STUDIES TOWARD THE TOTAL SYNTHESIS OF CARBA ANALOGUE OF MOTIF C OF M.tb CELL WALL AG COMPLEX, INTEGRASTATINS AND A DOUBLE-SUZUKI APPROACH FOR SYNTHESIS OF SUBSTITUTED DIARYLMETHYLIDENEFLUORENES

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(Research Guide)

ORGANIC CHEMISTRY DIVISION

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Studies Toward the Total Synthesis of Carba Analogue of Motif C of M.tb Cell wall AG Complex, Integrastatins and A Double-Suzuki Approach for Synthesis of Substituted Diarylmethylidenefluorenes.

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
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TO
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(Research Guide)

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NATIONAL CHEMICAL LABORATORY
PUNE-411008

APRIL 2008

DEDICATED
TO
MY BELOVED
PARENTS,
SISTER AND UNCLE

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Deputy Director, and Head, 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
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April 2008

(Mr. Challa Nageswara Reddy)

राष्ट्रीय रासायनिक प्रयोगशाला
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CERTIFICATE

The research work presented in thesis entitled "Studies toward the total synthesis of Carba analogue of motif C of M.tb cell wall AG Complex, integrastatins and A double-suzuki approach for synthesis of substituted diarylmethylidenefluorenes" has been carried out under my supervision and is a bonafide work of **Mr. Challa Nageswara Reddy**. 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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Finally, I thank Director, National Chemical Laboratory, Pune for providing infrastructure facilities to complete my work successfully. I am also thankful to UGC, New Delhi for the financial assistance in the form of fellowship.

- Nageswara Reddy.

Ac	-	Acetyl
AcOH	-	Acetic acid
AIBN	-	Azoisobutyronitrile
Ac_2O	-	Acetic anhydride
Ara	-	Arabinose
Ara*f*	-	Arabinofuranosyl
Ag_2O	-	Silveroxide
aq.	-	Aqueous
BCl_3	-	Boron trichloride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BF_3.Et_2O$	-	Boron trifluoride diethyl ether complex
BuLi	-	Butyl lithium
Bu_3SnH	-	Tributyl tin hydride
BzOH	-	Benzoyl alcohol
BzCl	-	Benzoyl chloride
CBr_4	-	Carbon tetrabromide
m-CPBA	-	*meta*-Chloroperbenzoic acid
COSY	-	Correlation Spectroscopy
$Cp_2Ti(CH_3)_2$	-	Bis(cyclopentadienyl) dimethyl titanium
$CpTiCl_3$	-	Cyclopentadienyl titanium trichloride
Cp_2TiCl_2	-	Bis(cyclopendienyl) titaniumdichloride
CsOAc	-	Cesium acetate
$(CH_3)_3SOI$	-	Trimethyl sulfoxonium iodide
$(COCl)_2$	-	Oxalyl chloride
DCC	-	Dicyclohexyl carbodiimide
DDQ	-	2,6-dichloro-3,5-dicyano quinone
DEAD	-	Diethyl azodicarboxylate
DTSCl	-	Dimethylthexylsilyl Chloride

DCM	-	Dichloromethane
DIBAL-H	-	Diisobutylaluminiumhydride
DIPT	-	Diisopropyl tartrate
DMP	-	2,2-Dimethoxypropane
DMF	-	*N*,*N*-Dimethylformamide
DMAP	-	4-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
EDA	-	Ethylene diamine
EtOH	-	Ethanol
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Et_3SiH	-	Triethyl silylhydride
$FeCl_3$	-	Ferric chloride
HMDS	-	Hexamethyl disilazane
HCOOH	-	Formic acid
$HClO_4$	-	Perchloric acid
Im	-	Imidazole
Ipc_2BH	-	Di isopinacampheyl borane
KHMDS	-	Potassium 1,1,1,3,3,3-hexamethyldisilazane
KF		Potassium flouride
LDA	-	Lithium diisopropylamide
LAH	-	Lithium aluminium hydride
m-CPBA	-	*meta*-Chloroperbenzoic acid
Ms	-	Methanesulfonyl
MeI	-	Methyl iodide
MnO_2	-	Manganese(IV) Oxide
$Mo(CO)_6$	-	Hexacarbonyl Molybdenum
$NaBH_4$	-	Sodium borohydride
$NaIO_4$	-	Sodium periodate
$NaNO_2$	-	Sodium nitrite

NBS	-	N–bromosuccinimide
NIS	-	N-Iodosuccinimide
NMO	-	*N*-Methyl morpholine *N*-oxide
NOESY	-	Nuclear overhauser effect spectroscopy
OsO_4	-	Osmium tetraoxide
ORTEP	-	Oak ridge thermal ellipsoid plot
PDC	-	Pyridinium dichromate
$Pd_2(dba)_3CHCl_3$	-	Tris(dibenzylideneacetone) dipalladium(0)-chloroform
$Pd(PPh_3)_2Cl_2$	-	Bis(triphenylphosphine) palladium(II)dichloride
$PhSO_2NO_2$	-	Phenyl sulfonyl nitromethane
PCC	-	Pyridinium chlorochromate
PPh_3	-	Triphenyl phosphine
$(Ph_3)_3RhCl$	-	Tris(triphenylphosphine) rhodium(I) chloride
$PdCl_2(MeCN)_2$	-	Bis(acetonitrile) dichloropalladium(II)
Py	-	Pyridine
P-TSA	-	*para*-Toluenesulfonic acid
rt	-	Room temperature
TBAF	-	Tetrabutylammonium flouride
TMG	-	1,1,3,3-Tetramethylguanidine
sat.	-	Saturated
TBDMS-Cl	-	*tert*-Butyldimethyl chlorosilane
TBHP	-	*tert*-Butyl hydroperoxide
TBS-Otf	-	*tert*-Butyldimethyl silyl trifluoromethane sulphonate
THF	-	Tetrahydrofuran
$TiCl_4$	-	Titanium(IV) chloride
$TfSO_3H$	-	Trifluoromethanesulfonic acid
TrCl	-	Trityl chloride
TsCl	-	*para*-Toluenesulphonyl chloride
$Vo(acac)_2$	-	Vanadium(IV) oxide bis(2,4-pentanedionate)

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 **"Studies toward the total synthesis of Carba analogue of motif C of M.tb cell wall AG complex, integrastatins and A double-suzuki approach for synthesis of substituted diarylmethylidenefluorenes"** has been divided into three chapters. Chapter I, describes studies toward the total synthesis of carba analogue of motif C of M.tb cell wall AG complex, Chapter II describes an expeditious one-step entry to the central core of integrastatins and Chapter III deals with a double-suzuki approach for synthesis of substituted diarylmethylidenefluorenes.

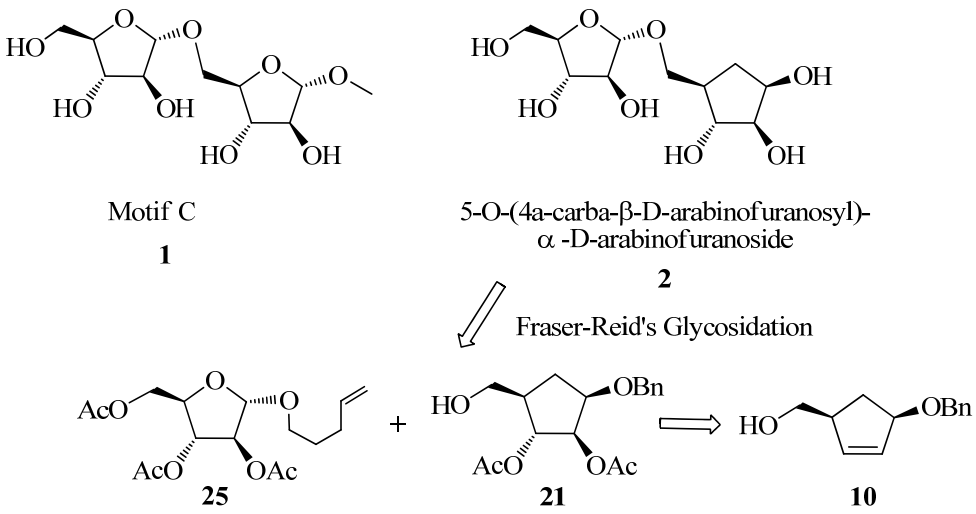
Chapter I

Studies toward the total synthesis of Carba analogue of motif C of M.tb cell wall AG complex.

The mycolic arabinogalactan (AG) complex present on the cell wall surface of *Mycobacterium tuberculosis* has unique structural features unknown in actinomycetes. The furanoside rings of AG complex are conformationally more mobile (than pyranosides) and are largely linked through primary hydroxyl groups. These characteristics enable the crowded AG complex to adopt a structure in which mycolic acids are closely arranged in parallel arrays. The AG complex is critical for the survival of *M. tuberculosis*. The hydrophobic AG complex acts as a strong barrier for the passage of antibiotics into the cell and therefore, plays an important role in developing the resistance of mycobacteria to many antibiotics. The drug ethambutol blocks the biosynthetic pathway of arabinose. The inhibition of biosynthetic pathway, involved in displacement of *M. tuberculosis* cells, is considered as an attractive strategy for drug development against *M. tuberculosis*. There has been increasing interest in the synthesis of "glycoconjugates" containing carbasugar residues for use as potential therapeutic agents. It is believed that such species will be more efficacious than their glycoside counterparts due to increased acidic and metabolic stability. Given that oligosaccharide analogues containing carbasugar residues have been shown to be competent glycosyltransferases, we postulated that arabinosyltransferase inhibitors containing carbasugar residues would be attractive synthetic targets. The logical extension of work was to develop a synthetic strategy to assemble carba analogue of disaccharide of motif C. The synthetic target of interest is 5-*O*-(4a-carba-β-D-arabinofuranosyl)-α-D-

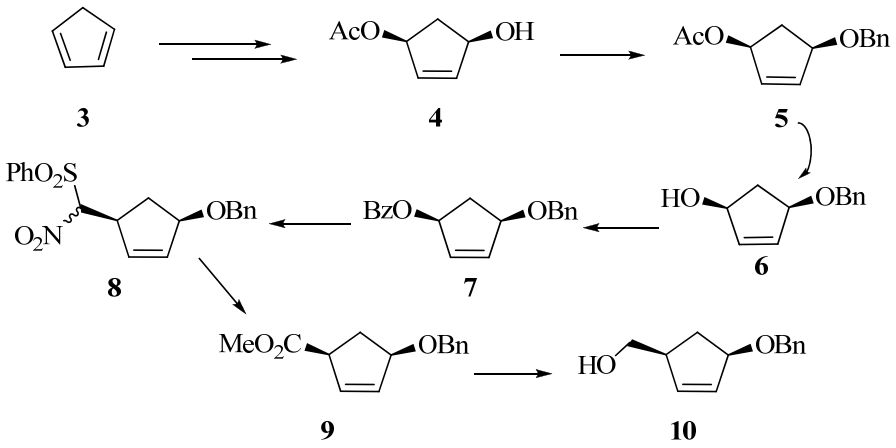
arabinofuranoside (**2**) as shown in Figure 1. The synthetic scheme for **2** was based on the *O*-glycosidation between two partners **21** and **25** *via* Fraser-reid's glycosidation reaction.

Figure 1



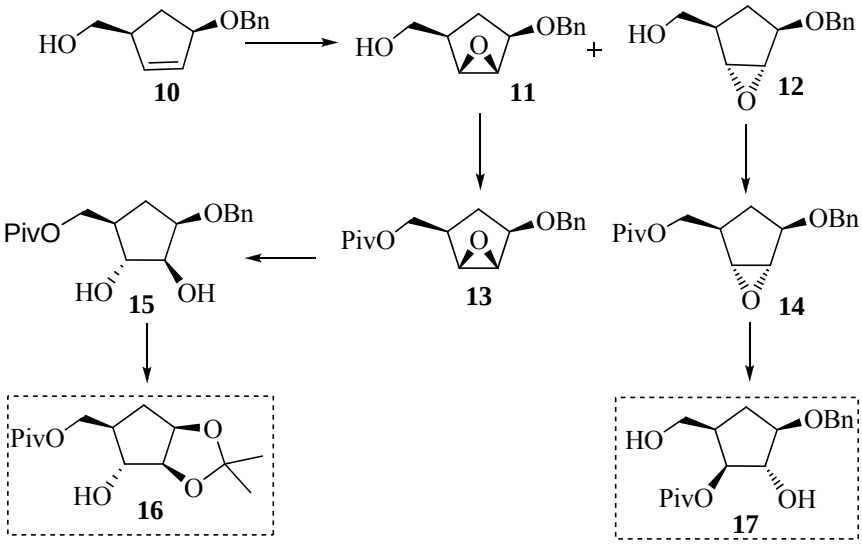
The synthesis of **10** was started from cyclopent-1,3-diene **3**, which was converted into (1*S*,4*R*)-4-(Benzyloxy)cyclopent-2-enyl acetate **5**. The benzylic derivative **5** was subjected to deacetylation by using K_2CO_3 in Methanol–H_2O (3:1) to furnish **6** (Scheme 1). The hydroxyl functionality in **6** was protected as its benzoate by using benzoyl chloride in the presence of Et_3N in CH_2Cl_2 to afford **7**. The benzoate **7** was subjected to a palladium (0) catalyzed cross-coupling reaction with a phenylsulfonyl nitromethane anion to afford **8** as a 1:1 diastereomeric mixture almost quantitatively. Treatment of **8** with tetramethylguanidine salt and tetrabutyl ammonium oxone (TBA-Oxone) in methanol/CH_2Cl_2 buffered with sodium carbonate gave the methyl ester **9**. The methyl ester **9** was treated with DIBAL-H in CH_2Cl_2 at –78 ^oC to procure the hydroxymethyl derivative **10** (Scheme 1).

