H), 6.72 (dt, *J* = 8.4, 2.9 Hz, 2H), 4.42 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 4.09–4.02 (m, 1H), 3.84–3.79 (m, 1H), 3.78 (s, 3H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.71 (dd, *J* = 15.5, 7.1 Hz, 1H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.49 (dd, *J* = 15.6, 5.0 Hz, 1H), 1.76–1.69 (m, 1H), 1.51–1.41 (m, 3H), 1.25 (m, 22H), 0.97 (s, 9H), 0.88 (s, 9H), 0.87 (t, *J* = 7.18 Hz, 3H), 0.17 (s, 6H), 0.04 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ –4.5 (q, 2C), –4.4 (q), –4.0 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t), 24.7 (t), 25.7 (q, 3C), 25.9 (q, 3C), 28.7 (t), 29.3 (t), 29.6 (t, 3C), 29.7 (t, 3C), 29.8 (t), 31.9 (t), 37.9 (t), 42.7 (t), 45.6 (t), 48.8 (t), 55.2 (q), 69.5 (d), 71.1 (t), 73.1 (d), 113.8 (d, 2C), 119.9 (d, 2C), 129.1 (d, 2C), 129.2 (d, 2C), 130.7 (s), 133.6 (s), 153.8 (s), 159.1 (s), 208.6 (s) ppm.
ESI-MS (*m/z*)	: 807.8 $[M+K]^+$.
Elemental Analysis	Calcd.: C, 71.82; H, 10.48. Found: C, 71.78; H, 10.40.

Aculeatin D (37)

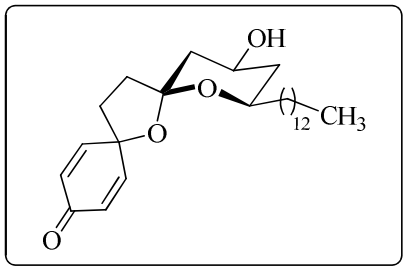


To a solution of PMB ether **93** (100 mg, 0.2 mmol) in DCM (10 mL) and buffer (2 mL), DDQ (45 mg, 0.18 mmol) was added portion wise at 0 °C and continued stirring

for another 30 min at the same temperature. The reaction mixture was filtered through a plug of filter aid, washed with DCM. Organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude (84 mg) was dissolved in dry THF (5 mL) and treated with TBAF (250 μL of 1M solution in THF, 0.25 mmol) at 0 °C. After stirring for 15 min at the same temperature, solvent was evaporated under reduced pressure. The crude ketal (50 mg) was dissolved in acetone/H_2O (2.5 mL, 10:1 v/v solution), was added PIFA (68 mg, 0.16 mmol) was added in one portion at room temperature. After stirring for 15 min in darkness, a saturated aqueous solution of $NaHCO_3$ (4 mL) was added and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash column chromatography (30% and 35% ethyl acetate in petroleum ether) to afford **38** (16 mg, 30%) and **37** (15 mg, 28%) as colorless oils

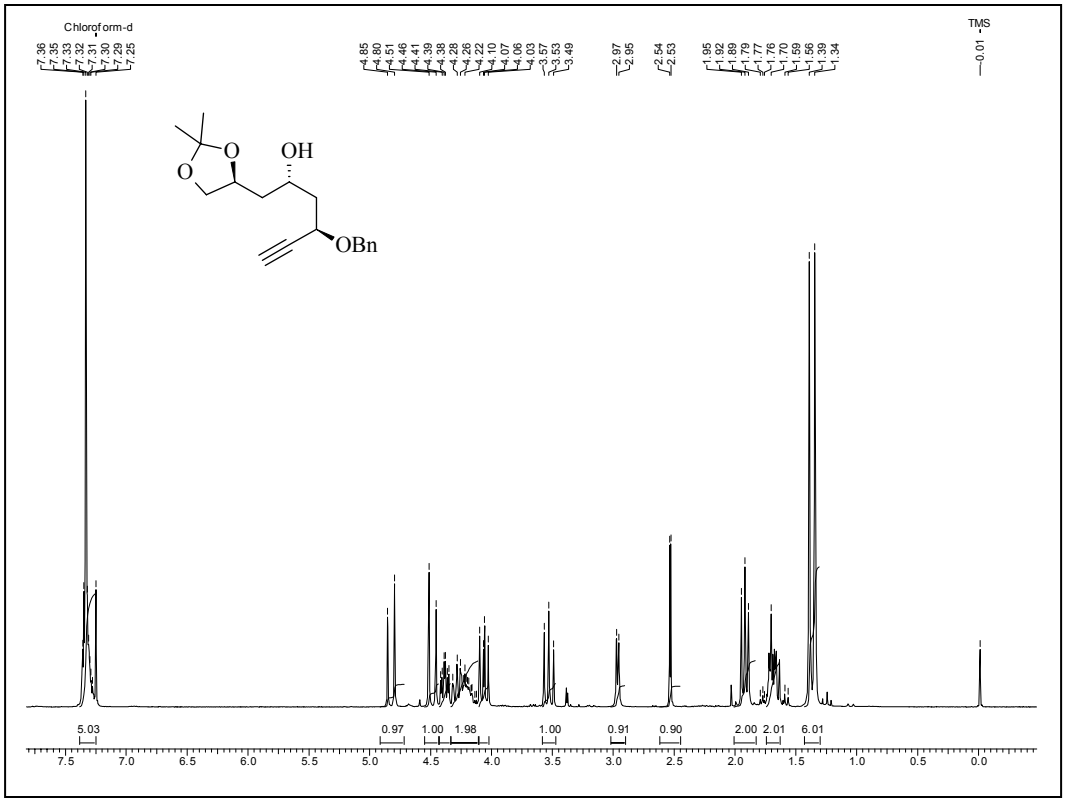
Mol. Formula	: $C_{26}H_{42}O_4$
$[\alpha]_D$	: +47.7 (*c* 0.2, $CHCl_3$) [lit +46.5 (*c* 1.0, $CHCl_3$)].
IR (Neat) $\tilde{\nu}$	: 3410, 2916, 2849, 1665, 1628, 1057, 1009 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 6.98 (dd, *J* = 10.5, 3.2 Hz, 1H), 6.77 (dd, *J* = 10.5, 3.2 Hz, 1H), 6.13 (dd, *J* = 10.3, 1.9 Hz, 1H), 6.12 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.88–3.80 (m, 1H), 3.40–3.32 (m, 1H), 2.39 (ddd, *J* = 12.7, 7.4, 2.0 Hz, 1H), 2.26 (ddd, *J* = 12.5, 11.3, 7.3 Hz, 1H), 2.12 (ddd, *J* = 12.1, 4.4, 1.6 Hz, 1H), 2.06 (ddd, *J* = 12.7, 8.4, 2.0 Hz, 1H), 1.95 (m, 1H), 1.87–1.75 (m, 2H), 1.69–1.57 (m, 1H), 1.53–1.43 (m, 2H), 1.35–1.23 (m, 22H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 14.1 (q), 22.7 (t), 25.9 (t), 29.3 (t), 29.4 (t), 29.6 (t), 29.6 (t, 2C), 29.7 (t, 3C), 31.9 (t), 33.4 (t), 34.9 (t), 35.7 (t), 40.8 (t), 43.6 (t), 66.8 (d), 71.6 (d), 78.1 (s), 109.2 (s), 127.2 (d), 127.4 (d), 148.8 (d), 151.5 (d), 185.5 (s) ppm.
ESI-MS (*m/z*)	: 441.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.60; H, 10.11. Found: C, 74.48; H, 10.00.

6-*epi*-Aculeatin D (38)

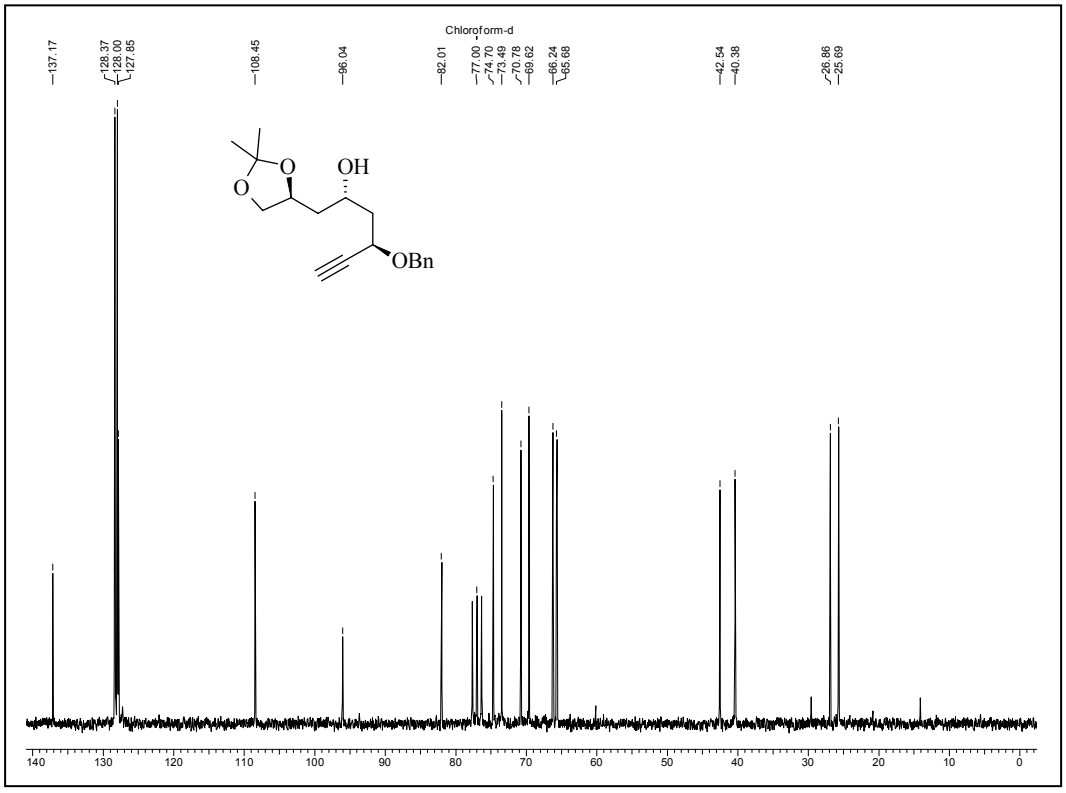


Mol. Formula	: $C_{26}H_{42}O_4$
$[\alpha]_D$	: +14.6 (*c* 0.2, $CHCl_3$) [lit +15.0 (*c* 1.0, $CHCl_3$)].
IR (Neat) $\tilde{\nu}$	: 3410, 2916, 2849, 1664, 1628, 1053, 1005 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 6.81 (dd, *J* = 10.4, 3.2 Hz, 1H), 6.76 (dd, *J* = 10.4, 3.2 Hz, 1H), 6.11 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.10 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.15–4.02 (m, 1H), 3.83–3.75 (m, 1H), 2.42–2.32 (m, 1H), 2.24 (dd, *J* = 10.3, 8.2 Hz, 1H), 2.08 (ddd, *J* = 12.4, 4.7, 1.6 Hz, 1H), 2.04–1.94 (m, 3H), 1.62 (dd, *J* = 11.8, 11.8 Hz, 1H), 1.52–1.41 (m, 2H), 1.32–1.22 (m, 22H), 1.18 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.6 (t), 29.7 (t, 6C), 31.9 (t), 34.6 (t), 35.9 (t), 38.8 (t), 40.6 (t), 43.0 (t), 65.3 (d), 69.1 (d), 79.0 (s), 108.9 (s), 127.0 (d), 127.1 (d), 149.2 (d), 151.4 (d), 185.5 (s) ppm.
ESI-MS (*m/z*)	: 441.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.60; H, 10.11. Found: C, 74.51; H, 10.02.