Scheme 1



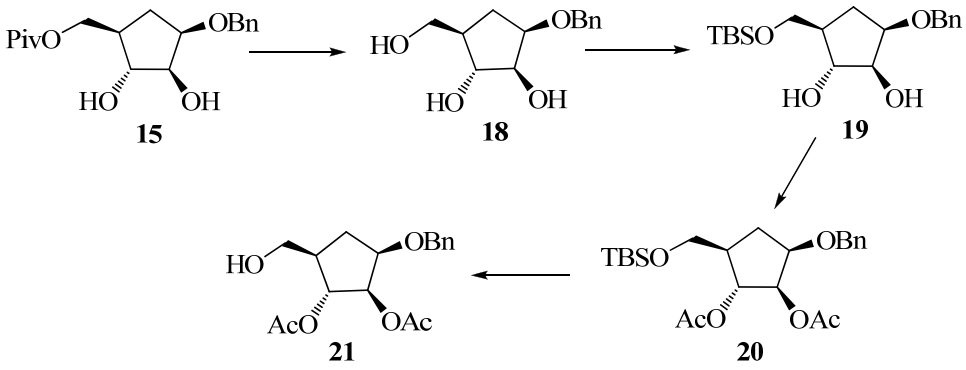
After having synthesized the key intermediate **10**, our next objective was to introduce the *trans* diol originating from the ring olefin of **10**. In that direction, treatment of **10** with *m*-CPBA gave a diastereomeric mixture of epoxides (α- and β- epoxides) in 3:7 ratio, which were separated by silica gel column chromatography. To determine the relative configuration of epoxides **11** and **12**, both the epoxides were independently treated with PivCl and Et_3N in CH_2Cl_2 to furnish the corresponding pivolate ester derivatives **13** and **14** (Scheme 2).

Scheme 2



The relative stereochemistry was assigned based on observed spatial interactions in NOESY/COSY experments. We proceeded with β-epoxide **13** for regioselctive epoxide opening. Epoxide **13** was subjected to hydrolysis with cat. $HClO_4$ in DMSO-H_2O (3:1) solvent mixture to afford the diol **15** quantitatively. To confirm whether the epoxide opening took place at C2 or C3 position, **15** was subjected to debenzylation using Pd/C (catalytic amount) in methanol under H_2 pressure to give intermediate triol. The *syn*-diol functionality of triol was protected as its acetonide using 2,2-dimethoxypropane in acetone with catalytic amount of *p*-TSA to give acetonide **16** (Scheme 2). The stereochemistry of **16** was unambiguously confirmed by its COSY/NOESY spectral analysis. Surprisingly, the acid catalyzed hydrolysis of the α-epoxide **14** gave exclusively **17** resulting from the pivoloyl participation and migration during the epoxide opening. The constitution and the configuration of **17** was confirmed by extensive spectral studies. The pivolate **15** was subjected to DIBAL-H reduction in CH_2Cl_2 at −78 ^oC to give triol **18**. Primary hydroxyl functionality of triol **18** was protected as its TBS ether using TBS-Cl and imidazole in CH_2Cl_2 to afford **19**. The diol **19** was acetylated using Ac_2O and pyridine in CH_2Cl_2 to procure the diacetate **20**. TBS deprotection of diacetate **19** using catalytic 0.8% H_2SO_4 completed the synthesis of the glycosyl acceptor **21** (Scheme 3).

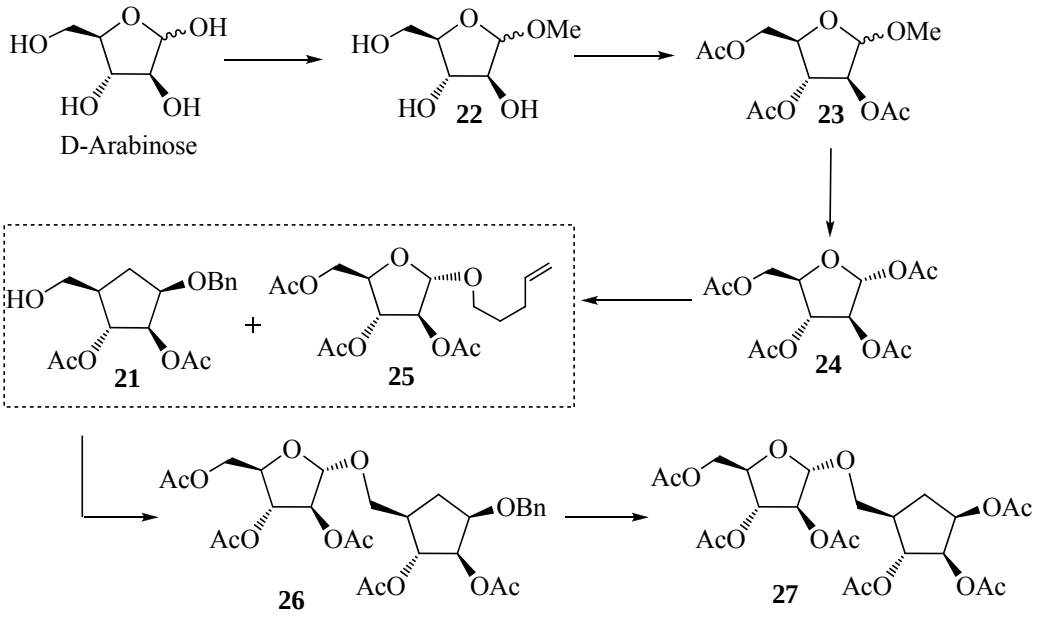
Scheme 3



Our next endeavor was to synthesize the *n*-pentenyl glycosyl donor **25** starting from D-arabinose and its glycosidation by employing glycosyl acceptor **21**. Methyl D-arabinofuranosides (**22**) were prepared from D-arabinose using methanolic HCl at room temperature, which was subsequently treated with Ac_2O, pyridine to afford methyl 2,3,5-

tri-*O*-acetyl-D-arabinofuranosides (**23**). The per-*O*-acetyl D-arabinose **24** was prepared from **23** using $Ac_2O/AcOH/H_2SO_4$ in quantitative yield. Following Fischer's glycosidation of **24** with 4-penten-1-ol with a catalytic amount of $BF_3{\cdot}OEt_2$ and 4Å MS powder in CH_2Cl_2 at room temperature furnished pentenyl glycosyl donor **25** (Scheme 4).

Scheme 4



The Fraser-Reid glycosidation reaction between glycosyl donor **21** and glycosyl acceptor **25** in the presence of NIS, TfOH (catalytic) and 4Å MS powder in CH_2Cl_2 at room temperature gave the disaccaharide **26** (Scheme 4). Finally the disaccharide **26** was subjected to benzyl deprotection using $Pd(OH)_2/C$ in MeOH at room temperature to give the alcohol which was subsequently acetylated using Ac_2O and pyridine to give hexa-acetyl disaccharide **27**.

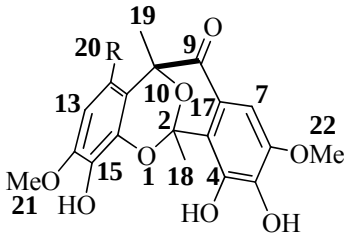
In summary we describe the first synthesis of carba analogue of motif C of arabinogalactan complex present in *M. tuberculosis* cell wall. The Pd(0) catalyzed allylic alkylation and Fraser-Reid's glycosidation are the two key reactions that were employed for the synthesis of central glycosyl acceptor unit and the glycosidation respectively. The biological and structural implications of this C-analogue will not be only interesting but significant from a drug development point of view.

Chapter II

An expeditious one-step entry to the central core of integrastatins

Construction of architecturally complex molecules from simple building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity. Accessing distinctive three-dimensional architectures by employing structurally simplifying transforms from simple or commercially available starting compounds remains as a challenging problem especially when the targets are required in a fewer steps. Domino reactions characterized by several bond formations through sequential intramolecular transformations are well outfitted to address the above issues. We illustrate such a domino process comprising a low valent titanium mediated pinacol cross coupling and an intramolecular trapping of the intermediate diol with suitably disposed carbonyl group resulting in a one step assembly of the central core of integrastatins. Integrastatin A (**28**) and B (**29**) are two recently discovered natural products isolated from both an unnamed fungal source (ATCC74478) and from an endophytic *Ascochtya* species (ATCC74477), which have been found to selectively inhibit the strand-transfer reaction of recombinant HIV-1 integrase at micromolar concentrations. They are based on a novel [6.6.6.6] tetracycle, and although they contain two chiral centers, they exist in nature in racemic form ((*R*,*R*)-form shown) (Figure 2).

Figure 2



Integrastatin A (**28**, R = CH_2OH)
Integrastatin B (**29**, R = CHO)

Inspired by the simplicity of the retrosynthetic strategy, the feasibility of projected transformation was examined by employing commercially available *o*-phthalaldehyde (**30**) and *o*-hydroxy benzaldehyde (**31**) (Scheme 5).

Scheme 5

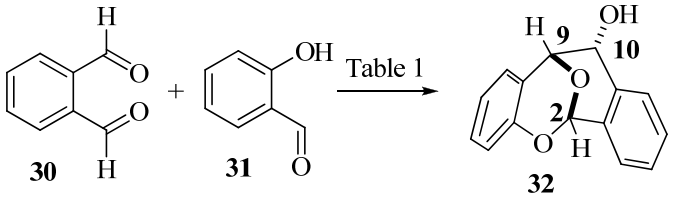


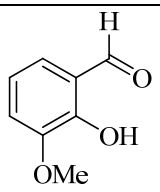
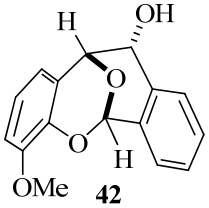
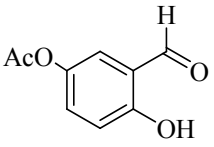
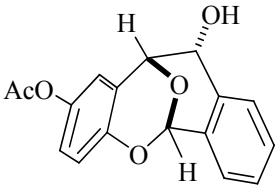
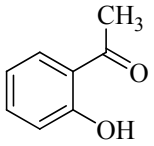
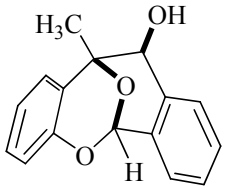
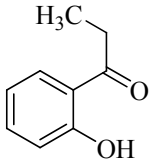
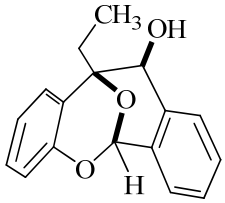
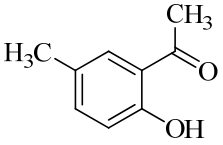
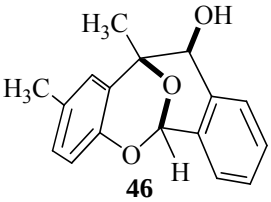
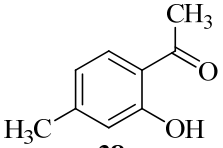
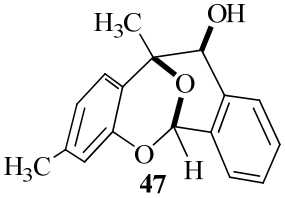
Table 1

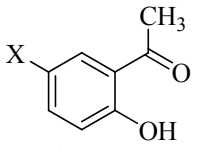
Entry	Conditions	Yield
1	15% aq.solution of $TiCl_3$, Acetone, rt	7%
2	Zn, $TiCl_4$, THF, 0 ^oC	21%
3	Mg(Hg), $TiCl_4$, THF, 0 ^oC	42%
4	Cat Cp_2TiCl_2, Zn, TMSCl, THF, rt	15%
5	Mg, TMSCl, Cat $InCl_3$, THF, rt	No reaction

As indicated in the table 1, the proposed transformation was found to be feasible with the low valent titanium reagent generated *in situ* by employing Zn-Cu, Zn, or Mg(Hg) the later being yielded better. The assigned *threo*-configuration for compound **32** was derived from the NMR studies. Finally, single crystal X-ray analysis of compound **32** proved the proposed stereochemistry beyond the doubt.

The generality of this transformation has been extended by employing various o-hydroxy aryl aldehydes (**33**, **34**) and aryl ketones (**35** – **41**). The corresponding tetracyclic derivatives **42** – **47** were obtained as a single diastereomers in moderate yields. Surprisingly, we could not isolate any expected products from the cross pinacol coupling reaction of **30** with halogen substituted acetophenones (entry 7).The *threo*-configuration for the products **42** and **43** resulted from the coupling of aryl aldehydes was assigned by comparing the chemical shifts and coupling constants with that of **32**. The single crystal X-ray structural analyses of **42** further confirmed the assigned structure. The stereochemistry of the tetracyclic compound **44** obtained from the cross pinacol coupling of *o*-hydroxy acetophenone (**35**) with **30** was established as *erythro* with the help of NOESY studies. A similar configuration for other related products **45** – **47** was proposed by considering their spectral data similarity with the spectral data of **44**.

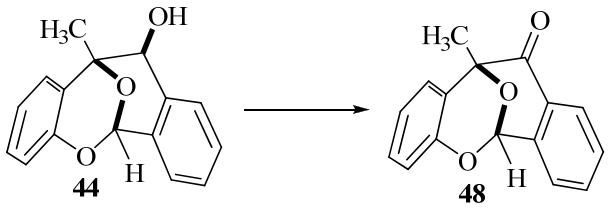
Table 2

Entry	Substrate	Product	Yield
1	 **33**	 **42**	47%
2	 **34**	 **43**	57%
3	 **35**	 **44**	49%
4	 **36**	 **45**	37%
5	 **37**	 **46**	43%
6	 **38**	 **47**	41%

7	 **39 - 41** X = F, Cl, Br	----	----

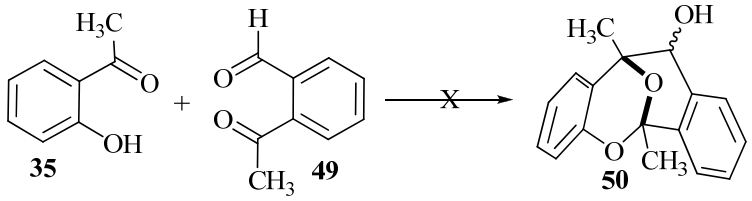
Oxidation of one of the compound **44** was carried out with MnO_2 to show the feasibility of projected benzylic-OH oxidation (Scheme 6) and corresponding keto compound **48** was obtained.

Scheme 6



Finally, when 2-formylacetophenone (**49**) and *o*-hydroxy acetophenone (**35**) despite being various reagents have been surveyed, the projected pinacol coupling of compound **49** and **35** to afford **50** was found to be a difficult proposition. In all the cases, the reactions afforded complex mixture of products (Scheme 7).

Scheme 7



In summary, inspired with the skeletol complexity and promising antiviral activity of integrastatins, herein we document a facile one-step approach for the central tetracyclic core by employing low valent titanium mediated pinacol cross coupling reaction and intramolecular acetal formation. The present approach characterized by consecutive formation of three bonds affording topologically complex tetracyclic compounds adds another dimension to the pinacol reaction and has the potential to be

extended for synthesis of hitherto unknown small molecules with multiple skeletons in fewer steps by judicious juxtaposition of reactive groups.

Chapter III

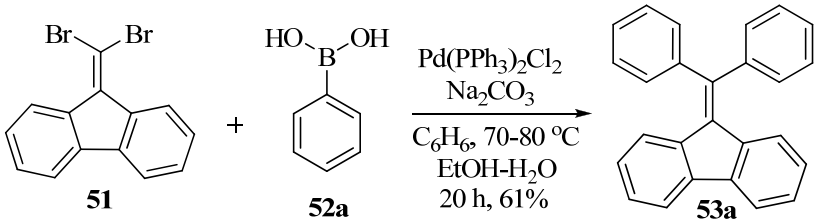
A double-Suzuki approach for synthesis of substituted diarylmethylidenefluorenes

There is great current interest in the chemistry of fluorenes and their polymers as electroluminescent compositions, and the alkylidene fluorene liquid crystalline semi-conducting polymers organic field effect transistor devices. While there appears to be a great deal of discussion about the derived transient intermediates by theoritical and experimental calculations, little has focused on the synthesis of these diarylmethylidenefluorene derivatives. We introduce a facile synthesis of diarylmethylidenefluorenes by means of Suzuki coupling of dibromomethylidenefluorene (**51**) with arylboronic acids **52**.

The Suzuki reaction of 1,1-dibromo-1-alkenes with alkenyl or arylboronic acids is known and used in the synthesis of tri- and tetrasubstituted olefins and also for the stereoselective formation of (*Z*)-1-aryl- or (*Z*)-alkenyl- 1-bromo-1-alkenes. Because a variety of organoboronic acid derivatives are now readily available, we examined the feasibility of a double Suzuki reaction with the known dibromomethylidenefluorene (**51**) to synthesize symmetric diarylmethylidenefluorene derivatives.

Our initial attempts to optimize the reaction conditions were carried out with simple phenylboronic acid (**52a**). After a careful examination of various reaction conditions, such as reaction temperature, reaction time, base, solvent, and amount of phenylboronic acid, we concluded that the best results for the intended double Suzuki reaction were achieved by using a suspension of benzene–ethanol–water as a solvent, sodium carbonate as a base, conducting the reaction at 70–80 °C and addition of the catalyst $Pd(PPh_3)_2Cl_2$ (7.5 mol%) and phenylboronic acid (1.5 equiv) twice to the reaction mixture with a 10 hour interval (Scheme 8).

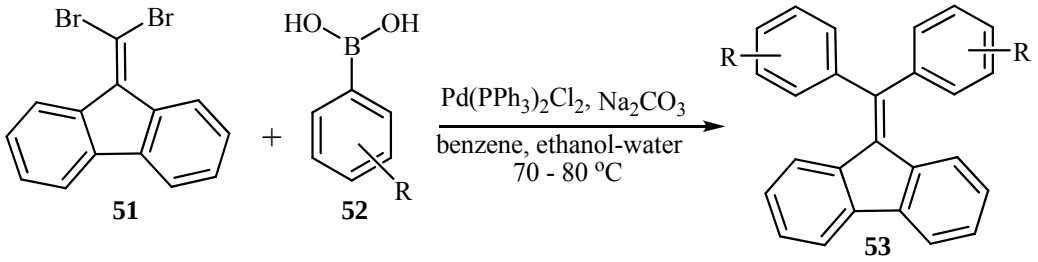
Scheme 8



51 **52a** **53a**

In order to show the generality of our double Suzuki approach, differently substituted aryl boronic acids **52b**–**i** were employed as the coupling partners with **51** under the conditions established and led to the synthesize previously known and a couple of unknown diarylmethylidenefluorene derivatives **53b**–**i** (Scheme 9).

Scheme 9



51 **52** **53**

52a	R =H	**53a**	R =H 61%
52b	R = *p*-Me	**53b**	R = *p*-Me 67%
52c	R = *p*-Cl	**53c**	R = *p*-Cl 81%
52d	R = *p*-NMe_2	**53d**	R = *p*-NMe_2 69%
52e	R = m-OMe	**53e**	R = *m*-OMe 73%
52f	R = *m*-NO_2	**53f**	R = *m*-NO_2 79%
52g	R = *m*,*p*-diOMe	**53g**	R = *m*,*p*-diOMe 44%
52h	R = *p*-$COCH_3$	**53h**	R = *p*-$COCH_3$ 88%
52i	R = *m*-$COCH_3$	**53i**	R = *m*-$COCH_3$ 81%

In summary a simple method for the synthesis of symmetric and substituted diarylmethylidenefluorenes has been reported using a double Suzuki reaction. Work in the direction of stepwise coupling of different boronic acids to address the synthesis of unsymmetric derivatives is in progress.

Chapter I

Studies Toward the Total Synthesis of Carba Analogue of Motif C of M.tb Cell wall AG Complex

Introduction

Tuberculosis: A global health crisis

The World Health Organization (WHO) estimates that the worldwide prevalence of tuberculosis (TB) exceeded 14 million in 2005, with more than 1.5 million deaths attributed to the disease during that year.[1] Perhaps even more staggering is the WHO estimate that one-third of the world's population currently harbors the causative bacterium of TB, *Mycobacterium tuberculosis,* with 5-10% (or more in those with concurrent immunodeficiency) of these individuals developing active TB during their lifetime. The economic burden of this epidemic is similarly astounding. An estimated $10 billion is spent annually on global TB control and, with more than 75% of TB deaths in the highest-burden nations occurring amongst working-aged 15-54 year-olds, TB causes a loss of productivity equal to 4-7% of gross domestic product.[2] As a plague upon individuals as well as nations, TB is a global health crisis in the twenty-first century. The vast majority of individuals with TB, more than 80%, live in India or Sub-Saharan Africa. Though incidence of TB is greatest in parts of Africa, the populous Asian countries of Bangladesh, China, India, Indonesia, and Pakistan account for nearly 50% of new cases worldwide.[3] Crowded living conditions and economic limitations often coincide with elevated TB incidence, indicating that socioeconomic factors are of paramount significance in the persistence of this disease for which effective medications are available.

In 2006, the alarming discovery of *M. tuberculosis* strains resistant to isoniazid, rifampicin, and three classes of second-line drugs, termed extensively drug-resistant (XDR), was reported, demonstrating that the dilemma of drug resistance in *M. tuberculosis* is worsening.[4] Following lines highlight a brief view to this growing public health threat in a chemist's perspective with little insight into biology.

History of Tuberculosis

In the late nineteenth century, Robert Koch and his team practically invented the field of bacteriology and the painstaking culturing techniques that go along with it. When

Koch released his article on the etiology of infectious diseases in 1879 and formalized the means of identifying an organism as an infectious agent in 1882 with what is known now as Koch's Postulates, he launched a novel field aiming to conclusively correlate microorganisms with disease.[5] The first of his great discoveries that connected illness with a specific microbe was revealed on March 24, 1882 when Koch announced to the Berlin Physiological Society that *Mycobacteriutn tuberculosis* was the causative agent of TB.[6]

Another important era of TB research occurred in the middle of the twentieth century, when the discovery of antibiotics provided the first pharmacological treatment for TB. In 1944 Selman Waksman discovered the fungus *Streptomyces griseus,* from which he isolated the first successful antibiotic against *M. tuberculosis,* known as streptomycin. By 1953, streptomycin was combined with isoniazid (discovered in 1950) in the first multi-drug, long-term chemotherapy for TB, a strategy reminiscent of the multi-drug therapies still used today.

Confidence in the new antibiotic age led the US Surgeon general to testify to Congress that we could "close the book on infectious diseases" in 1965.[7] By the early 1990s, after decades of culminating apathy towards infectious diseases, it became apparent that TB had reemerged as an epidemic killer. However, TB remains a major burden of human suffering with crippling economic impact worldwide as reported cases remain in the millions annually**.**

Introduction to *Mycobacteria*

The genus mycobacterium contains three important bacterial pathogens *Mycobacterium* (*M.*) *tuberculosis*, *M. leprae*, *M. avium*, and an important fast growing non-pathogenic research species *M. smegmatis*. Mycobacteria, although strictly speaking gram-positive, are readily distinguished from other bacteria by their unique cell wall, which confirms neither to the classical gram-positive nor gram-negative cell wall but includes features of both.[8] *M. tuberculosis* has a very slow growth cycle (dividing every 24 hours, compared with every 20 minutes for *Escherichia coli*), a complex cell envelope, the ability to colonize macrophages and the ability to remain quiescent and then reactivate decades later.[9]

M. tuberculosis is transmitted almost exclusively by air-borne route and "infectious unit" is a small bacillus-containing particle called a droplet nucleus. When a droplet nucleus containing one or two viable bacilli is inhaled by an immuno compromised person, it is deposited in the alveolar surface where the bacilli begin to multiply. Initially, the infecting organism meets only limited resistance from the host, as phagocytosis by alveolar macrophages has little effect on the bacilli, which continue to multiply intracellularly in the human host. After several weeks of infection, the number of leukocytes in the area decreases and the mononuclear cells predominate; these crowd together and contain pale, foamy, cytoplasmic material which is rich in lipid. The resulting unit is called a tubercle, the fundamental lesion of tuberculosis.

The primary structure of the cell wall

The basic cell wall structure of *M. tuberculosis* does not differ from that of other nonpathogenic mycobacteria. It consists of three interconnected "macromolecules".[10] The outermost of these are mycolic acids, unique 70-90 carbon branched fatty acids, which form outer lipid layer similar to, but differing from, the classical outer membrane of gramnegative bacteria. The mycolic acids are esterified to the middle component, arabinogalactan (AG), a polymer composed primarily of D-galactofuranosyl and D-arabinofuranosyl residues. AG is connected *via* a linker disaccharide phosphate to the 6-position of a muramic acid residue of the peptidoglycan. The peptidoglycan is the inner most of the three cell wall core macromolecules. The major polysaccharide components are arabinogalactan (AG) and a lipoarabinomannan (LAM) in which all of the galactose and arabinose residues are present in the furanose form.