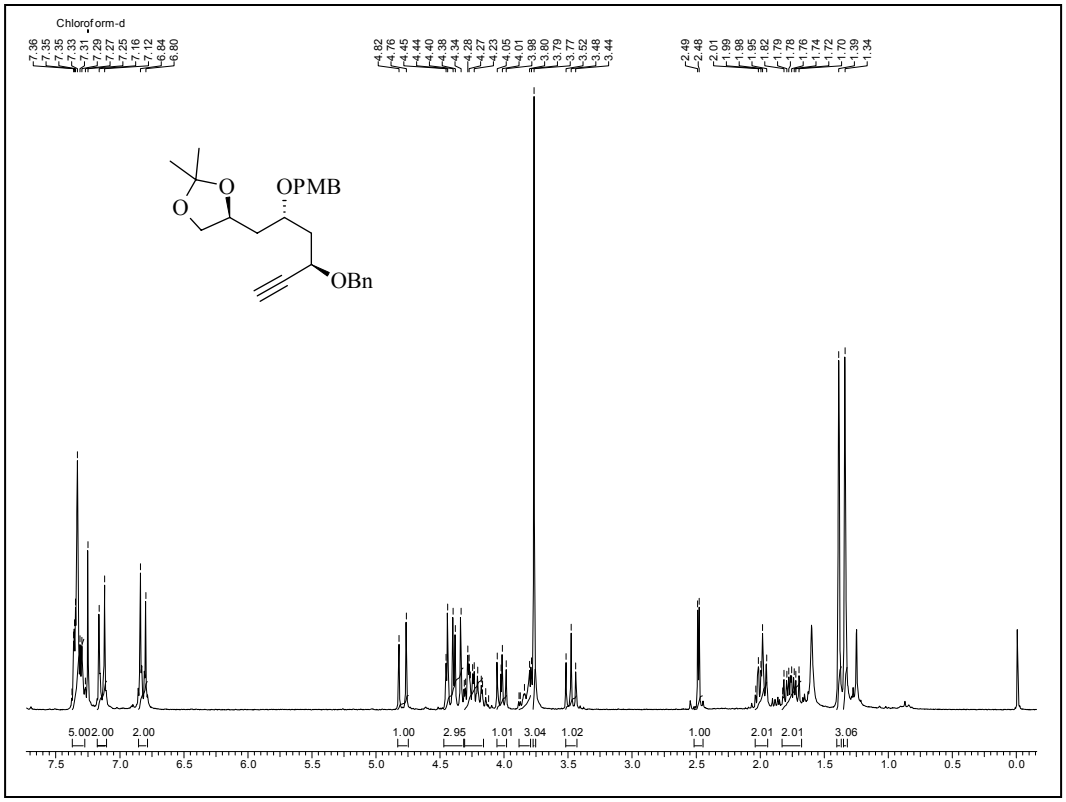
Spectroscopic Data



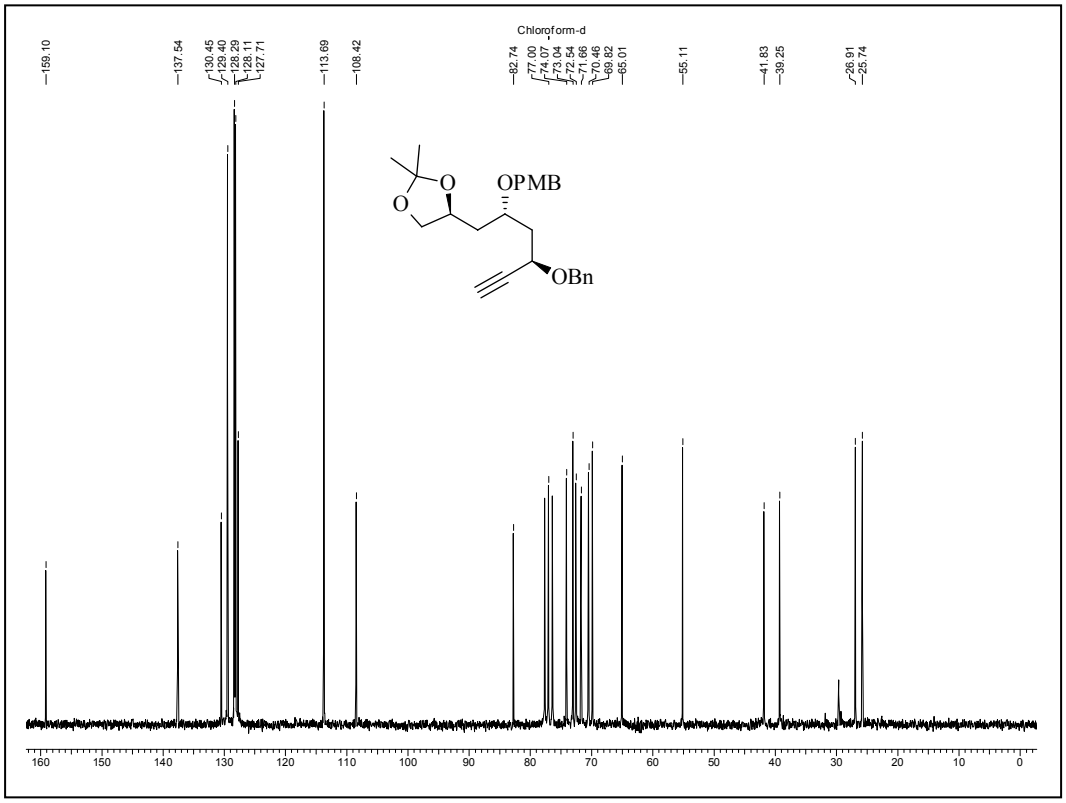
^{1}H NMR Spectrum of 81 in $CDCl_3$



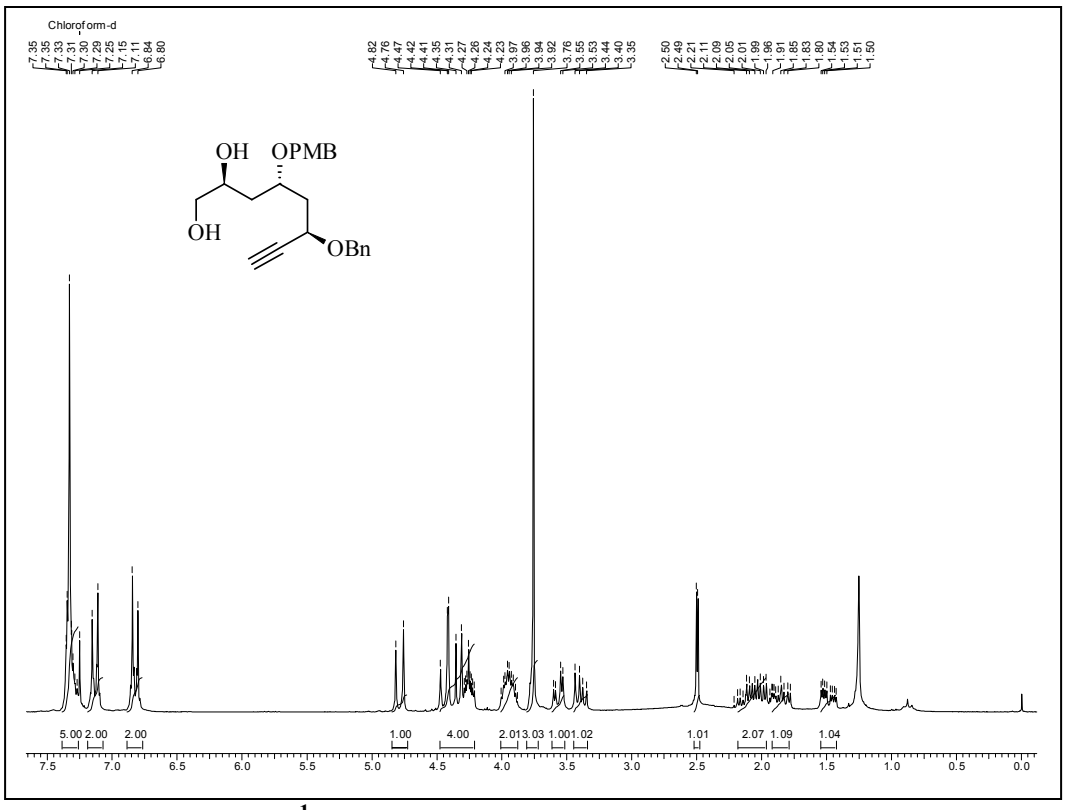
^{13}C NMR Spectrum of 81 in $CDCl_3$



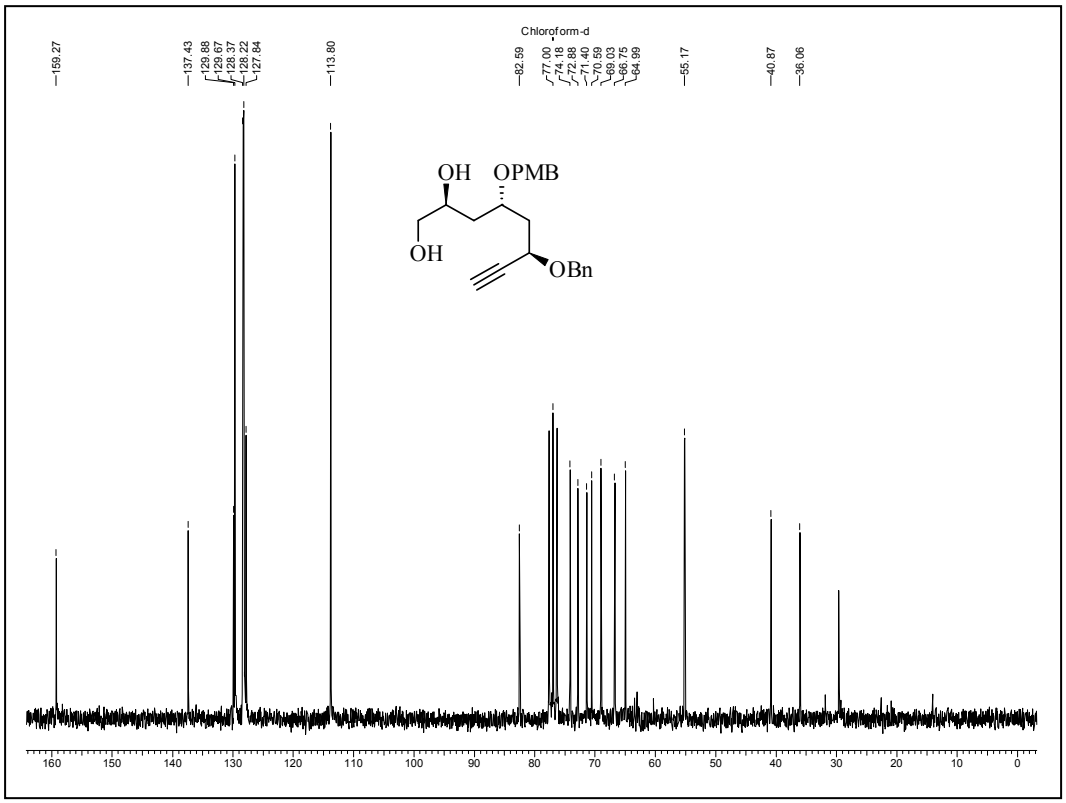
^{1}H NMR Spectrum of 82 in $CDCl_3$



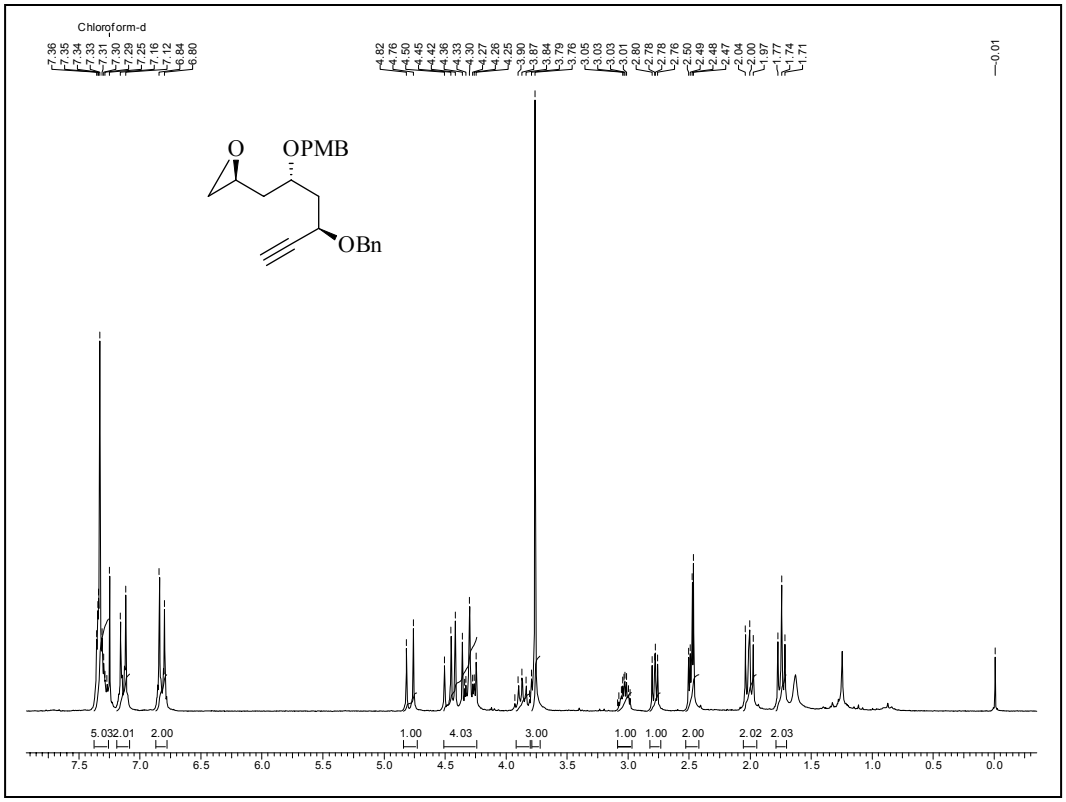
^{13}C NMR Spectrum of 82 in $CDCl_3$



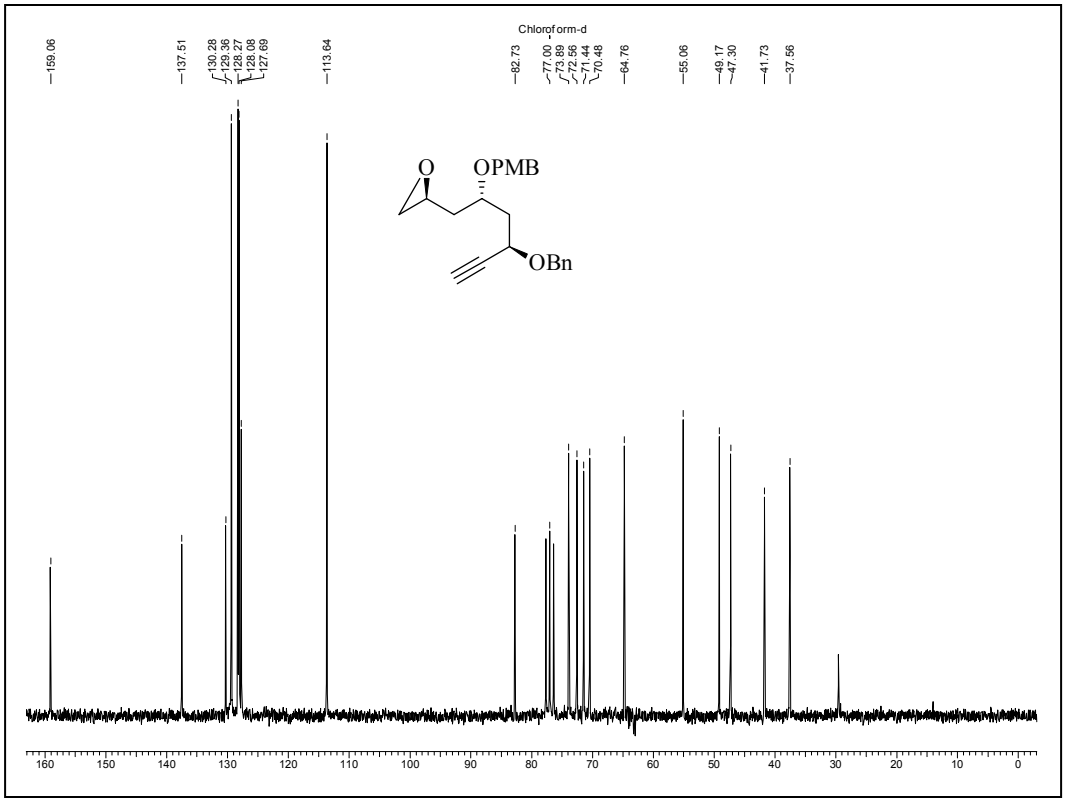
^{1}H NMR Spectrum of 83 in $CDCl_3$



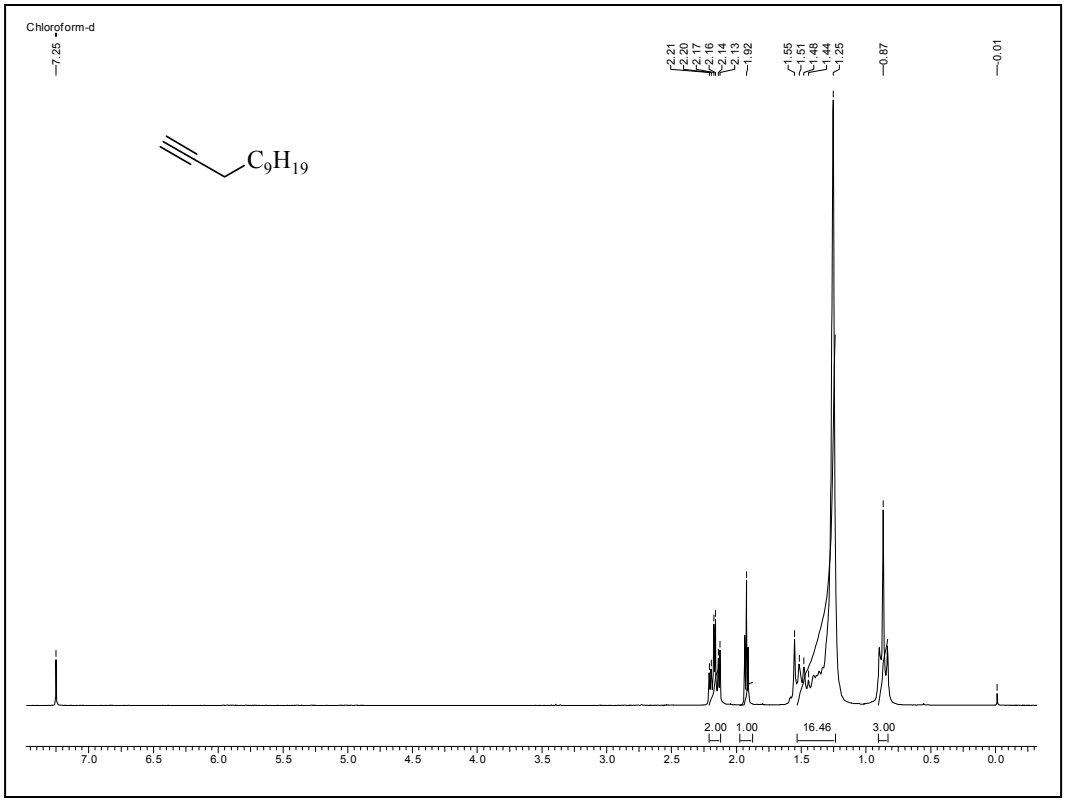
^{13}C NMR Spectrum of 83 in $CDCl_3$



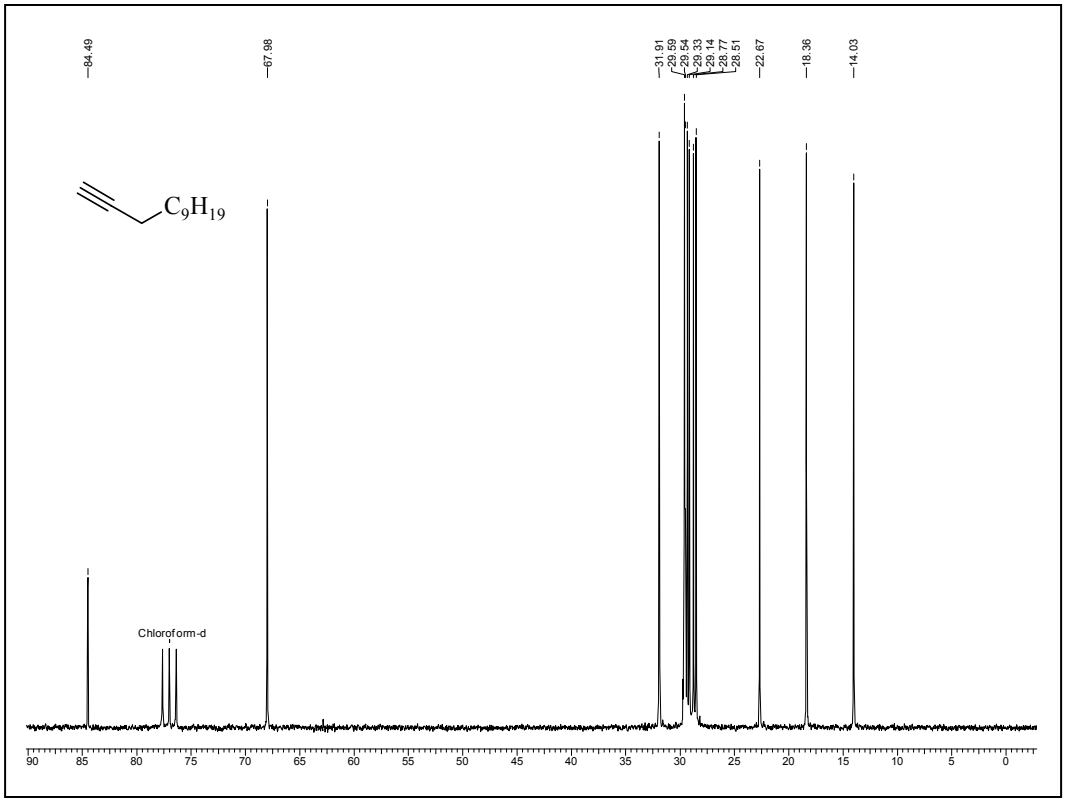
^{1}H NMR Spectrum of 77 in $CDCl_3$



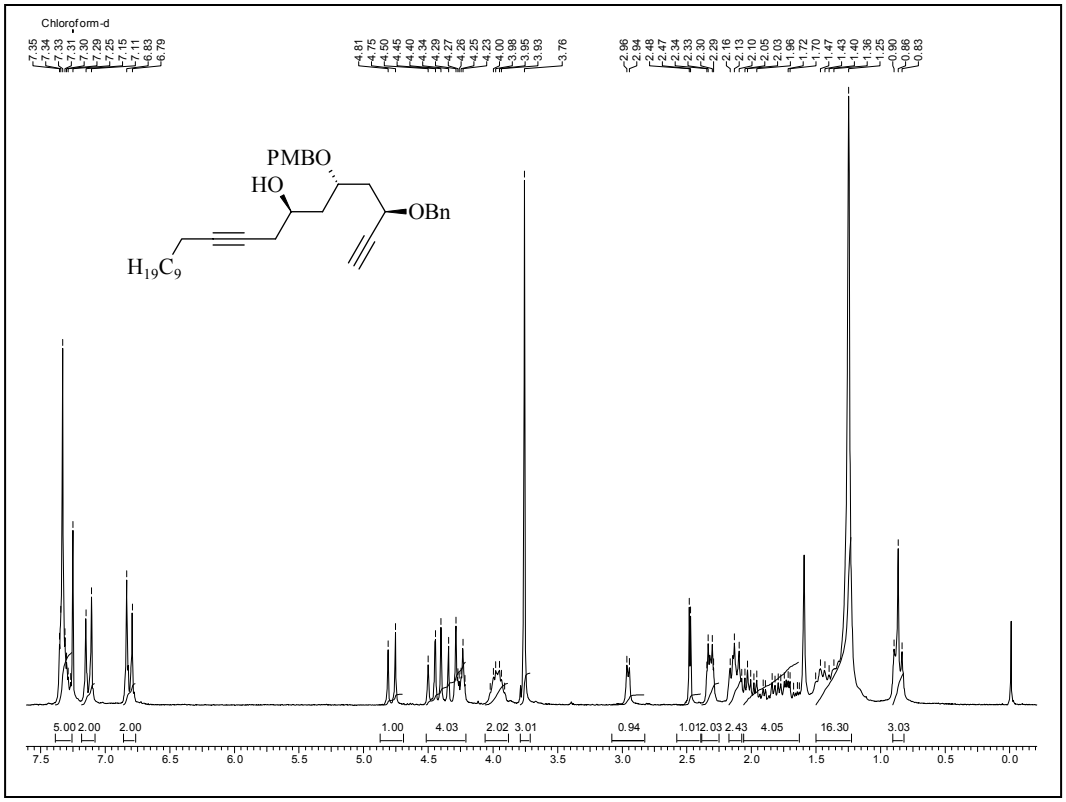
^{13}C NMR Spectrum of 77 in $CDCl_3$



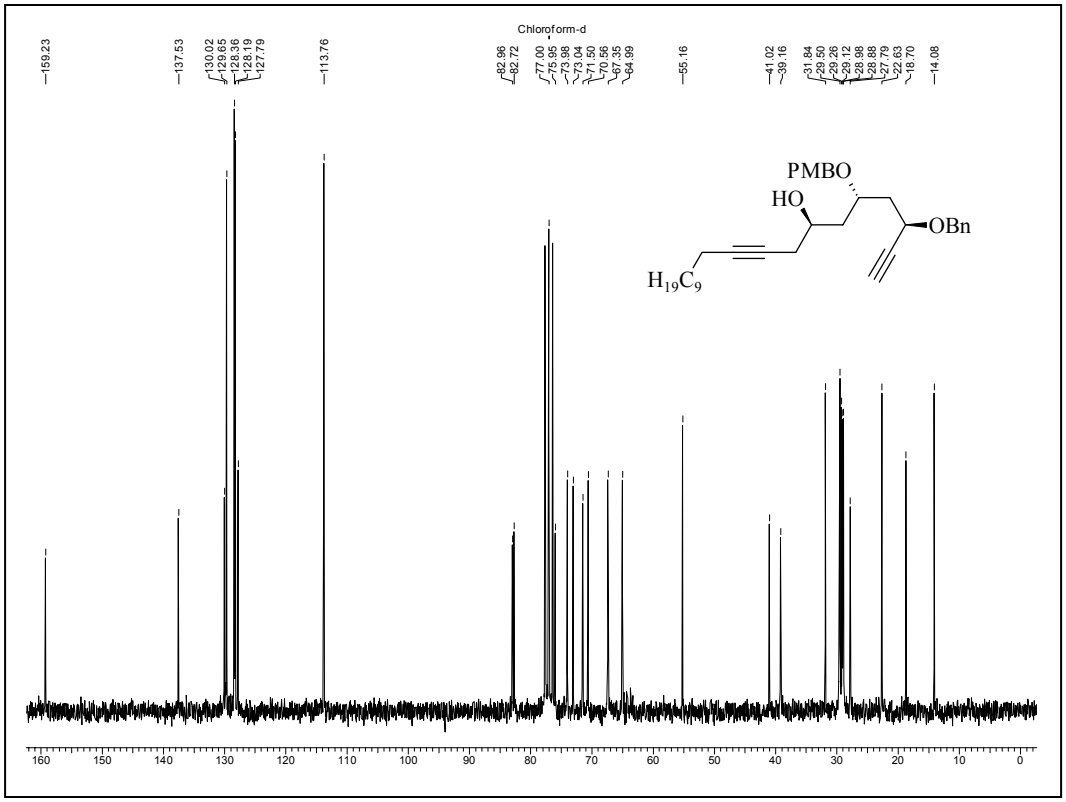
^{1}H NMR Spectrum of 84 in $CDCl_3$



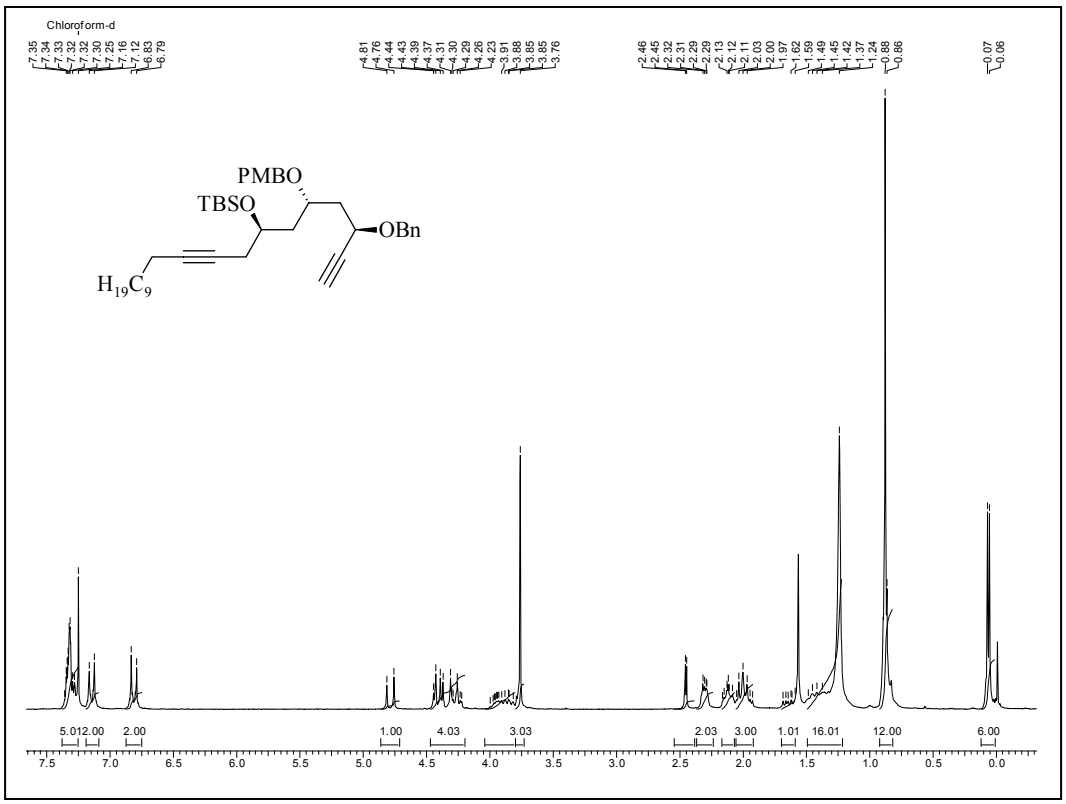
^{13}C NMR Spectrum of 84 in $CDCl_3$



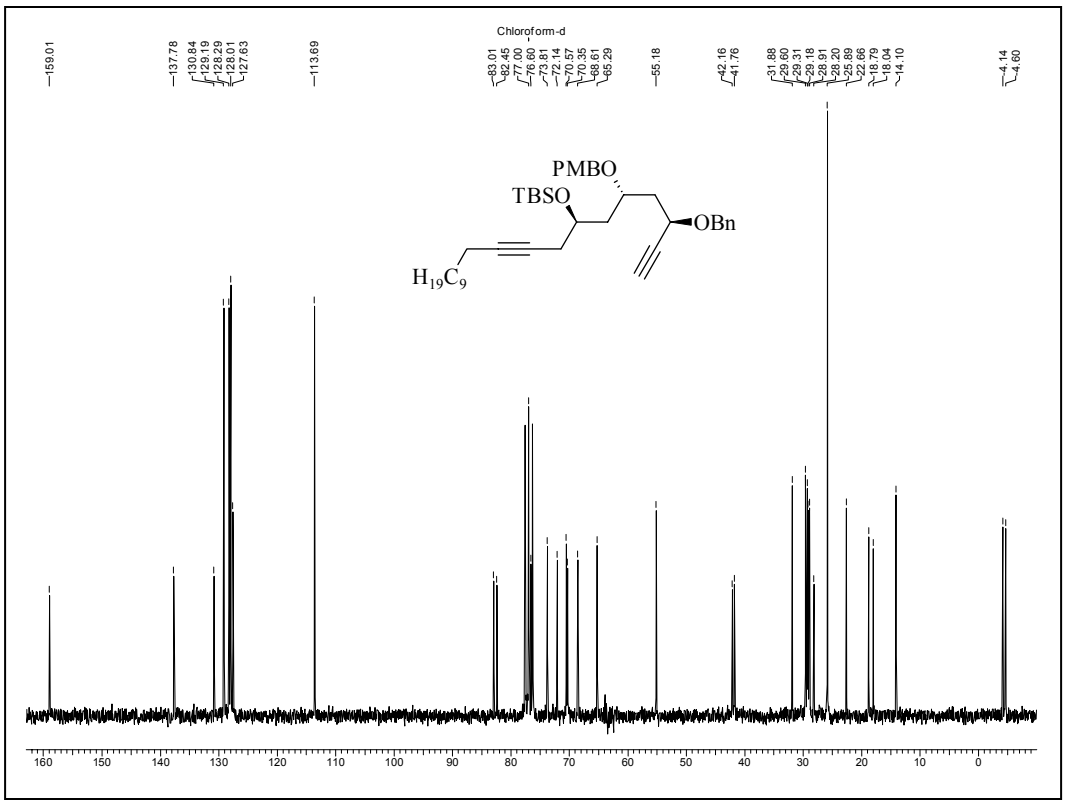
^{1}H NMR Spectrum of 85 in $CDCl_3$



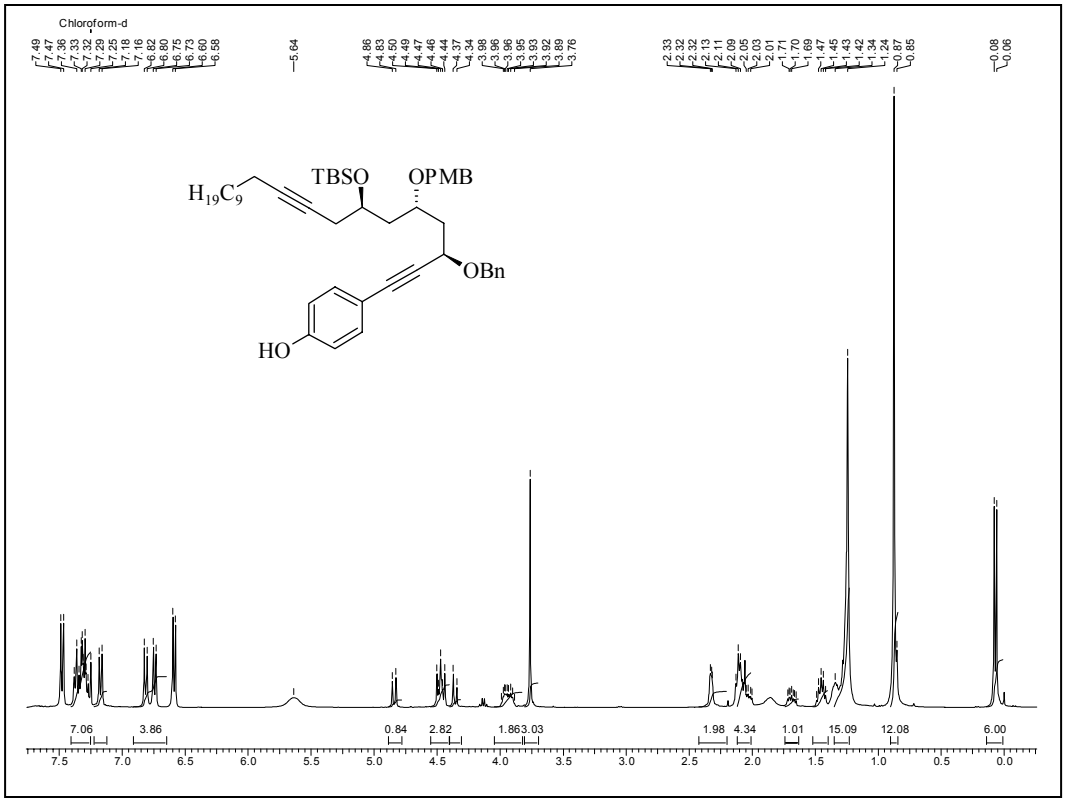
^{13}C NMR Spectrum of 85 in $CDCl_3$



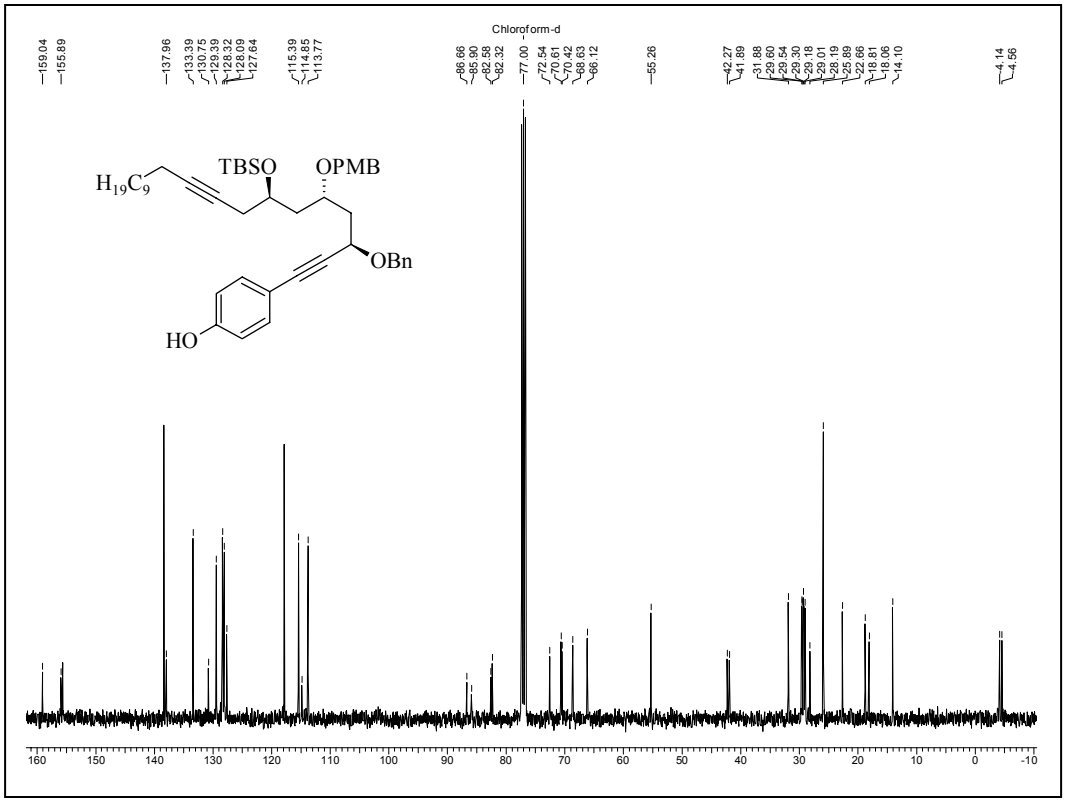
^{1}H NMR Spectrum of 86 in $CDCl_3$



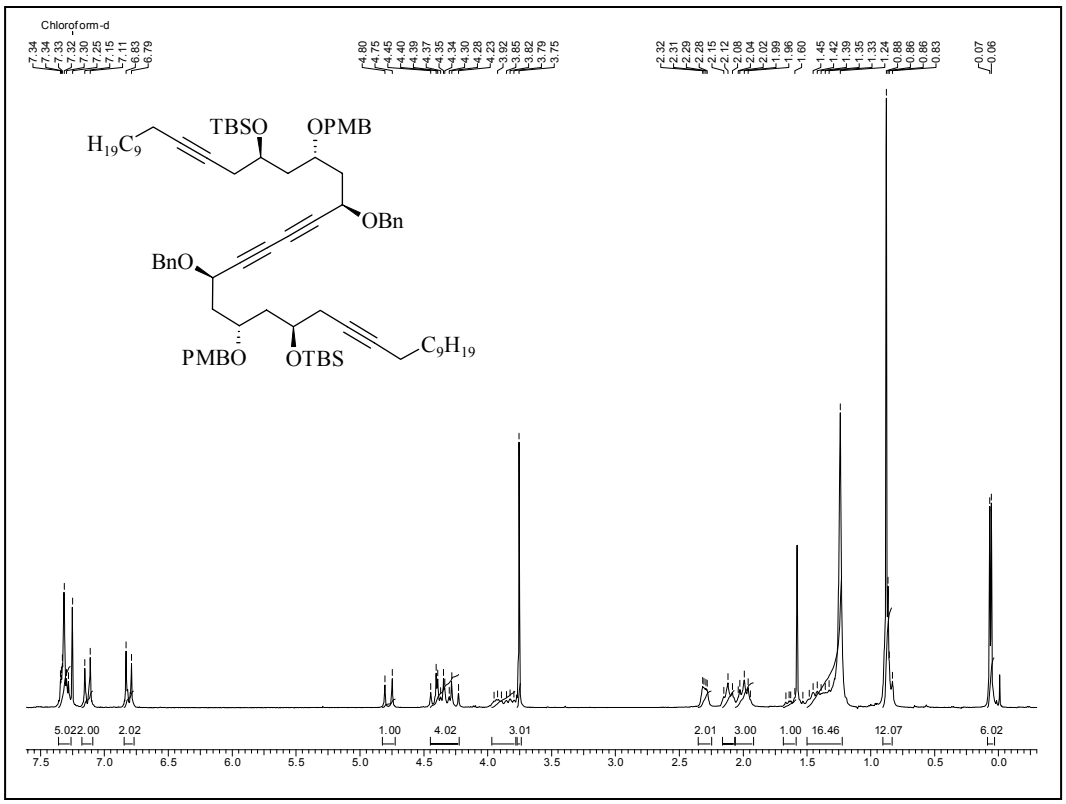
^{13}C NMR Spectrum of 86 in $CDCl_3$



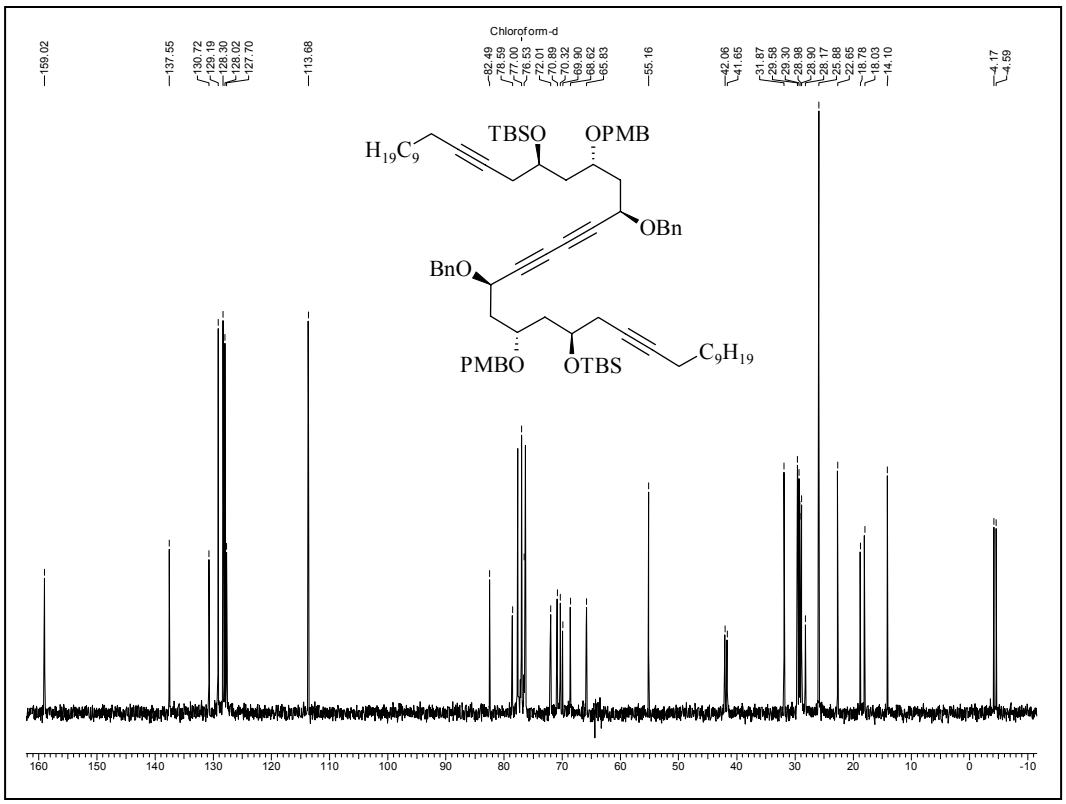
^{1}H NMR Spectrum of 87 in $CDCl_3$



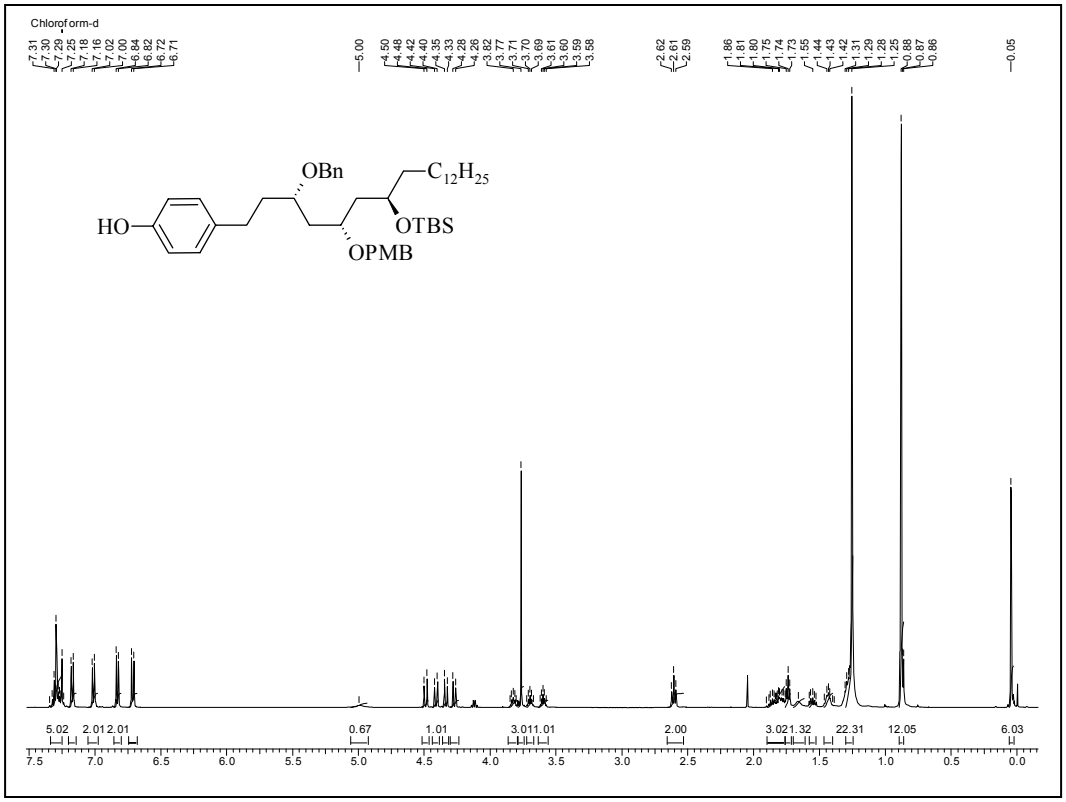
^{13}C NMR Spectrum of 87 in $CDCl_3$



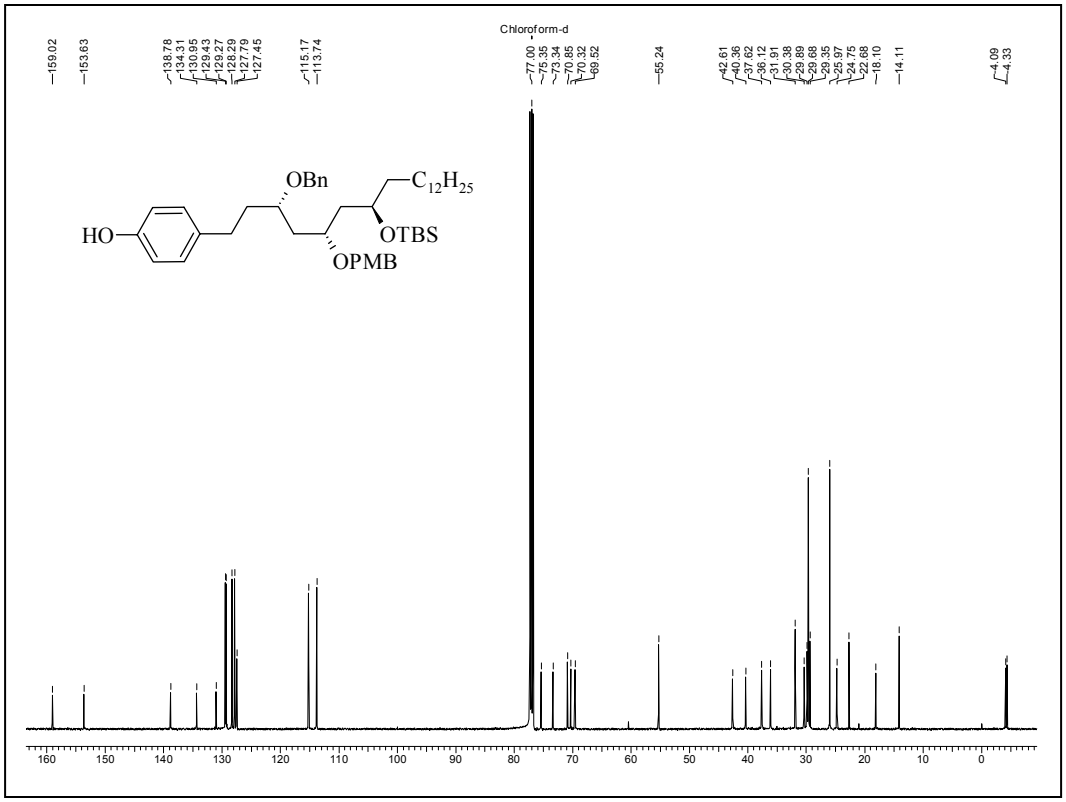
^{1}H NMR Spectrum of 88 in $CDCl_3$



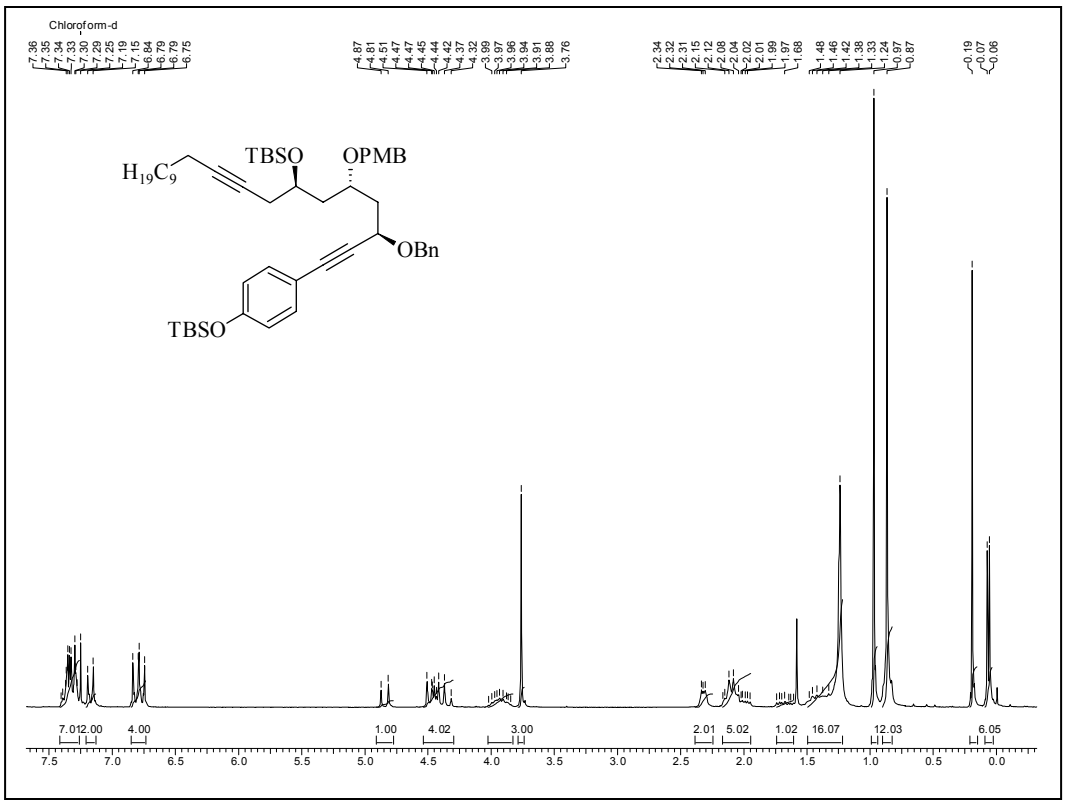
^{13}C NMR Spectrum of 88 in $CDCl_3$



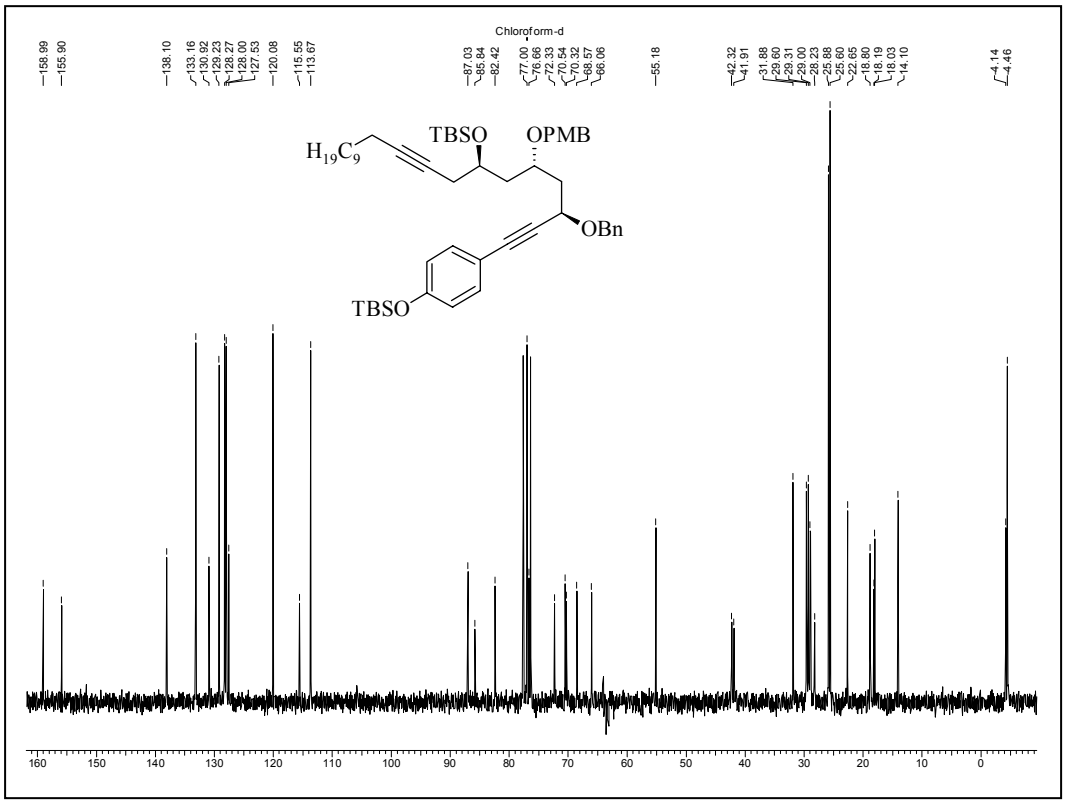
^{1}H NMR Spectrum of 89 in $CDCl_3$



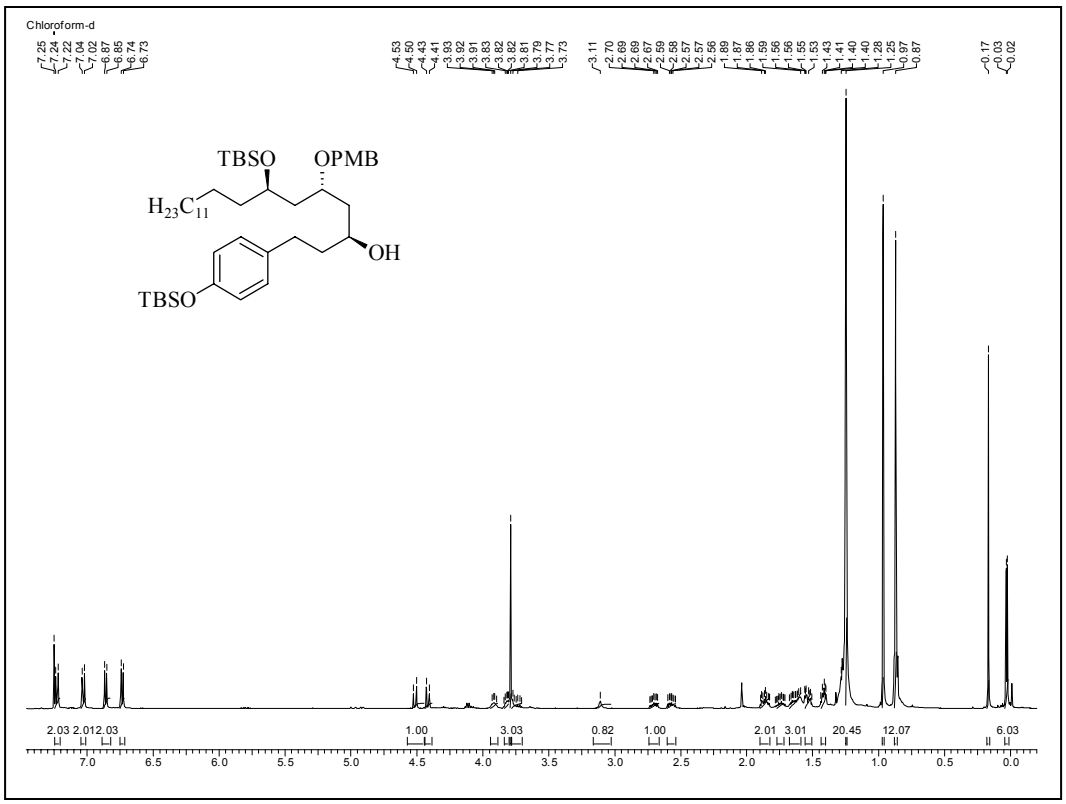
^{13}C NMR Spectrum of 89 in $CDCl_3$



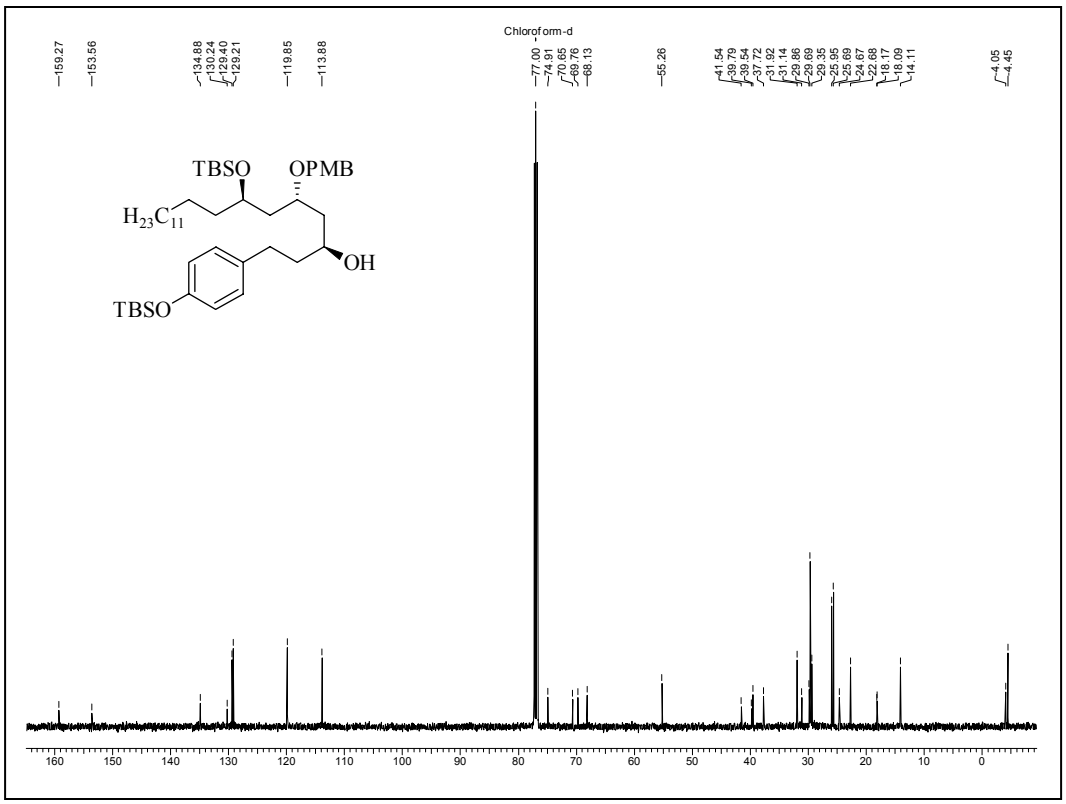
^{1}H NMR Spectrum of 91 in $CDCl_3$



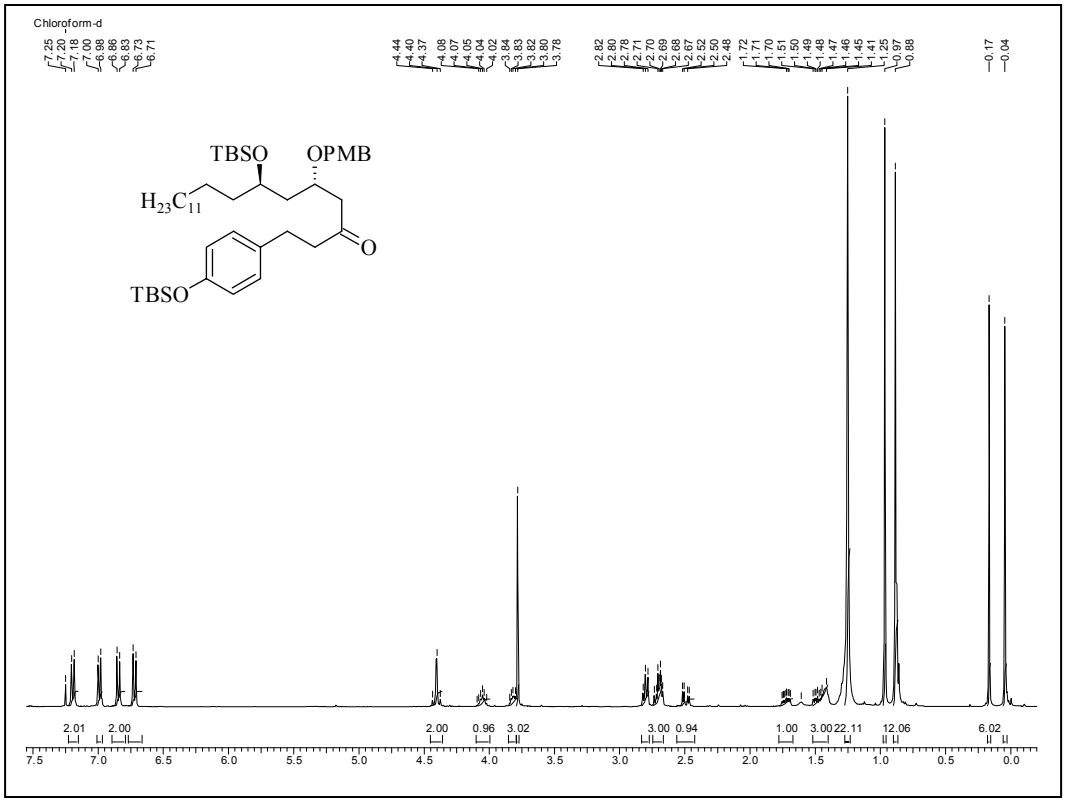
^{13}C NMR Spectrum of 91 in $CDCl_3$



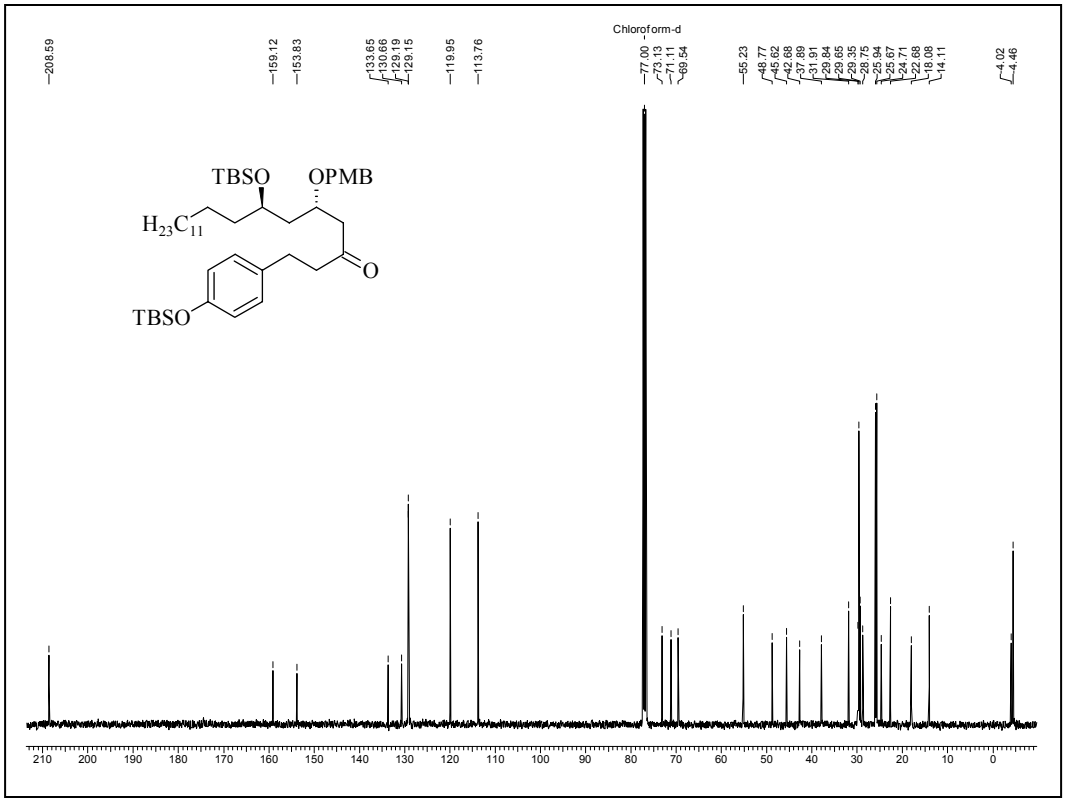
^{1}H NMR Spectrum of 92 in $CDCl_3$



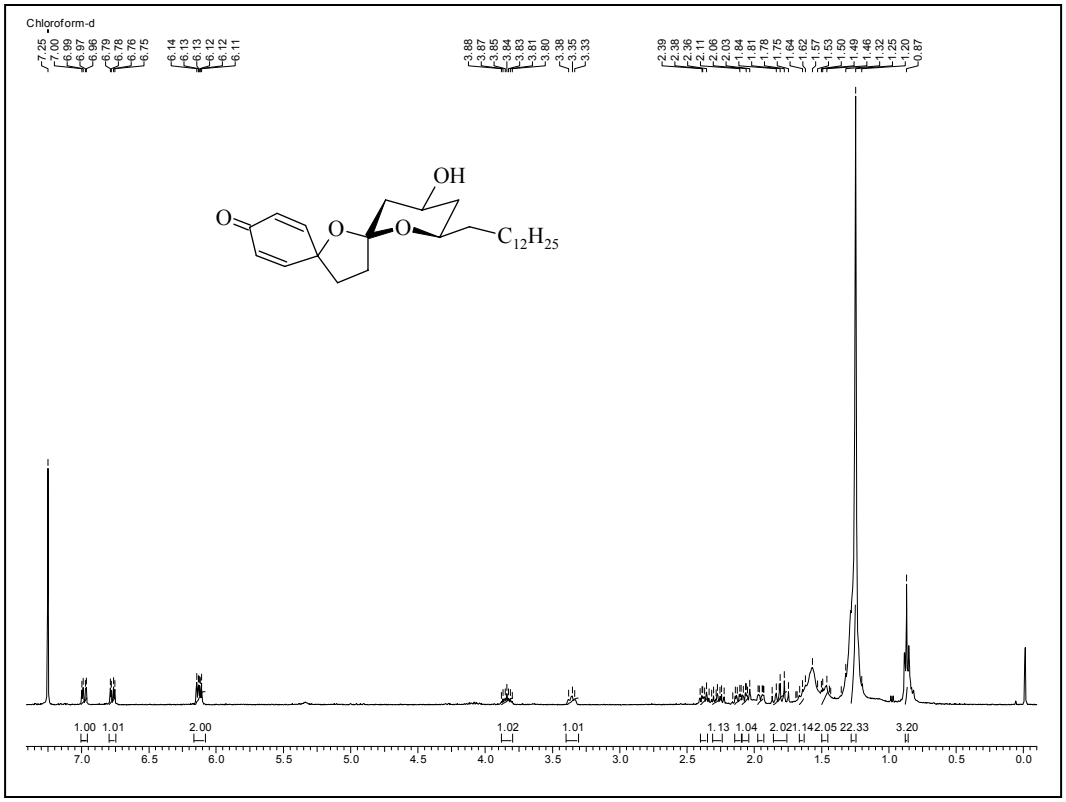
^{13}C NMR Spectrum of 92 in $CDCl_3$



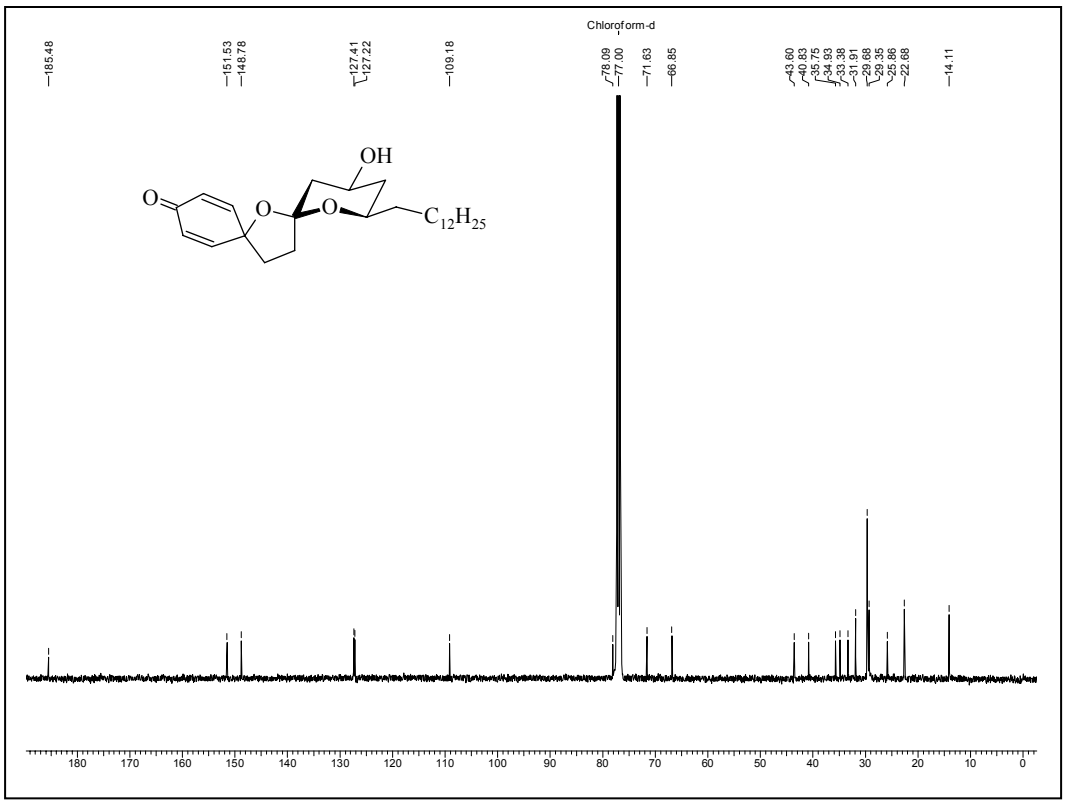
^{1}H NMR Spectrum of 93 in $CDCl_3$



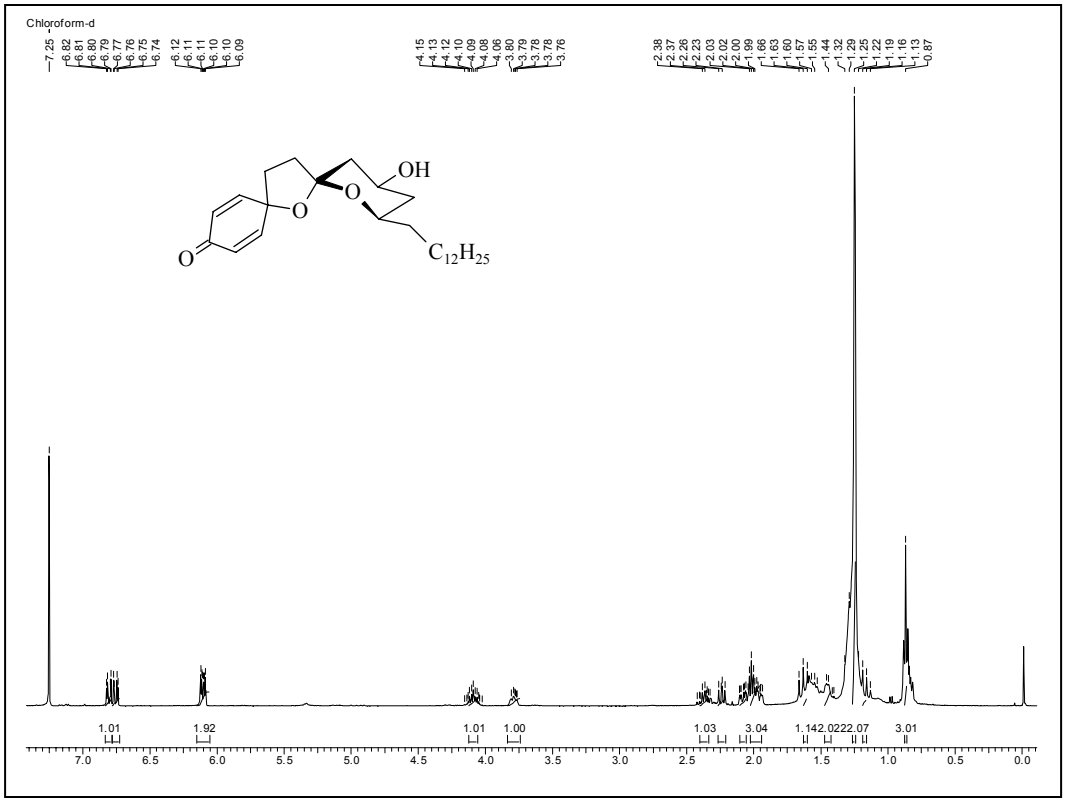
^{13}C NMR Spectrum of 93 in $CDCl_3$



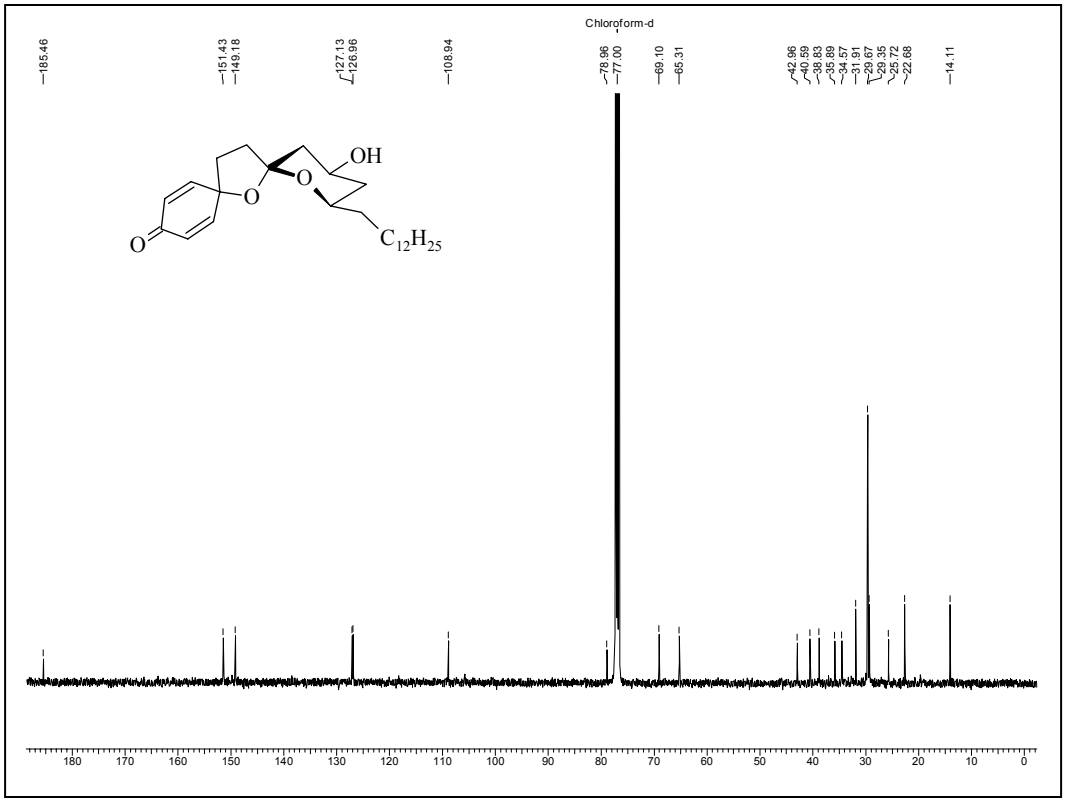
^{1}H NMR Spectrum of 37 in $CDCl_3$



^{13}C NMR Spectrum of 37 in $CDCl_3$



^{1}H NMR Spectrum of 38 in $CDCl_3$



^{13}C NMR Spectrum of 38 in $CDCl_3$

References

1. After much consideration, it has been decided to use the more popular term "spiroketal" and not "spiroacetal" although the latter is more correct by IUPAC standards.
2. (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617-1661. (b) Vaillan, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. The Total Synthesis of Natural Products; John Wiley & Sons: New York, **1992**, *8*, 533-691.
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Chapter III

Cycloisomerization of Sugar Alkynols

Introduction

Basic concepts of transition metal catalysis

A catalyst is a substance which can accelerate (positive catalyst or promoter) or decelerate (negative catalyst or inhibitor) chemical reactions without being consumed or permanently changed chemically. A catalyst provides alternative paths with higher or lower activation barriers without changing equilibrium constants. Therefore, the equilibrium is attained more rapidly by using catalysts. In addition to the enhanced reaction time, using transition-metal catalyst in organic syntheses offers innumerable advantages. For example, by the choice of ligands and metals in catalysts, we can control chemo-, regio- and diastreoselectivity of the reactions.[1]

Catalysts with transition elements have been widely applied in organic syntheses. It is because transition metals can form stable compounds with more than one oxidation states. They can gain or lose electrons without high energetic penalty. Therefore, oxidation states of transition metal complexes can be changed smoothly and transition metal complexes act as the media to push reactions forward. More specifically, palladium-catalyzed methodology has been extensively utilized in recent years.[2] The ability to create multiple carbon-carbon bonds from simple starting materials, the regio- and stereospecificity of the reactions, the exceptional tolerance for functional groups, the insensitivity to air or moisture, and the procedural ease with which the reactions can be carried out have all contributed to the success of palladium in organic synthesis.

Transition metal catalyzed cyclizations have proven to be a powerful tool in organic synthesis. These cyclizations often use π systems as reactive moieties. Some of such notable and important cyclization reactions include ene-yne/ene-allene cyclizations, intramolecular allyl-olefin couplings, intramolecular Heck reactions, ring-closing metathesis reactions, catalytic Pauson-Khand reactions etc. All these reactions are extensively used in organic synthesis and have become an integral part of synthesis of complex molecules.

The Larock group have shown a series of recent papers that palladium-catalyzed cyclisation or annulation methodology[3] can be effectively employed for the synthesis of

indoles, isoindolo-[2,1-α]indoles, benzofurans, benzopyrans, isocoumarins, α-pyrones, isoquinolines, carbolines and polycyclic aromatic hydrocarbons with a wide variety of substituent patterns.

The ability of palladium to activate C≡C bonds has been used extensively in organic synthesis. In recent years, palladium-catalyzed C≡C activation has received considerable attention. Since Reppe's pioneering research on the nickel-catalyzed alkyne oligomerization, the transition metal-mediated reactions of alkyne have grown explosively to embrace a wide variety of chemical transformations.[4] The unique reactivity of alkynes in the presence of transition metals stem from its good coordinating ability to transition metals and a large amount of energy stored in the triple bond.

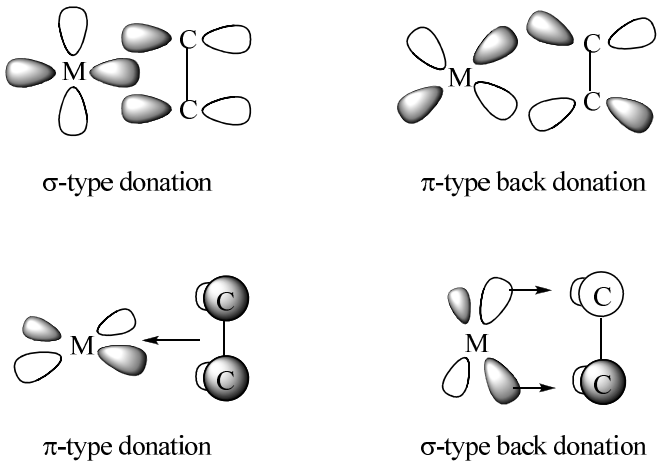


Figure 1: *Orbital interactions of Alkyne-Metal complex*

Alkynes can coordinate to transition metals in various ways depending on the number of metals present and electronic environment of metals or alkynes. Typically, the coordination of a transition metal to an alkyne, which is the first event of many alkyne reactions, results in a distortion of the alkyne group toward olefin geometry and elongation of the carbon-carbon bond, which is often explained by the Dewar-Chatt-Duncanson model as depicted in Figure 1. The σ-type donation occurs through the interactions between the filled π bonding orbital of alkyne and a proper acceptor orbital on the metal. On the other hand, the π-type back donation is established when a filled

metal d-orbital is aligned with π* orbital of the alkyne. The combined effect is weakening the carbon-carbon triple bond. In general, the σ-type donation orbital interactions predominate with early transition metals or metals with high oxidation state and electron rich alkynes and the π-type back donation becomes increasingly more important with later, lower-oxidation state transition metals and electron poor alkynes.

The major difference in bonding with transition metals between alkenes and alkynes is that the latter has a second occupied π orbital perpendicular to the bonding plane. These secondary orbital interactions further strengthen the metal-alkyne linkage, and therefore, alkynes tend to bind more tightly to transition metals than alkenes.[5] Alkynes also can form a complex with two metal centers, providing two electrons to each metal. Some metal clusters of this type are so strongly bound that they can be utilized as a protecting group for alkyne functionality.[6] For this reason, many early reactions of alkynes often required a stoichiometric amount of metals, except for polymerization reactions. However, with the recent development of transition metal chemistry, many chemical transformations can be achieved catalytically. In addition, chemo- and regioselectivity associated with these transformations are addressed with the development of the new catalyst systems.

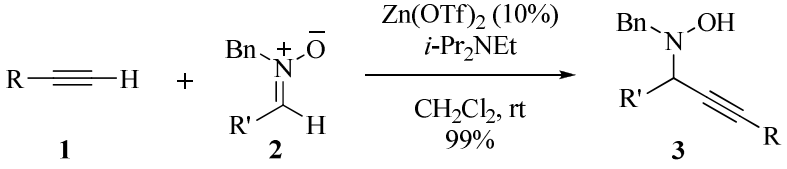
Alkyne is becoming increasingly important as a fundamental building block in organic synthesis due to its relative robustness and ease of substrate preparation, for example, by deprotonation of terminal alkynes or activation of propargylic positions. A number of review articles are available covering the usage of this simple structural motif, such as the regioselective addition reactions,[7] heterocycle formations,[8] alkyne reactions *via* vinylidene- or allylidene-complexes,[9] and various carbon-carbon bond formations.[10] The synthetic utility of alkyne substrates induced by transition metal catalysis is reviewed with particular attention to the catalytic reactions, for which the interaction of transition metal catalysts and alkyne substrates is the critical mechanistic trigger for the transformation.

Transition Metal-Catalyzed Reactions of Alkynes

- **Nucleophilic activation of alkynes**

The π-coordination of transition metals, such as zinc, copper and silver activate terminal alkynes toward deprotonation under the mild conditions. This phenomenon was appreciated early on and subsequently utilized in many important carbon-carbon bond forming reactions, such as Castro-Stephens, Cadiot-Chodkiewicz, Sonogashira, and Carreira coupling reactions.

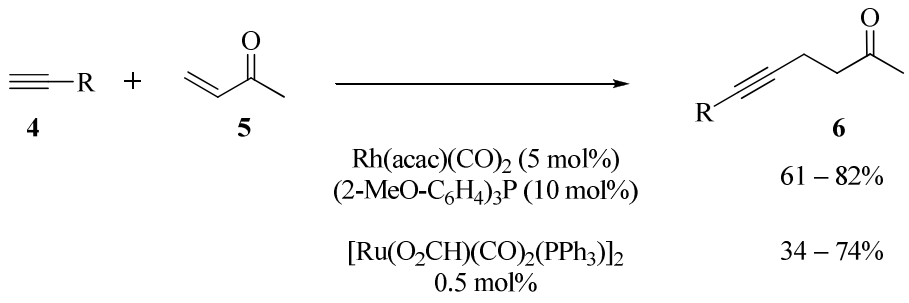