Structural features of Lipoarabinomannan (LAM)

The LAM, which is an antigenic polymer, contains about 120 sugar residues, 71 of which are arabinoses and 49 of which are mannoses. Distinct features are:

1. Within LAM, all *ara* are in furanose form and *man* are in pyranosyl form.
2. The terminal end is a branched hexaarabinofuranoside with the structure [β-D-ara*f*-(1→2)-α-D-ara*f*)] $_2$-3,5-α-D-ara*f*-(1→5)-α-D-ara*f*, similar to that in AG
3. A linear β-D-ara*f*-(1→2)-α-D-ara*f*-(1→5)-α-D-ara*f*

4. *Ara* termini are extensively capped with man*p* residues
5. Mycolic acids are not present in LAM

Structural features of Arabinogalactan (AG)

Partial depolymerisation of the per-*O*-alkylated polysaccharide and analysis of the generated oligomers by GC-MS and FAB MS has established[11] the fine structure of Arabinogalactan as depicted in the AG, which is a structural polymer, contains approximately 100 sugar residues, 69 of which are arabinofuranoses and 31 of which are galactofuranoses. Salient features are:

Figure 1

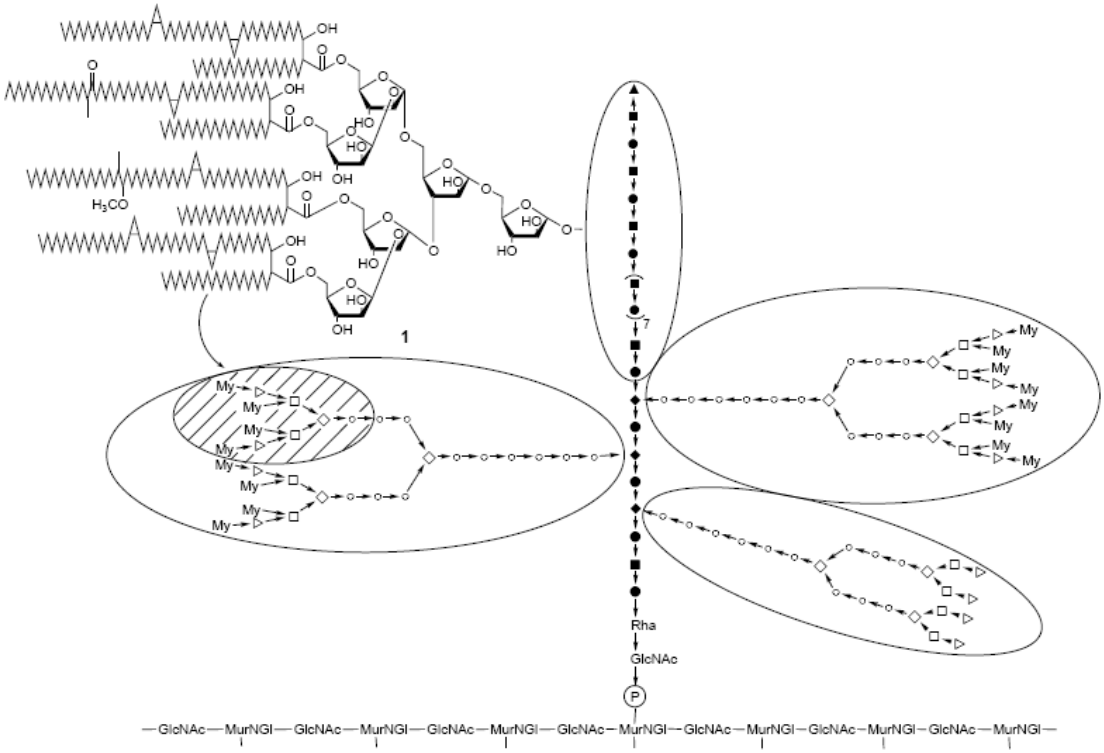


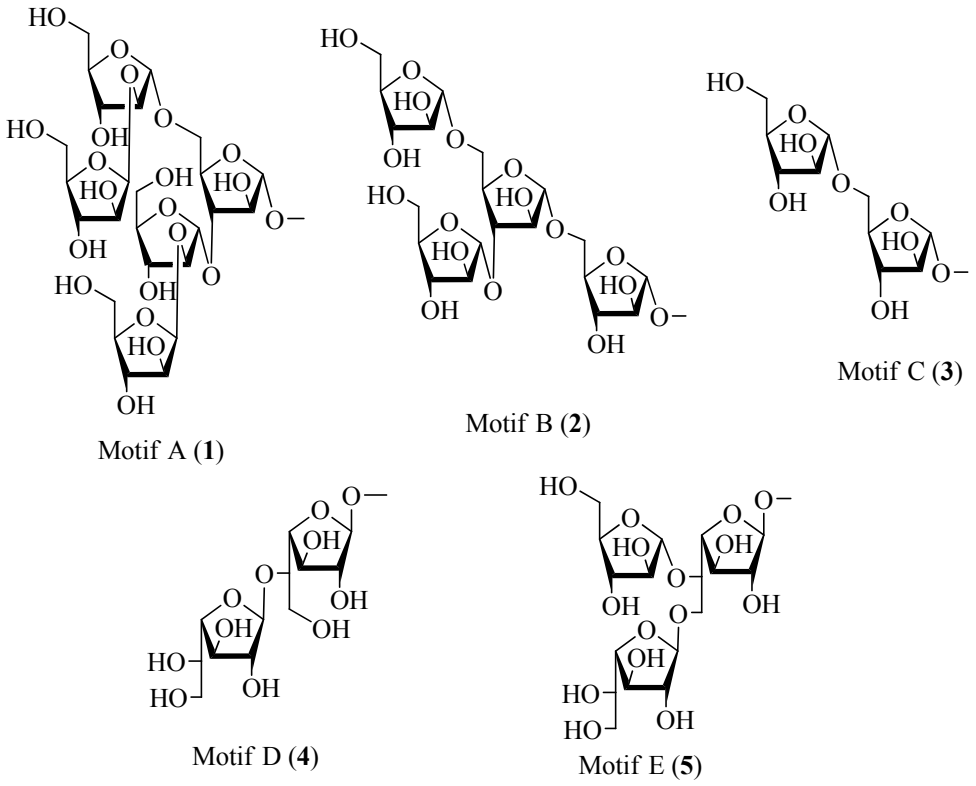
Fig. 1 Schematic diagram of the proposed illustration of the macro structural motifs of the cell wall arabinogalactan. My, Mycolic acid; (▼) t-β-D-Ara*f*; (□) 2-α-D-Ara*f*; (◇) 3, 5-α-D-Ara*f*; (▲) t-β-D-Gal*f*; (■) 6-β-D-Gal*f*; (●) 5-β-D-Gal*f*; (◆) 5,6-β-D-Gal*f*; GlcNAc, *N*-acetylglucosamine; Rha, rhamnose; MurNGl, *N*-glycolylmuramic acid.

1. Within AG, all *ara* and *gal* are in the furanose form.
2. The non-reducing termini of arabinan consist of a branched pentaarabinofuranosyl structure [β-D-ara*f*-(1→2)-α-D-ara*f*] 2-3,5-α-D-ara*f*-(1→5)-

3. The majority of the arabinan consists of 5-linked α-D-ara*f* residues with branching introduced by 3,5-α-D-ara*f* residues replaced at both branched positions with 5-α-D-ara*f*
4. The arabinan chains are attached to the galactan core through the C-5 of some of the 6-linked alternating 5-and 6-linked β-D-gal*f* moieties.
5. The galactan of AG is linked to the C-6 of some muramyl residues of peptidoglycan *via* the glycophosphoryl bridge L-Rha*p*-(1→3)-D-GlcNAc-(1→*p*)

The mycolic acids are located in clusters of four on the terminal pentaarabinofuranosyl units.

Figure 2: Five major Structural motifs A-E of AG



The major *ara*-containing degradation products were the hexaarabinofuranoside and linear disaccharide, α-D-ara*f*-(1→5)-D-ara*f*. Oligosaccharide fragments containing upto 23 *ara* residues were obtained by gentle acid hydrolysis of the per-*O*-methylated AG

and all the major structural motifs of AG, namely motifs A-E were as represented in figure 2.

Synthesis of these motifs provide tremendous opportunities to understand their role in the survival and pathogenicity of these organisms. The structural analysis revealed that motifs A, B, and C are composed of arabinofuranose units having subtle differences between them with respective *O*-glycosidic linkage. Structure of motif A is significant due to the presence of two 1→2 *cis* linkages[12], whereas structural motifs B and C account for the bulk of internal portions of the arabinan segments of the arabinogalactan and structural motif D, composed of alternating 6-linked and 5-linked galactofuranosyl residues, is supported by the presence of the disaccharide, 6-*O*-β-D-galactofuranosyl-D-galactose. Among the products of the degradation of AG, motif E is unique in that it contains both arabinofuranose and galactofuranose residues and both 5-and 6-positions of the galactofuranose component are linked with arabinofuranosyl and galactofuranosyl residues, respectively.

A major impetus for the study of the cell wall core molecule AG arises from the need for new drugs against *M. tuberculosis* and *M. avium*.[13] AG of *M. tuberculosis* has special interest for two fundamental reasons, 1) it appears to be essential for viability and 2) three out of the four sugars of which it is composed, D-Ara*f*, D-Gal*f* and L-Rha*p* are not found in humans. Thus any of a score or more of enzymes involved in the formation of sugar donors and their polymerization are potential drug targets. The isolation and expression of the genes for these enzymes is a high research priority. Inhibitors of the resultant enzymes can be obtained by using "high through put" screens and by enzyme characterization (ultimately X-ray analysis) and the subsequent design of "rational" inhibitors.

The terminal ends of both AG and LAM are capped with a pentaarabinofuranosyl motif A, which is linked to the remainder of the polymer *via* a α-(1→5)-linked linear chain of arabinofuranosyl residues. This motif A serves as an attachment site for other functionalities present in the cell wall. These groups are located at the periphery of the cell wall complex and are therefore interface between the microorganisms and the environment.[14] In LAM, the primary hydroxyl groups in motif A are often substituted with mannopyranosyl oligosaccharides, which have been implicated in the initial stages

of infection through their interaction with human mannose binding proteins.[15] In the AG, the same hydroxyl groups are esterified with mycolic acids, branched, long chain fatty acids. Through the tight packing of the alkyl chains, the mycolic acids form a protective hydrophobic façade that in some cases is nearly crystalline.

The peptidoglycan-bound arabinogalactan of a virulent strain of *M. tuberculosis* was per-*O*-methylated, partially hydrolyzed with acid and the resulting oligosaccharides were separated by high pressure liquid chromatography and the structures of all those 43 constituent oligosaccharide fragments were identified by exhaustive NMR studies.[16] Based on availability of sugars and number of glycosyl linkages, the fine structure of AG polymer has been characterized. It has been proven that arabinosyl residues are responsible for the antigenicity of AG, and that serological activity resides largely in fraction containing 2-linked arabinosyl residues. Thus it is logical to speculate that part, or all, of structural motif A is the major humoral immunological epitope of arabinogalactan and, consequently, of whole mycobacteria.[17] Monoclonal antibodies raised against lipoarabinomannan also react with purified cell walls, suggesting an arabinose-containing epitope common to lipoarabinomannan and arabinogalactan.

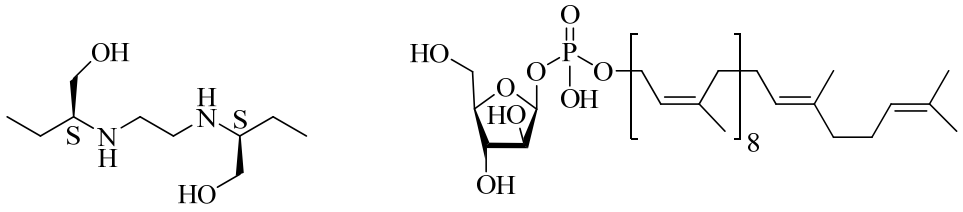
As the distal ends of both polymers (AG and LAM) are terminated with motif A, this motif is believed to play critical role in both infection by and survival of the organism in the human host. Ethambutol (**6**) (Figure 3), one of the drugs currently used to treat tuberculosis, has recently been shown to be an arabinosyltransferase inhibitor.[18] Thus, new compounds that act, as does Ethambutol (**6**), in preventing complete arabinan biosynthesis are likely to be potent antimycobacterial agents. Furanosyl oligo-and polysaccharides are not found in mammalian glycoconjugates and therefore inhibitors of the biosynthetic pathways leading to their formation are particularly attractive drug candidates.

Attention is now being focused on understanding mycobacterial cell wall biosynthesis but there is still much to be learned concerning the details of this process, especially the assembly of the arabinan component. Decaprenol arabinofuranosyl phosphate (**7**) has been identified as the source of the arabinose in mycobacteria[19] and there is presumably an array of glycosyl transferases that use **7** and various oligosaccharide acceptors to produce the glycan. None of these putative

arabinosyltransferases have yet been isolated or purified however, an assay for their activity using mycobacterial membrane preparations as the enzyme source has been developed.[20]

The transfer of arabinose from **7** to an arabinofuranosyl dimer and trimer has been evaluated using this assay; the effect of the aglyconic group (*e.g.* methyl vs. octyl) was also investigated.[21]

Figure 3



Ethambutol (**6**)

β-D-arabinofuranosyl-1-mono phosphoryldecaprenol (**7**)

However, a major limiting factor in these studies is the lack of availability of discrete oligosaccharide structures that can be used for unraveling the biosynthetic pathways, including the isolation and purification of the enzymes and the development of individual assays for their activity. Such compounds are most easily obtained *via* chemical synthesis but synthetic studies are rare. Thus the current endeavor stands as a pivotal point in this direction.