In 1999, Carreira et al. reported a Zn^{II}-catalyzed process for the addition of terminal alkynes to *N*-benzylnitrones, in which stoichiometric generation of alkynylide in a separate step was not required (Scheme 1).[11a] The related Zn^{II}-catalyzed asymmetric addition reaction of aldehydes was achieved by using *N*-methylephedrine as a chiral ligand, expanding the scope of the direct activation of the acetylenic C–H bonds by transition metals. In the proposed mechanism, zinc triflate coordinates to terminal alkyne to form a π-complex, thereby acidifying the acetylenic C–H bond. The amine base subsequently removes the proton to provide the corresponding zinc alkynylide.



Scheme 1: Zn^{II}-catalyzed addition of terminal alkyne to nitrone

The acetylenic C–H bond can be activated by transition metals toward conjugate addition. Whereas conventional copper-catalyzed conjugate addition of acetylenic nucleophiles is difficult due to the low transferability of the alkynyl substituents on organocuprates.[11b] In these reactions Rh^{I} or Ru^{II} catalysts are thought to activate the alkyne by oxidative insertion into the acetylenic C–H bond after η^2-coordination of the alkyne to the metal center. The coordination of **4** to the enone **5** leads to the formation of the carbon-carbon bond by a migratory insertion, and a subsequent reductive elimination

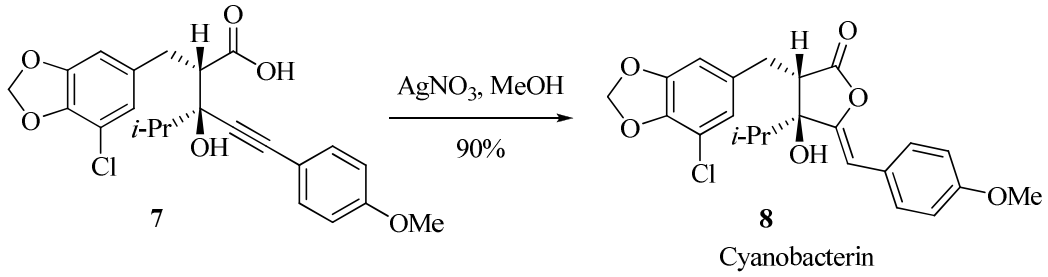
releases the 1,4-addition product **6** (Scheme 2). The γ,δ-alkynyl ketone products, obtained are useful intermediates for the synthesis of furans and pyrroles.



Scheme 2: Metal-catalyzed conjugate addition of terminal alkyne

- **Electrophilic activation of alkynes**

The addition of a tethered nucleophile onto the transition metal coordinated alkyne is a powerful method for the synthesis of heterocyclic and carbocyclic compounds. In these reactions, transition metal act as "carbophilic" Lewis acid and form electrophilic metal-η^2-alkyne complexes. These complexes are then attacked by a nucleophile usually in an *anti* fashion. Late transition metals are usually employed since the oxophilicity of these metals allow better compatibility with many functional groups in substrates, in comparison to early transition metals.

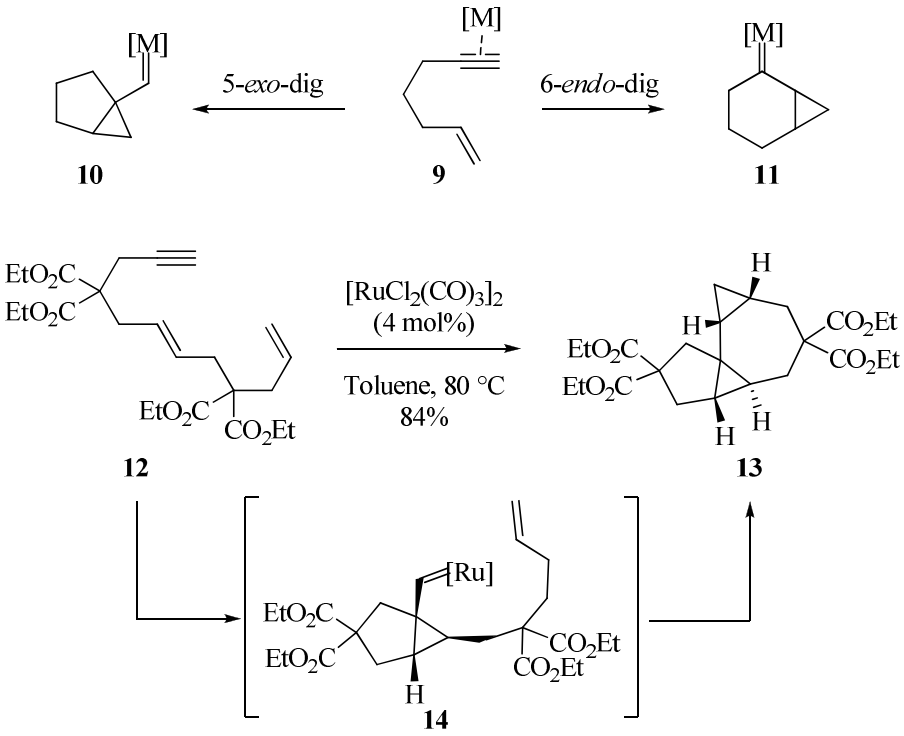


Scheme 3: Ag^I-catalyzed lactone formation

The *anti* mode of addition is evident in the Ag^I-catalyzed lactonization reaction shown in Scheme 3.[12] In a study toward the total synthesis of cyanobacterin, Williard et

al. observed the formation of γ-butyrolactone of (**8**) with high regio- and stereoselectivity under the Ag^{I}-catalysis. On the contrary, the Hg^{II}-catalyzed cyclization of the same substrate **7** led to the corresponding six-membered ring lactone selectively.

- **Reactions involving carbene species**



Scheme 4: Cyclopropyl carbene formation from enyne and Ru^{II}-catalyzed cycloisomerization of dieneyne

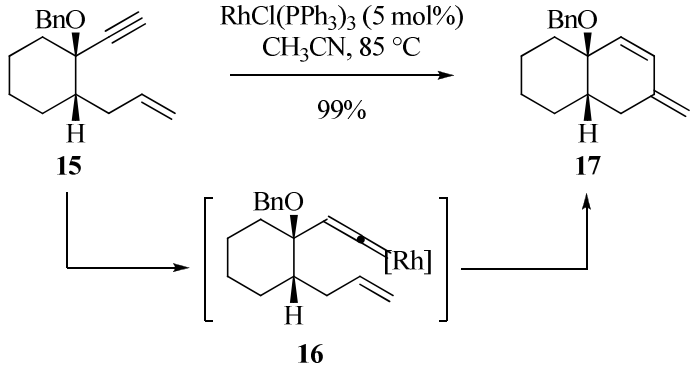
The activation of alkynes with carbophilic transition metals can trigger a nucleophilic attack by a carbon-carbon double bond. In this case, two reaction pathways are possible. If the metal coordinates to the alkyne and alkene simultaneously, an oxidative cyclometallation can occur providing metalla-cyclopentene intermediate. On the other hand, if the metal preferentially coordinates to the alkyne followed by intramolecular attack of the alkene in an *anti* manner through an *endo*- or *exo*- dig pathway, cyclopropyl carbene species **10** or **11** is generated (Scheme 4). This carbene

species is then quenched by way of various processes such as 1,2-H-shift, skeletal rearrangement, and cyclopropane formation if additional alkene is available.[13a,b]

These tandem processes allow the rapid buildup of complexity in the molecule by placing an appropriately tethered olefin in the starting material. One such process is exemplified in Scheme 4, wherein the cyclopropyl carbenoid **14** generated from the 5-*exo* reaction pathway undergoes intramolecular cyclopropanation to give the tetracyclic compound **13** in high yield.[13c]

- **Reactions involving vinylidene species**

The rearrangement of free acetylene to a vinylidene isomer is a thermodynamically disfavored process. A theoretical study estimates that vinylidene is 44~47 kcal/mol less stable than acetylene. However, the coordination of transition metals to terminal alkynes often leads to the formation of a metal vinylidene complex. This reactive species can be formed either by 1,2-hydrogen migration from the alkyne-metal complex or the initial oxidative addition of a metal into the acetylenic C–H bond, followed by 1,3-hydrogen migration. A rhodium-catalyzed cycloisomerization reaction of 1,6-enynes reported by Kim and Lee, was thought to proceed by [2+2] cycloaddition of the intermediate rhodium vinylidene complex **16**.[14]

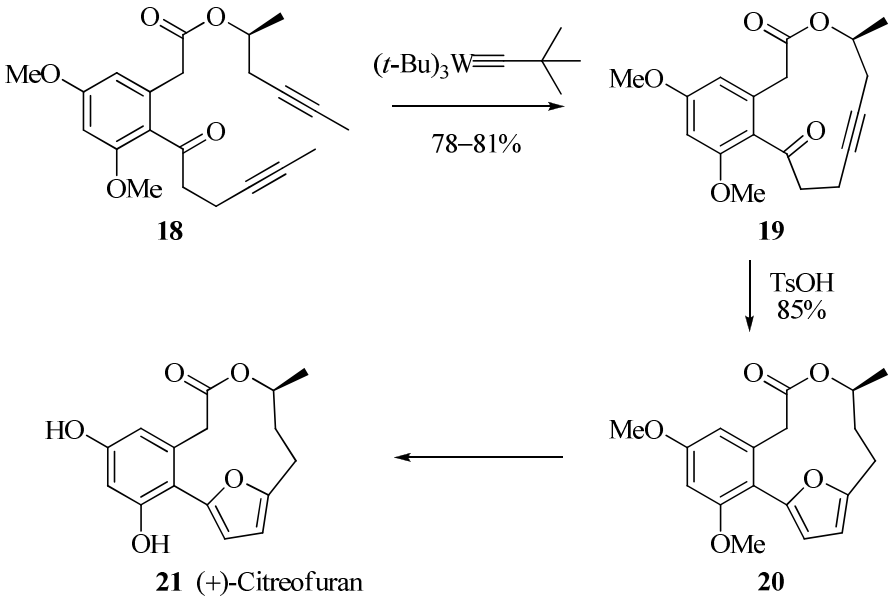


Scheme 5: Rh-catalyzed cycloisomerization *via* [2+2] cycloaddition

- **Alkyne metathesis**

Closely related to carbene complexes, the transition metal-carbyne complexes are also catalytically active for the metathesis reaction. However, unlike olefin metathesis, the utility of intramolecular alkyne metathesis is limited to the macrocyclization for geometrical restriction associated to the linear structure of the alkyne being produced. It was Furstner's contribution that revealed the real potential of alkyne metathesis reaction. Specifically, Furstner and co-workers demonstrated that, by manipulating the alkyne products, the alkenes with defined *E*- or *Z*-geometry could be obtained in a predictable manner.

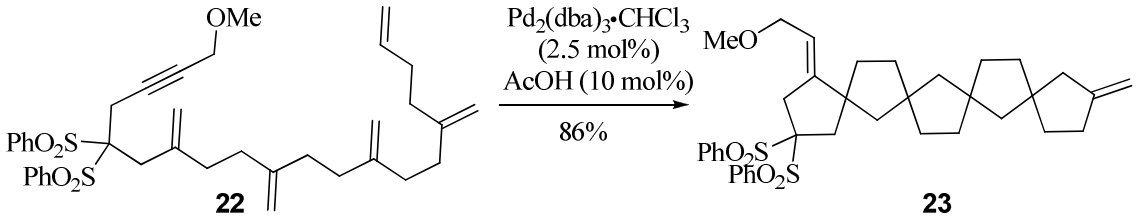
In addition to the utility as a precursor of a geometrically defined olefin, the internal alkyne provided by alkyne metathesis serves as a useful functional group that can be further manipulated. One such utilization is demonstrated in the total synthesis of (+)-citreofuran (**21**), in which a ring-closing alkyne metathesis is generated an alkynyl ketone **19** which is well-positioned for the acid-mediated annulation reaction to afford the corresponding furan **20** (Scheme 6).[15]



Scheme 6: Total synthesis of (+)-Citreofuran

- **Reactions involving migratory insertion to alkynes**

Organotransition metal complexes are capable of addition to carbon-carbon multiple bonds. In the reaction, the metal-carbon or metal-hydrogen bonds are added in a *syn* manner and the regiochemistry reflects both steric and electronic effects. In addition, the alkene or alkyne acceptors usually don't require much polarization, contrary to the main group organometallic addition. The addition or migratory insertion of transition metal complexes to alkynes leads to the corresponding vinyl metal species that are reactive enough to undergo further transformations such as addition to π-bonds, reductive elimination, and β-hydride elimination. A palladium-catalyzed Zipper reaction is a wonderful example, in which the organopalladium species initially generated by addition of a hydridopalladium complex onto the alkyne, was iteratively trapped by carbon-carbon double bond suitably positioned across the linear substrate **22**, affording a polycycle (**23**) (Scheme 7).[16]



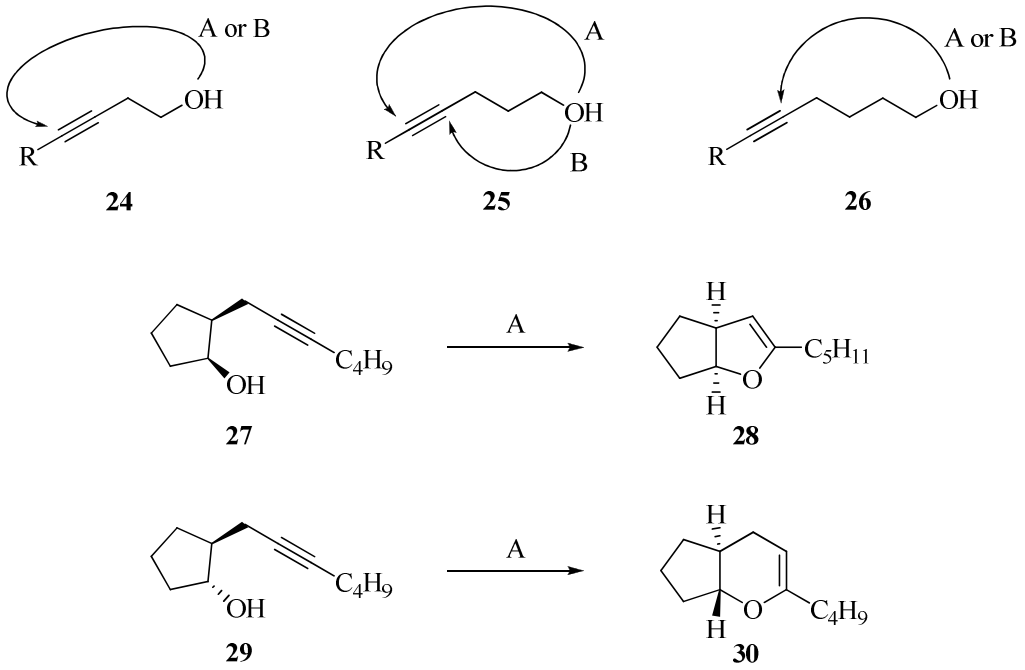
Scheme 7: Pd-catalyzed Zipper reaction

On the other hand, when two π-bonds are coordinated to a metal center, a metallacyclization can occur. This process is very general with coordinatively unsaturated metal species. Once it is formed, the metallacycle can undergo β-hydride elimination, reductive elimination, or addition to π-bonds.

Cycloisomerization:

The word cycloisomerization will be defined as a reaction where a section of an organic molecule containing at least one unsaturated C-C bond is isomerized with concomitant loss of atleast one site of unsaturation and no formal loss or gain of any atoms, and is accompanied by the formation of one or more rings.

Regioslectivity:

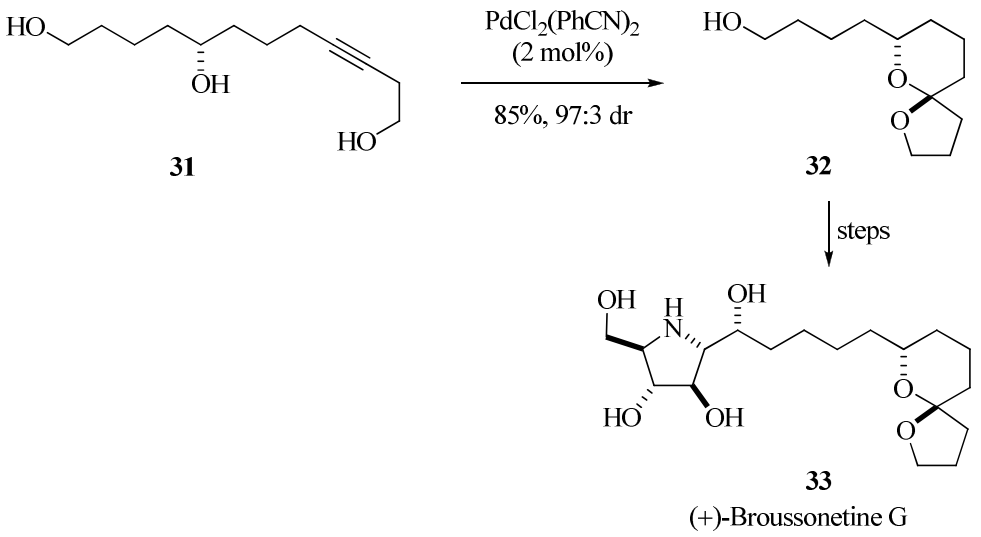


Scheme 8: Pd^{II}-catalyzed cyclization of hydroxyalkynes

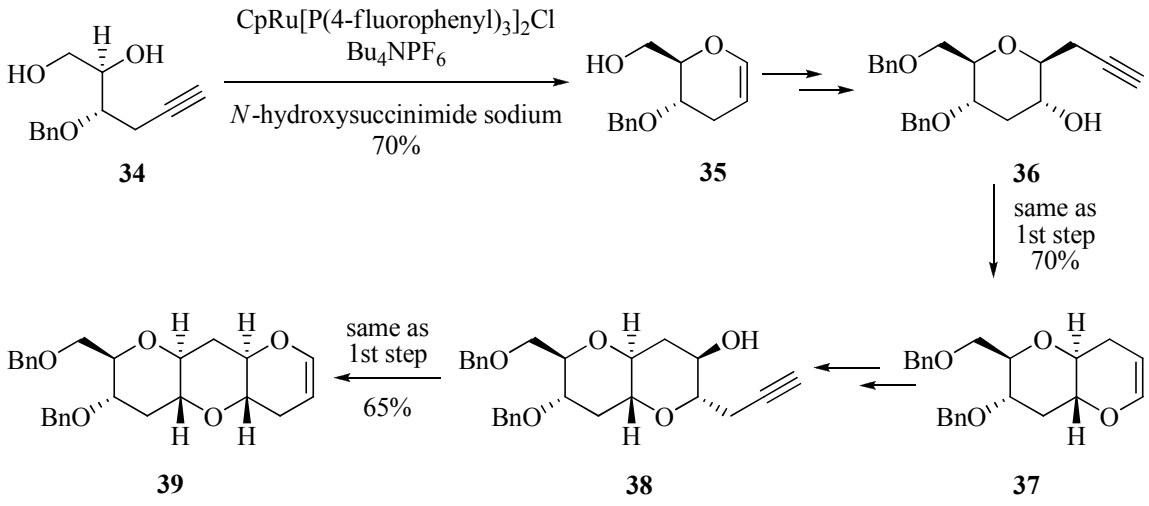
Reagents & Conditions: (A) $PdCl_2(PhCN)_2$ (1~3 mol%), anhydrous Et_2O, rt; (B) $PdCl_2$ (1~5 mol%), aq. CH_3CN, reflux.

The transition metal-catalyzed cycloisomerization reaction of hydroxyalkynes and aminoalkynes has been studied extensively, because it provides straightforward access to various heterocycles of biological importance, such as furans, pyrans, pyrroles and indoles. In one of the pioneering publications in this area, Utimoto et al. utilized $PdCl_2$ as a catalyst to form various heterocycles.[17] In this transformation, the alkyne serves as a latent ketone functional group, and the regioselectivity was governed by the tether length,

or by the relative stereochemistry of substituents in bicyclic formation as shown in (Scheme 8). The power of this methodology was elegantly demonstrated in the synthesis of bicyclic ether-containing natural products, such as *exo*-brevicomin, frontalin, and broussonetine G (**33**) (Scheme 9).[17,18]



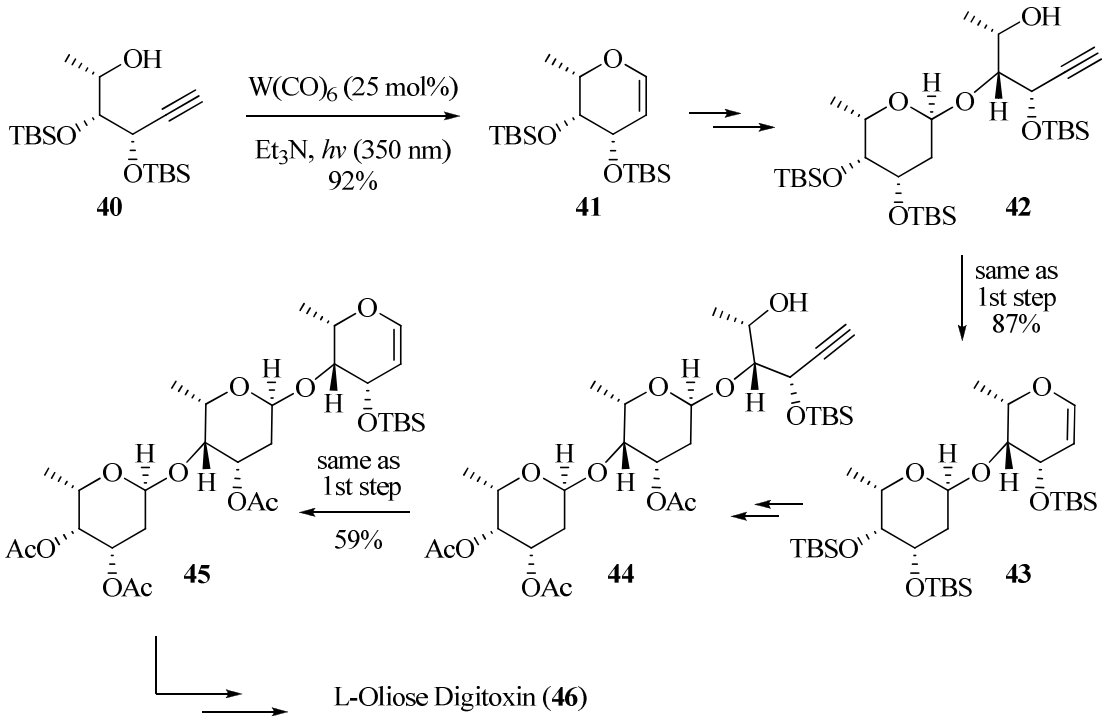
Scheme 9: Total synthesis of (+)-Broussonetine G



Scheme 10: Iterative cycloisomerization approach toward *trans*-fused polycyclic tetrahydropyrans

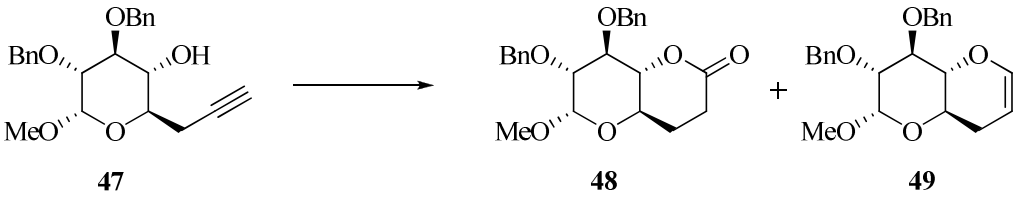
The cycloisomerization of bis-homopropargylic alcohols to dihydropyrans, when applied iteratively, provides efficient access to natural products with fused tetrahydropyran structure (Scheme 10).[19] The dihydropyran **35** obtained from the first cycloisomerization was transformed to the substrate **36** for the second ruthenium catalysis by a stereoselective epoxidation and the regioselective opening of the epoxide with allenylmagnesium bromide. In this approach, the second and third cycloisomerization reactions were carried out with similar efficiency to afford the tricyclic compound (**39**).

On the other hand, McDonald et al. used a similar strategy to synthesize L-oliose trisaccharide using a tungsten-catalyzed alkynol cycloisomerization (Scheme 11).[20] The cycloisomerization reaction required irradiation of the reaction mixture to achieve the catalyst turnover; however, the cycloisomerization could be carried out iteratively in a reliable way, providing all-α-linked L-oliose digitoxin stereoisomer (**46**).



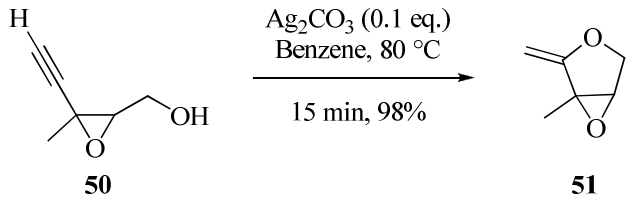
Scheme 11: Synthesis of L-Oliose Digitoxin *via* iterative cycloisomerization approach

An interesting divergence of reactivity was observed in the ruthenium-catalyzed reactions of bis-homopropargylic alcohols (Scheme 12).[21] In particular, the electron-poor phosphine in the presence of Bu_4NPF_4 and *N*-hydroxysuccinimide sodium salt provided the dihydropyran (**49**) selectively, whereas the electron-rich phosphine mainly led to the oxidation of the intermediate carbene species affording the δ-lactone (**48**).



Scheme 12: Ru-catalyzed divergence

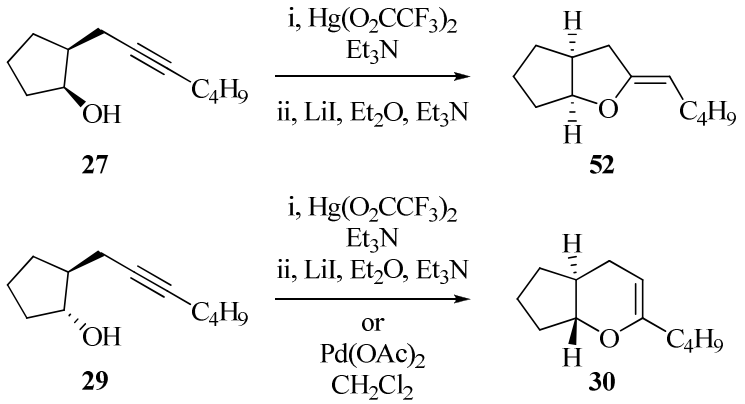
Several metal catalyzed cyclization of alkynyl alcohols to give cyclic enol ethers. Pale and Chuche[22] (Scheme 13) found that silver (I) promoted cyclization of alkynol **50** to give the exocyclic enol ether (**51**). The mild conditions tolerated epoxide functionality.



Scheme 13: Silver-mediated alkynol cyclization

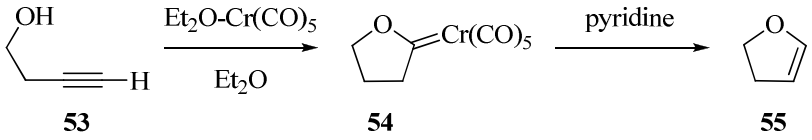
Riediker and Schwartz[23] used catalytic Hg(II) salts to prepare the *cis*-fused exocyclic enol ether **52** from alkynol **27**. The *trans*-fused cyclopentanol **29** gave the thermodynamically favored endocyclic enol ether **30** upon treatment with catalytic Hg(II) or Pd(II) salts. In the case of *cis*-fused alkynols such as **27**, cyclization to the five-

membered ring is kinetically favored over cyclization to the six-membered ring resulting in *exo*-cyclization to the *cis*-fused 5,5-bicyclic enol ether (**52**). In the case of *trans*-fused alkynol **29**, strain disfavors formation of the *trans*-fused 5,5-exocyclic product and *endo*-cyclization to the 5,6-endocyclic product (**30**) occurs (Scheme 14).



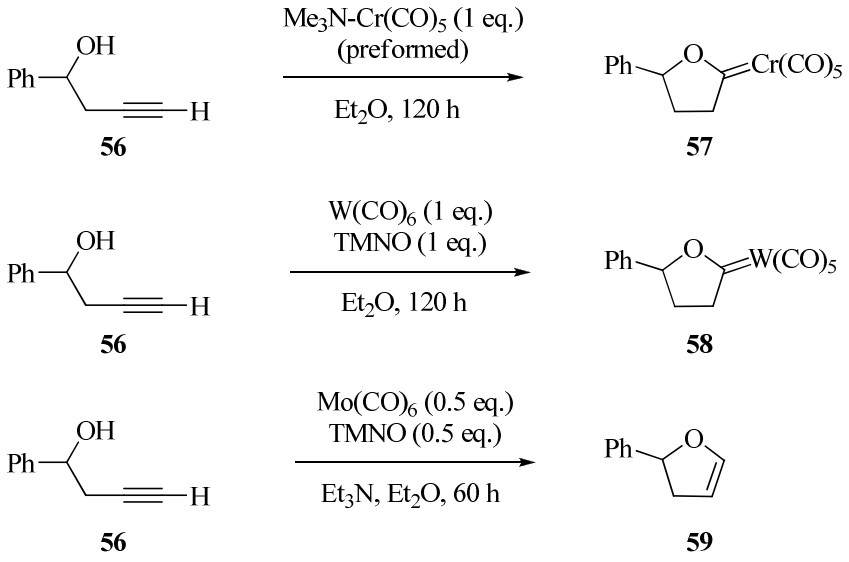
Scheme 14: Hg(II)- and Pd(II)-mediated alkynol cyclization

Chisholm and Clark[24] first reported the cyclization of 1-alkyn-4-ols with platinum complexes to give cyclic oxacarbenes in 1972. More recently, this concept has been extended to other transition metal complexes. Alkynol cyclizations to oxacarbenes have been applied toward the synthesis of natural products. Oxacarbenes of group VI metals react with tertiary amine bases to give enol ethers. For instance, treatment of (2-oxacyclopentylidene)pentacarbonylchromium(0) **54** with pyridine salts affords dihydrofuran (**55**) providing a two-step route to dihydrofurans from alkynols (Scheme 15).



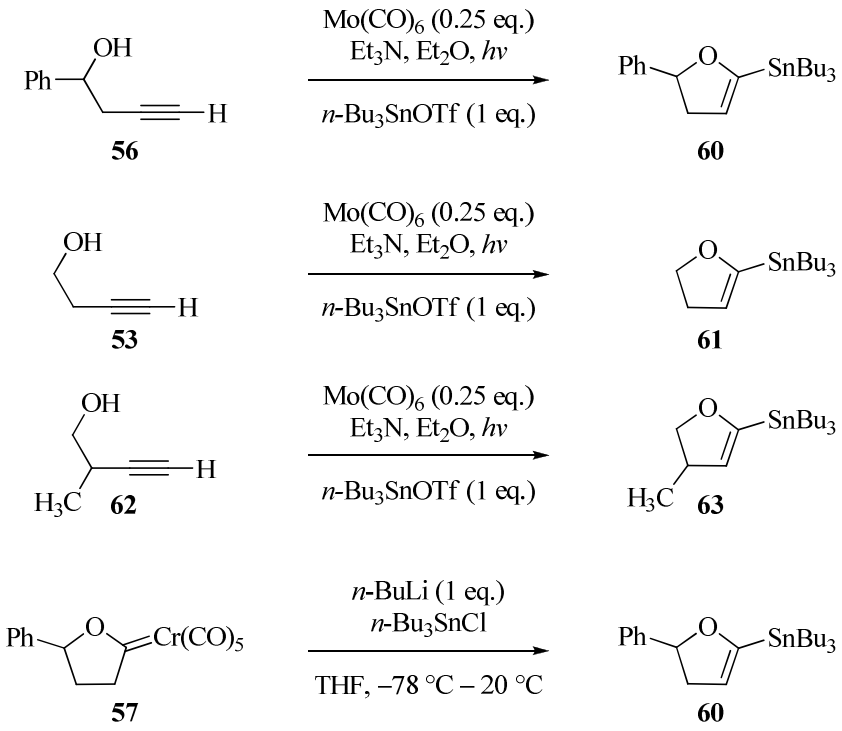
Scheme 15: Alkynol cyclization *via* oxacarbenes

Molybdenum pentacarbonyl-trialkylamine complexes catalyze the cyclization of alkynyl alcohol to endocyclic enol ethers in a single step (Scheme 16).[25] Treatment of alkynol **56** with trialkylamine-chromium pentacarbonyl and trialkylamine-tungsten pentacarbonyl complexes resulted in formation of cyclic oxacarbenes (**57**) and (**58**). However, treatment of the alkynol **56** with trialkylamine-molybdenum pentacarbonyl resulted in formation of the enol ether (**59**). The reaction was modestly catalytic in molybdenum, and the presence of tertiary amine base was necessary for the reaction to proceed. The reaction was inhibited by the presence of oxygen but tolerated water in the reaction mixture.



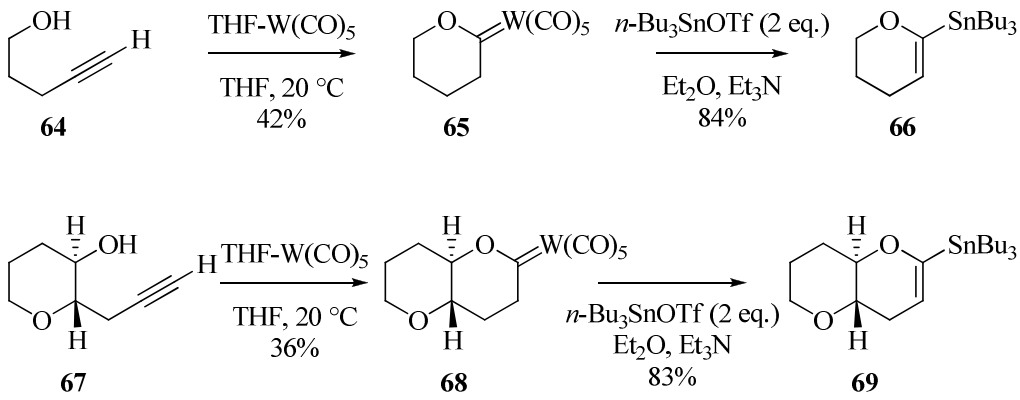
Scheme 16: Molybdenum-catalyzed alkynol cyclization

Trapping of molybdenum carbene anion intermediates with tributyltin triflate resulted in formation of α-stannyl enol ether (**60**) (Scheme 17).[26] Typically, primary alcohols such as **53** and **62** were unreactive to molybdenum cycloisomerization conditions. In the presence of tributyltin triflate, however, cyclic stannyl enol ether products (**61**) and (**63**) were obtained. Chromium carbene **57** provided α-stannyl enol ether (**60**) upon kinetic deprotonation with *n*-butyllithium and addition of tributyltin chloride or under mild conditions employing triethylamine and tributyltin triflate.



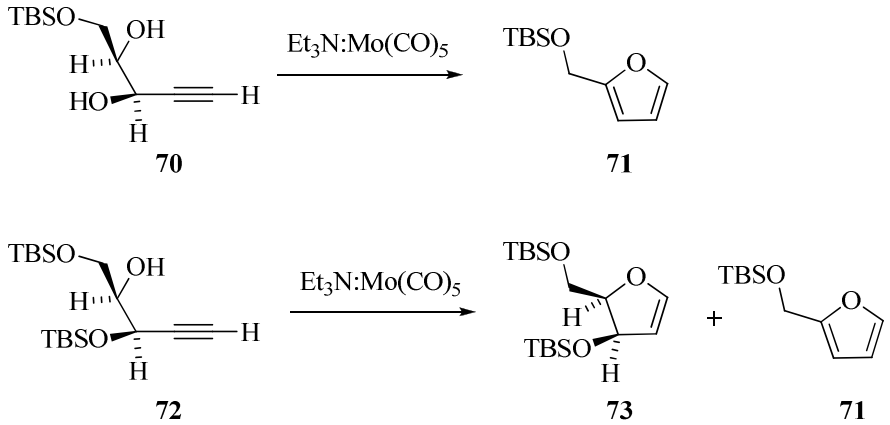
Scheme 17: Carbene anion trapping with tributyltin triflate

Tungsten pentacarbonyl-tetrahydrofuran complexes induce cyclization of alkynol **64** to provide dihydropyranylidene carbene **65** providing the first general route to six-membered cyclic oxacarbenes of group VI metals.[27] Primary, secondary, and tertiary alcohols successfully undergo cyclization. The resulting carbene **65** can be converted to the α-stannyl dihydropyran (**66**) with triethylamine and tributyl triflate. The method was used to prepare bicyclic oxacarbene **68** from alkynol **67** which was converted to the α-stannyl enol ether (**69**) (Scheme 18).



Scheme 18: Alkynol cyclization to dihydropyrans

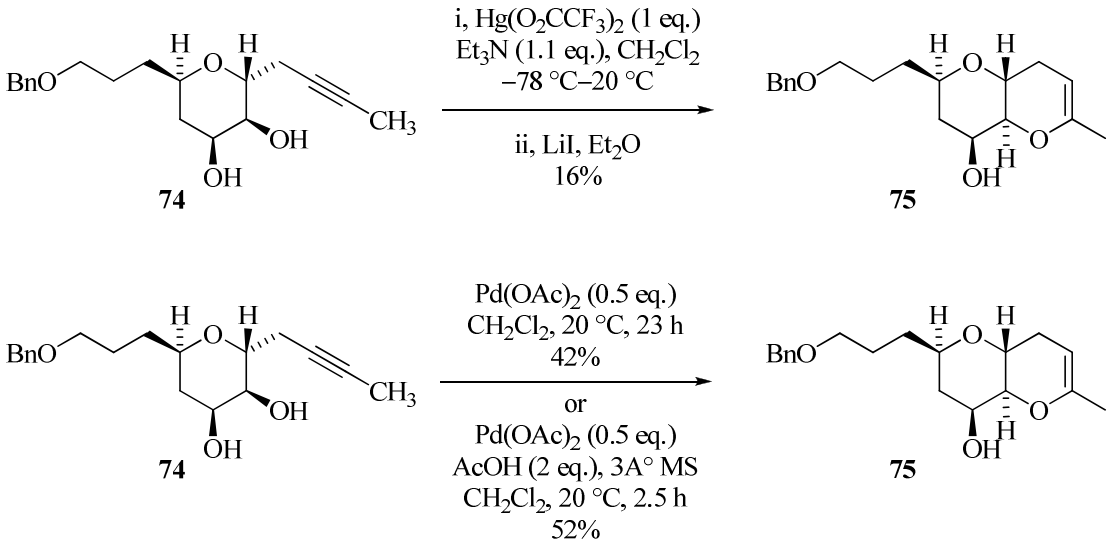
Propargylic heteroatom substituents undergo elimination to give furans upon subjection to cycloisomerization conditions. Alkynols with good leaving groups at the propargylic position such as azide, amine and hydroxyl eliminate to give furans. Reaction of the propargylic alcohol **70** with triethylamine-molybdenum pentacarbonyl resulted in formation of furan (**71**) (Scheme 19). When the alcohol was protected as the silyl ether **72**, the elimination to (**71**) occurred, but dihydrofuran (**73**) was the major product.



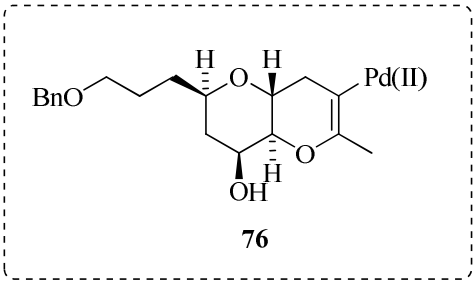
Scheme 19: Cyclization of alkynol with propargylic substituents

Treatment of alkynyl diol **74** (4:1 mixture of diastereomeric diols) with Hg(II) trifluoroacetate[28] provided bicyclic enol ether (**75)** in low yield along with decomposition

materials. Whereas treatment of diol **74** with Pd(II) acetate provided higher yields of bicyclic enol ether (**75**) as a single isomer. This material was identical to the compound obtained from Hg(II) cyclization. Addition of acetic acid and molecular sieves to the Pd(II) acetate cyclization reaction resulted in rate acceleration and an increase in the isolated yield of enol ether **75** (Scheme 20).



Scheme 20: Cyclization of alkynol



Scheme 21: Hypothetical alkynol cyclization intermediate

Conclusion:

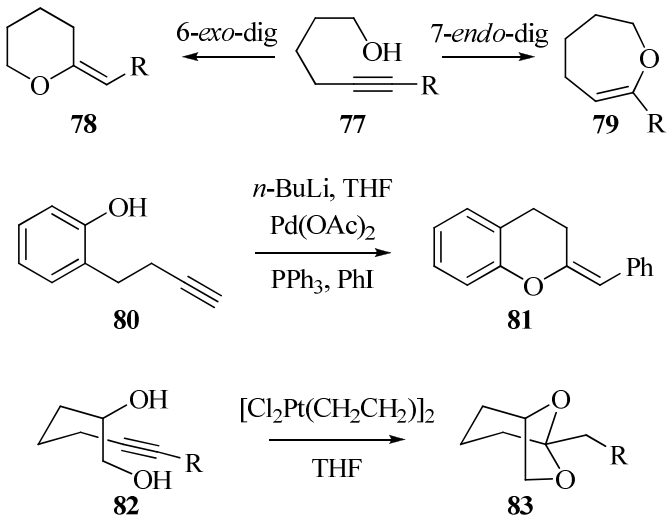
The development of transition metal catalysis has enabled the discovery of effective yet mild chemical methods suitable for complex molecule synthesis. Alkynes, with high polarizability and cylindrical symmetry, possess superior coordinating ability to π-acids. The development of new synthetic methodology based on transition metal catalysts in the past two decades have revealed the diverse reactivity concealed in alkynes and allowed the synthetic community to enjoy the rich chemical properties of this highly energetic functional group. By the action of transition metals, alkynes have been activated toward nucleophiles, electrophiles, carbene species, and neutral organometallic species, which can undergo further useful transformations. Not only alkynes have played a significant role in this area as reacting substrates but also as controlling elements in some reactions. An alkyne is an attractive building block in synthetic organic chemistry as a masked form of a carbonyl group or geometrically defined olefin functionality, and yet it is easily accessible and synthetically robust, which make it capable functional group in designing a complex molecule synthesis. Surely, continued development in transition metal catalysts and synthetic strategies to take advantage of the promising chemical properties of alkynes is expected.

Present Work

The intramolecular addition of carbon and heteroatom nucleophiles across the alkynes falls under the broad category of cycloisomerization reactions.[29] The cycloisomerization is projected as a tool for syntheses of oxygen-containing heterocycles encompassing functionalized furan, pyran, benzopyran and spiroketal skeletons.[30] Various transition metals like palladium, gold, platinum, tungsten, molybdenum, ruthenium, rhodium, and iridium are explored for cycloisomerization reaction as catalysts.[31] The key issue of the cycloisomerization reactions is the mode of cyclization *i.e. exo*-dig *vs. endo*-dig.[32] In this context, recently from our group, a systematic investigation dealing with the influence of electronic and steric factors over competitive 5-*exo*-dig *vs.* 6-*endo*-dig cyclizations mediated by $Pd[CH_3CN]_2Cl_2$ complex is reported.[33,34] Using a large set of substrates for the projected cycloisomerization reaction, we noticed that Pd promoted cycloisomerization reactions were substantially influenced by electronic factors that is in contrast with the base promoted cycloisomerizations.[34] From the results obtained, we concluded that competitive balance between –I effect of furanose ring and +M effect of the aryl substituents influence the mode of cyclization. The presence of a +M substituent (–OMe) on the aromatic ring in general enforced a 6-*endo*-dig while –M group ($–NO_2$) favored 5-*exo*-dig modes of cyclization. In case if the *exo*-mode of ring closure is disfavoured due to ring strain we noticed exclusive 6-*endo* cyclization.[34b]

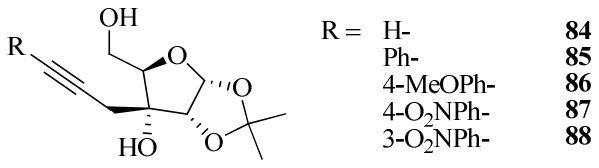
Compared to competitive 5-*exo*-dig/6-*endo*-dig, reports concerning the 6-*exo*-dig/7-*endo*-dig cyclizations are less frequent.[35] The seminal publications by Utimoto et al. on the Pd mediated cycloisomerization of ω-alkynols show that 5-*exo* and 6-*exo*-dig cyclizations are more favored over their competitive *endo*-dig cyclizations.[31] A one pot Sonogashira coupling and cycloisomerization of 3-, 4-, and 5-alkynols with aryl halides was studied by Santelli and co-workers using *tedicyp* ligand.[35a] In general, 6-*exo*-dig mode of cyclizations were documented and the cyclizations are favored only with electron deficient aryl halides whereas with electron rich aryl halides, only coupling products were isolated. Results published by Luo et al. showed that oxypalladation and cross-coupling of acetylenic alkoxides generally prefer to

undergo 6-*exo*-ring closure.[33g] Liu and de Brabander reported regiochemical control in the cycloisomerization of electronically unbiased internal alkynes by selecting appropriate catalyst and conditions.[35d] During our work in progress, Ley and co-workers reported the selective 7-*endo* cyclization of alkyne diols by employing $PtCl_4$ as the catalyst.[35e] With sugar derived alkynols, Vasella and co-workers have reported that in general these cyclizations favor a 6-*exo*-dig mode of cyclization.[36]



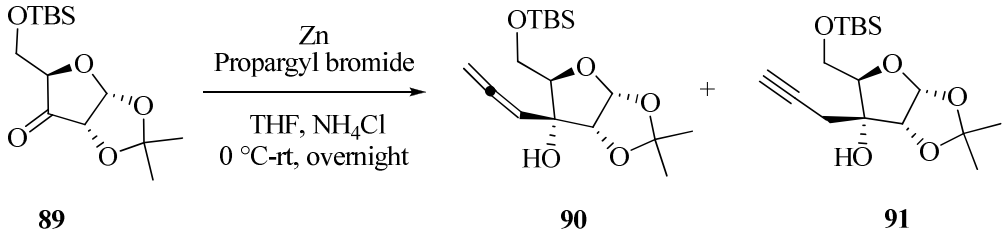
Scheme 1: Representatives for competitive 6-*exo*-dig vs 7-*endo*-dig cyclizations

In continuation, we describe our investigations dealing with electronic control over competitive 6-*exo*-dig *vs* 7-*endo*-dig mode of cyclizations employing 3-*C*-propargylfuranosyl derivatives (Scheme 2) **84**–**88**. With this set of compounds **84**–**88**, the cycloisomerization should lead to [3.4.0] or [3.5.0]dioxabicyclic enol ether derivatives.



Scheme 2: Designed substrates for projected cycloisomerization

The synthesis of the requisite model 3-*C*-propargyl-*ribo*-furanose derivatives **84**–**88** started with the known 3-ulose derivative **89**.[37] Propargylation of 3-ulose derivative **89** under Barbier conditions using Zn and propargyl bromide in THF:NH_4Cl afforded **91** along with the allene **90** (Scheme 3).[38] The assigned structure of allene **90** was deduced from the NMR spectroscopy. For example, three well separated olefinic-H resonating at 4.93 (d, J = 6.2 Hz), 4.95 (d, J = 7.4 Hz) and 5.24 (dd, J = 6.2, 7.4 Hz) ppm were observed in the ^{1}H NMR spectrum of **90** thus confirming the presence of an allene moiety attached to a quaternary carbon. This was further supported by the resonance of a quaternary olefinic carbon at extreme down field region 207 (s) and a secondary olefinic carbon at 78.7 (t) and a tertiary carbon at 90.3 (d) in ^{13}C NMR spectrum of compound **90**. IR, Mass and elemental analysis also supported the assigned structure.

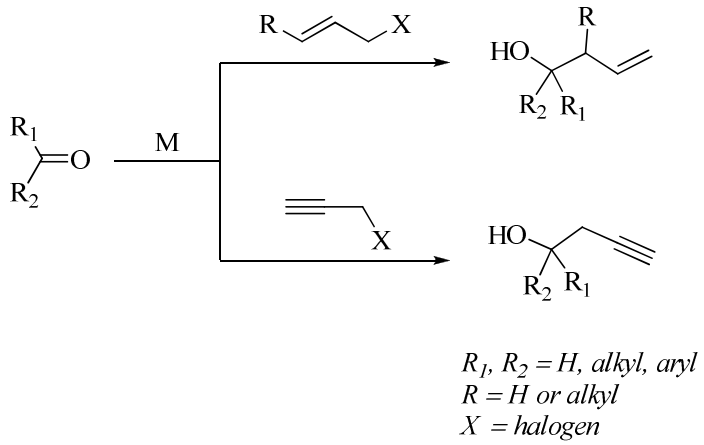


Scheme 3: Barbier propargylation

The structure of the major product **91** of the Barbier reaction was analyzed with the help of NMR spectroscopy. The ^{1}H NMR spectrum of compound **91** showed the characteristic acetylene proton as a triplet at 2.03 (J = 2.7 Hz) ppm, and well separated propargylic CH_2 protons at 2.35 (ddd, J = 17.1, 2.7, 0.7 Hz) and 2.57 (dd, J = 17.1, 2.7 Hz) ppm. The assigned structure of compound **91** was further supported by the ^{13}C NMR spectrum where the characteristic signals of propargylic CH_2 (t, 22.9 ppm), terminal acetylenic carbon (d, 71.1 ppm) and internal acetylenic carbon (s, 79.1 ppm) appeared at the expected positions. IR, Mass and elemental analysis further supported the assigned constitution for compound **91**.

Short account of Barbier reaction[38]

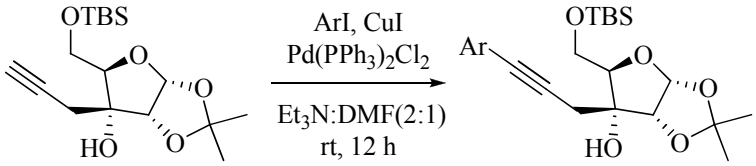
The reaction between an alkyl halide and a carbonyl group (aldehyde or a ketone) in the presence of metals like aluminium, zinc, indium, tin, samarium etc., or their salts is termed as Barbier reaction. The reaction product is a secondary or a tertiary alcohol. The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier is a one-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compound. Barbier reactions are nucleophilic addition reactions that take place with relatively inexpensive and water insensitive metals or metal compounds in contrast to Grignard reagents or organolithium reagents. For this reason it is possible in many cases to run the reaction in water, which makes this procedure part of green chemistry. The Barbier reaction is named after Victor Grignard's teacher Philippe Barbier.



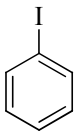
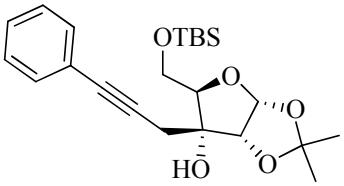
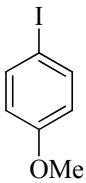
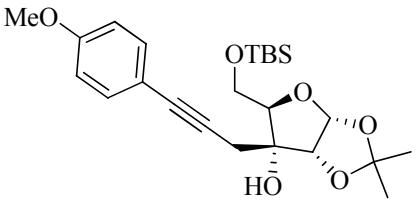
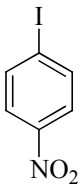
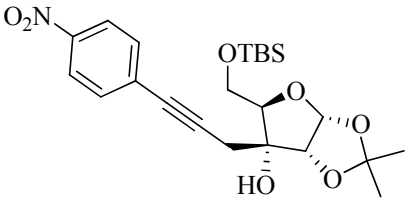
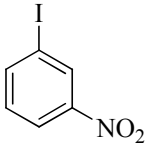
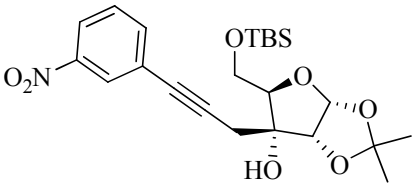
Scheme 4: Barbier reaction

To prepare the other proposed substrates, the Sonogashira coupling[39] reaction of **91** with different aryl iodides was carried out in presence of catalytic CuI and $Pd(PPh_3)_2Cl_2$ in Et_3N:DMF to afford compounds **92–95** (Scheme 5). The aryl iodides

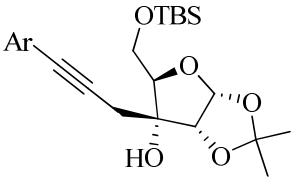
employed for the Sonogashira coupling were of two types namely iodides with NO_2 (–M effect) as the substituent on the arene and iodides with OMe (+M effect) as the substituent. The assigned structures for **92–95** were well supported by spectral and analytical data. The ^{1}H NMR data of **92–95** are summarized in Table 1.



91 **92-95**

ArI	Product	Yield
		**92**; 84%
		**93**; 83%
		**94**; 85%
		**95**; 72%

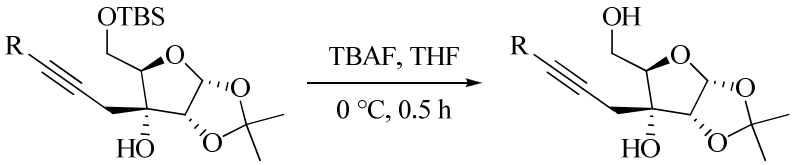
Scheme 5: Synthesis of Sonogashira products **92–95**



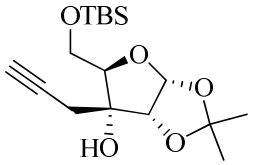
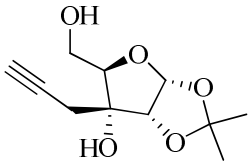
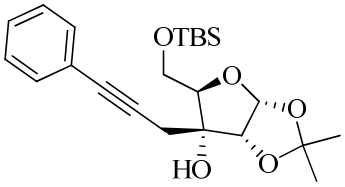
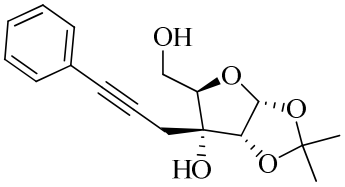
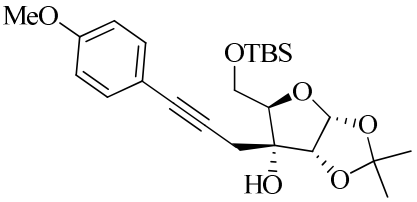
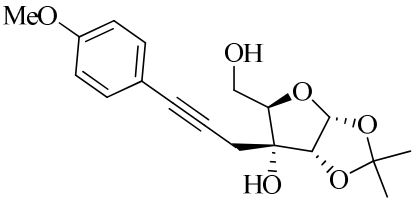
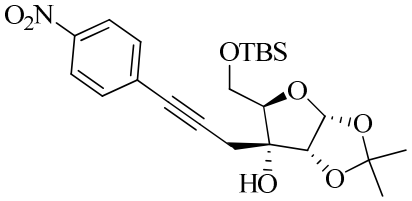
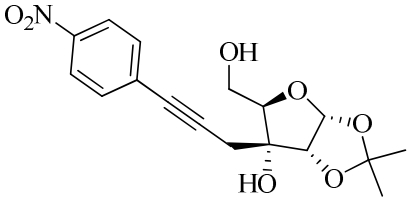
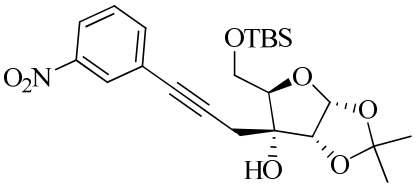
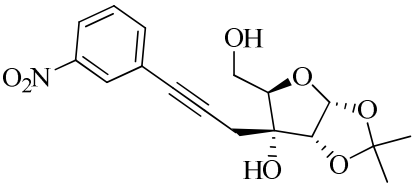
		C_1–H	C_2–H	propargylic $-CH_2$	aromatic δ (ppm)
92	Ar = Ph-	5.81 (d)	4.51 (d)	2.57 (d) 2.75 (d)	7.20–7.27 (m) 7.33–7.40 (m)
93	4-MeOPh-	5.83 (d)	4.53 (d)	2.58 (d) 2.76 (d)	6.79 (dt) 7.33 (dt)
94	4-O_2NPh-	5.84 (d)	4.49 (d)	2.64 (d) 2.85 (d)	7.55 (dt) 8.16 (dt)
95	3-O_2NPh-	5.84 (d)	4.51 (d)	2.62 (d) 2.84 (d)	7.47 (t), 7.71 (dt) 8.14 (ddd), 8.26 (t)

Table 1: ^{1}H NMR chemical shifts of **92**–**95**.

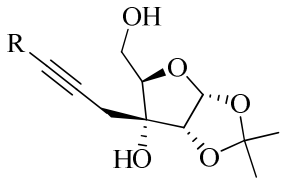
Having Sonogashira products in the hand, the stage was set for deprotection of TBS group present at *O*-5 of **91**–**95**. Treatments of compounds **91**–**95** with TBAF in THF at 0 °C afforded the projected set of cycloisomerization substrates **84**–**88** (Scheme 6). The assigned structures for **84**–**88** were well supported by spectral and analytical data. The ^{1}H NMR data of **84**–**88** are summarized in Table 2.



91–95 **84–88**

S. M	Product	Yield
		**84**; 92%
		**85**; 91%
		**86**; 93%
		**87**; 90%
		**88**; 91%

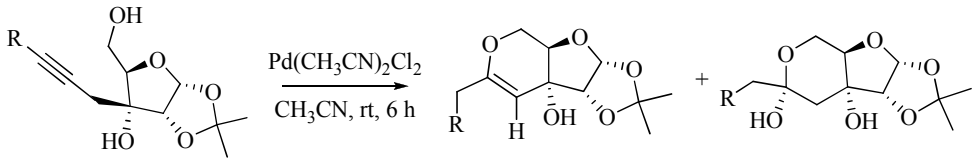
Scheme 6: Synthesis of cycloisomerization substrates **84–88**

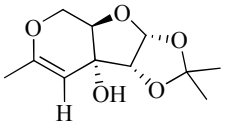
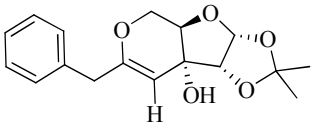
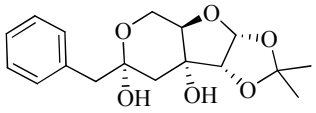
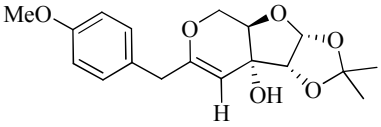
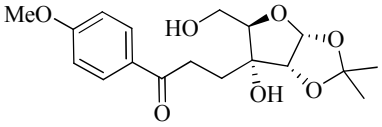
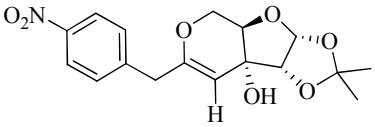
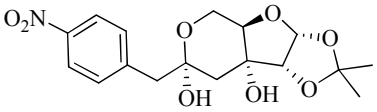
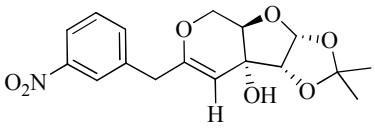
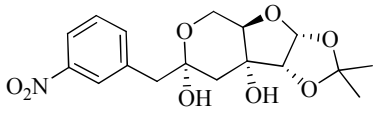


		C_1–H	C_2–H	propargylic –CH_2	aromatic δ (ppm)
84	R = H	5.81 (d)	4.48 (d)	2.38 (dd) 2.56 (dd)	-- -- -- --
85	Ph-	5.86 (d)	4.52 (d)	2.61 (d) 2.76 (d)	7.25–7.31 (m) 7.36–7.43 (m)
86	4-MeOPh-	5.86 (d)	4.53 (d)	2.60 (d) 2.76 (d)	6.81 (dt) 7.34 (dt)
87	4-O_2NPh-	5.87 (d)	4.51 (d)	2.66 (d) 2.85 (d)	7.55 (dt) 8.16 (dt)
88	3-O_2NPh-	5.85 (d)	4.50 (d)	2.62 (d) 2.81 (d)	7.46 (t), 7.70 (dt) 8.13 (ddd), 8.24 (t)

Table 2: ^{1}H NMR chemical shifts of **84**–**88**

The palladium-catalyzed cycloisomerization reactions of model 3-*C*-propargyl-*ribo*-furanose derivatives **84**–**88** were carried out in the presence of $Pd(CH_3CN)_2Cl_2$ in MeCN at room temperature. The results are summarized in Scheme 7. The parent compound **84** gave exclusively the fused dihydropyran (**96**) resulting from the double bond isomerization of the intermediate *exo*-methylene derivative. A doublet resonating at 1.79 (d, J = 0.8 Hz) ppm in the ^{1}H NMR spectrum of compound **96** indicated the presence of a methyl group attached to an olefin. There is one additional signal in the down field region 4.40 (br q, J = 0.8 Hz) ppm of the ^{1}H NMR spectrum of compound **96** along with the furan ring protons and is characterized as internal olefinic proton. This indicated that the initial 6-*exo*-dig cyclization product was isomerized to more stable endocyclic dihydropyran derivative. The assigned structure of **96** was further supported by ^{13}C NMR spectrum where signals corresponding to the primary methyl and endocyclic tertiary olefinic -CH and endocyclic quaternary carbon appeared at 20.3 (q), 95.0 (d), and 156.2 (s) ppm respectively.



Substrate/ R =	Cycloisomerization products	Olefin-H δ (ppm)	Hydrolysis products
84 H-	 **96** (64%)	4.40	-- --
85 Ph-	 **97** (60%)	4.40	 **98** (19%)
86 4-MeOPh-	 **99** (16%)	4.40	 **100** (55%)
87 4-O_2NPh-	 **101** (60%)	4.51	 **102** (14%)
88 3-O_2NPh-	 **103** (53%)	4.53	 **104** (13%)

Scheme 7: Cycloisomerization of alkynols **84**–**88**

Cycloisomerization of alkynol **85** afforded the *endo*-product (**97**) along with small amounts of the hemiketal (**98**) resulting from the hydrolysis of **97**. Whilst the cycloisomerization of the alkynol **86** gave dihydropyran (**99**) (16%) and the major product was found to be the keto derivative (**100**) (55%). Formation of hemiketals (**102**) and (**104**) was also noticed with the cycloisomerization of alkynols **87** and **88** respectively, along with the major dihydropyran derivatives **101** and **103** (Scheme 7). The similar NMR spectral pattern noticed for **96**, **97**, **99**, **101** and **103** confirmed the assigned structures. The structures of hemiketals **98**, **102** and **104** were proposed based on ^{1}H, ^{13}C, mass and elemental analysis. The single crystal X-ray study of *endo*-product **97**, **102** and **104** unambiguously proved assigned structures.