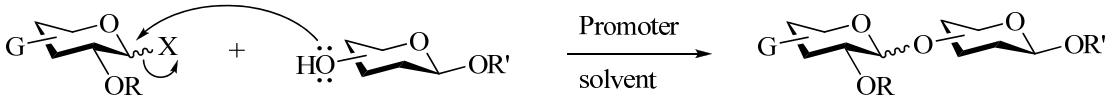
Glycosylation methods in oligosaccharide synthesis

The area of organic chemistry that deals with the study, preparation and biological role of sugars, from monosaccharides to complex oligosaccharides and their analogues, is called Glycobiology. The important role of carbohydrates in Biology and Biomedicine has been a major incentive for devising new methods for the chemical and enzymatic synthesis of this class of molecules. The biological role of sugars depends on many factors. Compared with other biopolymers such as nucleic acids, proteins and peptides, in which their biological activity depends on their sequence of nucleotides or amino acids, in the case of oligosaccharides, the situation is more complex. For oligosaccharides,

besides the sequence of the monomeric structures, other aspects such as the functional groups and their stereochemistry, the conformation of the sugars ramification, the stereoselective formation of glycosidic linkages, etc. must be considered. All these facts have made the area of oligosaccharide synthesis an ideal and challenging area for the development and testing of new synthetic methodologies[22].

A glycosidic bond is formed by a nucleophilic displacement of a leaving group (X) attached to the anomeric carbon of a sugar moiety by an alcohol ROH, or by the OH group of a partially protected sugar moiety. The compound that "gives" the glycosyl moiety is called the *glycosyl donor*, and the alcohol that receives it, is known as *glycosyl acceptor*. The reaction generally is performed in the presence of an activator called "promoter". The role of the promoter is to assist the departure of the leaving group. Promoters are often used in catalytic amounts, although in some instances they are used stoichiometrically. In some cases, other additives such as molecular seives or any base that may act as acid scavenger are used. There are many methods available for glycosidic bond formation (Scheme 1).

Scheme 1: Glycosidation reaction



Glocosyl donor (electrophile) Glocosyl acceptor (nucleophile)

Glycosylation method	**X**	**Promoter**
Köenings-Knorr[24]	Bromide, Chloride	Ag_2O, Ag_2CO_3, $HgBr_2$, $Hg(CN)_2$, AgOTf
Mukaiyama[25]	Fluoride	$SnCl_4$-$AgClO_4$
Fraser-Ried[26]	*n*-Pentenyl	NIS/$BF_3.OEt_2$
Schimdt[27]	Trichloroacetamidate	$BF_3.OEt_2$, AgOTf
Phenylseleno[28]	-SePh	IDCP, NIS-TfOH, AgOTf
Lemieux, Thiem, Danishefsky (With glycals)[29]	-	I_2, DMDO

The synthesis of disaccharides and oligosaccharides in general, involves the linking of two polyfunctional compounds. It is much more complicated than the synthesis of other biopolymers such as peptides or nucleic acids because of the greater number of possibilities for the combination of monomeric units and because the glycosidic linkages have to be introduced in a stereospecific way. The success of a coupling reaction between two sugars depends on the reactivity of the donor and acceptor, on the promoter, on the kind of substituents on both saccharide units and, of course, on the preferred selectivity of the reaction towards the α- or the β-anomeric form[23].

Synthesis of the sugar components of AG of *M. tuberculosis* has been a topic of immense activity. The first major contribution appeared from our laboratory and reported the synthesis of the pentaarabinofuranoside of motif A. Subsequently Lowary et al. reported a series of publications on motifs A, B, and C and studied their ring conformation by NMR techniques. Very recently Prandi et al. also published the synthesis of the pentaarabinofuranosyl structure of motif A.

A brief introduction to carba sugars

The search for new derivatives with analogues or even improved biological properties compared to those of the parent structures (the *carbohydrate mimetics*) appears to be a logical matter of research.[30] The term "*carbohydrate mimetic*" is frequently used to refer to any carbohydrate derivative or other compound that has multiple hydroxy groups and thus resembles a sugar or a saccharide. However, some authors prefer to reserve this term for compounds that have been demonstrated to truly mimic the structural and functional aspects of a known target. The ***carbasugars*** (*vide infra*) fall within this category, since they are endowed with important biological properties.

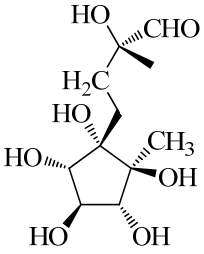
G. E. McCasland's group prepared a series of derivatives in which the ring oxygen of a monosaccharide had been replaced by a methylene group and they coined the term *pseudosugars* for this family of compounds, although they are currently known as ***carbasugars***.[31] They postulated that their structural resemblance to the parent sugars would facilitate their recognition by enzymes or other biological systems in place of the related *true* sugars. This subtle change constituted an appealing possibility, since, while

guaranteeing a high similarity with the *true* sugar, it would lead to compounds more stable toward endogenous degradative enzymes.

Natural occurrence of carbafuranoses

Carbafuranoses have not been found free in Nature but are subunits of products isolated from natural sources, in particular carbanucleosides. These compounds have been the subject of several recent reviews.[32] It should be pointed out, however, that five-membered cyclitols, such as caryose (**8**) or calditol (**9**) (Figure 4), have been isolated as natural products. No other examples of five-membered carbocyclic carbohydrate analogues from natural sources have been reported.

Figure 4: Naturally occurring carbafuranoses



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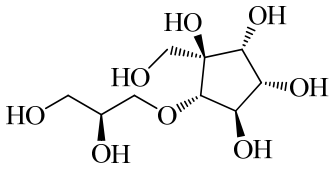

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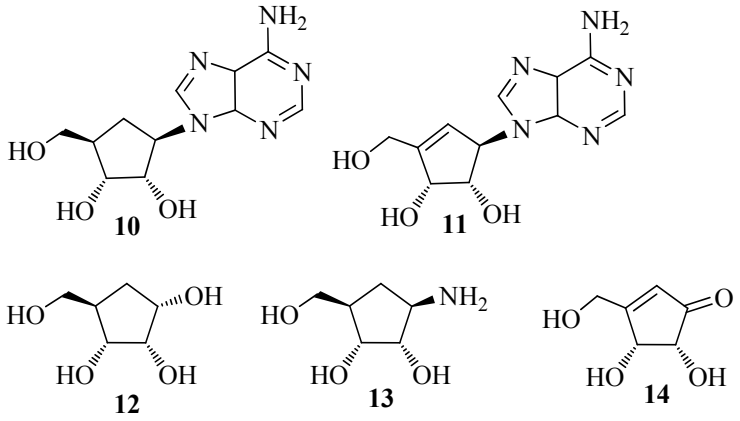
Biosynthesis of carbafuranoses

The biosynthesis of carbapentofuranoses has only been considered in the literature in connection with the more biologically relevant carbocyclic nucleosides.[33] Early biosynthetic studies on aristeromycin (**10**) and neplanocin A (**11**) (Figure 5) had established that the carbocyclic ribose ring was derived from D-glucose. On the basis of isotopically labeled precursors incorporation experiments, Parry et al.[34] were able to demonstrate that cyclization occurs between C2 and C6. Subsequent isotope dilution experiments identified the saturated tetrol **12** and aminotriol **13** as putative intermediates produced by *Srteptromyces citricolor*. More recent work suggests that, contrary to this previous proposal, the saturated carbocycles **12** and **13** do not lie on the central

biosynthetic pathway of the carbocyclic nucleosides, and instead enone **14** is postulated as the first-formed carbocyclic intermediate from D-glucose.

Figure 5: Aristeromycin (**10**), Neplanocin A (**11**), and some proposed intermediates in their biosynthesis, **12-14**

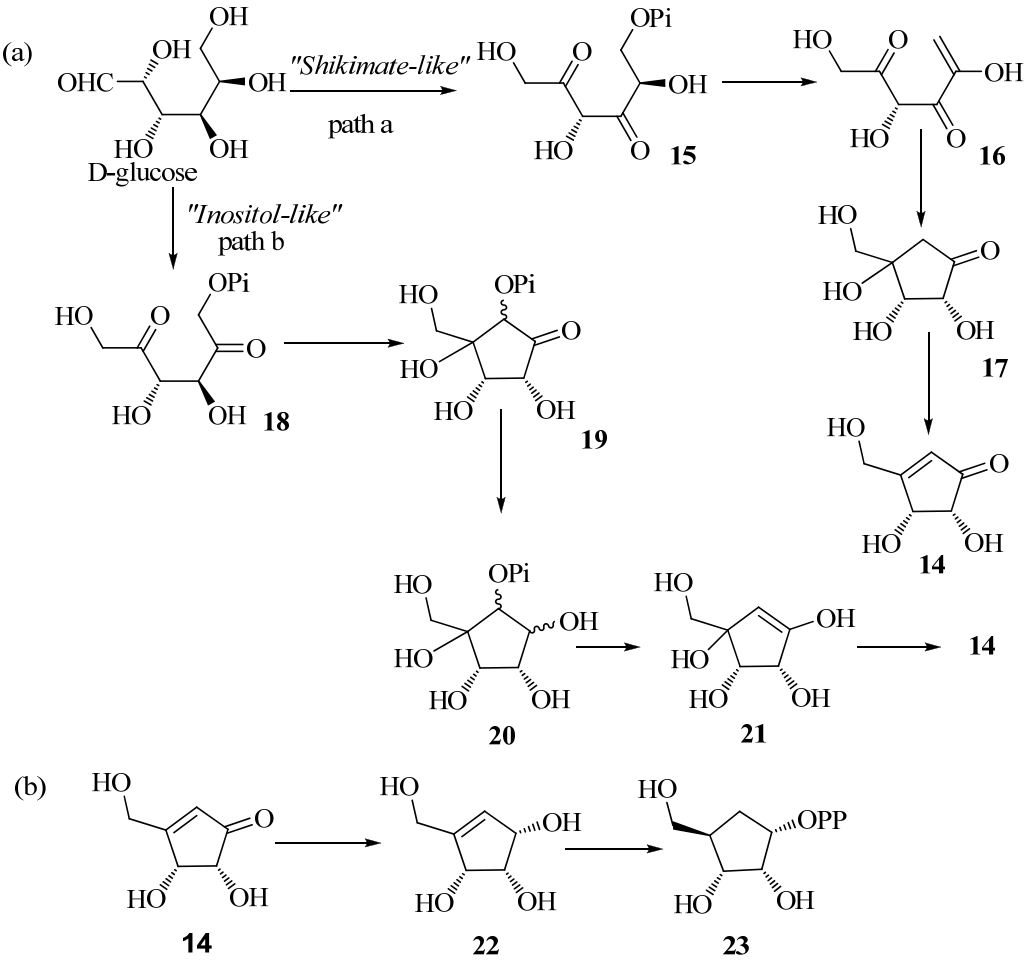


Two plausible mechanisms were postulated for the formation of the cyclopentane ring, and in both the cyclization reaction was presumed to proceed via a fructose derivative (Scheme 2a). In the first proposed mechanism, a "*shikimate-like*" pathway (Scheme 2, path a), isomerization to fructose-6-phosphate is followed by oxidation at C4 to yield compound **15**. Elimination of the phosphate group then leads to enol **16** followed by a 5-[enol-*endo*]-[*exo-trig*] cyclization. Reduction of the keto group would yield the carbocycle **17,** which could undergo dehydration, with stereospecific removal of the 6-pro-*S*-hydrogen atom, to introduce the double bond, thus generating the enone **14**.

The alternative "inositol-like" process (Scheme 2, path b) begins with the oxidation of the C5 hydroxyl group to give the diketone **18**. Cyclization can then proceed by stereospecific loss of the 6-pro-*S*-hydrogen atom followed by an aldoltype ring closure. Subsequent epimerization at C4 would yield the carbocycle **19**. Reduction of **19** followed by elimination of the phosphate moiety in **20** would lead to **21**, which could undergo an extended elimination reaction to give enone **14**. Reduction of the ketone function in **14** will then give the unsaturated carbocyclic derivative **22** (Scheme 2b), whose double bond could be reduced in an *anti* fashion with subsequent reduction of the

carbonyl group and phosphorylation to produce the carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate, **23**.

Scheme 2: Proposed biosynthetic pathways to carbapentofuranoses

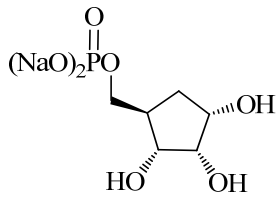


On the other hand, very little evidence has been obtained on the identity of the intermediates between D-glucose and the carbocyclic analogue of ribose **23**. The determination of the structure of such compounds will allow firm conclusions to be drawn regarding the biosynthesis of these five-membered rings.

Biological activity of carbafuranoses

The only report[35] regarding the biological activity of carbafuranoses was devoted to evaluating the enzymatic inhibitory activity of the carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP **24**, Figure 6) against the enzyme 5-phosphoribosyl-R-1-pyrophosphate (PRPP) synthetase. This enzyme reacts with ATP in the presence of Mg ion to give PRPP, a compound involved in the biosynthesis of histidine and tryptophan. From a biological point of view, there is evidence that the activity of PRPP synthetase is elevated in tumors. Then, inhibitors of this enzyme show antineoplastic activity. Compound **24** inhibits PRPP synthetase with a *K*i of 186 μM (human type PRPP synthetase) and a *K*i of 3811 mM (*Bacillus subtilis* PRPP synthetase).