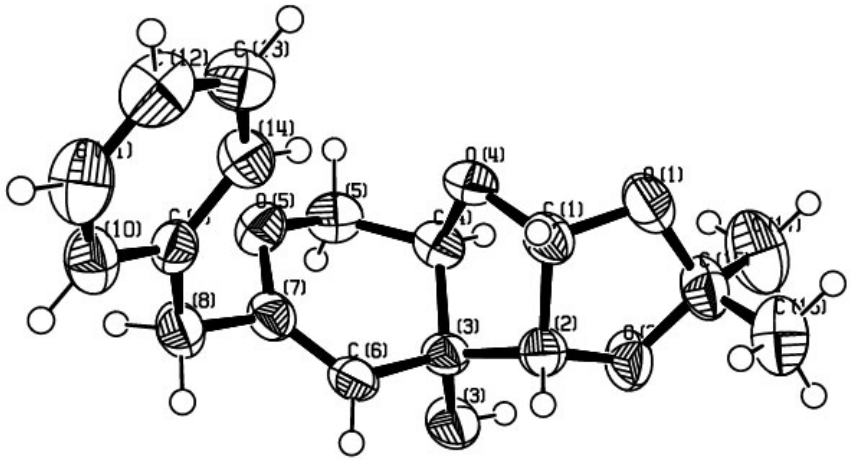


Figure 1. *ORTEP structure of the bicylic enol ether* **97**

The structure of compound **97** was analyzed by NMR spectroscopy which shows the characteristic benzylic protons at 3.36 (d, J = 16.5 Hz), 3.40 (d, J = 16.5 Hz) ppm, and at 4.40 (br d, J = 1.1 Hz) ppm for endocyclic olefinic proton in ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, signals resonated at δ 40.5 (t) for the benzylic CH_2, δ 96.2 (d) for olefinic CH, and at δ 158.5 (s) for the quaternary olefinic carbon indicating the 6-*exo*-dig cyclization followed by isomerization of double bond. IR, Mass and elemental analysis also supported the assigned structure. The structure of compound **97** was also evidenced

from its single crystal X-ray (Figure 1). The compounds **99**, **101** and **103** showed the similar NMR splitting pattern.

The structure of compound **98** was assigned by NMR spectroscopy which shows the characteristic internal methylene protons of pyran at 1.57 (d, J = 14.1 Hz), 1.69 (d, J = 14.1 Hz) ppm, and for benzylic CH_2 protons at 2.82 (d, J = 13.6 Hz), 3.03 (d, J = 13.6 Hz) ppm in ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, signals were observed at δ 37.0 (t) for internal CH_2, δ 47.5 (t) for benzylic CH_2, δ 95.5 (s) for hemiketal carbon indicating the hydrolysis of cycloisomerized product. The compounds **102**, **104** showed the similar NMR splitting pattern. The structures of compounds **102** and **104** were unambiguously proved by its single crystal X-ray (Figure 2 and 3). The structure of keto product **100** was analyzed by NMR spectroscopy which shows the characteristic methylenic protons at δ 1.89 (dd, J = 8.5, 6.3 Hz), 1.94 (dd, J = 8.5, 6.3 Hz), 2.99 (ddd, J = 17.7, 8.5, 6.3 Hz), and 3.25 (ddd, J = 17.7, 8.5, 6.3 Hz) ppm in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, signals located at δ 24.5 (t) for α–C to keto, δ 31.9 (t) for β–C to keto, and at δ 198.3 (s) for keto carbon indicates the presence of keto moiety in assigned structure **100**. IR, Mass and elemental analysis also supported the assigned structure.

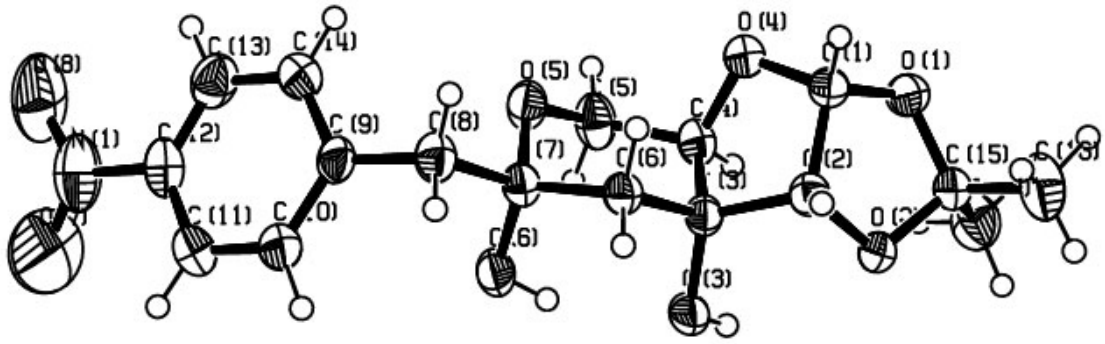


Figure 2: *ORTEP structure of the bicylic ketal* **102**

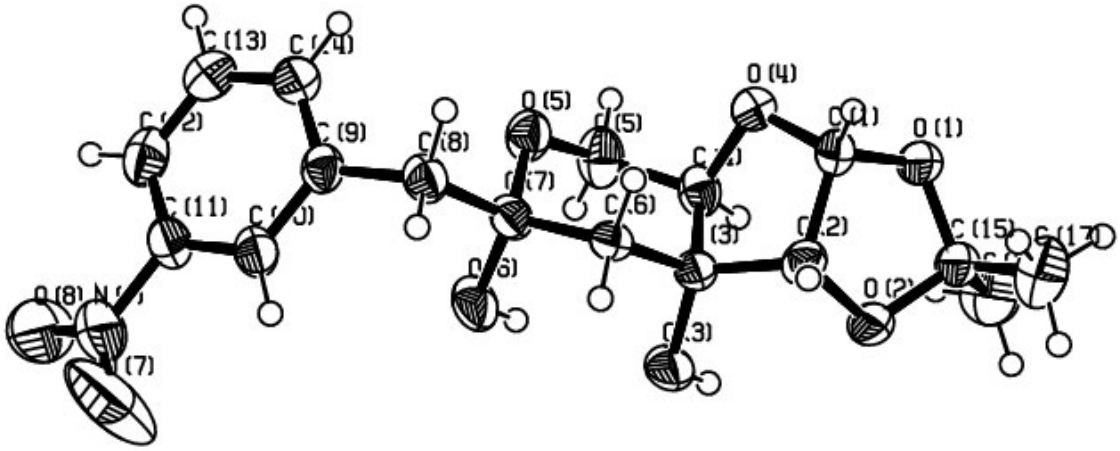


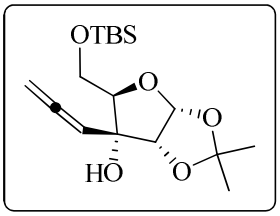
Figure 3: *ORTEP structure of bicylic ketal* **104**

Conclusion:

In summary, electronic control over the 6-*exo*-dig *vs.* 7-*endo*-dig modes of cyclizations in Pd-mediated cycloisomerization reaction has been studied in detail. 3-*C*-propargyl *ribo*furanose derivatives with systematic variation of functional groups at the other side of alkyne were employed to understand the competitive balance between inductive effect of furanose ring and mesomeric effect of aryl substituent. Unlike with 3-*C*-alkynyl *allo*- and *ribo*furanose derivatives where the regioselectivity of the cyclization were inline with the electronic control, with 3-*C*-propargyl *ribo*-derivatives we observed complete 6-*exo*-dig selectivity without an electronic interference. However, intermediate exocyclic enol ethers isomerized to more stable endocyclic enol ethers.

Experimental

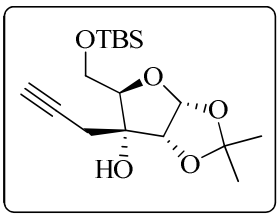
1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(propadienyl)-*α*-D-ribofuranose (90)



Zn (5.05 g, 77.69 mmol), propargyl bromide (4.15 mL, 46.62 mmol), in THF (50 mL) was stirred vigorously for 30 min, to which a solution of ketone **89** (4.7 g, 15.53 mmol) in THF (50 mL) was added and the stirring was continued for another 30 min. The reaction mixture was cooled to 0 °C and saturated NH_4Cl (25 mL) was added dropwise for 30 min and stirring was continued overnight. Reaction mixture was filtered through *Celite* pad and the solvent was evaporated under vacuum and extracted with ethyl acetate washed with brine, dried (Na_2SO_4), concentrated. Purification of the crude by column chromatography (10% ethyl acetate in petroleum ether) afforded **90** (1.8 g, 34%) as semi-solid and **91** (2.7 g, 51%) as colorless syrup respectively.

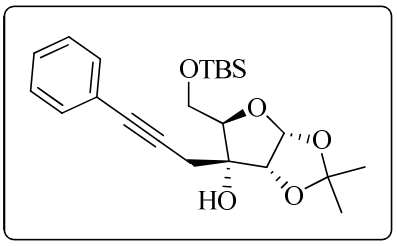
Mol. Formula	: $C_{17}H_{30}O_5Si$
$[\alpha]_D$	: +14.2 (*c* 1.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3547, 2931, 1957, 1376, 1216, 1086, 838, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.07 (s, 6H), 0.88 (s, 9H), 1.34 (s, 3H), 1.59 (s, 3H), 2.76 (br s, 1H), 3.77 (s, 1H), 3.80 (s, 1H), 3.97 (dd, *J* = 5.4, 1.0 Hz, 1H), 4.35 (d, *J* = 3.7 Hz, 1H), 4.93 (d, *J* = 6.2 Hz, 1H), 4.95 (d, *J* = 7.4 Hz, 1H), 5.24 (dd, *J* = 7.4, 6.2 Hz, 1H), 5.69 (d, *J* = 3.7 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.4 (q), –5.3 (q), 18.3 (s), 25.9 (q, 3C), 26.6 (q), 26.7 (q), 62.1 (t), 78.0 (s), 78.7 (t), 82.1 (d), 83.3 (d), 90.3 (d), 104.0 (d), 112.7 (s), 207.0 (s) ppm.
ESI-MS (*m/z*)	: 365.6 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 59.61; H, 8.83. Found: C, 59.54; H, 8.73.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-[prop-2'-ynyl]-*α*-D-ribofuranose (91)



Mol. Formula	: $C_{17}H_{30}O_5Si$
$[\alpha]_D$	: +7.6 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3503, 3311, 2253, 1375, 1255, 1101, 838, 735, 648 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.06 (s, 6H), 0.88 (s, 9H), 1.37 (s, 3H), 1.58 (s, 3H), 2.03 (t, *J* = 2.7 Hz, 1H), 2.35 (ddd, *J* = 17.1, 2.7, 0.7 Hz, 1H), 2.57 (dd, *J* = 17.1, 2.7 Hz, 1H), 2.79 (br d, *J* = 0.8 1H), 3.77–3.90 (m, 3H), 4.48 (d, *J* = 3.9 Hz, 1H), 5.79 (d, *J* = 3.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.5 (q), −5.4 (q), 18.2 (s), 22.9 (t), 25.8 (q, 3C), 26.5 (q), 26.6 (q), 60.8 (t), 71.1 (d), 78.1 (s), 79.1 (s), 81.8 (d), 82.0 (d), 103.7 (d), 112.4 (s) ppm.
ESI-MS (*m/z*)	: 365.6 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 59.61; H, 8.83.
	Found: C, 59.55; H, 8.75.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-[3'-phenyl-prop-2'-ynyl]-*α*-D-ribofuranose (92)

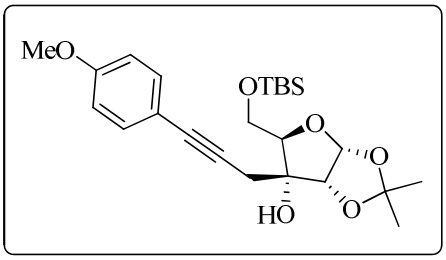


To a solution of alkyne **91** (500 mg, 1.46 mmol), iodobenzene (0.16 mL, 1.46 mmol), in Et_3N (5 mL) and DMF (2.5 mL), TPP (38 mg, 0.14 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (102 mg, 0.14 mmol), and the reaction mixture was flushed with argon for 30 min. CuI (33 mg, 0.17 mmol) was added and flushed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate, water and the organic layer was separated washed with brine, dried (Na_2SO_4), and concentrated.

The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to obtain **92** (515 mg, 84%) as a white solid.

Mol. Formula	: $C_{23}H_{34}O_5Si$
M. P.	: 56–57 °C.
$[\alpha]_D$	: +22.3 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3543, 2954, 1599, 1491, 1375, 1254, 837, 778, 691 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.04 (s, 6H), 0.85 (s, 9H), 1.33 (s, 3H), 1.55 (s, 3H), 2.57 (d, *J* = 17.2 Hz, 1H), 2.75 (d, *J* = 17.2 Hz, 1H), 2.82 (br s, 1H), 3.83–3.86 (m, 2H), 3.92 (dd, *J* = 6.2, 4.0 Hz, 1H), 4.51 (d, *J* = 3.9 Hz, 1H), 5.81 (d, *J* = 3.9 Hz, 1H), 7.20–7.27 (m, 3H), 7.33–7.40 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.4 (q), –5.2 (q), 18.3 (s), 24.0 (t), 25.9 (q, 3C), 26.7 (q), 26.7 (q), 61.1 (t), 78.6 (s), 82.2 (d, 2C), 83.2 (s), 84.5 (s), 104.0 (d), 112.5 (s), 123.2 (s), 127.9 (d), 128.2 (d, 2C), 131.7 (d, 2C) ppm.
ESI-MS (*m/z*)	: 441.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 65.99; H, 8.19.
	Found: C, 65.80; H, 8.32.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyl-dimethylsilyl)-3-*C*-[3'-(4-methoxyphenyl)-prop-2'-ynyl]-*α*-D-ribofuranose (93)

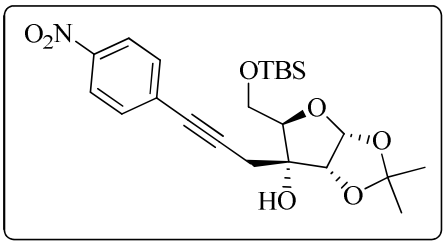


To a solution of alkyne **91** (480 mg, 1.40 mmol), iodoanisole (360 mg, 1.54 mmol), in Et_3N (8 mL) and DMF (4 mL), TPP (36 mg, 0.14 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (98 mg, 0. 14 mmol), and the reaction mixture was flushed with argon for 30 min. CuI (40 mg, 0.21 mmol) was added, flushed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate, water and the organic layer was separated washed with ethyl acetate, brine, dried (Na_2SO_4), and

concentrated. Purification of the residue by column chromatography (15% ethyl acetate in petroleum ether) afforded **93** (520 mg, 83%) as colorless syrup.

Mol. Formula	: $C_{24}H_{36}O_6Si$
$[\alpha]_D$	: +5.3 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3500, 2931, 1607, 1510, 1248, 835, 778, 665 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.08 (s, 6H), 0.89 (s, 9H), 1.37 (s, 3H), 1.59 (s, 3H), 2.58 (d, *J* = 17.1 Hz, 1H), 2.76 (d, *J* = 17.1 Hz, 1H), 2.75–2.85 (br s, 1H), 3.79 (s, 3H), 3.85–3.89 (m, 2H), 3.94 (dd, *J* = 6.5, 3.6 Hz, 1H), 4.53 (d, *J* = 3.9 Hz, 1H), 5.83 (d, *J* = 3.9 Hz, 1H), 6.79 (dt, *J* = 8.8, 2.6 Hz, 2H), 7.33 (dt, *J* = 8.8, 2.6 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.5 (q), –5.4 (q), 18.2 (s), 23.8 (t), 25.8 (q, 3C), 26.5 (q), 26.6 (q), 54.9 (q), 61.0 (t), 78.4 (s), 82.2 (d), 82.2 (d), 82.7 (s), 82.8 (s), 103.8 (d), 112.2 (s), 113.6 (d, 2C), 115.2 (s), 132.9 (d, 2C), 159.2 (s) ppm.
ESI-MS (*m/z*)	: 471.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 64.25; H, 8.09.
	Found: C, 64.13; H, 7.95.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyl-dimethylsilyl) -3-*C*-[3'-(4-nitrophenyl)-prop-2'-ynyl]-*α*-D-ribofuranose (94)

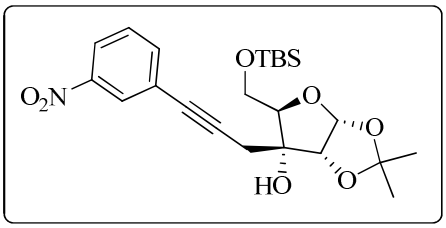


To a solution of alkyne **91** (480 mg, 1.40 mmol), 4-iodonitrobenzene (348 mg, 1.40 mmol), in Et_3N (6 mL) and DMF (3 mL), TPP (36 mg, 0.14 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol), and the reaction mixture was flushed with argon for 30 min. CuI (40 mg, 0.21 mmol) was added and flushed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate, water and the organic layer was separated washed with brine, dried (Na_2SO_4), and

concentrated. The residue obtained was purified by column chromatography (15% ethyl acetate in petroleum ether) to give **94** (550 mg, 85%) as yellow syrup.

Mol. Formula	: $C_{23}H_{33}NO_7Si$
$[\alpha]_D$	: +10.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3542, 2930, 1594, 1520, 1343, 1106, 838, 751, 688 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.08 (s, 6H), 0.90 (s, 9H), 1.39 (s, 3H), 1.60 (s, 3H), 2.64 (d, *J* = 17.3 Hz, 1H), 2.85 (d, *J* = 17.3 Hz, 1H), 2.85 (br d, *J* = 0.6 Hz, 1H), 3.85–3.89 (m, 2H), 3.92 (dd, *J* = 6.4, 3.0 Hz, 1H), 4.49 (d, *J* = 3.9 Hz, 1H), 5.84 (d, *J* = 3.9 Hz, 1H), 7.55 (dt, *J* = 8.9, 2.2 Hz, 2H), 8.16 (dt, *J* = 8.9, 2.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.4 (q), –5.3 (q), 18.3 (s), 24.1 (t), 25.9 (q, 3C), 26.5 (q), 26.7 (q), 60.8 (t), 78.5 (s), 81.4 (s), 82.0 (d, 2C), 90.9 (s), 103.8 (d), 112.6 (s), 123.4 (d, 2C), 130.1 (s), 132.4 (d, 2C), 146.9 (s) ppm.
ESI-MS (*m/z*)	: 486.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 59.59; H, 7.17; N, 3.02.
	Found: C, 59.47; H, 7.14; N, 3.09.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyl-dimethylsilyl) -3-*C*-[3'-(3-nitrophenyl)-prop-2'-ynyl]-*α*-D-ribofuranose (95)

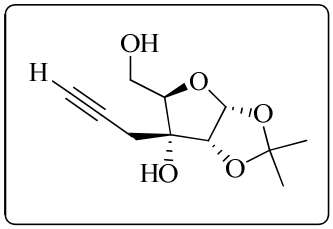


To a solution of alkyne **91** (500 mg, 1.46 mmol), 3-iodonitrobenzene (399 mg, 1.60 mmol), in Et_3N (8 mL) and DMF (4 mL), TPP (38 mg, 0.14 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (102 mg, 0.14 mmol), and the reaction mixture was flushed with argon for 30 min. CuI (41 mg, 0.22 mmol) was added and flushed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate, water and the organic layer was separated washed with brine, dried (Na_2SO_4), and

concentrated. The residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to obtain **95** (490 mg, 72%) as yellow syrup.

Mol. Formula	: $C_{23}H_{33}NO_7Si$
$[\alpha]_D$	: +9.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3543, 2930, 1532, 1351, 1100, 838, 758, 673 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.09 (s, 6H), 0.90 (s, 9H), 1.39 (s, 3H), 1.60 (s, 3H), 2.62 (d, *J* = 17.3 Hz, 1H), 2.84 (d, *J* = 17.3 Hz, 1H), 2.85 (d, *J* = 0.8 Hz, 1H), 3.86–3.95 (m, 3H), 4.51 (d, *J* = 4.0 Hz, 1H), 5.84 (d, *J* = 4.0 Hz, 1H), 7.47 (t, *J* = 8.0, Hz, 1H), 7.71 (dt, *J* = 7.7, 1.3 Hz, 1H), 8.14 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.26 (t, *J* = 1.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.4 (q), –5.3 (q), 18.3 (s), 23.9 (t), 25.9 (q, 3C), 26.5 (q), 26.7 (q), 60.9 (t), 78.4 (s), 80.7 (s), 82.0 (d), 82.1 (d), 88.0 (s), 103.8 (d), 112.6 (s), 122.6 (d), 125.0 (s), 126.4 (d), 129.1 (d), 137.3 (d), 148.0 (s) ppm.
ESI-MS (*m/z*)	: 486.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 59.59; H, 7.17; N, 3.02.
	Found: C, 59.65; H, 7.24; N, 3.12.

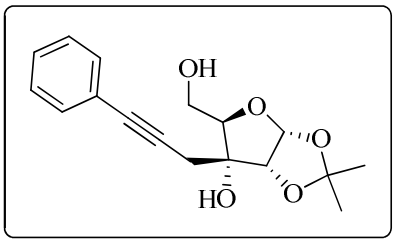
1,2-*O*-Isopropylidene-3-*C*-[prop-2'-ynyl]-*α*-D-ribofuranose (84)



To a cooled solution (0 °C) of **91** (515 mg, 1.50 mmol) in THF (10 mL), TBAF (1.8 mL, 1.80 mmol, 1 M solution) was added and the reaction mixture was warmed to rt and stirred for 0.5 h. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to obtain **84** (315 mg, 92%) as thick syrup.

Mol. Formula	: $C_{11}H_{16}O_5$
$[\alpha]_D$	: +20.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3500, 3301, 2260, 1355, 1245, 1110, 837, 740, 650 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.37 (s, 3H), 1.57 (s, 3H), 2.08 (t, *J* = 2.7 Hz, 1H), 2.38 (dd, *J* = 17.1, 2.6 Hz, 1H), 2.56 (dd, *J* = 17.1, 2.7 Hz, 1H), 2.93 (s, 1H), 3.69–4.04 (m, 4H), 4.48 (d, *J* = 3.9 Hz, 1H), 5.81 (d, *J* = 3.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 22.6 (t), 26.3 (q), 26.4 (q), 59.7 (t), 71.4 (d), 78.1 (s), 78.9 (s), 81.5 (d), 81.7 (d), 103.5 (d), 112.6 (s) ppm.
ESI-MS (*m/z*)	: 251.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 57.88; H, 7.07.
	Found: C, 57.80; H, 7.10.

1,2-*O*-Isopropylidene-3-*C*-[3'-phenyl-prop-2'-ynyl]-*α*-D-ribofuranose (85)



To a cooled solution (0 °C) of **92** (240 mg, 0.57 mmol) in THF (8 mL), TBAF (0.687 mL, 0.69 mmol, 1 M solution) was added and the reaction mixture was warmed to rt and stirred for 0.5 h. Solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (50% ethyl acetate in petroleum ether) to yield **85** (158 mg, 91%) as white solid.

Mol. Formula	: $C_{17}H_{20}O_5$
M. P.	: 121–122 °C.
$[\alpha]_D$	: +23.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 3018, 1734, 1490, 1376, 1216, 875, 755, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.38 (s, 3H), 1.60 (s, 3H), 2.19 (br s, 1H), 2.61 (d, *J* = 17.1 Hz, 1H), 2.76 (d, *J* = 17.1 Hz, 1H), 2.97 (br s, 1H), 3.80–3.90 (m, 2H), 3.98 (dd, *J* = 6.4, 3.7 Hz, 1H), 4.52 (d, *J* = 3.9 Hz, 1H), 5.86 (d, *J* = 3.9 Hz, 1H), 7.25–7.31 (m,

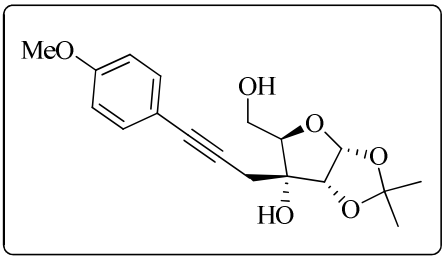
3H), 7.36–7.43 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 23.9 (t), 26.6 (q), 26.7 (q), 60.2 (t), 78.5 (s), 82.0 (d), 82.3 (d), 83.4 (s), 84.1 (s), 103.8 (d), 112.7 (s), 123.1 (s), 128.1 (d), 128.2 (d, 2C), 131.7 (d, 2C) ppm.

ESI-MS (*m/z*) : 327.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 67.09; H, 6.62.
Found: C, 66.95; H, 6.67.

1,2-*O*-Isopropylidene-3-*C*-[3'-(4-methoxy-phenyl)-prop-2'-ynyl]-*α*-D-ribofuranose (86)



To a cooled solution (0 °C) of **93** (718 mg, 1.60 mmol) in THF (15 mL), TBAF (1.92 mL, 1.92 mmol, 1 M solution) was added and the reaction mixture was warmed to rt and stirred for 0.5 h. Solvent was evaporated under reduced pressure. The residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to yield **86** (500 mg, 93%) as white solid.

Mol. Formula : $C_{18}H_{22}O_6$

M. P. : 120–121 °C.

$[\alpha]_D$: +23.5 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3461, 2937, 1606, 1509, 1247, 1031, 833, 755, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.38 (s, 3H), 1.59 (s, 3H), 1.90–1.99 (br, 1H), 2.60 (d, *J* = 17.1 Hz, 1H), 2.76 (d, *J* = 17.1 Hz, 1H), 2.89 (br s, 1H), 3.79 (s, 3H), 3.86–3.93 (m, 2H), 4.00 (dd, *J* = 6.6, 3.8 Hz, 1H), 4.53 (d, *J* = 3.9 Hz, 1H), 5.86 (d, *J* = 3.9 Hz, 1H), 6.81 (dt, *J* = 8.8, 2.8 Hz, 2H), 7.34 (dt, *J* = 8.8, 2.8 Hz, 2H) ppm.

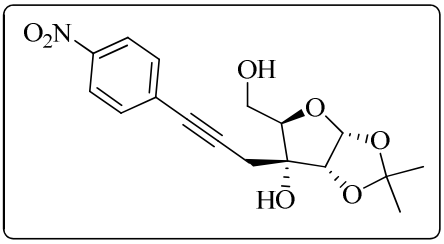
^{13}C NMR ($CDCl_3$, 125 MHz) : δ 23.8 (t), 26.5 (q), 26.5 (q), 55.2 (q), 60.1 (t), 78.5 (s), 81.8 (d), 82.2 (d), 82.4 (s), 83.1 (s), 103.7 (d), 112.6 (s), 113.8 (d, 2C), 115.0 (s), 133.0 (d, 2C), 159.3 (s) ppm.

ESI-MS (*m/z*) : 357.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 64.66; H, 6.63.

Found: C, 64.45; H, 6.47.

1,2-*O*-Isopropylidene-3-*C*-[3'-(4-nitro-phenyl)-prop-2'-ynyl]-*α*-D-ribofuranose (87)



To a cooled solution (0 °C) of **94** (930 mg, 2.00 mmol) in THF (15 mL), TBAF (2.4 mL, 2.40 mmol, 1M solution) was added and the reaction mixture was warmed to rt and stirred for 0.5 h. Solvent was evaporated under reduced pressure. The residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to afford **87** (630 mg, 90%) as yellowish syrup.

Mol. Formula : $C_{17}H_{19}NO_7$

$[\alpha]_D$: +32.9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3548, 3020, 1594, 1520, 1344, 1215, 855, 757, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.39 (s, 3H), 1.60 (s, 3H), 1.86 (br, 1H), 2.66 (d, *J* = 17.3 Hz, 1H), 2.85 (d, *J* = 17.3 Hz, 1H), 2.93 (br s, 1H), 3.86–3.94 (m, 2H), 3.98 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.51 (d, *J* = 3.9 Hz, 1H), 5.87 (d, *J* = 3.9 Hz, 1H), 7.55 (dt, *J* = 8.9, 2.2 Hz, 2H), 8.16 (dt, *J* = 8.9, 2.2 Hz, 2H) ppm.

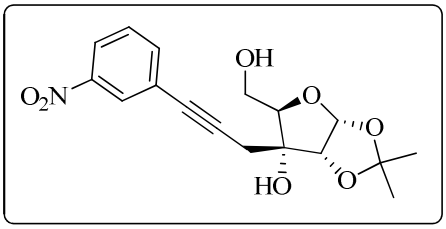
^{13}C NMR ($CDCl_3$, 125 MHz) : δ 23.9 (t), 26.4 (q), 26.6 (q), 60.0 (t), 78.4 (s), 81.6 (s), 81.7 (d), 81.9 (d), 90.3 (s), 103.6 (d), 112.8 (s), 123.4 (d, 2C), 129.9 (s), 132.4 (d, 2C), 146.9 (s) ppm.

ESI-MS (*m/z*) : 372.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 58.45; H, 5.48; N, 4.01.

Found: C, 58.25; H, 5.59; N, 4.18.

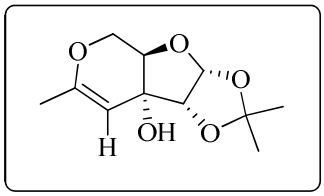
1,2-*O*-Isopropylidene-3-*C*-[3'-(3-nitrophenyl-)-prop-2'-ynyl]-*α*-D-ribofuranose (88)



To a cooled solution (0 °C) of **95** (950 mg, 2.05 mmol) in THF (15 mL), TBAF (2.46 mL, 2.46 mmol, 1 M solution) was added and the reaction mixture was warmed to rt and stirred for 0.5 h. Solvent was evaporated under reduced pressure. The residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to yield **88** (650 mg, 91%) as yellowish syrup.

Mol. Formula	: $C_{17}H_{19}NO_7$
$[\alpha]_D$	: +25.2 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3491, 2991, 1531, 1352, 1216, 1005, 874, 758, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.39 (s, 3H), 1.59 (s, 3H), 2.06 (br s, 1H), 2.62 (d, *J* = 17.3 Hz, 1H), 2.81 (d, *J* = 17.3 Hz, 1H), 2.96 (br s, 1H), 3.84–3.92 (m, 2H), 3.96 (dd, *J* = 6.7, 3.5 Hz, 1H), 4.50 (d, *J* = 3.9 Hz, 1H), 5.85 (d, *J* = 3.9 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.70 (dt, *J* = 7.7, 1.3 Hz, 1H), 8.13 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.24 (t, *J* = 1.8 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 23.6 (t), 26.4 (q), 26.5 (q), 59.9 (t), 78.3 (s), 80.9 (s), 81.7 (d), 81.9 (d), 87.4 (s), 103.6 (d), 112.8 (s), 122.8 (d), 124.8 (s), 126.4 (d), 129.2 (d), 137.4 (d), 147.9 (s) ppm.
ESI-MS (*m/z*)	: 372.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.28; H, 5.20; N, 4.12.

1,2-*O*-Isopropylidene-3-*C*-(2'-hydroxy-prop-1-enyl)-2',5-anhydro-*α*-D-ribofuranose (96)



A solution of **84** (90 mg, 0.39 mmol) and $Pd(CH_3CN)_2Cl_2$ (10 mg, 0.04 mmol) in acetonitrile (10 mL) was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and purified by silica gel chromatography (15% ethyl acetate in petroleum ether) to obtain **96** (58 mg, 64%) as syrup.

Mol. Formula : $C_{11}H_{16}O_5$

$[\alpha]_D$: –31.3 (*c* 2.5, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3432, 3019, 1672, 1376, 1216, 1116, 876, 756, 667 cm^{-1}.

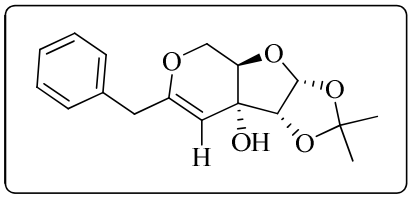
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.35 (s, 3H), 1.56 (s, 3H), 1.79 (d, *J* = 0.8 Hz, 3H), 2.89 (br s 1H), 3.90 (dd, *J* = 12.6, 1.2 Hz, 2H), 4.19 (d, *J* = 3.7 Hz, 1H), 4.31 (dd, *J* = 12.6, 1.6 Hz, 1H), 4.40 (br q, *J* = 0.8 Hz, 1H), 5.72 (d, *J* = 3.7 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 20.3 (q), 26.8 (q), 27.0 (q), 63.1 (t), 71.3 (s), 76.9 (d), 83.5 (d), 95.0 (d), 104.2 (d), 112.7 (s), 156.2 (s) ppm.

ESI-MS (*m/z*) : 251.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 57.88; H, 7.07.
Found: C, 57.83; H, 7.05.

1,2-*O*-Isopropylidene-3-*C*-(2'-hydroxy-2'-benzyl-*E*-vinyl)-2',5-anhydro]-α-D-ribo-furanose (97)



A solution of **85** (100 mg, 0.33 mmol) and $Pd(CH_3CN)_2Cl_2$ (8 mg, 0.03 mmol) in acetonitrile (10 mL) was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and the residue obtained was purified by silica gel chromatography (20%, 30% ethyl acetate in petroleum ether) to obtain **97** (60 mg, 60%) and **98** (20 mg, 19%) as colorless solids.

Mol. Formula : $C_{17}H_{20}O_5$

M. P. : 118–119 °C.

$[\alpha]_D$: –67.8 (*c* 1.0, $CHCl_3$).

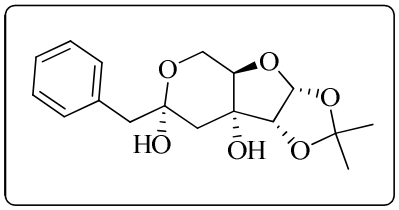
IR ($CHCl_3$) $\tilde{\nu}$: 3533, 3019, 1669, 1376, 1216, 1115, 875, 756, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.35 (s, 3H), 1.57 (s, 3H), 2.89 (br s, 1H), 3.36 (d, *J* = 16.5 Hz, 1H), 3.40 (d, *J* = 16.5 Hz, 1H), 3.84 (d, *J* = 12.3 Hz, 1H), 3.92 (br d, *J* = 1.1 Hz, 1H), 4.16 (d, *J* = 3.7 Hz, 1H), 4.33 (dd, *J* = 12.4, 1.4 Hz, 1H), 4.40 (br d, *J* = 1.1 Hz, 1H), 5.71 (d, *J* = 3.7 Hz, 1H), 7.18–7.29 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 26.8 (q), 27.0 (q), 40.5 (t), 63.4 (t), 71.3 (s), 77.1 (d), 83.4 (d), 96.2 (d), 104.2 (d), 112.7 (s), 126.5 (d), 128.4 (d, 2C), 129.0 (d, 2C), 137.0 (s), 158.5 (s) ppm.
ESI-MS (*m/z*)	: 327.0 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 67.09; H, 6.62.
	Found: C, 67.10; H, 6.78.

Crystallographic data for 97. ($C_{17}H_{20}O_5$): M = 304.33, Crystal dimensions 0.65 x 0.25 x 0.11 mm^3, orthorhombic, space group $P\ 2_12_12_1$, a = 6.0693(14), b = 12.689(3), c = 20.174(5) Å, V = 1553.7(6) $Å^3$, Z = 4, ρ_{calcd} = 1.301 gcm^{-3}, μ (Mo-K_α) = 0.095 mm^{-1}, *F(000)* = 648, $2\theta_{max}$ = 50.00°, T = 297(2) K, 7855 reflections collected, 2722 unique, 2507 observed ($I > 2\sigma(I)$) reflections, 202 refined parameters, R value 0.0323, $wR2$ = 0.0697 (all data R = 0.0362, $wR2$ = 0.0725), S = 1.101, minimum and maximum transmission 0.9410 and 0.9893; maximum and minimum residual electron densities +0.117 and –0.137 e $Å^{-3}$.

Data of 98:

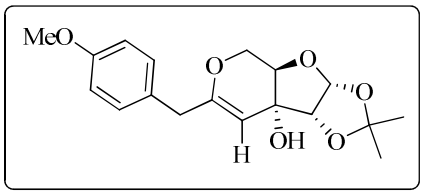
1,2-*O*-Isopropylidene-3-*C*-(2'-oxo-3'-phenyl-propyl)-*α*-D-ribofuranose-(2'-*C*,5-*O*)-hemiketal (98)



Mol. Formula	: $C_{17}H_{22}O_6$
M. P.	: 144–145 °C.
$[\alpha]_D$	: –8.4 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3522, 3019, 1684, 1376, 1216, 1010, 875, 756, 668 cm^{-1}.
^{1}H NMR	: δ 1.33 (s, 3H), 1.55 (s, 3H), 1.57 (d, *J* = 14.1 Hz, 1H),

($CDCl_3$, 400 MHz)	1.69 (d, *J* = 14.1 Hz, 1H), 2.82 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 13.6 Hz, 1H), 3.20 (br s, 1H), 3.69 (s, 1H), 3.81 (s, 1H), 3.96 (d, *J* = 13.8 Hz, 1H), 4.06 (d, *J* = 3.7 Hz, 1H), 4.12 (dd, *J* = 13.8, 1.8 Hz, 1H), 5.74 (d, *J* = 3.7 Hz, 1H), 7.21–7.28 (m, 5H) ppm.
^{13}C NMR	: δ 26.5 (q, 2C), 37.0 (t), 47.5 (t), 57.6 (t), 74.1 (d), 74.5 (s), 82.7 (d), 95.5 (s), 103.7 (d), 112.8 (s), 126.9 (d), 128.2 (d, 2C), 130.9 (d, 2C), 135.1 (s) ppm.
($CDCl_3$, 100 MHz)	
ESI-MS (*m/z*)	: 345.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 63.34; H, 6.88.
	Found: C, 63.28; H, 6.82.

1,2-*O*-Isopropylidene-3-*C*-[2'-hydroxy-2'-(4-methoxybenzyl)-*E*-vinyl]-2',5-anhydro-α-D-ribofuranose (99)



A solution of **86** (120 mg, 0.36 mmol) and $Pd(CH_3CN)_2Cl_2$ (9 mg, 0.04 mmol) in acetonitrile (10 mL) was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and residue obtained was purified by silica gel chromatography (20%, 60% ethyl acetate in petroleum ether) to obtain **99** (20 mg, 16%) and **100** (70 mg, 55%) as colorless syrups.

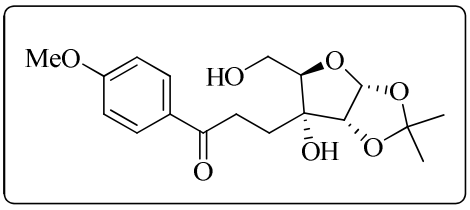
Mol. Formula	: $C_{18}H_{22}O_6$
$[\alpha]_D$	: –49.8 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3479, 2926, 1741, 1669, 1512, 1248, 875, 757, 666 cm^{-1}.
^{1}H NMR	: δ 1.35 (s, 3H), 1.57 (s, 3H), 2.89 (br s, 1H), 3.29 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 17.3 Hz, 1H), 3.78 (s, 3H), 3.84 (dd, *J* = 12.4, 0.9 Hz, 1H), 3.94 (dd, *J* = 3.0, 1.6 Hz, 1H), 4.19 (d, *J* = 3.7 Hz, 1H), 4.34 (ddd, *J* = 12.4, 2.0, 0.6 Hz, 1H), 4.40 (d, *J* = 0.9 Hz, 1H), 5.73 (d, *J* = 3.7 Hz, 1H), 6.82 (dt, *J* = 8.7, 2.9 Hz, 2H), 7.11 (dt, *J* = 8.7, 2.9 Hz,
($CDCl_3$, 200 MHz)	

2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.7 (q), 27.0 (q), 39.6 (t), 55.2 (q), 63.4 (t), 71.3 (s), 77.1 (d), 83.4 (d), 95.9 (d), 104.2 (d), 112.8 (s), 113.8 (d, 2C), 129.0 (s), 130.0 (d, 2C), 158.3 (s), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 357.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 64.66; H, 6.63.
	Found: C, 64.58; H, 6.55.

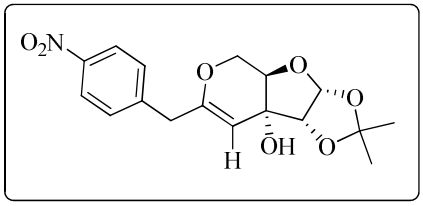
Data of 100:

1,2-*O*-Isopropylidene-3-*C*-[3'-oxo-3'-(4-methoxyphenyl)-propyl]-*α*-D-ribofuranose (100)



Mol. Formula	: $C_{18}H_{24}O_7$
$[\alpha]_D$	: +13.3 (*c* 2.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3491, 2936, 1673, 1601, 1512, 1171, 877, 755, 666 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.34 (s, 3H), 1.57 (s, 3H), 1.89 (dd, *J* = 8.5, 6.3 Hz, 1H), 1.94 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.85 (br s, 1H), 2.99 (ddd, *J* = 17.7, 8.5, 6.3 Hz, 1H), 3.25 (ddd, *J* = 17.7, 8.5, 6.3 Hz, 1H), 3.78–3.84 (m, 2H), 3.86 (s, 3H), 3.94 (dd, *J* = 6.6, 4.1 Hz, 1H), 4.22 (d, *J* = 3.9 Hz, 1H), 5.81 (d, *J* = 3.9 Hz, 1H), 6.91 (dt, *J* = 8.9, 2.9 Hz, 2H), 7.94 (dt, *J* = 8.9, 2.9 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.5 (t), 26.4 (q, 2C), 31.9 (t), 55.4 (q), 60.5 (t), 78.6 (s), 81.0 (d), 82.7 (d), 103.6 (d), 112.5 (s), 113.7 (d, 2C), 129.7 (s), 130.3 (d, 2C), 163.5 (s), 198.3 (s) ppm.
ESI-MS (*m/z*)	: 375.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 61.35; H, 6.86.
	Found: C, 61.30; H, 6.82.

1,2-*O*-Isopropylidene-3-*C*-[2'-hydroxy-2'-(4-nitrobenzyl)-*E*-vinyl]-2',5-anhydro-*α*-D-ribofuranose (101)

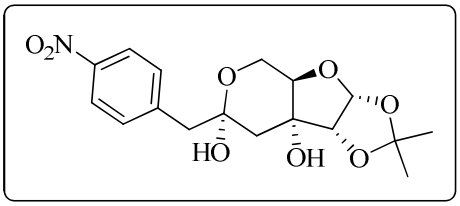


A solution of **87** (100 mg, 0.29 mmol) and $Pd(CH_3CN)_2Cl_2$ (7 mg, 0.03 mmol) in acetonitrile (10 mL) was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and the crude residue obtained was purified by silica gel chromatography (25%, 30% ethyl acetate in petroleum ether) to obtain **101** (60 mg**,** 60%) as yellow syrup and **102** (15 mg, 14%) as yellow solid.

Mol. Formula	: $C_{17}H_{19}NO_7$
$[\alpha]_D$	: −61.0 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3505, 2988, 2923, 1671, 1519, 1347, 875, 733, 648 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.56 (s, 3H), 2.99 (br s, 1H), 3.43 (d, *J* = 16.3 Hz, 1H), 3.51 (d, *J* = 16.3 Hz, 1H), 3.84 (dd, *J* = 12.4, 0.8 Hz, 1H), 3.93 (dd, *J* = 3.2, 1.8 Hz, 1H), 4.21 (d, *J* = 3.7 Hz, 1H), 4.34 (ddd, *J* = 12.4, 2.0, 0.6 Hz, 1H), 4.51 (d, *J* = 1.8 Hz, 1H), 5.73 (d, *J* = 3.7 Hz, 1H), 7.36 (dt, *J* = 8.7, 2.5 Hz, 2H), 8.13 (dt, *J* = 8.7, 2.5 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.6 (q), 26.8 (q), 40.3 (t), 63.5 (t), 71.2 (s), 76.7 (d), 83.1 (d), 97.2 (d), 104.0 (d), 112.9 (s), 123.6 (d, 2C), 129.6 (d, 2C), 144.8 (s), 146.8 (s), 156.7 (s) ppm.
ESI-MS (*m/z*)	: 372.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 58.45; H, 5.48; N, 4.01.
	Found: C, 58.40; H, 5.43; N, 4.02.

Data of 102:

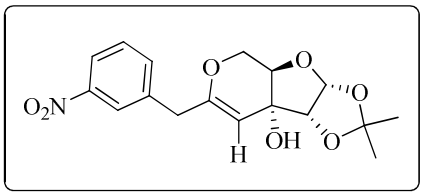
1,2-*O*-Isopropylidene-3-*C*-[2'-oxo-3'(4-nitrophenyl)-propyl]-*α*-D-ribo-furanose-(2'-*C*,5-*O*)-hemiketal (102)



Mol. Formula	: $C_{17}H_{21}NO_8$
M. P.	: 149–150 °C.
$[\alpha]_D$	: −11.6 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3397, 2923, 1597, 1511, 1345, 1043, 862, 733, 648 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.34 (s, 3H), 1.55 (s, 3H), 1.61 (d, *J* = 14.1 Hz, 1H), 1.71 (d, *J* = 14.1 Hz, 1H), 2.96 (d, *J* = 13.6 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 3.08 (br s, 1H), 3.67 (br s, 1H), 3.99 (d, *J* = 14.0 Hz, 1H), 4.07 (d, *J* = 3.8 Hz, 1H), 4.12 (dd, *J* = 14.0, 2.2 Hz, 1H), 4.44 (s, 1H), 5.78 (d, *J* = 3.8 Hz, 1H), 7.47 (dt, *J* = 8.7, 2.4 Hz, 2H), 8.14 (dt, *J* = 8.7, 2.4 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 26.3 (q), 26.4 (q), 37.0 (t), 47.1 (t), 57.5 (t), 73.7 (d), 74.7 (s), 82.1 (d), 95.1 (s), 103.6 (d), 113.0 (s), 123.1 (d, 2C), 131.7 (d, 2C), 143.4 (s), 147.0 (s) ppm.
ESI-MS (*m/z*)	: 390.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.55; H, 5.74; N, 3.75.

Crystallographic data for 102. ($C_{17}H_{21}NO_8$): *M* = 367.35, Crystal dimensions 0.77 x 0.31 x 0.18 mm^3, monoclinic, space group *P* 2_1, *a* = 5.4991(14), *b* = 17.126(4), *c* = 9.123(2) Å, β = 95.765(4), *V* = 854.9(4) $Å^3$, *Z* = 2, ρ_{calcd} = 1.427 gcm^{-3}, μ (Mo-K_α) = 0.114 mm^{-1}, *F(000)* = 388, $2\theta_{max}$ = 50.00°, *T* = 297(2) K, 6696 reflections collected, 3262 unique, 3100 observed ($I > 2\sigma(I)$) reflections, 297 refined parameters, *R* value 0.0355, *wR*2 = 0.0881 (all data *R* = 0.0374, *wR*2 = 0.0902), S = 1.045, minimum and maximum transmission 0.9172 and 0.9797; maximum and minimum residual electron densities +0.295 and –0.138 e $Å^{-3}$.

1,2-*O*-Isopropylidene-3-*C*-[2'-hydroxy-2'-(3-nitrobenzyl)-*E*-vinyl]-2',5-anhydro-*α*-D-ribo-furanose (103)



A solution of **88** (150 mg, 0.43 mmol) and $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) in acetonitrile (15 mL) was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and the residue obtained was purified by silica gel chromatography (25%, 30% ethyl acetate in petroleum ether) to obtain **103** (80 mg, 53%) as yellow syrup and **104** (20 mg, 13%) as yellow solid.

Mol. Formula : $C_{17}H_{19}NO_7$

$[\alpha]_D$: –49.7 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3506, 2989, 1671, 1530, 1351, 1215, 874, 756, 667 cm^{-1}.

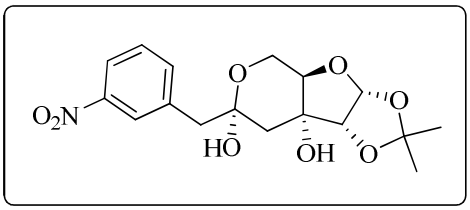
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.36 (s, 3H), 1.57 (s, 3H), 2.98 (s, 1H), 3.44 (d, *J* = 16.4 Hz, 1H), 3.52 (d, *J* = 16.4 Hz, 1H), 3.86 (dd, *J* = 12.4, 0.9 Hz, 1H), 3.94 (dd, *J* = 3.2, 1.8 Hz, 1H), 4.23 (d, *J* = 3.7 Hz, 1H), 4.35 (ddd, *J* = 12.4, 2.0, 0.6 Hz, 1H), 4.53 (d, *J* = 1.9 Hz, 1H), 5.78 (d, *J* = 3.7 Hz, 1H), 7.46 (dt, *J* = 8.6, 2.5 Hz, 1H), 7.54 (dt, *J* = 7.7, 1.4 Hz, 1H), 8.06–8.11 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.6 (q), 26.8 (q), 40.0 (t), 63.4 (t), 71.2 (s), 76.7 (d), 83.1 (d), 97.2 (d), 104.0 (d), 112.8 (s), 121.7 (d), 123.6 (d), 129.2 (d), 135.0 (d), 139.2 (s), 148.2 (s), 156.7 (s) ppm.

ESI-MS (*m/z*) : 372.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 58.45; H, 5.48; N, 4.01.
Found: C, 58.41; H, 5.42. N, 3.99.

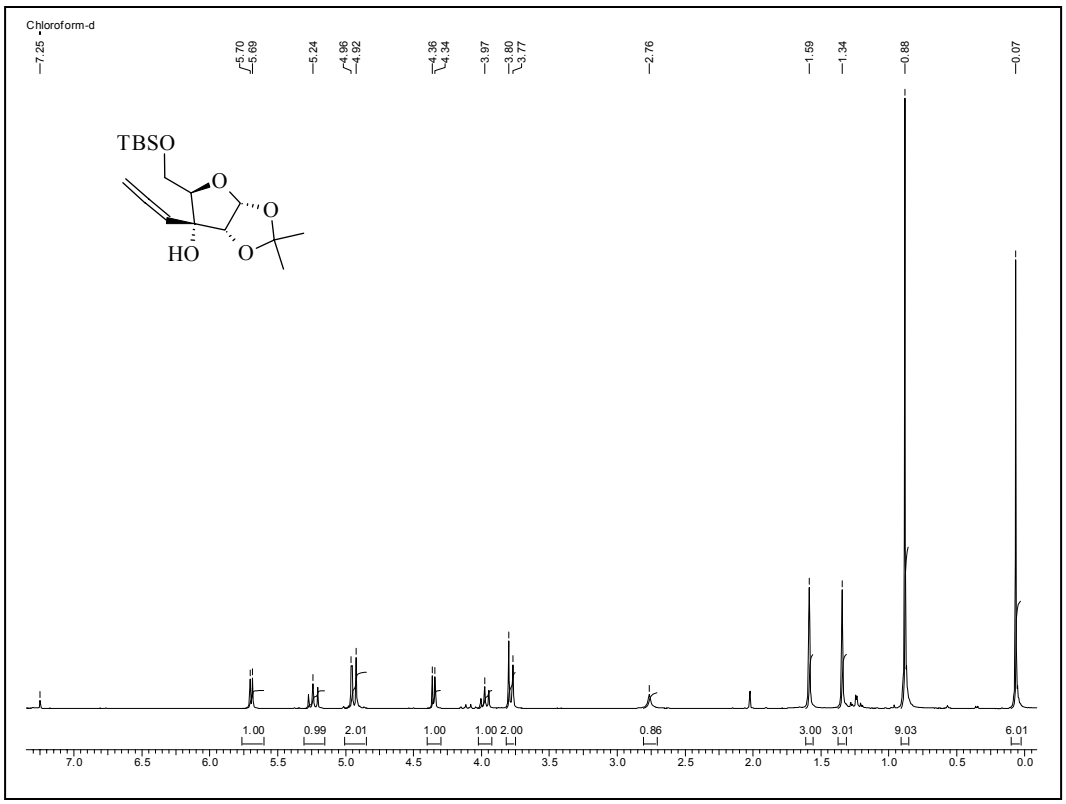
1,2-*O*-Isopropylidene-3-*C*-[2'-oxo-3'-(3-nitrophenyl)-propyl]-*α*-D-ribo-furanose-(2'-*C*,5-*O*)-hemiketal (104)



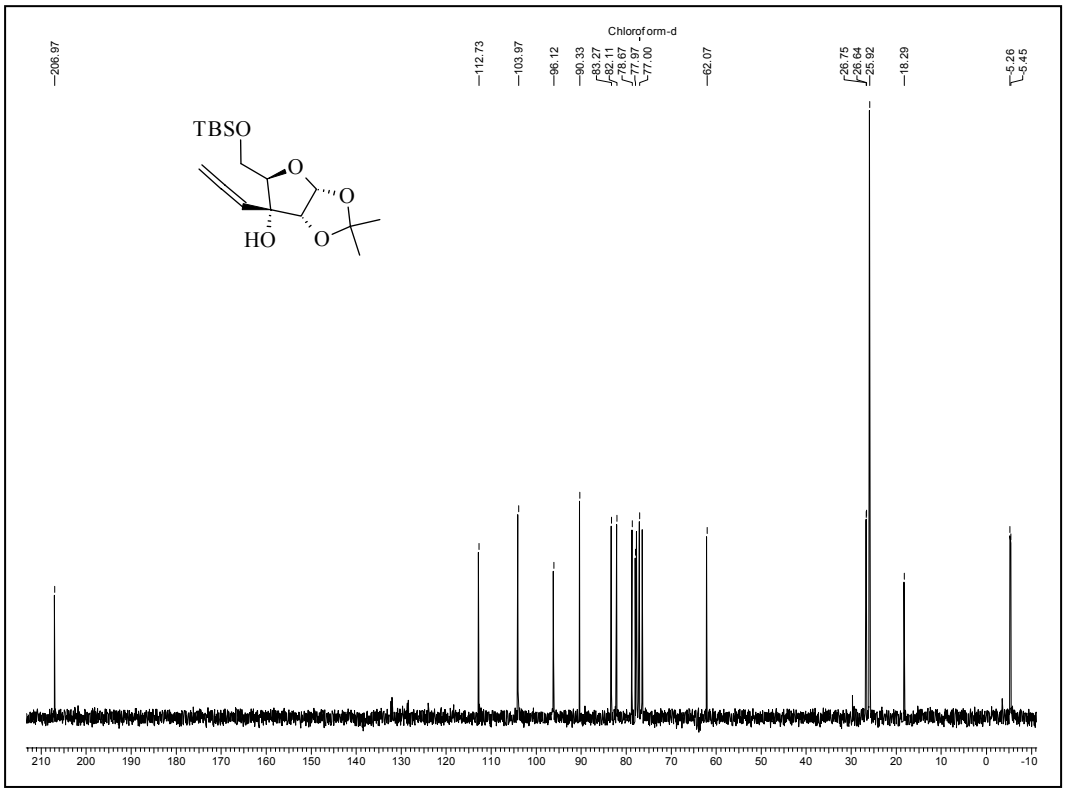
Mol. Formula	: $C_{17}H_{21}NO_8$
M. P.	: 152–153 °C.
$[\alpha]_D$	: −14.0 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3478, 2929, 1529, 1351, 1216, 1052, 876, 757, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.33 (s, 3H), 1.55 (s, 3H), 1.61 (d, *J* = 14.0 Hz, 1H), 1.73 (d, *J* = 14.0 Hz, 1H), 2.94 (d, *J* = 13.6 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 3.11 (br s, 1H), 3.68 (br s, 1H), 3.98 (d, *J* = 14.0 Hz, 1H), 4.08 (s, 1H), 4.13 (dd, *J* = 12.4, 2.1 Hz, 1H), 4.45 (s, 1H), 5.79 (d, *J* = 3.8 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.66 (dt, *J* = 7.7, 1.2 Hz, 1H), 8.10 (ddd, *J* = 8.1, 2.3, 1.1 Hz, 1H), 8.16 (t, *J* = 1.8 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 26.2 (q), 26.3 (q), 36.9 (t), 46.9 (t), 57.5 (t), 73.7 (d), 74.6 (s), 82.1 (d), 95.0 (s), 103.6 (d), 112.9 (s), 121.8 (d), 125.6 (d), 128.8 (d), 137.1 (d), 137.6 (s), 148.0 (s) ppm.
ESI-MS (*m/z*)	: 390.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.53; H, 5.70; N, 3.75.

Crystallographic data for 104. ($C_{17}H_{21}NO_8$): *M* = 367.35, Crystal dimensions 0.97 x 0.05 x 0.03 mm^3, orthorhombic, space group *P* $2_12_12_1$, *a* = 5.5126(16), *b* = 16.461(5), *c* = 19.369(6) Å, *V* = 1757.5(9) $Å^3$, *Z* = 4, ρ_{calcd} = 1.388 gcm^{-3}, μ (Mo-K_α) = 0.111 mm^{-1}, *F(000)* = 776, $2\theta_{max}$ = 50.00°, *T* = 297(2) K, 8849 reflections collected, 3087 unique, 2292 observed ($I > 2\sigma(I)$) reflections, 237 refined parameters, *R* value 0.0494, *wR*2 = 0.0852 (all data *R* = 0.0770, *wR*2 = 0.0945), S = 1.029, minimum and maximum transmission 0.8999 and 0.9965; maximum and minimum residual electron densities +0.173 and –0.178 e $Å^{-3}$.