Figure 6: Carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP)



24

Regarding the importance of this carbasugars here we would like to discuss the earlier methods for the synthesis of carbasugars.

Past work: Carbasugars

In fact, the racemic synthesis[36] of arysteromycin (**10**), the first natural carbafuranose related compound reported, preceded its isolation, and likewise, 5a-carba-α-D-galactopyranose was discovered as a naturally occurring compound 7 years after McCasland's first synthesis. Since then, the synthesis of such compounds has attracted considerable interest and a plethora of synthetic approaches have been developed. In this a brief discussion of earlier synthesis of carbafuranoses.

Synthesis of carbafuranoses

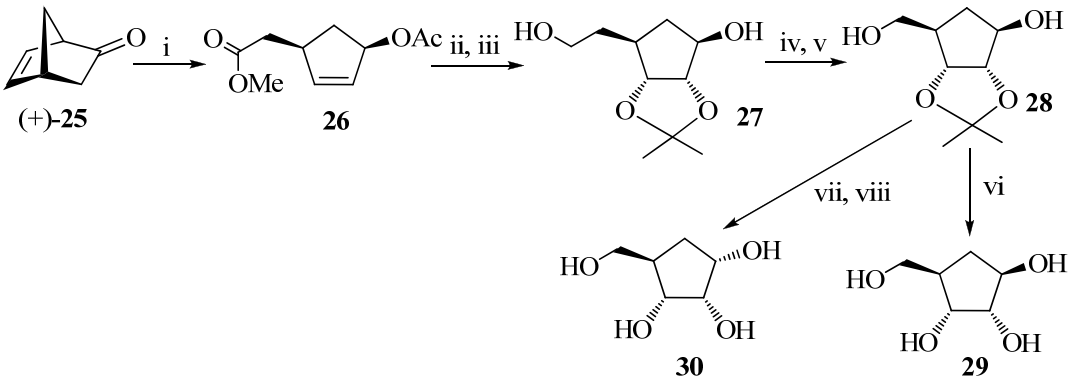
The different synthetic strategies will be classified according to the type of compounds employed as starting materials: (i) from bicyclic compounds; and (ii) from cyclopentadiene.

(i) From bicyclic compounds: Griengl and coworkers described in 1990,[37] the first synthesis of carbapentofuranoses from non-carbohydrate precursors, employing norborn-5-en-2-one (**25**) as the starting material.

(a) Synthesis of 4a-Carba-α-and -β-D-ribofuranoses (29 and 30) by Griengl's Group[38]

The compound **25** was subjected to alkaline Baeyer-Villiger reaction later followed by esterification and acetylation provided the unsaturated carbahexofuranuronic acid derivative **26**. Stereoselective dihydroxylation of **26** with OsO_4/NMO and protection of the ensuing diol as a dioxolane was followed by reduction with LAH to give compound **27**. Side-chain degradation was performed by a sequence of elimination, degradative oxidation, and reduction to the protected 4a-carba-β-D-ribofuranose (**28**).

Scheme 3



***Reagents and conditions*:** (i) (a). H_2O_2, NaOH, H_2O, Et_2O; (b). MeI, DMF; (c). Ac_2O, Py, DMAP, CH_2Cl_2, 71%; (ii) (a). OsO_4, NMO, acetone; (b). 2,2- dimethoxypropane, *p*-TsOH, 77%; (iii) LAH, Et_2O, 0 °C, 97%; (iv) (a). Ph_3P, Br_2, Et_3N; (b). 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (c). H_2O_2, THF; (d). Ac_2O, Py, DMAP, CH_2Cl_2, 61%; (v) (a). OsO_4, $NaIO_4$, H_2O, Et_2O; (b). LAH,

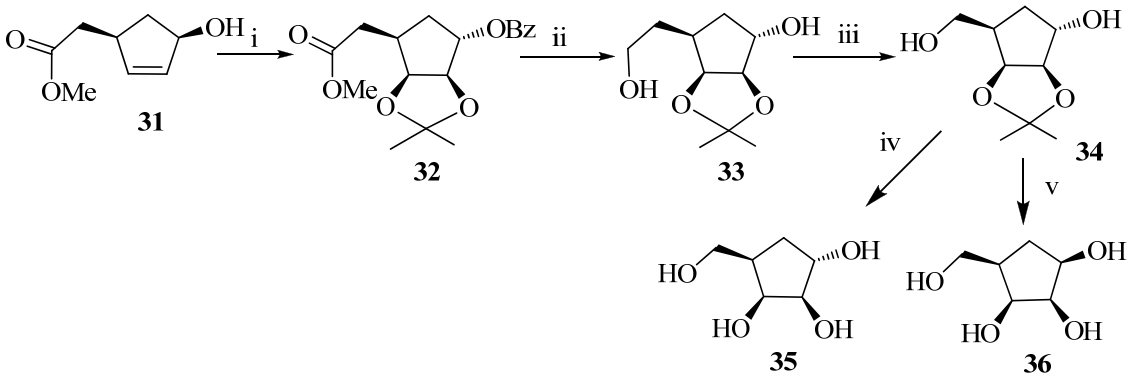
Et_2O, 88%; (vi) BCl_3, CH_2Cl_2, -78 °C, 95%. (vii) (a). triphenylchloromethane, Py, DMAP, CH_2Cl_2; (b). PDC, 77%; (viii) (a). $NaBH_4$, MeOH; (b). BCl_3, CH_2Cl_2, -78 °C, 58%.

Deprotection of the latter with BCl_3 paved the way to 4a-carba-β-D-ribofuranose (**29**). In order to obtain the α-anomer from **28**, the required inversion of C_1 was performed by a three step sequence, including protection of the primary hydroxy group, pyridinium dichromate (PDC) oxidation of the secondary alcohol, and stereoselective reduction with $NaBH_4$. Finally, deprotection with BCl_3 yielded the desired 4a-carba-α-D-ribofuranose (**30**) (Scheme 3).

(b) Synthesis of 4a-Carba-α-and-β-D-lyxofuranoses (35 and 36) by Griengl's Group[39]

Inversion of the configuration at C_1 in **31** was carried out by Mitsunobu reaction, leading to the corresponding benzoate. The latter, on treatment with OsO_4/NMO and protection, gave exclusively the desired stereoisomer **32**, which was reduced to give dioxolane **33**. The side-chain degradation to **34** and deprotection achieved 4a-carba-α-D-lyxofuranose (**35**) (Scheme 4). The β-anomer, 4a-carba-β-D-lyxofuranose (**36**), was also prepared from **34** using the same oxidation/reduction protocol.

Scheme 4

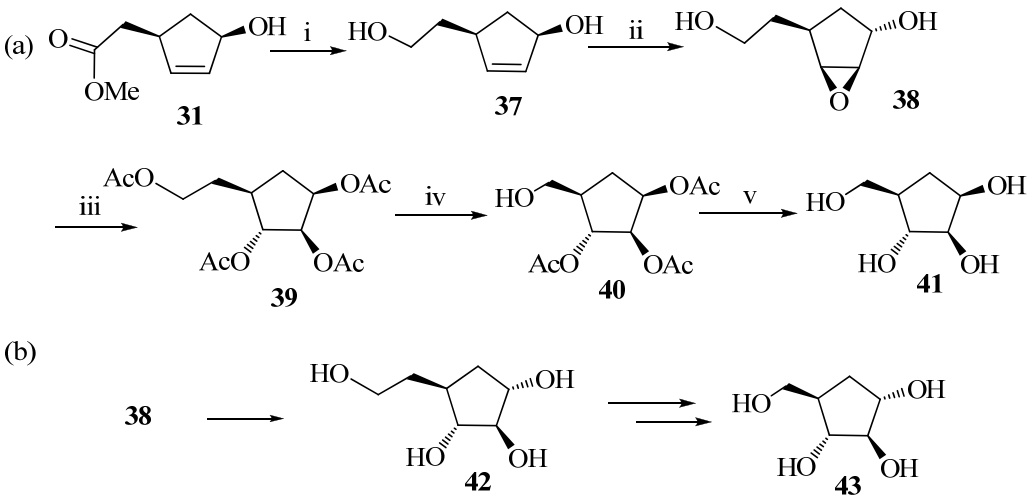


***Reagents and conditions*:** (i) (a). Ph_3P, DEAD, BzOH, THF; (b). OsO_4, NMO, acetone; (c). 2,2-dimethoxypropane, TsOH, 40% from **31**; (ii) LAH, Et_2O, 86%; (iii) (a). Ph_3P, Br_2, Et_3N, CH_2Cl_2, 76%; (b). 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (c). H_2O_2, EtOH, 86% (two steps); (d). OsO_4, $NaIO_4$, Et_2O, H_2O; (e). $NaBH_4$, MeOH, 61% (two steps); (iv) HOAc, 80%, reflux; (v) (a). TrCl, Py, CH_2Cl_2, 62%; (b). DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (c). $NaBH_4$, MeOH, 0 °C, 93%; (d). HOAc, reflux, 80%.

(c) Synthesis of 4a-Carba-DL-arabinofuranoses 41 and 43 by Griengl and Co-workers (Only D-Enantiomers are shown)[40]

Reduction of (±)-**31** gave allylic alcohol (±)-**37**, which, after Sharpless epoxidation, gave epoxide (±)-**38** as a single diastereomer. Treatment of (±)-**38** with aqueous perchloric acid resulted regioselective oxirane opening, leading, after acylation, to (±)-**39** with the desired β-arabino configuration. Conversion of (±)-**39** to 4a-carba-β-DL-arabinofuranose [(±)-**41**] proceeded as shown before, albeit, in the present, the cleavage of the terminal double bond was achieved via ozonolysis/reduction. The α-arabino configuration was obtained by inversion of configuration at C_1, after protection of the primary alcohol of (±)-**38** followed by addition of cesium acetate. The opening of the epoxide moiety required the presence of a free C_1-OH, because a C_1-OAc directs the attack of the oxygen nucleophile at C_2 rather than at C_3. Conversion of (±)-**42** into 4a-carba-α-DL-arabinofuranose [(±)-**43**] was carried out (Scheme 5).

Scheme 5

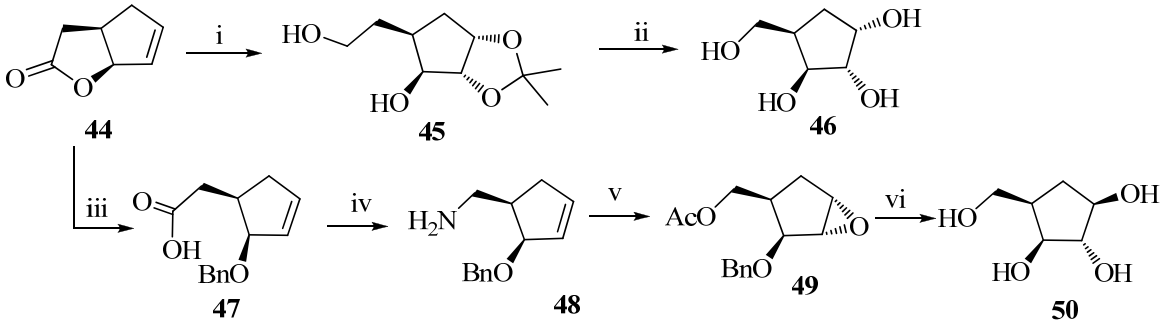


***Reagents and conditions*:** (i) LAH, Et_2O, 90%; (ii) $Vo(acac)_2$, *t*-BuOOH, CH_2Cl_2, 70%; (iii) (a). $HClO_4$, H_2O; (b). Ac_2O, Py, DMAP, CH_2Cl_2, 94%; (iv) (a). NaOMe, MeOH, 94%; (b). TrCl, Py, CH_2Cl_2, 90%; (c). Ac_2O, Py, DMAP, CH_2Cl_2, 86%; (d). H_2, 10% Pd-C, EtOH; (e). Ph_3P, Br_2, Et_3N, CH_2Cl_2; (f). 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (g). H_2O_2, EtOH; (h). O_3, MeOH, -80 to 0 °C; (i) $NaBH_4$, MeOH, 0 °C, 18% overall; (v) NaOMe, MeOH, 83%.

(d) Synthesis of 4a-Carbaxylofuranoses 46 and 50 by Griengl's Group (When Racemic, Only D-Enantiomers are shown)

cis-hydroxylation of **44** yielded an α-xylo diol, which was protected as a dioxolane whereas the lactone was reduced to diol **45**. 4a-Carba-α-D-xylofuranose (**46**) was obtained from compound **45**.[41] Compound (±)-**44** was converted into acid (±)-**47**. Curtius degradation gave amine (±)-**48**, which was stereoselectively transformed into the epoxide (±)-**49**. Regioselective ring opening of (±)-**49** with perchloric acid and deprotection gave 4a-carba-β-D-Lyxofuranose (±)-**50** (Scheme 6).