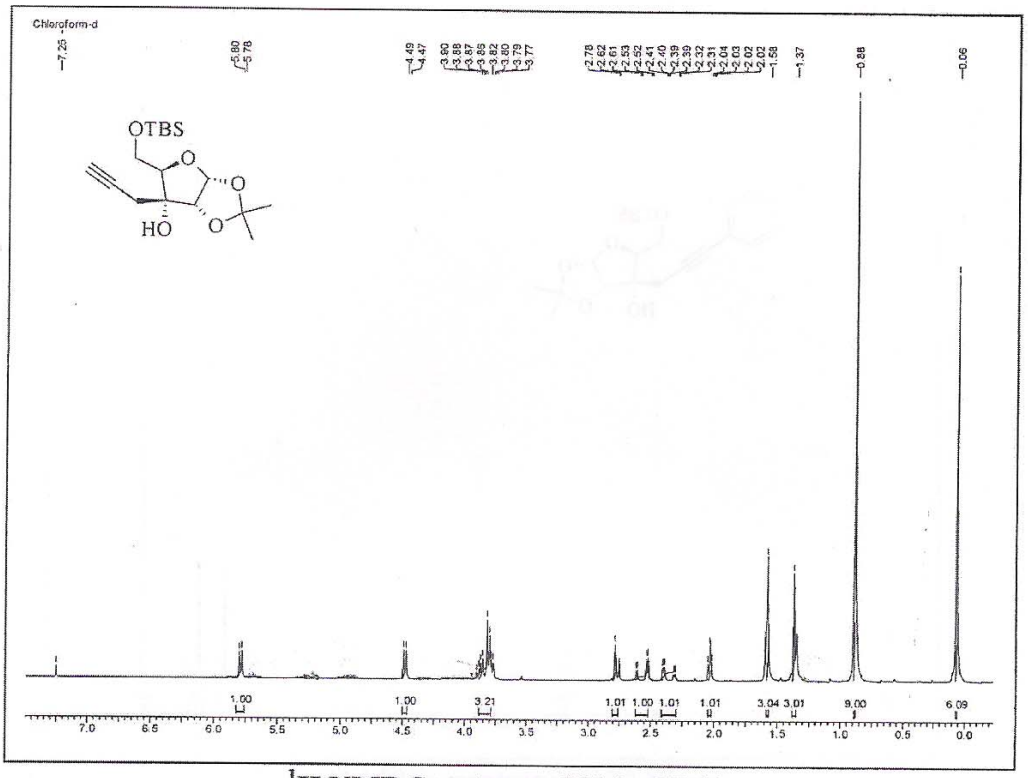
Spectroscopic Data



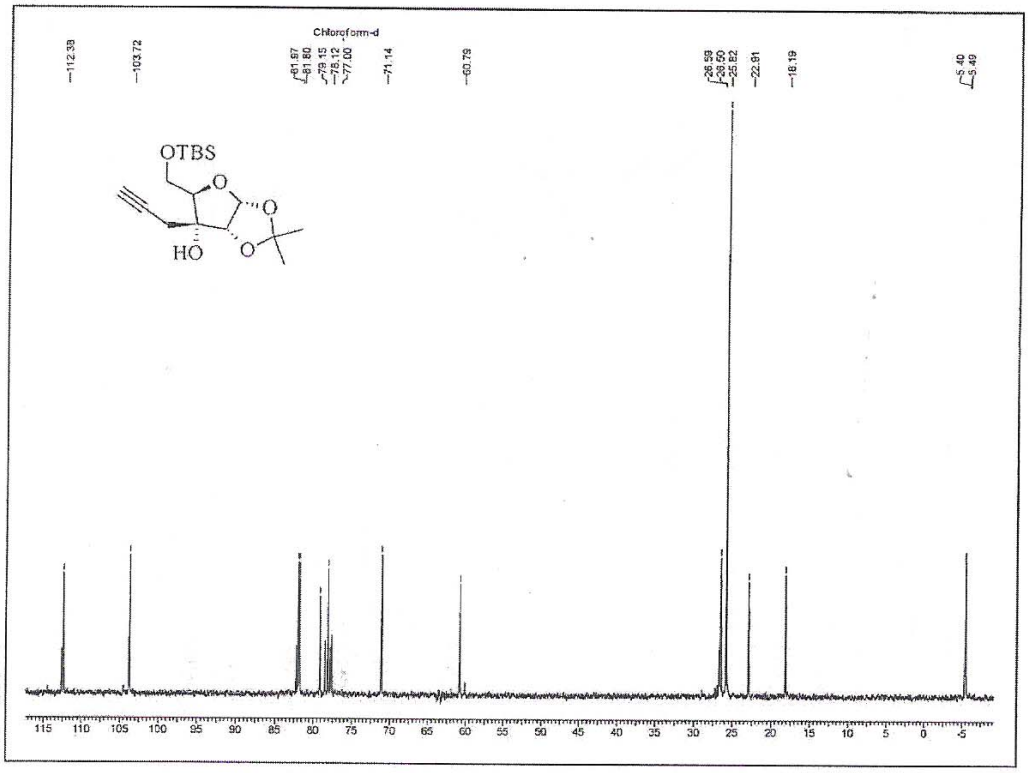
^{1}H NMR Spectrum of 90 in $CDCl_3$



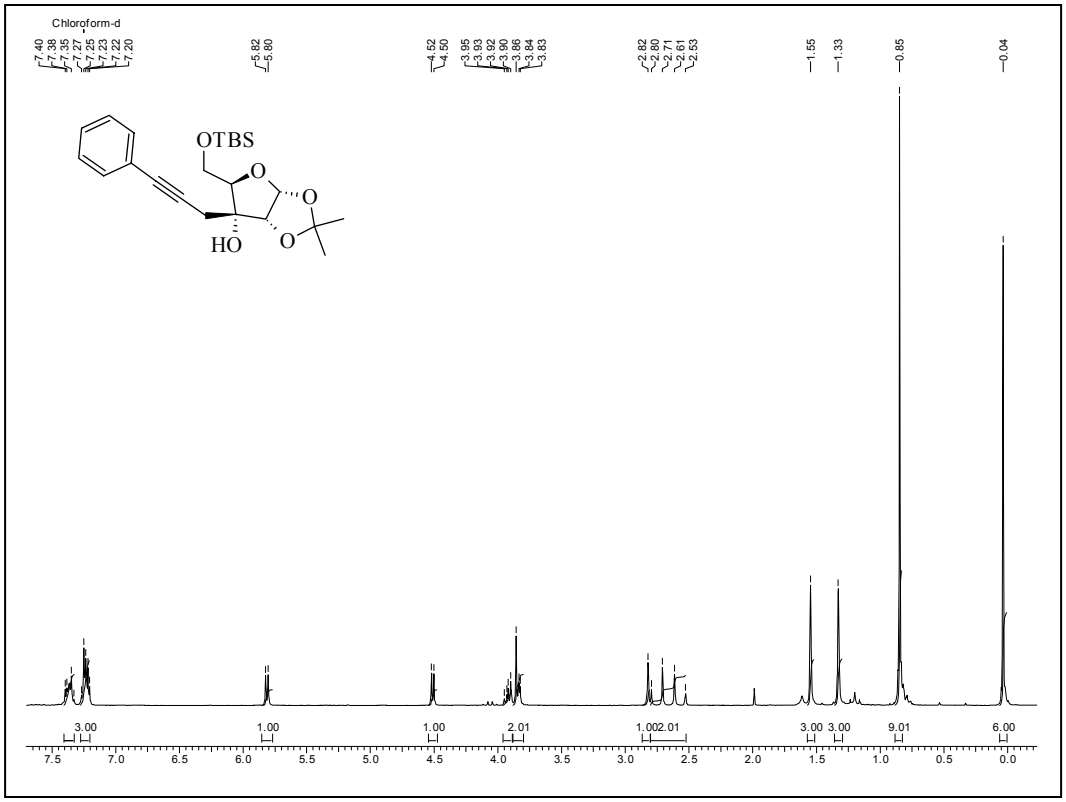
^{13}C NMR Spectrum of 90 in $CDCl_3$



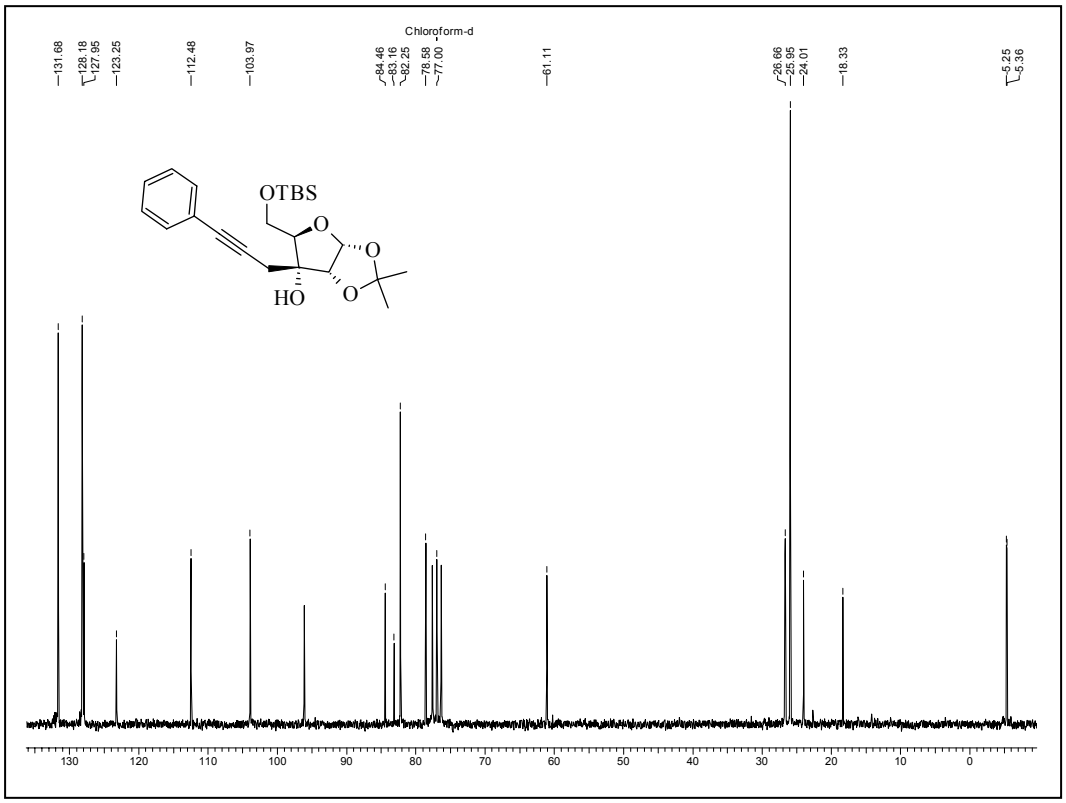
^{1}H NMR Spectrum of 91 in $CDCl_3$



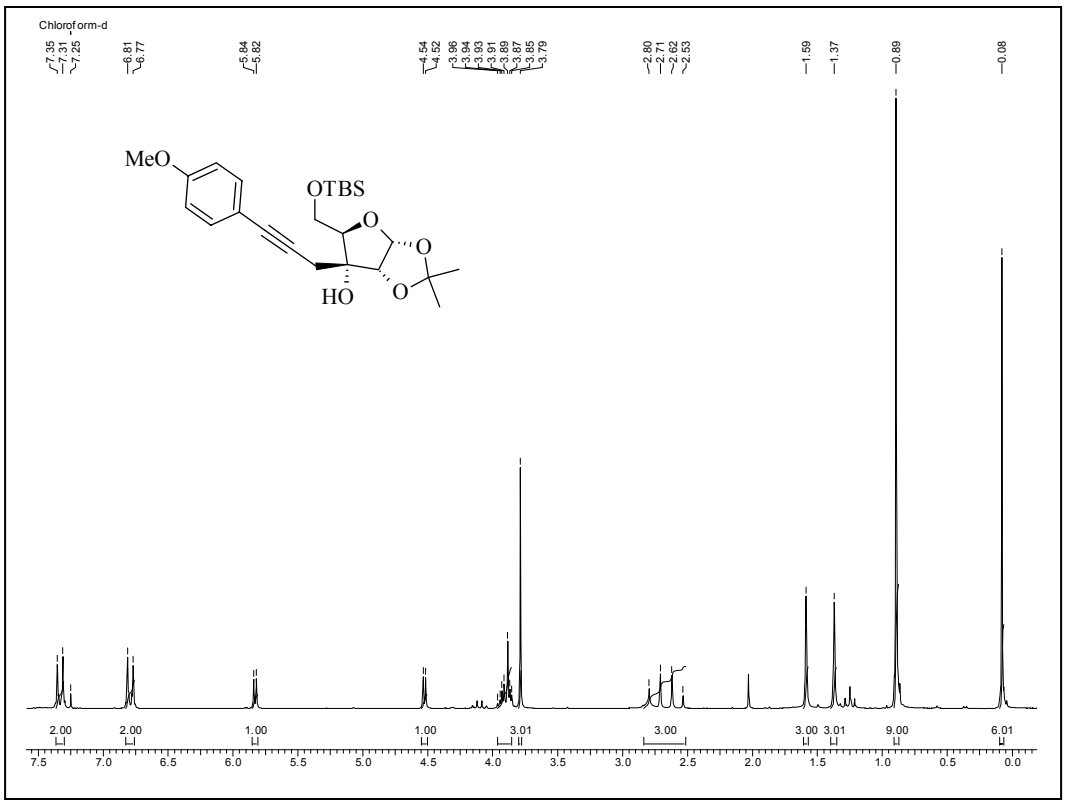
^{13}C NMR Spectrum of 91 in $CDCl_3$



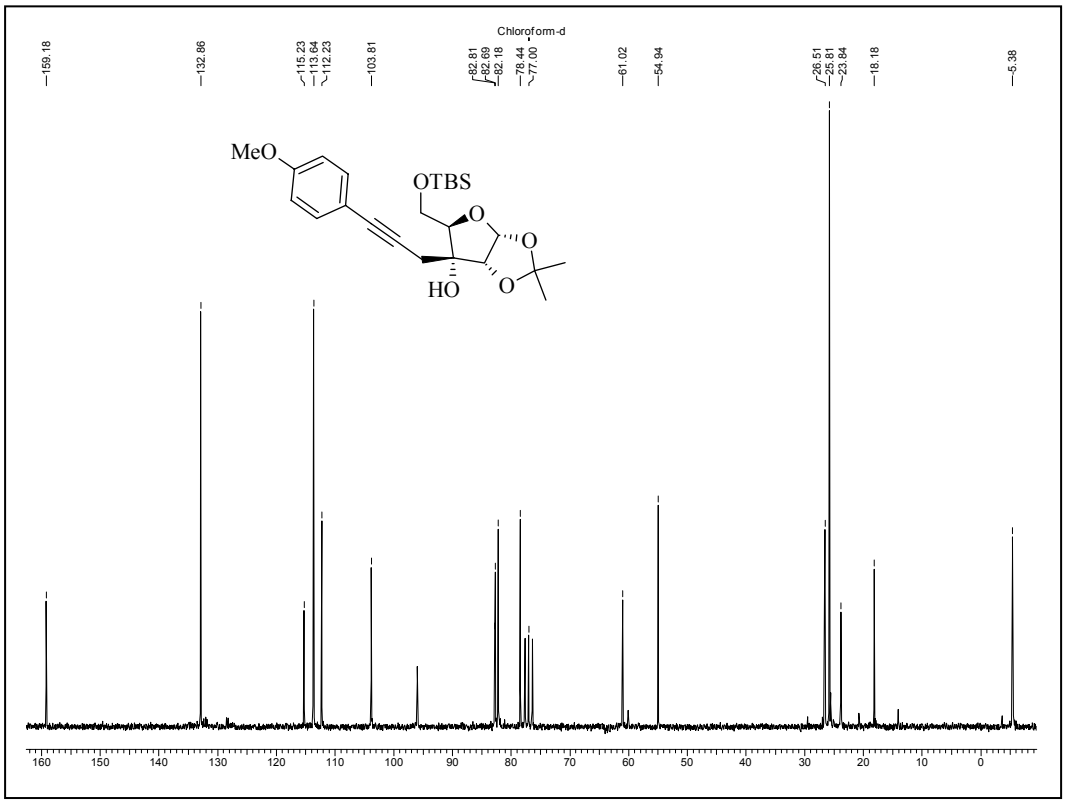
^{1}H NMR Spectrum of 92 in $CDCl_3$



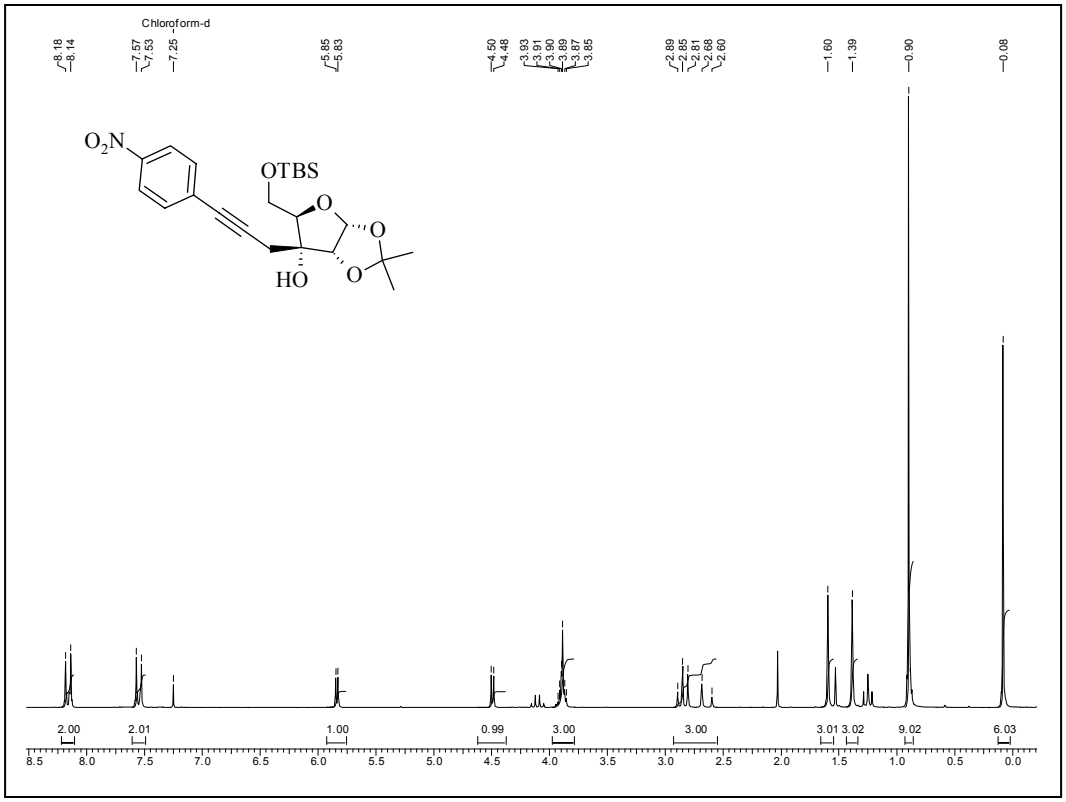
^{13}C NMR Spectrum of 92 in $CDCl_3$



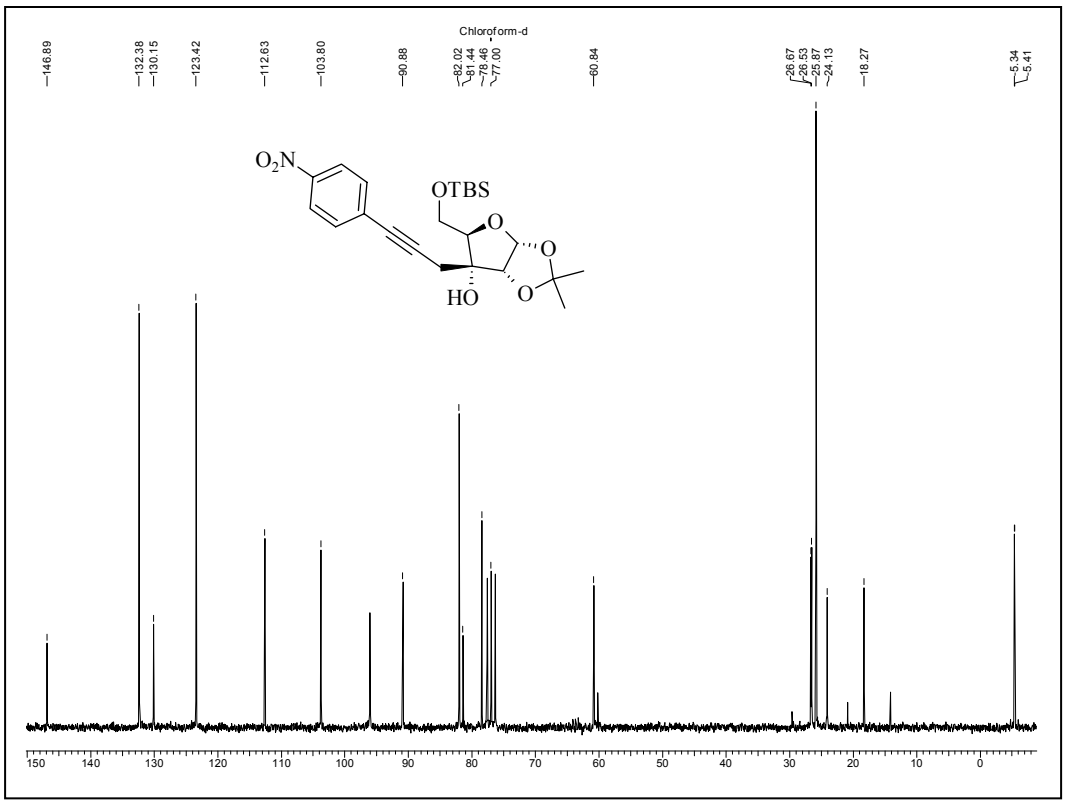
^{1}H NMR Spectrum of 93 in $CDCl_3$



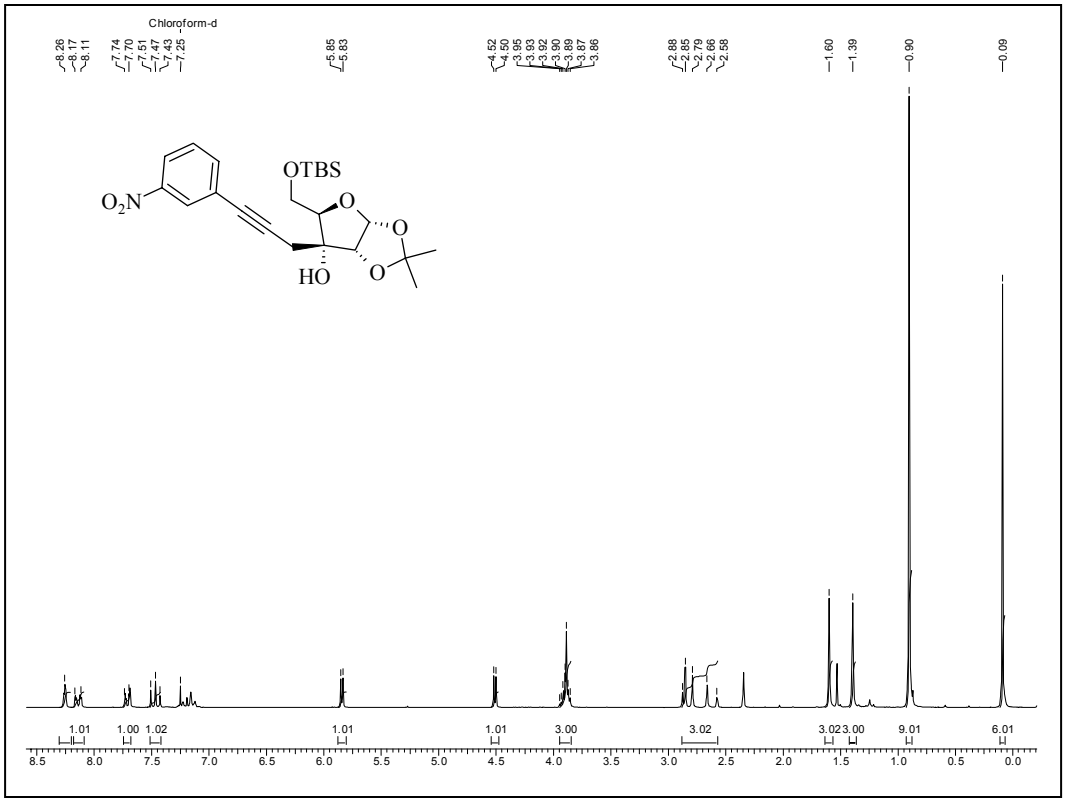
^{13}C NMR Spectrum of 93 in $CDCl_3$



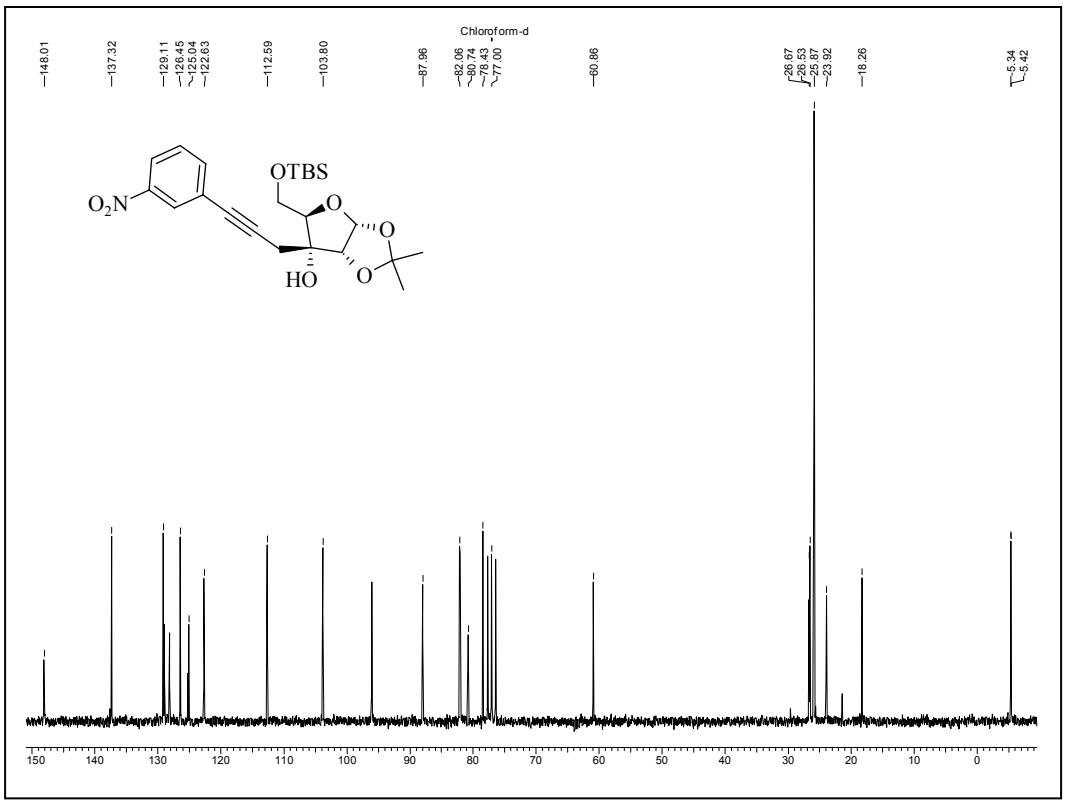
^{1}H NMR Spectrum of 94 in $CDCl_3$



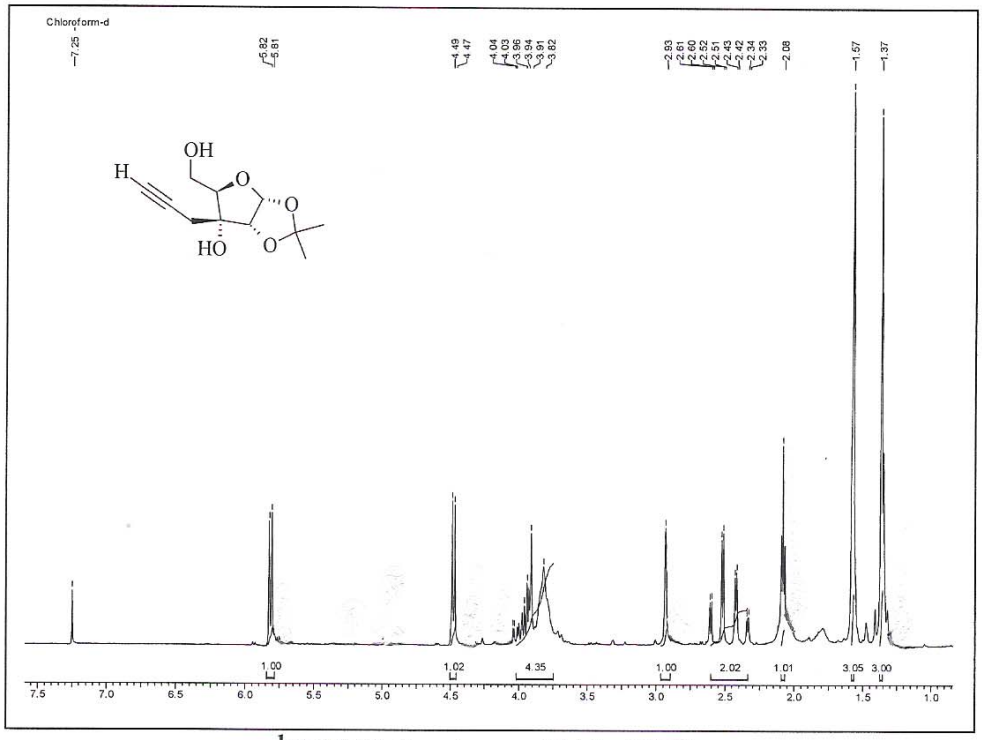
^{13}C NMR Spectrum of 94 in $CDCl_3$



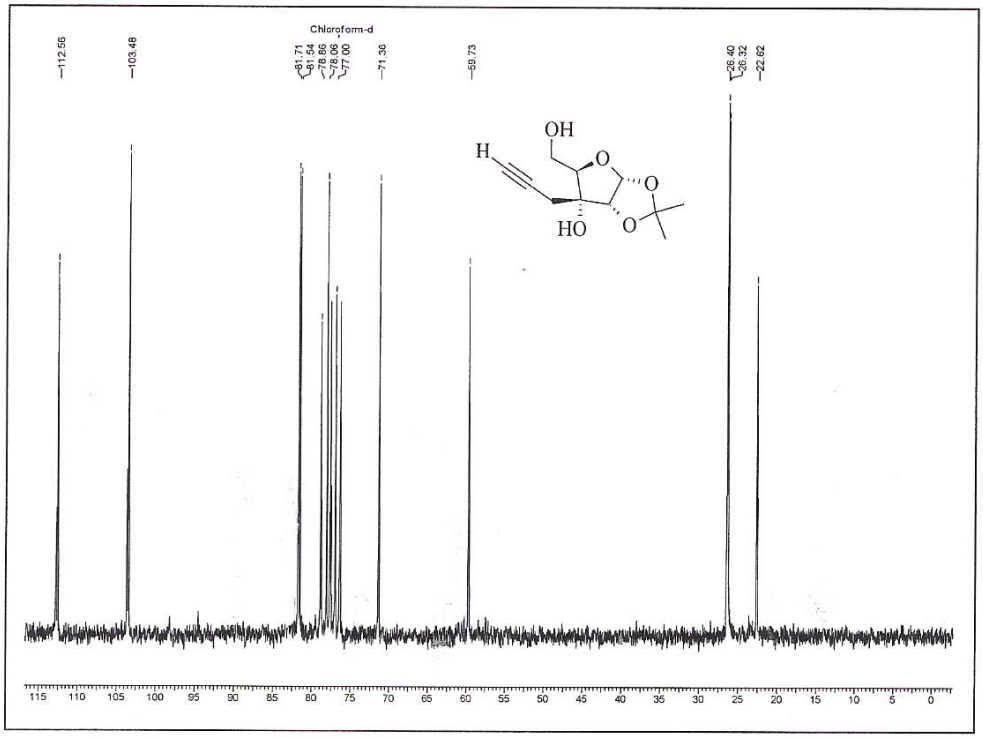
^{1}H NMR Spectrum of 95 in $CDCl_3$



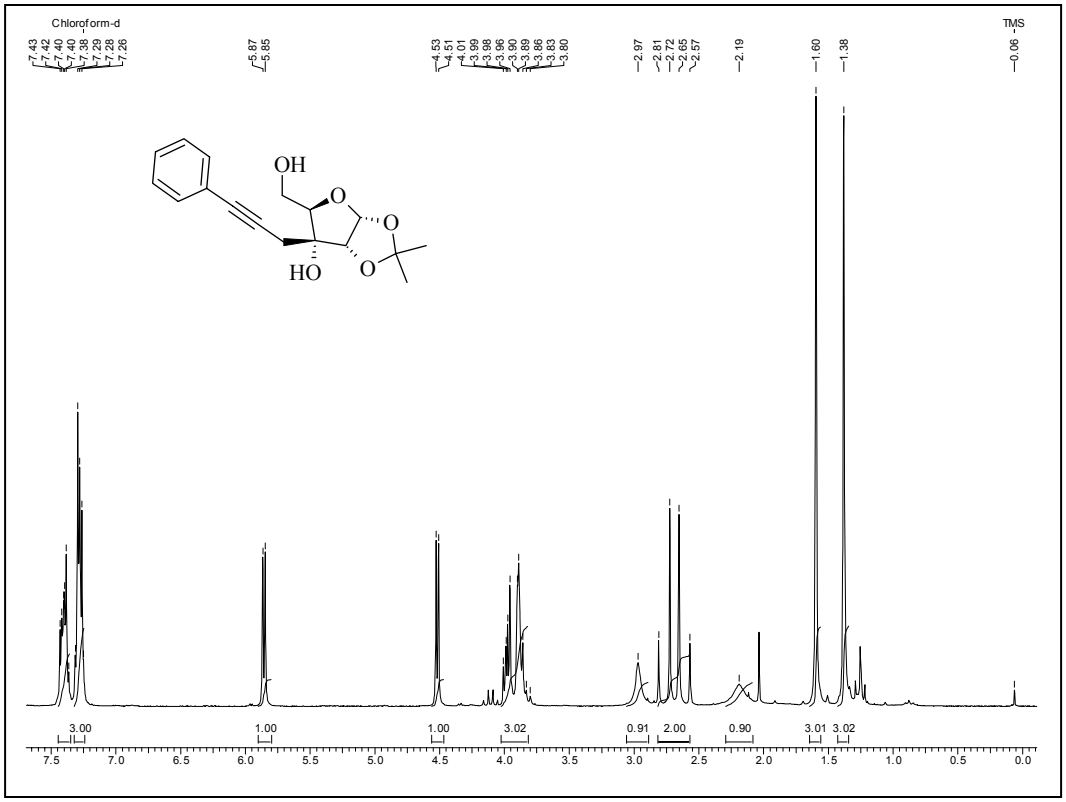
^{13}C NMR Spectrum of 95 in $CDCl_3$



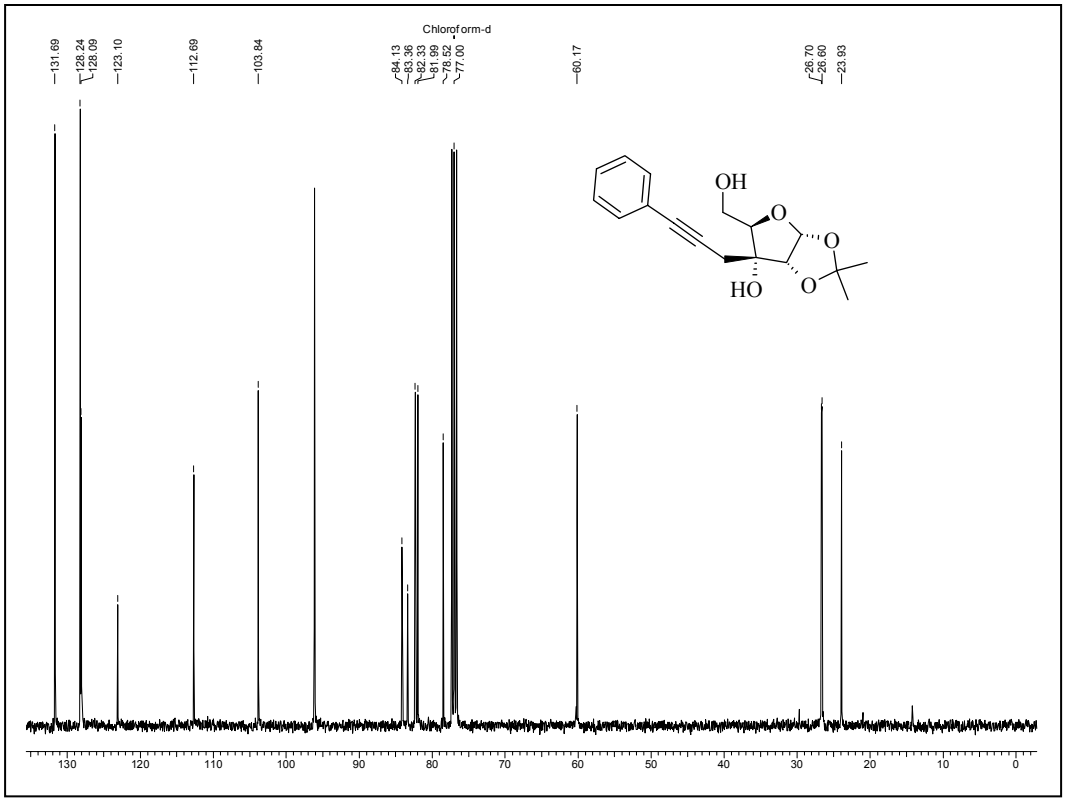
^{1}H NMR Spectrum of 84 in $CDCl_3$



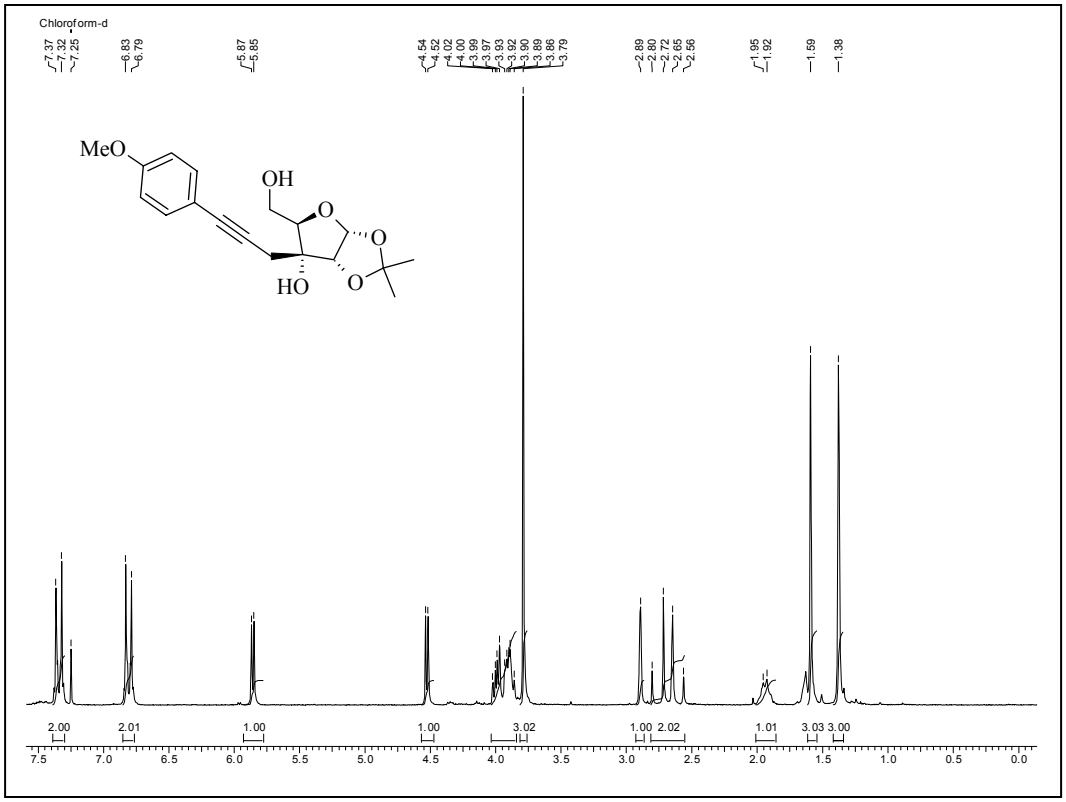
^{13}C NMR Spectrum of 84 in $CDCl_3$



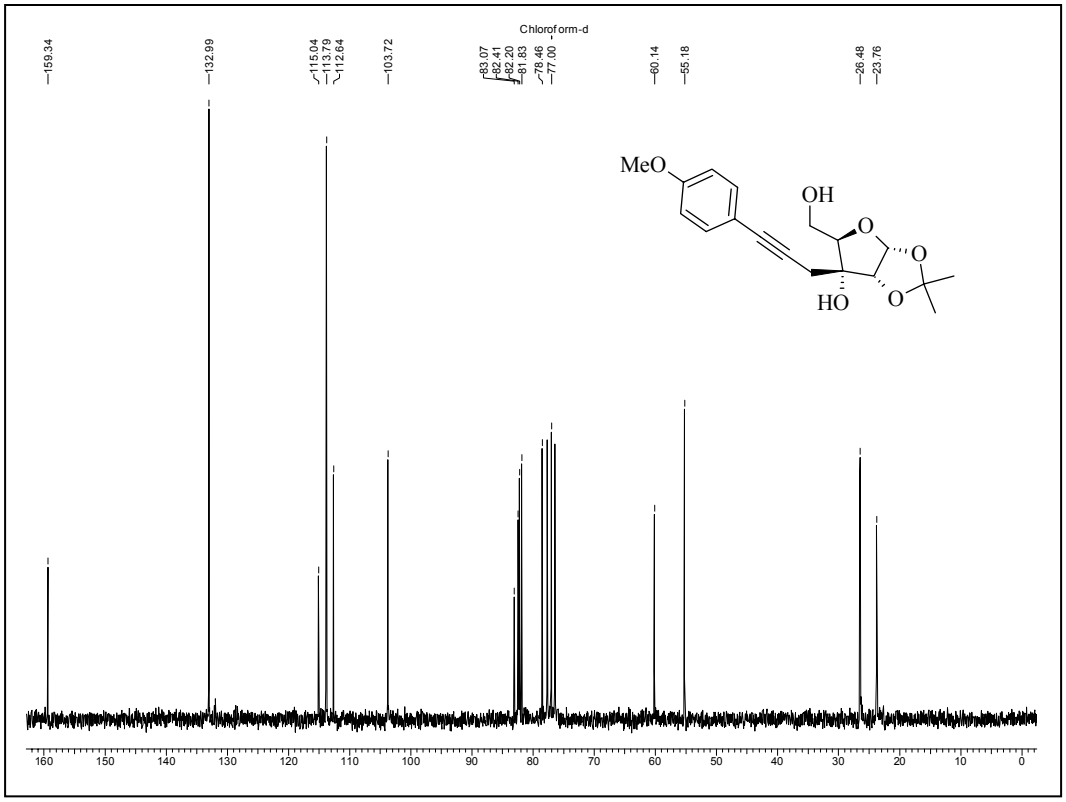
^{1}H NMR Spectrum of 85 in $CDCl_3$



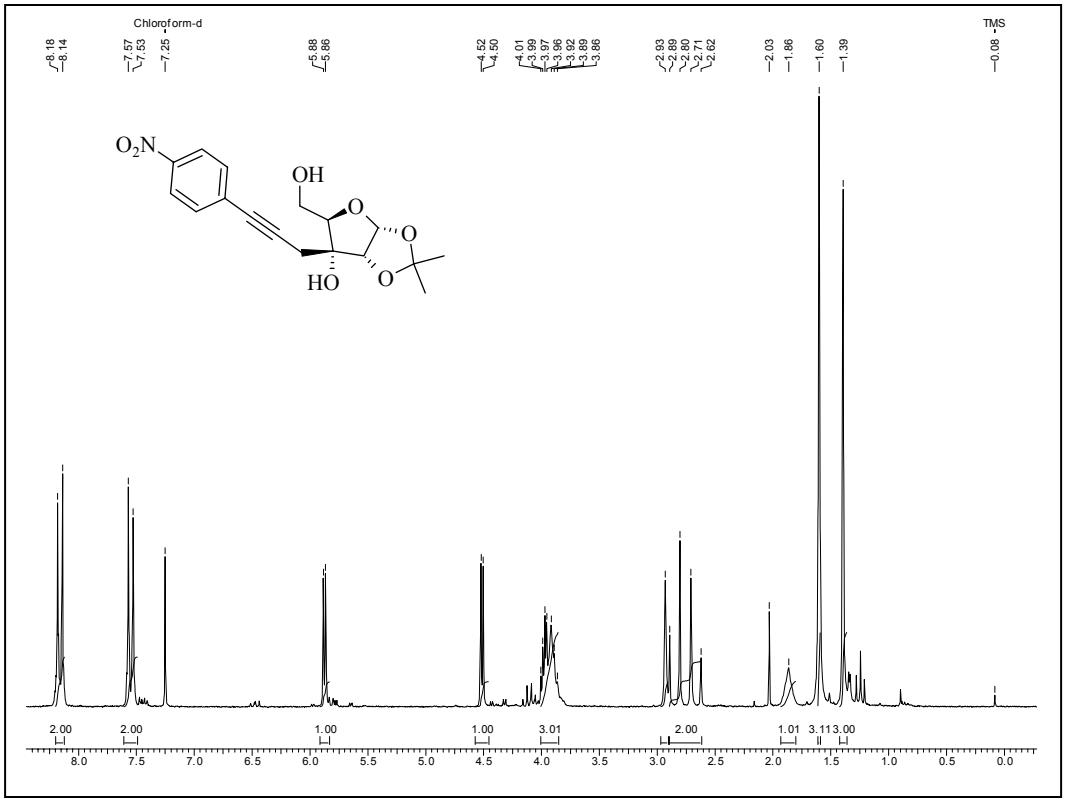
^{13}C NMR Spectrum of 85 in $CDCl_3$



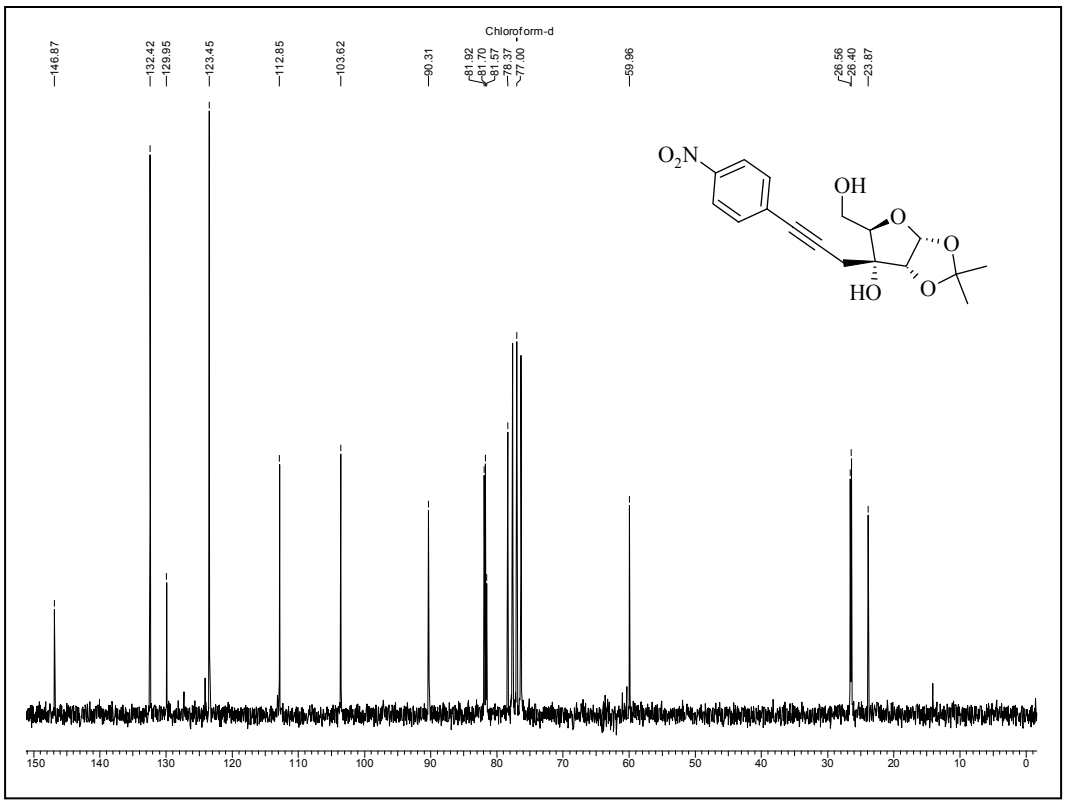
^{1}H NMR Spectrum of 86 in $CDCl_3$



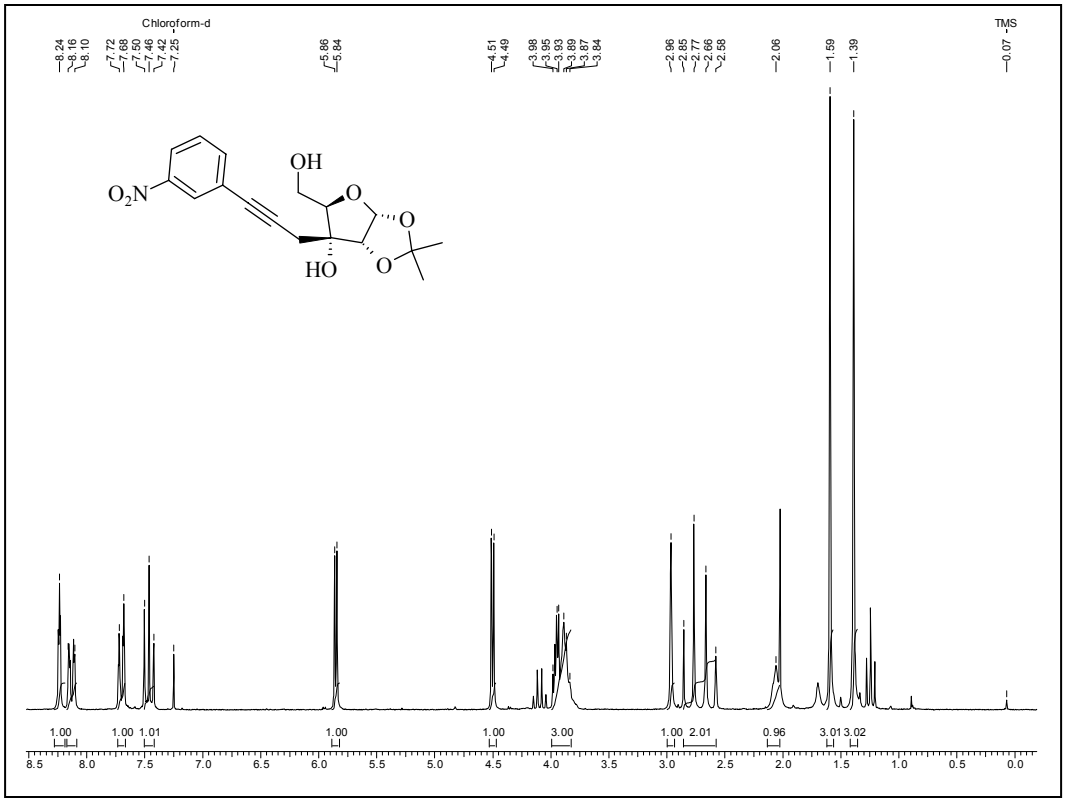
^{13}C NMR Spectrum of 86 in $CDCl_3$



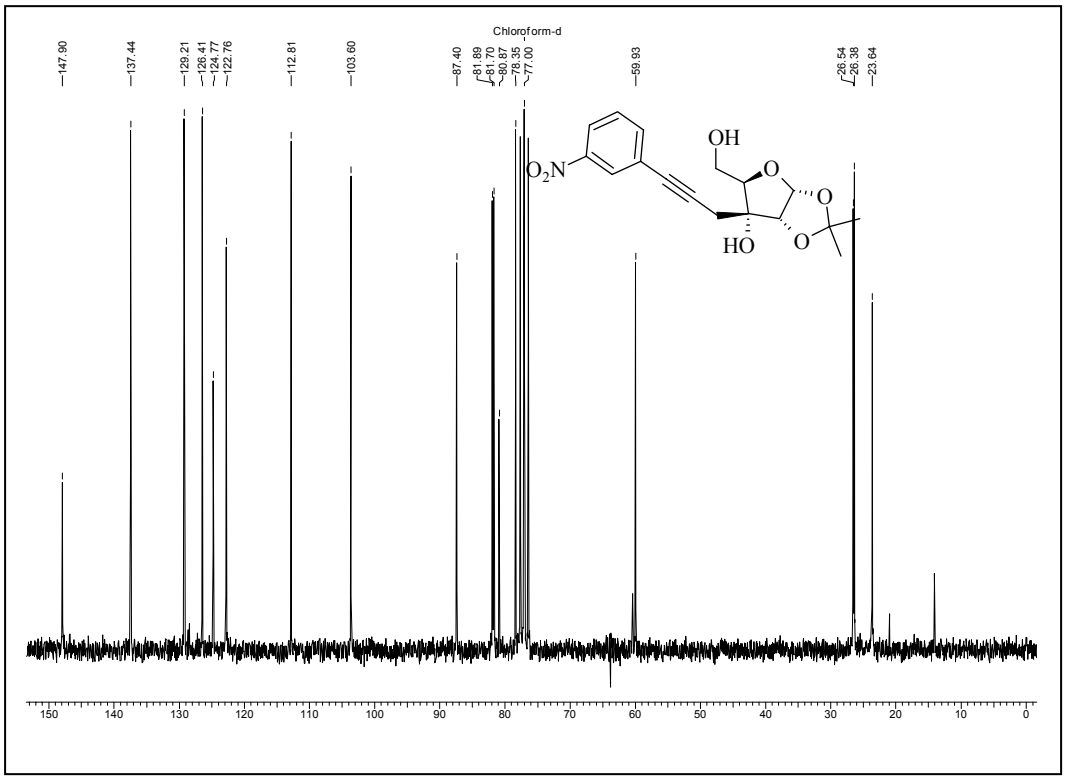
^{1}H NMR Spectrum of 87 in $CDCl_3$



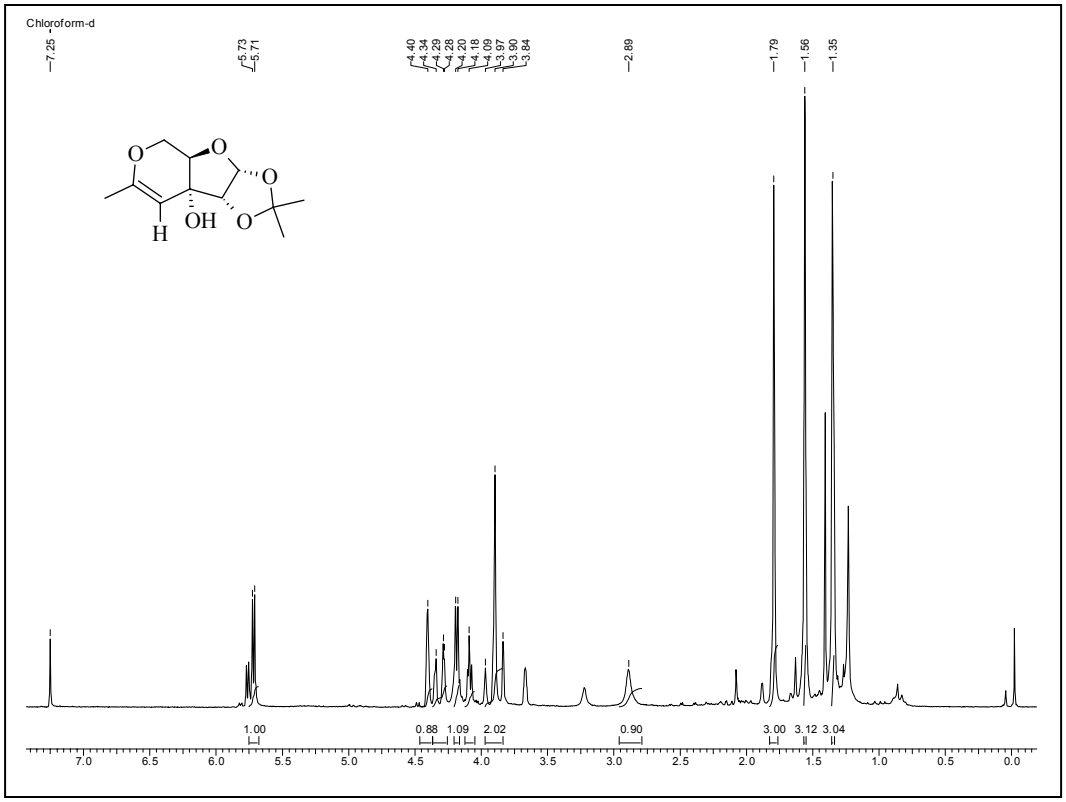
^{13}C NMR Spectrum of 87 in $CDCl_3$



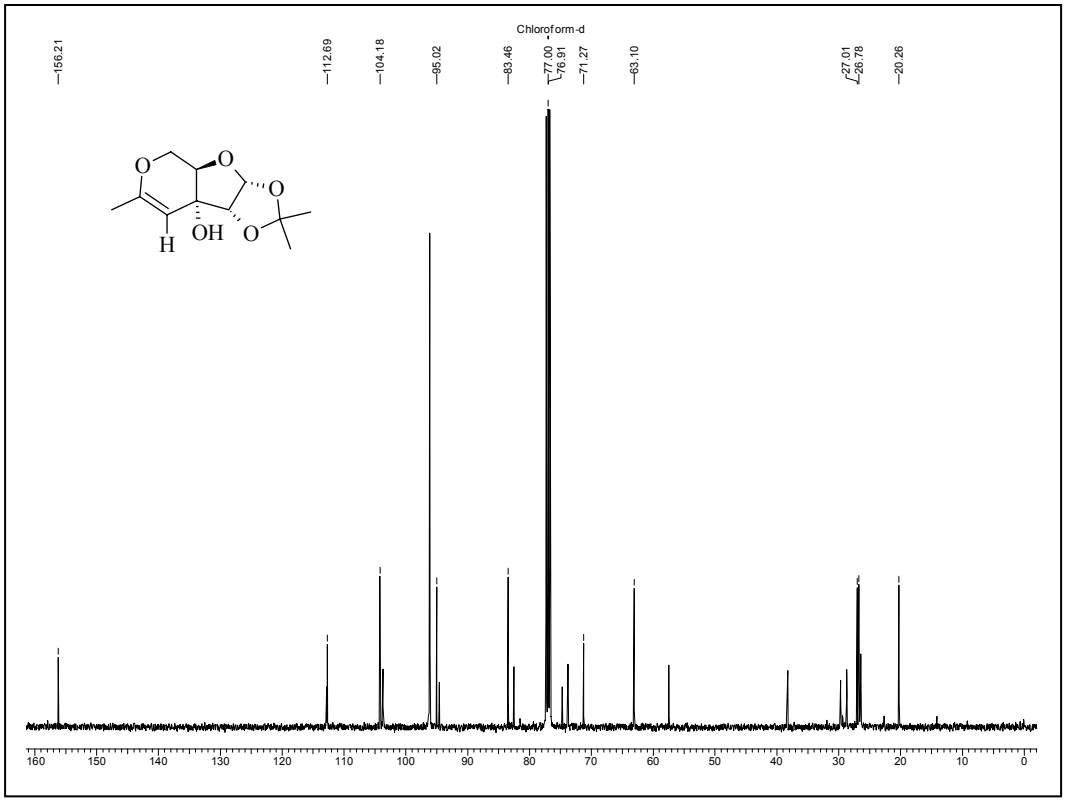
^{1}H NMR Spectrum of 88 in $CDCl_3$



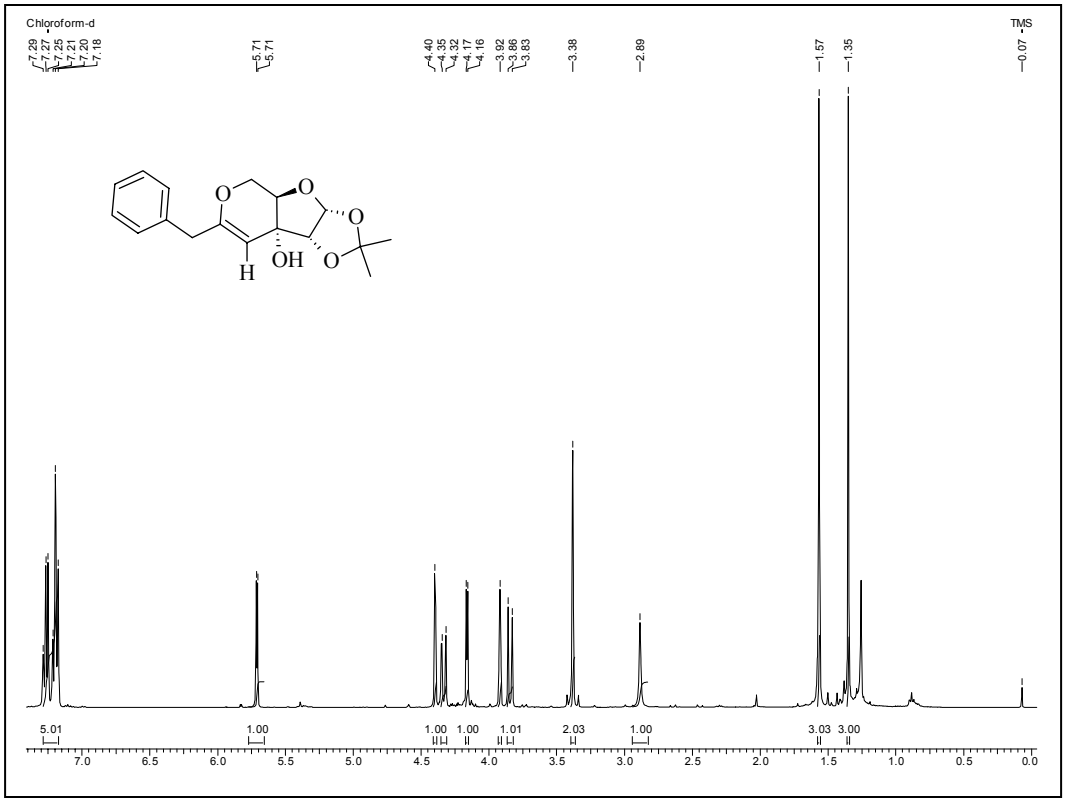
^{13}C NMR Spectrum of 88 in $CDCl_3$



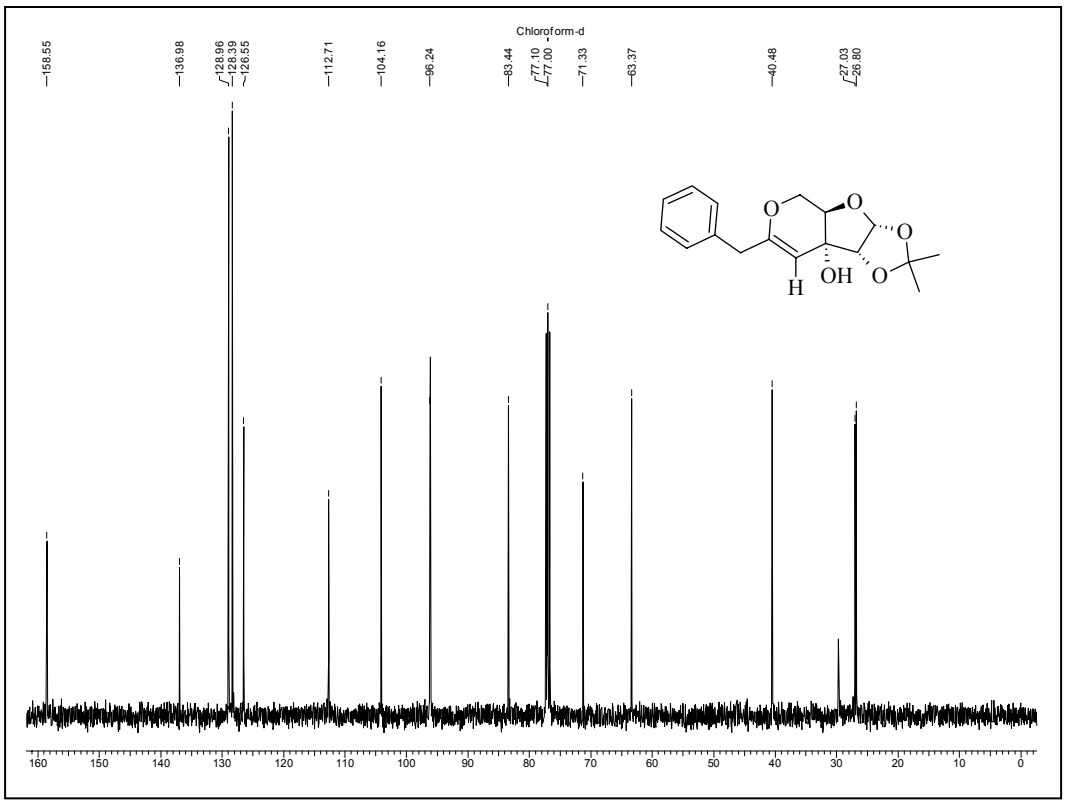
^{1}H NMR Spectrum of 96 in $CDCl_3$



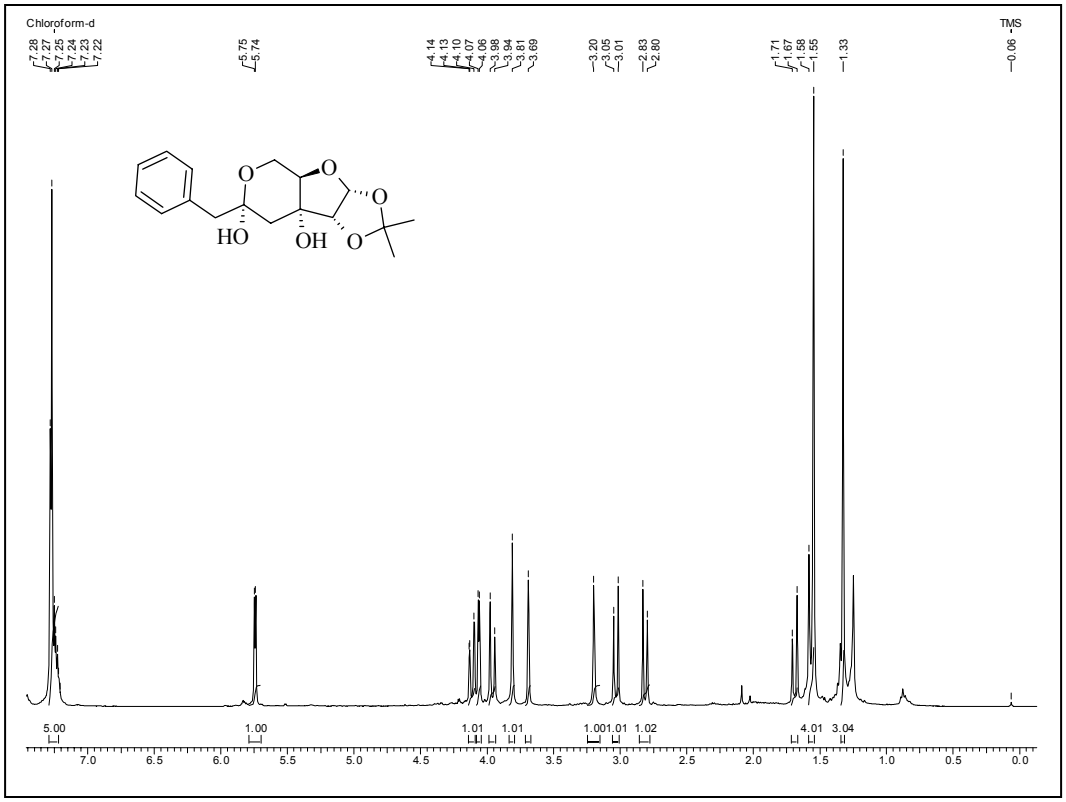
^{13}C NMR Spectrum of 96 in $CDCl_3$



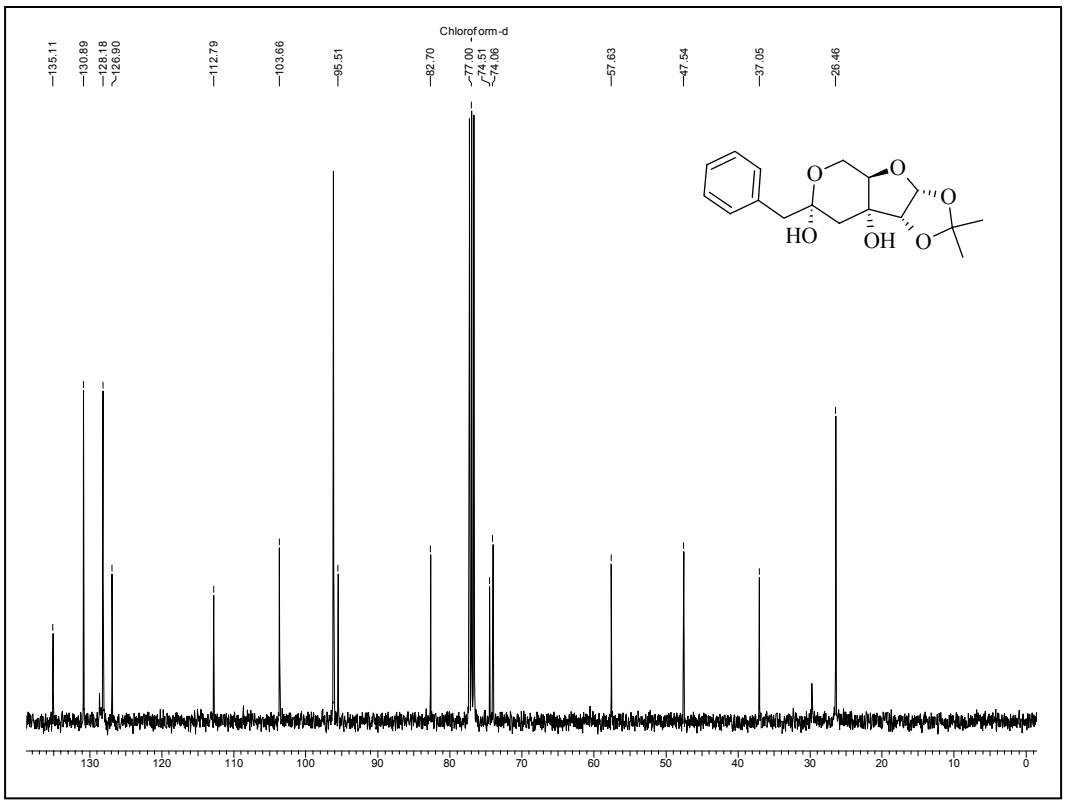
^{1}H NMR Spectrum of 97 in $CDCl_3$



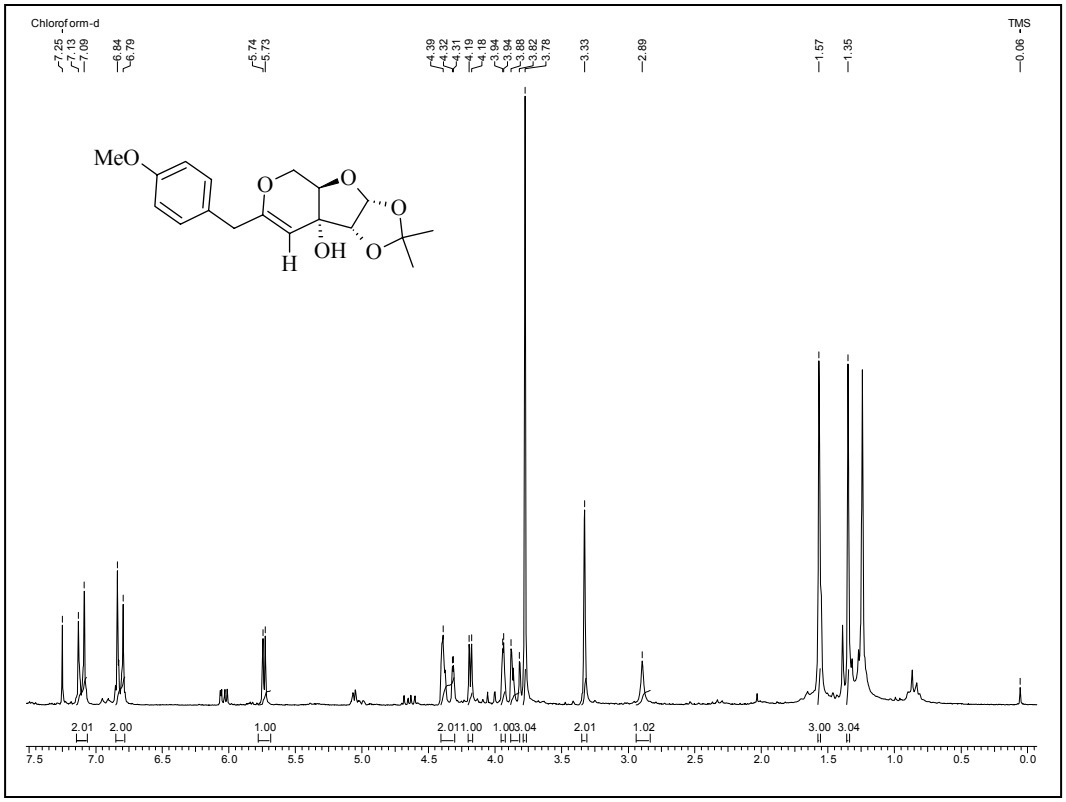
^{13}C NMR Spectrum of 97 in $CDCl_3$



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



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



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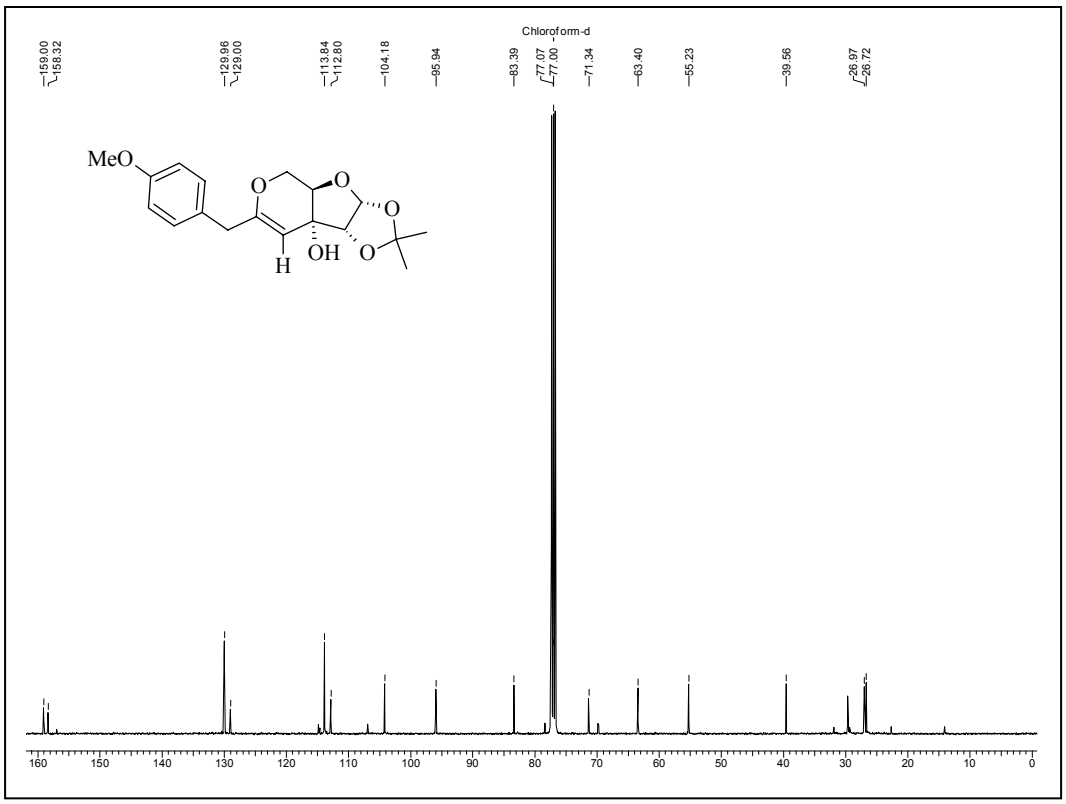
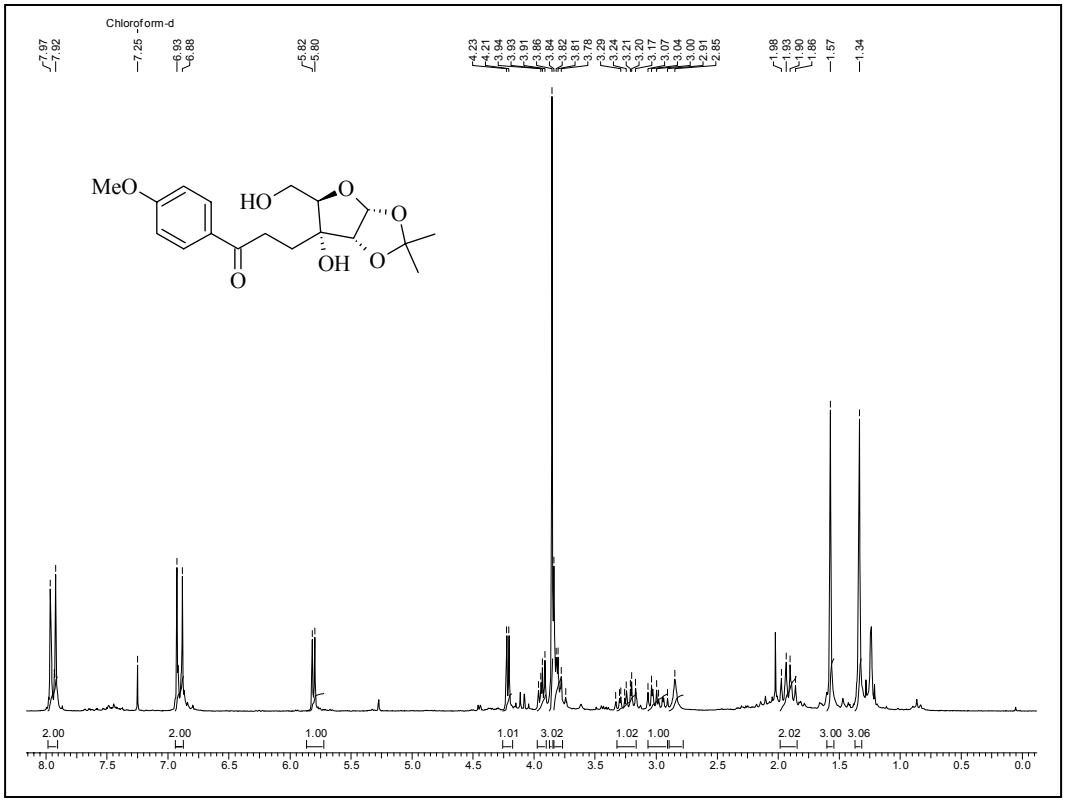
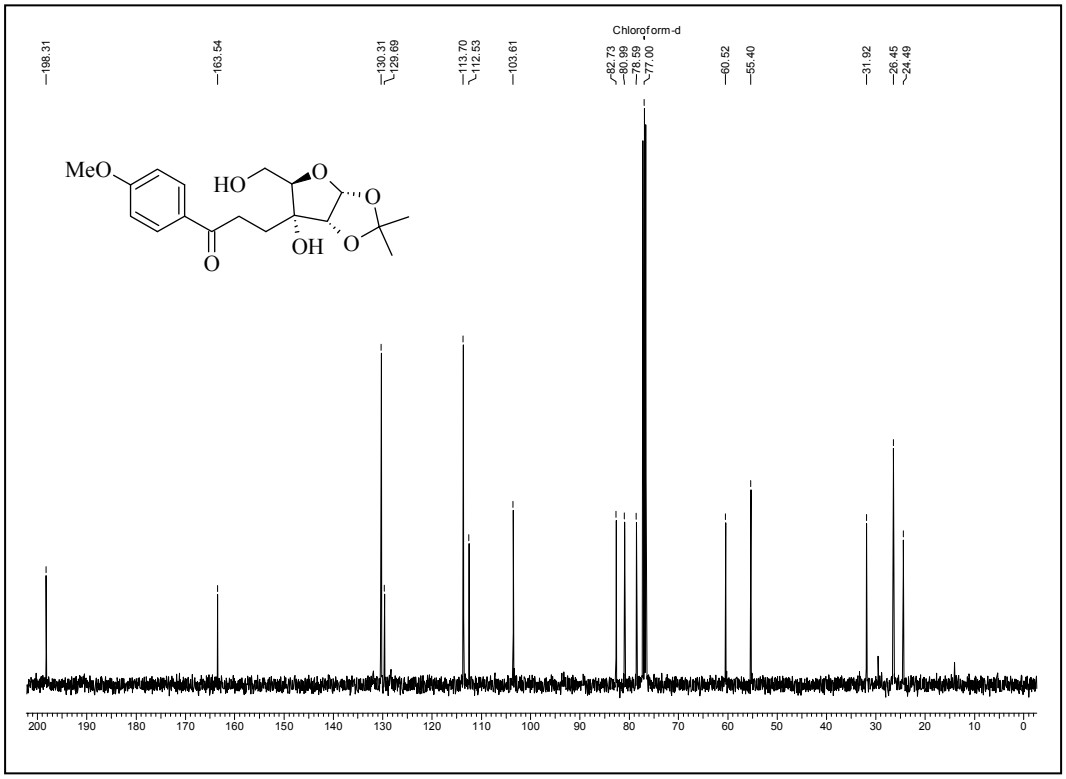


^{13}C NMR Spectrum of 99 in $CDCl_3$



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



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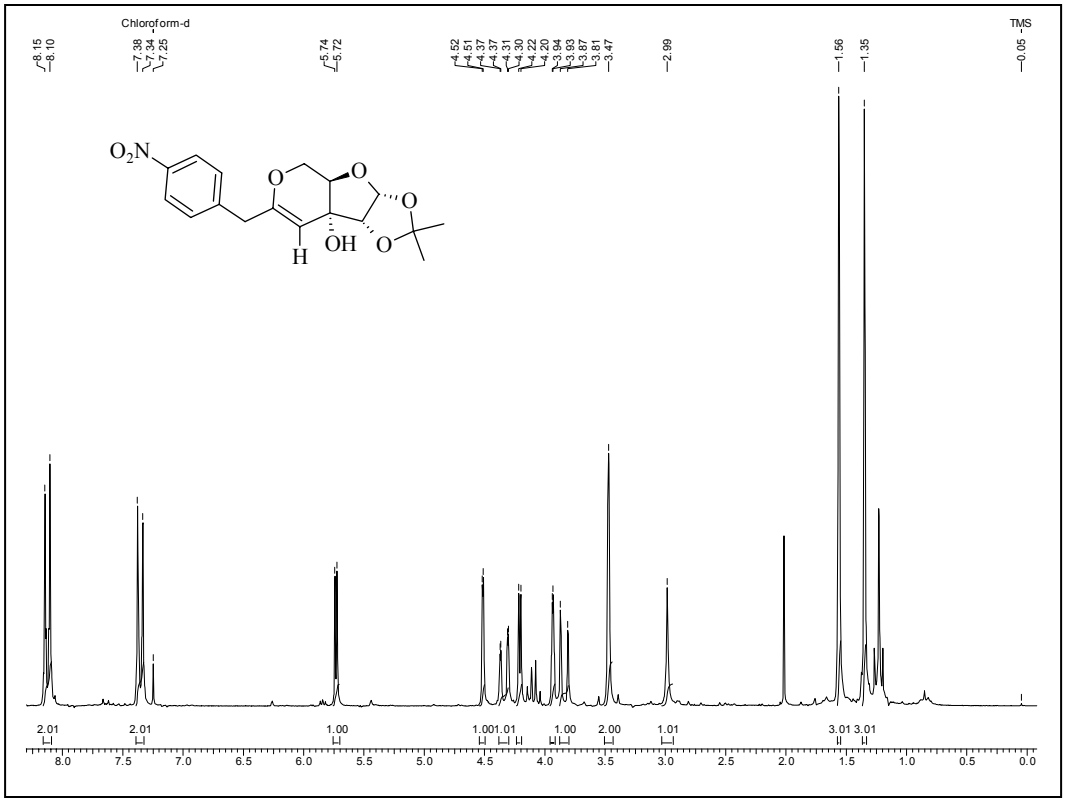
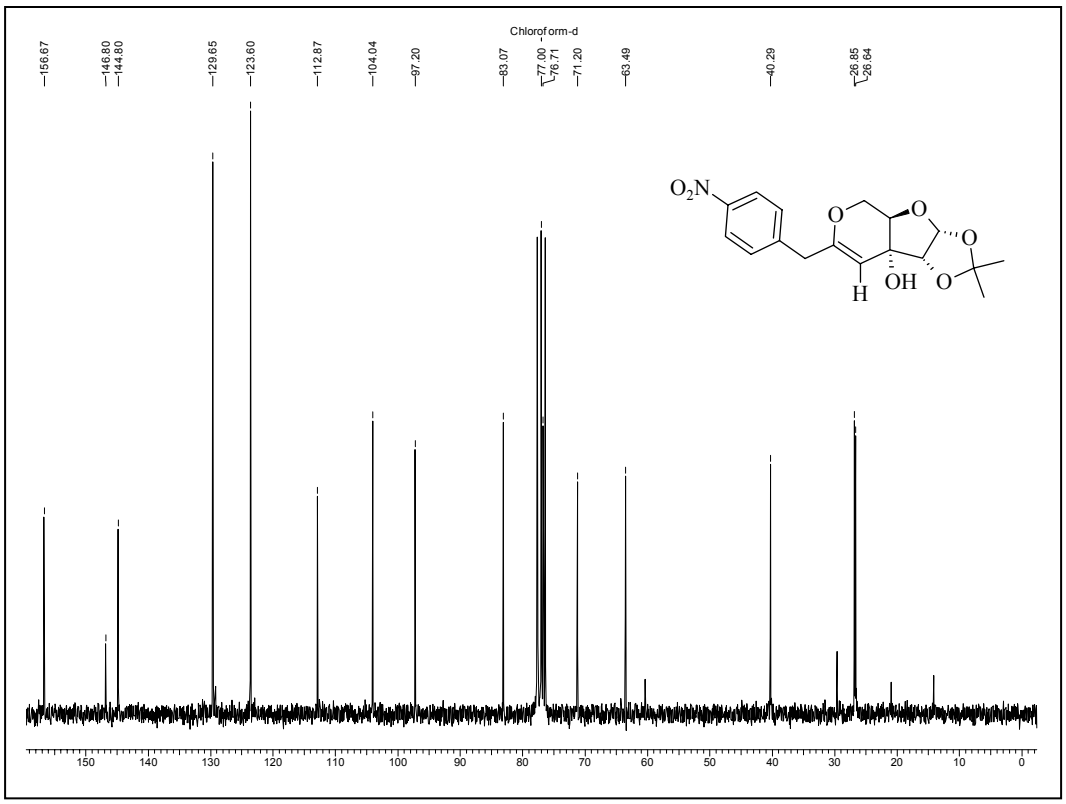
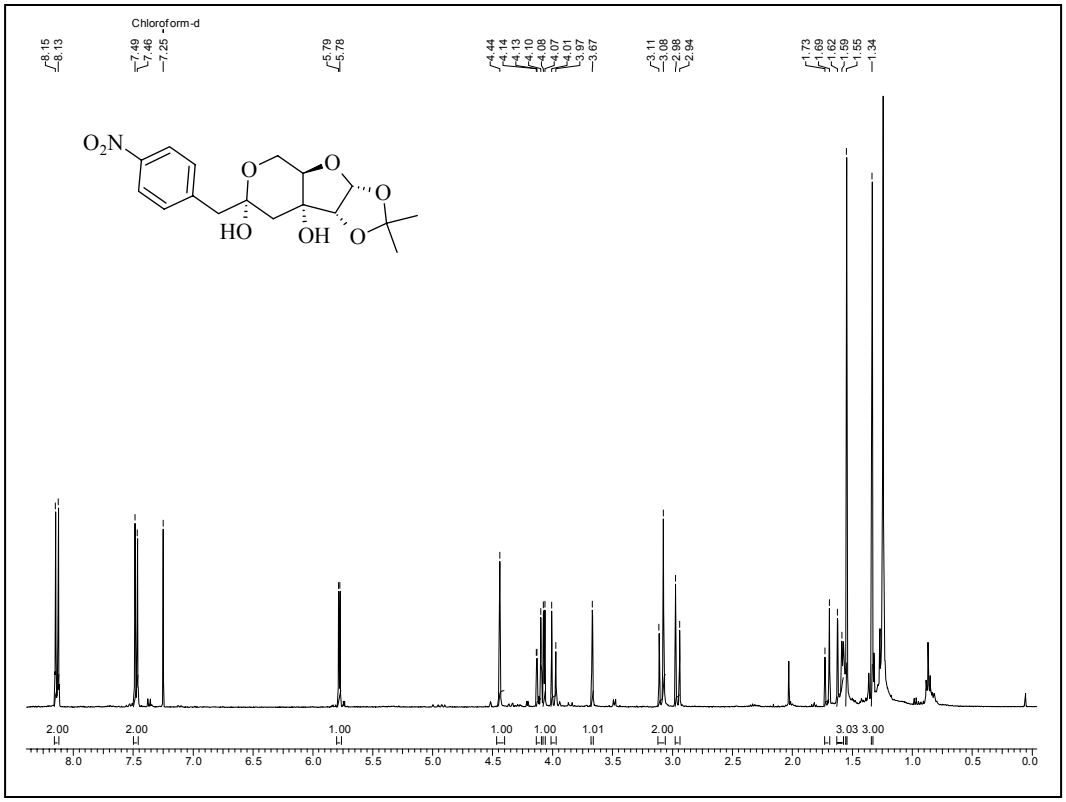


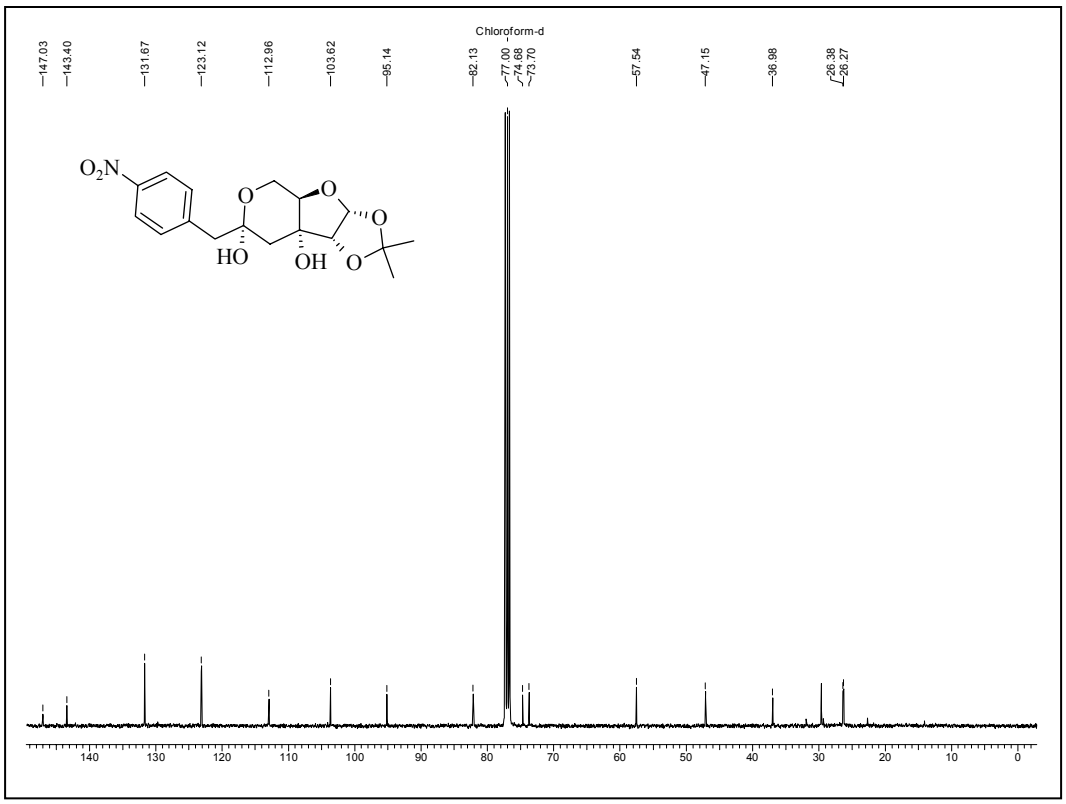
^{1}H NMR Spectrum of 101 in $CDCl_3$



^{13}C NMR Spectrum of 101 in $CDCl_3$



^{1}H NMR Spectrum of 102 in $CDCl_3$



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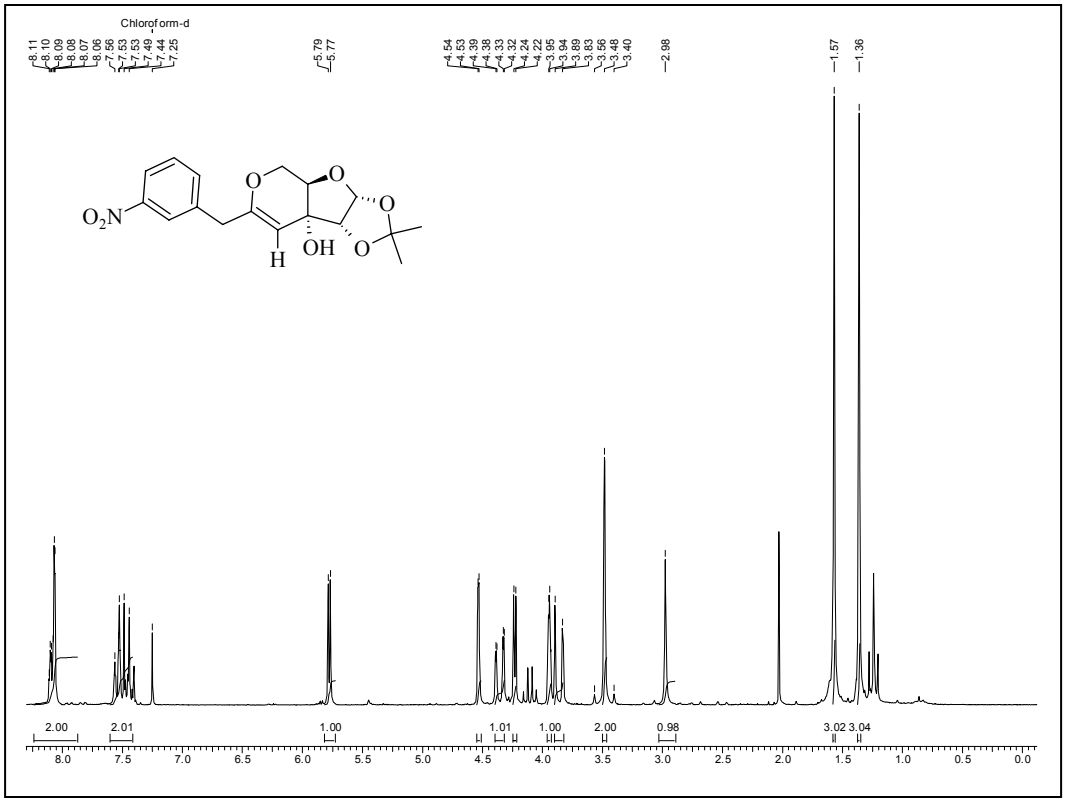

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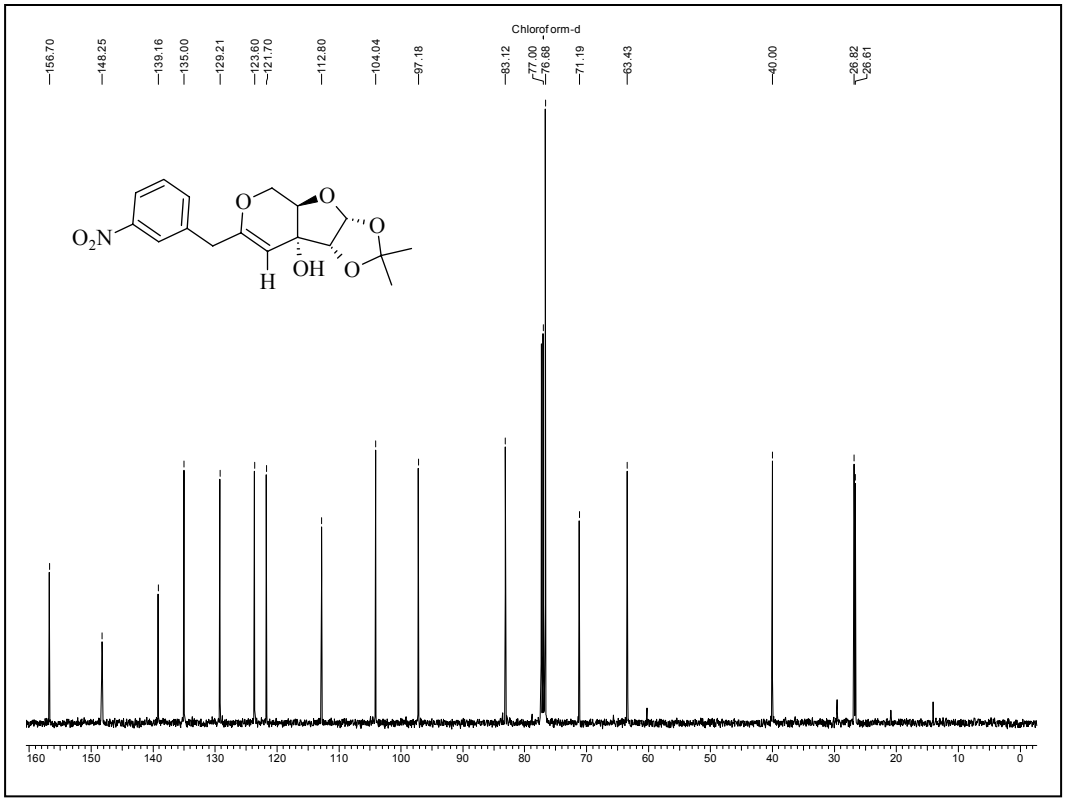
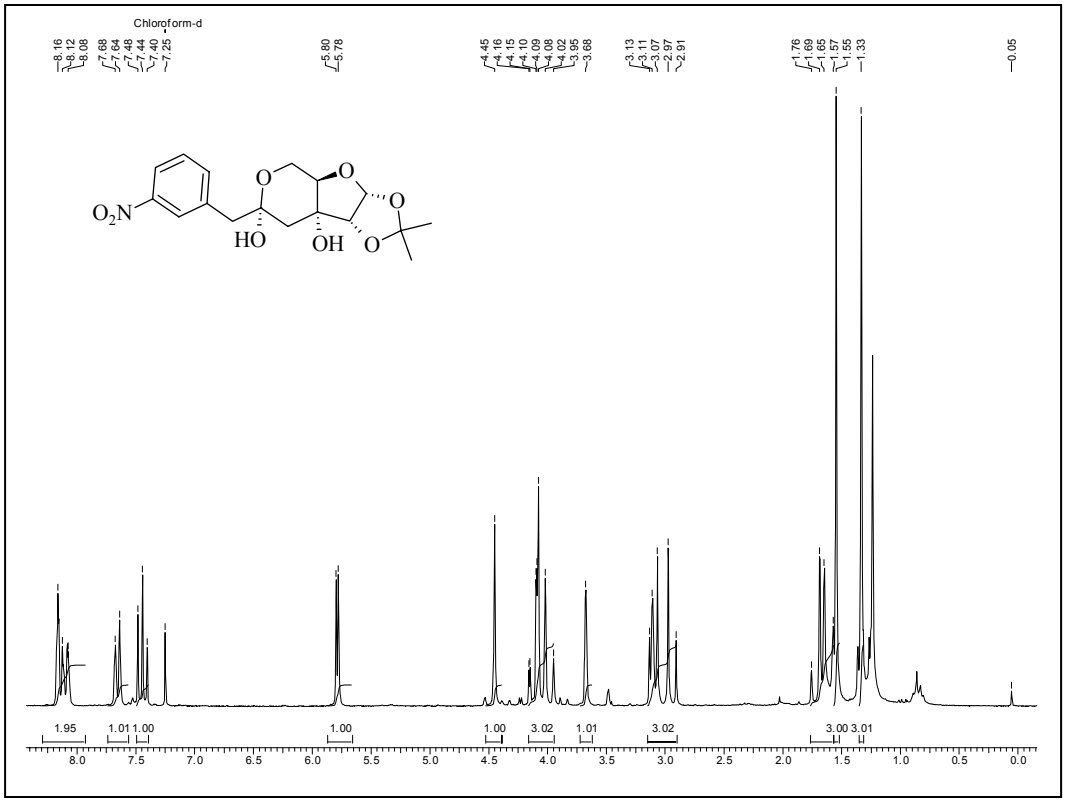
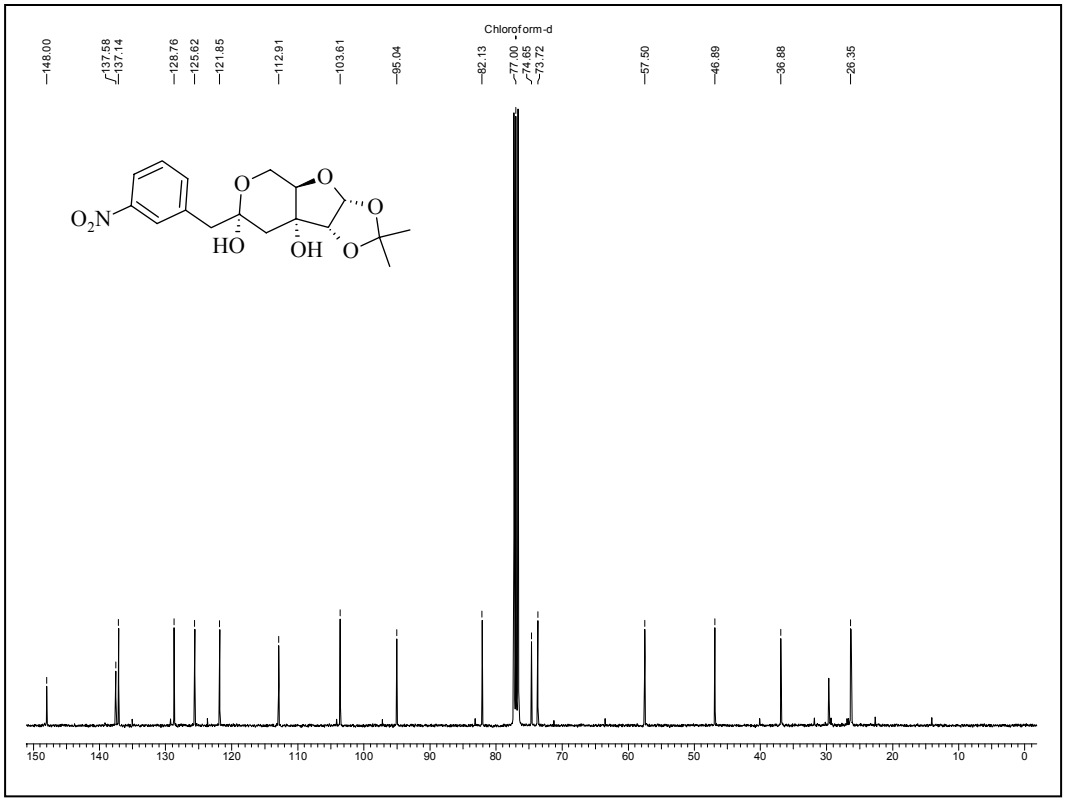


^{13}C NMR Spectrum of 103 in $CDCl_3$



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



^{13}C NMR Spectrum of 104 in $CDCl_3$

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List of publications

LIST OF PUBLICATIONS

1. A Carbohydrate-Based Approach for the Total Synthesis of 1,3-Polyol/α-Pyrone Antifungal Natural Products- *J. Org. Chem.* **2005**, *70*, 8216.
2. A Carbohydrate-Based Approach for the Total Synthesis of Aculeatin D and 6-*epi*-Aculeatin D- *J. Org. Chem.* **2008**. (Article in press).
3. The influence of electronic factors on Palladium mediated cycloisomerization: A systematic investigation of competitive 6-*exo*-dig *vs* 7-*endo*-dig cyclizations of sugar alkynols- *Org. Biomol. Chem.* **2008** (communicated).