Scheme 6



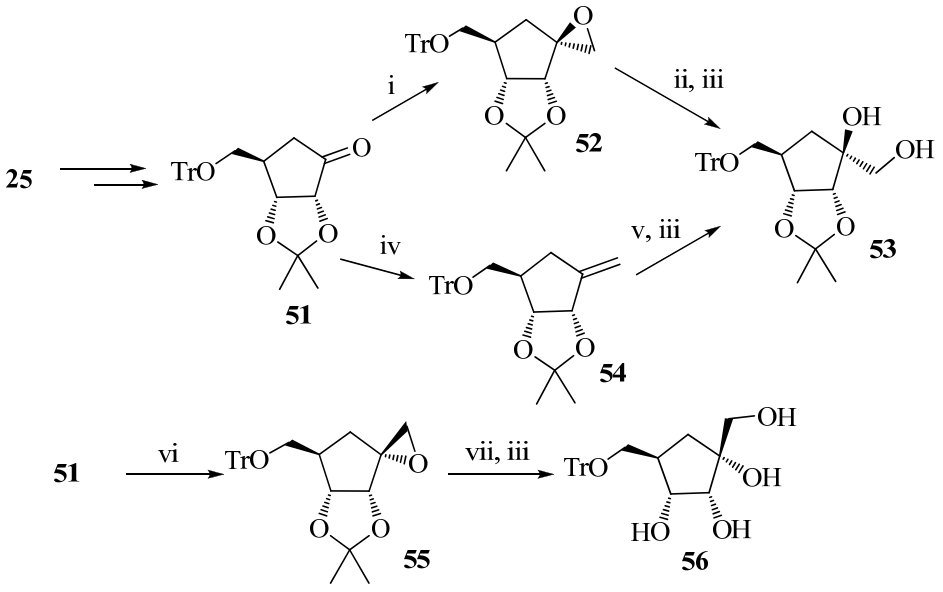
***Reagents and conditions*:** (i) (a). OsO_4, NMO, acetone; (b). 2,2-dimethoxypropane, TsOH; (c). LAH, Et_2O, 69% (three steps); (ii) (a). Ph_3P, Br_2, Et_3N, CH_2Cl_2; (b). 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (c). H_2O_2, EtOH, $Vo(acac)_2$, *t*-BuOOH, CH_2Cl_2; (d). OsO_4, $NaIO_4$, Et_2O, H_2O; (e). HOAc, reflux, 13% (five steps); (iii) KOH, BnBr, dioxane, reflux; (iv) (a). Ethyl chloroformate, Et_3N, acetone, NaN_3; (b). $PhCH_3$, reflux, 97%, two steps; (v) (a). $NaNO_2$, HOAc, NaOAc; (b). *m*-CPBA, CH_2Cl_2, 46% (two steps); (vi) (a). $HClO_4$, H_2O; (b). Ac_2O, Py, DMAP, CH_2Cl_2; (c). H_2, 10% Pd/C, EtOH; (d). NaOMe, MeOH, 53% (four steps).

(e) Synthesis of Carba-DL-ribo-2-ulofuranoses (53 and 56) by Griengl's Group (Only D-Enantiomers are shown)[42]

In the first case, the required one-carbon side chain was introduced either via dimethylsulfoxonium methylide addition, which takes place from the more hindered α-side, and nucleophilic opening of the oxirane **52** or via methylenation with Tebbe's reagent and *cis*-hydroxylation. α-Epoxide **55** was prepared by stereoselective β-bromomethyllithium addition followed by nucleophilic bromine displacement (Scheme

7). Opening of oxirane **55** followed by deprotection gave α-DL-ribocarba-2-ulofuranose (**56**).

Scheme 7



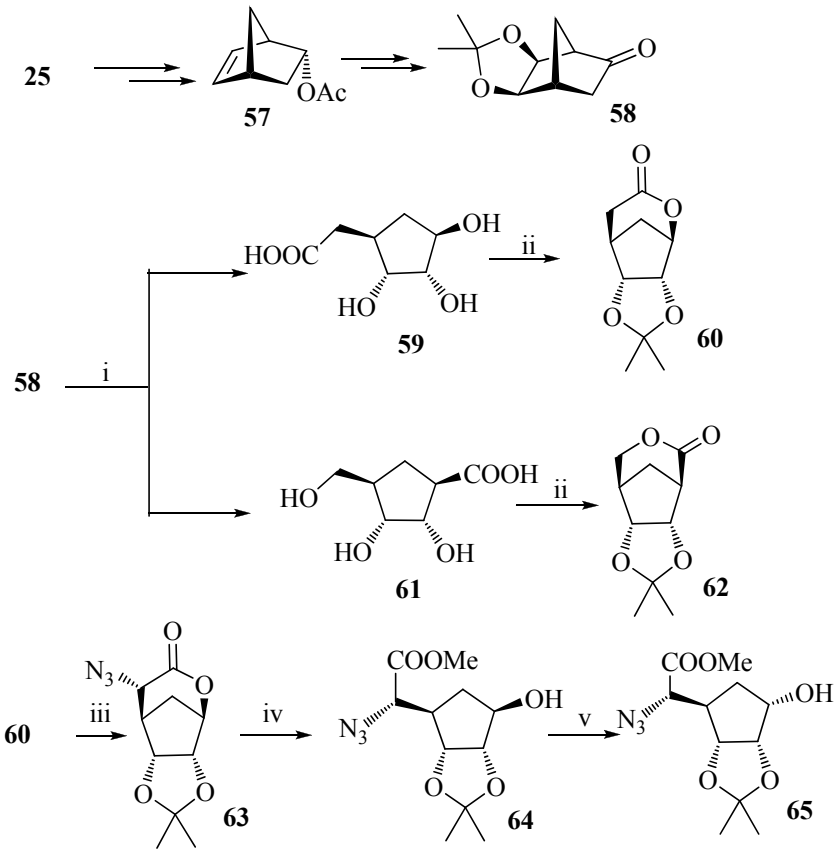
***Reagents and conditions*:** (i) NaH, $(CH_3)_3SOI$, DMSO, THF; (ii) NaOAc, DMF, 140 °C or CsOAc, DMF, 80 °C; (iii) (a). Amberlite IR-120, CH_3CN, H_2O, 50 °C; (b). Ac_2O, Py, DMAP, CH_2Cl_2; (c). MeOH, NaOMe; (iv) $Cp_2Ti(CH_3)_2$, $PhCH_3$, 60-70 °C; (v) oxone, acetone, 18-crown-6, $NaHCO_3$, H_2O, CH_2Cl_2 or *m*-CPBA, PhH, reflux; (vi) CH_2Br_2, *n*-BuLi, THF, -80 °C to rt; (vii) CsOAc, DMF, 90 °C.

(f) Synthesis of a Carbocycle Analogue to the Sugar Portion of Polyoxins (Only D-Enantiomers are shown)

Griengl and co-workers also described the synthesis of the carbocyclic analogue of the sugar portion of the antibiotics nikkomycins and polyoxins.[43] The enantiomerically enriched starting material norborn-5-en-2-yl acetate (**57**) was easily obtained from racemic (±)-**25**, and the key step was the Baeyer-Villiger oxidation of **58**. When the oxidation step was carried out in neutral or alkaline media, a mixture of lactones **60** and **62** were formed, but the undesired **62** was dominant. In acidic media, the percentage of **60** could be raised to 81% although the acetal moiety was cleaved and the products were a mixture of acids **59** and **61**. After acetalization and lactonization, the azido functionality

was introduced in **60** and opened to hydroxy ester **64**, which through an oxidation-reduction sequence gave the desired carbasugar derivative **65** (Scheme 8).

Scheme 8



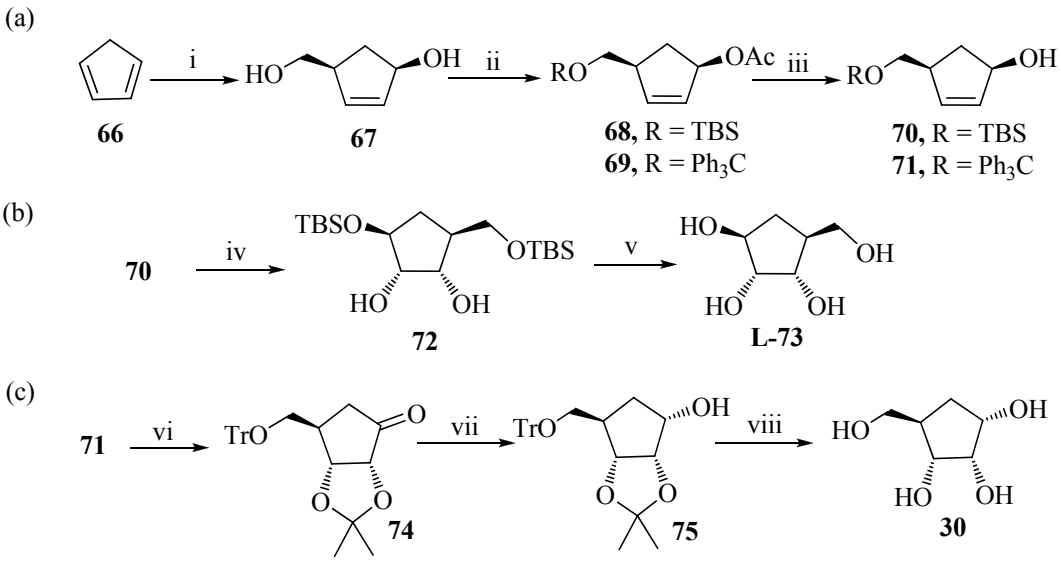
***Reagents and conditions*:** (i) *m*-CPBA, H_2O, 80 °C; (ii) acetone, conc. HCl, then Et_3N, ClC(O)OEt, 81% **61**, 19% **63**; (iii) KHMDS, 2,4,6-triisopropylbenzenesulphonyl azide, then HOAc, 79%; (iv) NaOMe, MeOH, 0 °C, 88%; (v) PCC, EtOAc, 80 °C, then $NaBH_4$, MeOH, 76%.

(ii) From Cyclopentadiene and Derivatives: Cyclopentadiene has also been a valuable starting material for the preparation of 4a-carbafuranoses and derivatives. It is a low cost compound with the required carbocyclic structure. On the other hand, as a drawback, its transformation to optically pure compounds requires the use of classical resolution processes or asymmetric bond-forming reactions.

(a) Synthesis of 4a-Carba-β-L-ribofuranose (L-73) and 4a-Carba-α-D-ribofuranose (30) by Roberts's Group

In 1992, Roberts and co-workers[44] reported a novel synthesis of 4a-carba-α-D-ribofuranose (**30**) in high optical purity. They used an enzyme-catalyzed esterification reaction to obtain a suitable chiral synthon from cyclopentadiene **66**. Treatment of **66** with formaldehyde in formic acid (Prins reaction) furnished racemic diol (±)-**67** in which the primary hydroxyl group was later protected as a trityl or *tert*-butyldimethylsilyl (TBS) ether and the secondary hydroxyl group was protected as an acetate. From these compounds, cyclopentenols (+)-**68** and (-)-**69** were obtained using an enzyme-catalyzed reaction. Furthermore, the alcohol (+)-**70** was converted into a bis *tert*-butyldimethylsilyl derivative and oxidized with osmium tetraoxide to give diol **72**. Deprotection, acetylation, and saponification gave 4a-carba-β-L-ribofuranose (L-**73**). In an analogues way, tritylated alcohol (-)-**71** was acetylated, bis-hydroxylated, and converted into ketone **74**. Reduction of the keto group permitted the overall inversion at C_1 to **75**, which, after deprotection, led to the desired 4a-carba- α-D-ribofuranose (D-**30**) (Scheme 9).

Scheme 9



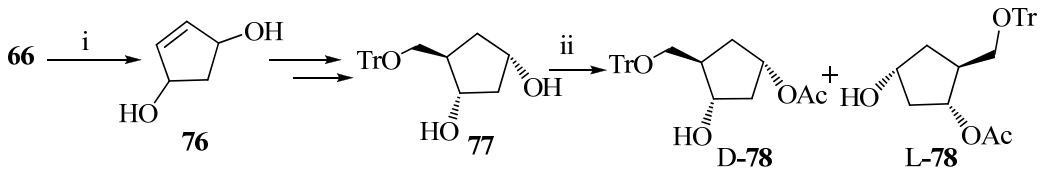
***Reagents and conditions*:** (i) HCHO, HCOOH; (ii) (a). TBSCl or TrCl; (b). Ac_2O; (iii) *Pseudomonas fluorescens* lipase, (+)-**70** (42%, >95% *ee*), (-)-**71** (46%, 95.5% *ee*); (iv) (a). TBSCl; (b) OsO_4, NMO; (v) (a). TBAF; (b). Ac_2O, 99%; (c). NaOMe, 90%; (vi) (a). Ac_2O; (b). OsO_4,

NMO; (c). 2,2- dimethoxypropane; (d). NaOMe; (e) PCC; (vii) $NaBH_4$; (viii) (a). aq. AcOH; (b). Amberlyst (H^+).

(b) Synthesis of 2-Deoxy-4a-carba-α-D-ribofuranose Derivative 78 by Moser's Group

Moser and co-workers[45] developed a related enzyme catalyzed acetylation for the synthesis of a carbocyclic 2-deoxyribose derivative. The trityl-protected precursor (±)-**77**, readily available from cyclopentadiene *via* 1,4-addition of singlet oxygen, hydroformylation, reduction, and tritylation, was subjected to enzymatic acyl transfer with *Chromobacterium viscosum* lipase, to give 2-deoxy-α-D-ribocarbafuranose derivative **78**, with high enantioselectivity (Scheme 10).

Scheme 10

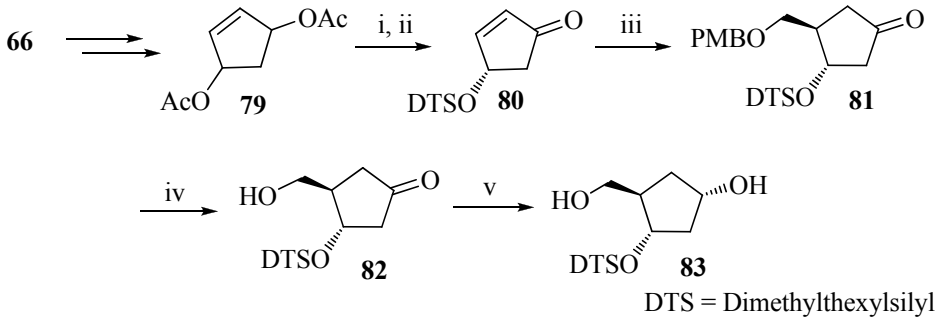


***Reagents and conditions*:** (i) *hv*, rose bengal, thiourea, MeOH, 59%; (ii) CVL, 49% for D-**78**, 26% for L-**78**.

(c) Synthesis of 2-Deoxy-4a-carba-α-D-ribofuranose Derivative 80 by Borthwick's Group

Borthwick and co-workers[46] used chiral cyclopentenone **80**, easily prepared in enantiomerically pure from cyclopentadiene **86**, as the starting material. 1,4- Addition of a one-carbon fragment to **80**, followed by stereoselective reduction with triacetoxyborohydride paved the way to the 2-deoxyribocarbafuranose derivative **83** (Scheme 11).

Scheme 11

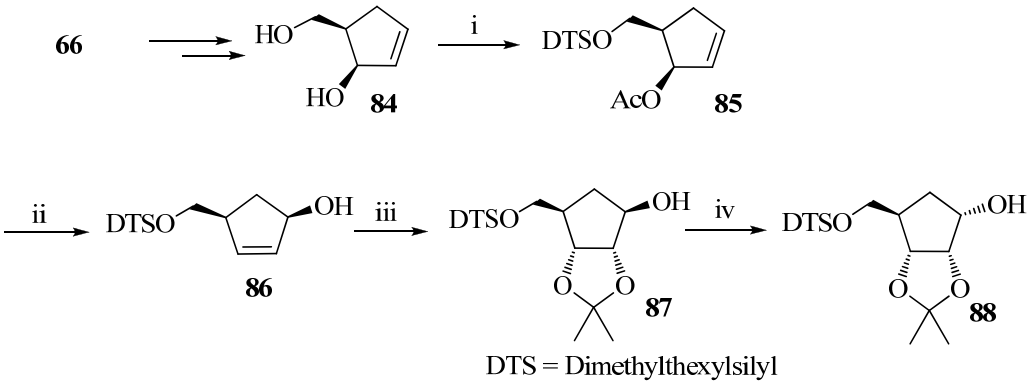


***Reagents and conditions*:** (i) (a). Baker's yeast; (b). MnO_2, petroleum ether-dioxane; (c). *wheat germ* lipase, 24%, three steps; (ii) DTSCl, Et_3N, DMAP; (iii) (2-Th)$(PMBOCH_2)CuCNLi_2$, TMSCl, THF, -78 °C, 69%; (iv) DDQ, CH_2Cl_2, 86%; (v) $NaBH(OAc)_3$, EtOAc, reflux, 75%.

(d) Synthesis of 4a-Carba-α-D-ribofuranose Derivative 88 by Shuto's Group

Shuto, Matsuda, and co-workers[47] have developed a related approach also starting from cyclopentadiene **66**. They used an optically active diol, **84**, prepared by resolution with *Pseudomonas fluorescens* lipase, as starting material. Protection of its hydroxyl groups led to **85**, which was subjected to an allylic rearrangement to generate compound **86**. Stereoselective *cis*-hydroxylation of the latter, followed by protection and deprotection steps, furnished alcohol **87**. Finally, an oxidation-reduction sequence at C_1-OH in **87** yielded the sought 4a-carba-α-D-ribofuranose derivative **88** (Scheme 12).

Scheme 12

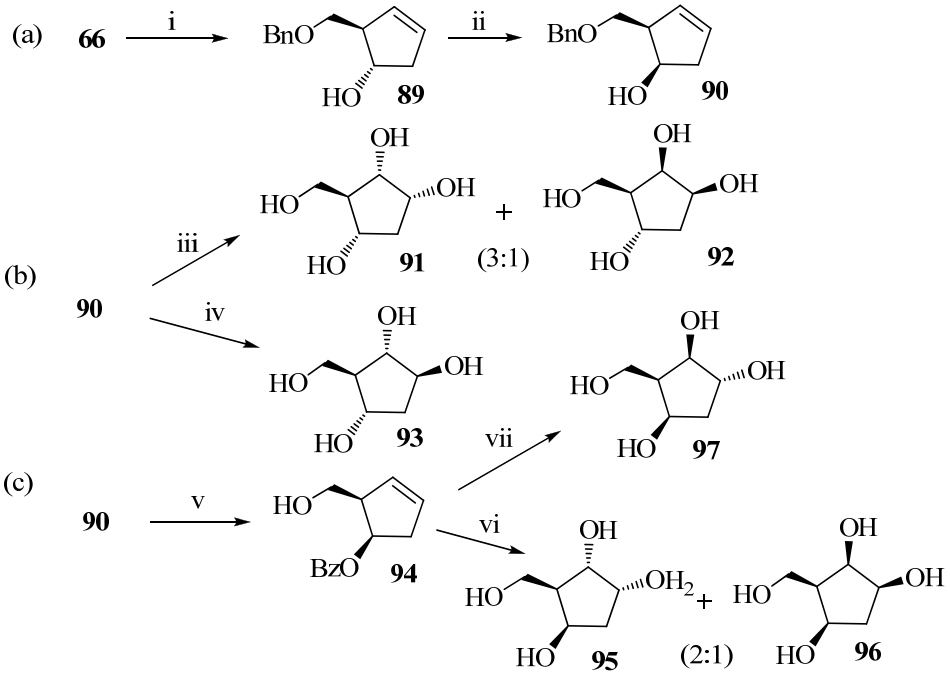


***Reagents and conditions*:** (i) (a). DTSCl, Et_3N, DMAP; (b). Ac_2O, Et_3N, 69%; (ii) $PdCl_2(MeCN)_2$, *p*-benzoquinone, 60%; (iii) (a). OsO_4, NMO, 55%; (b). 2,2-dimethoxypropane, TsOH; (c). K_2CO_3, MeOH; (iv) (a). PDC, 92%; (b). $NaBH_4$, 88%.

(e) Synthesis of Carbafuranose Derivatives by Jorgensen's Group

Jorgensen and co-workers[48] have described the preparation of six optically active carbocyclic furanose derivatives from cyclopentadiene (**66**) and using an enantioselective hydroboration reaction as the key step, by which the first two stereogenic centers were introduced. The newly formed stereocenters are used to guide the formation of the remaining stereogenic centers in the carbocyclic skeleton. Cyclopentadiene (**66**) was deprotonated and treated with benzyl chloromethyl ether and then hydroborated with diisopinocamphenylborane.[49] Oxidative workup of the organoborane gave alcohol **89** (94% *ee*), which was then converted into alcohol **90** by inversion of the secondary hydroxyl by the Mitsunobu protocol. The six carbasugar analogues **91**-**93** and **95**-**97** were then prepared from these precursors by either osmylation or epoxidation/opening sequences (Scheme 13).

Scheme 13



***Reagents and conditions*:** (i) (a). $BnOCH_2Cl$, NaH; (b). Ipc_2BH; (c). H_2O_2, 94% *ee*; (ii) (a). Ph_3P, BzOH, DEAD; (b). NaOH, MeOH; (iii) (a). NaH, BnBr, 95%; (b). OsO_4, NMO, 70%; H_2, Pd/C, 59-62%; (iv) (a). *t*-BuOOH, $Mo(CO)_6$, 95%; (b). $HClO_4$, 95%; H_2, Pd/C, quant; (v) (a). PPh_3, BzOH, DEAD, 85%; (b). $FeCl_3$, 88%; (vi) (a). NaOH, 99%; (b). $Me_2C(OMe)_2$, 99%; (c). OsO_4, NMO, 94%; (vii) (a). *t*-BuOOH, $Mo(CO)_6$, 96%; (b). $HClO_4$, 94%; H_2, Pd/C, quant.

Importance and synthesis of carba analogues of AG complex

Besides the sweetness of pseudo-sugars, a pseudo-sugar may have a biological activity, owing to its structural close resemblance to a true sugar. They are stable to enzymatic hydrolysis in biological systemes, and often display a range of biological activities, particularly as glycosidase inhibitors.[50]

There has been increasing interest in the synthesis of "glycoconjugates" containing carbasugar residues for use as potential therapeutic agents. It is believed that such species will be more efficacious than their glycoside counterparts due to increased acidic and metabolic stability. The approach has already been validated in that many carbasugar-containing nucleoside analogues have been demonstrated to possess antiviral activity. Given that oligosaccharide analogues containing carbasugar residues have been shown to be competent glycosyl tranferases, we postulated that arabinosyltransferase inhibitors containing carbsugar residues would be attractive synthetic targets.[52]

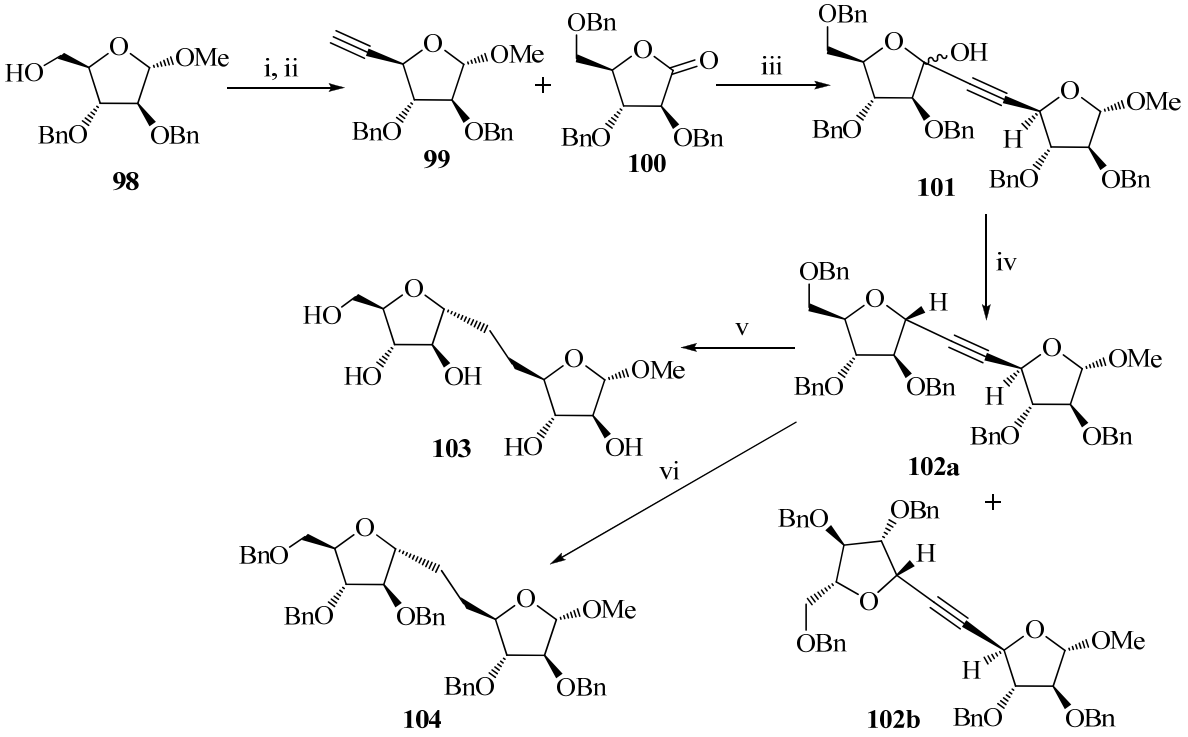
Because of this importance we would like to discuss the earlier methods for syntheis of carba disaccharides.

Past work

(a) Using acetylenic intermediate[51]

Wightman et al. synthesised the *C*-glycoside related to motif C. Swern oxidation of **98**, followed by treatment of the aldehyde with CBr_4–Ph_3P gave the dibromoalkene, which on treatment with *n*-BuLi gave alkyne **99** (75%). Reaction of the lithio-derivative of **99** with lactone **100** gave hemiacetal **101** (87%), which on treatment with Et_3SiH and $BF_3{\cdot}Et_2O$ gave **102a** (66%) and **102b** (20%), separable by chromatography. Catalytic hydrogenation of **102a** gave the *C*-saccharide **103** (Scheme 14).

Scheme 14

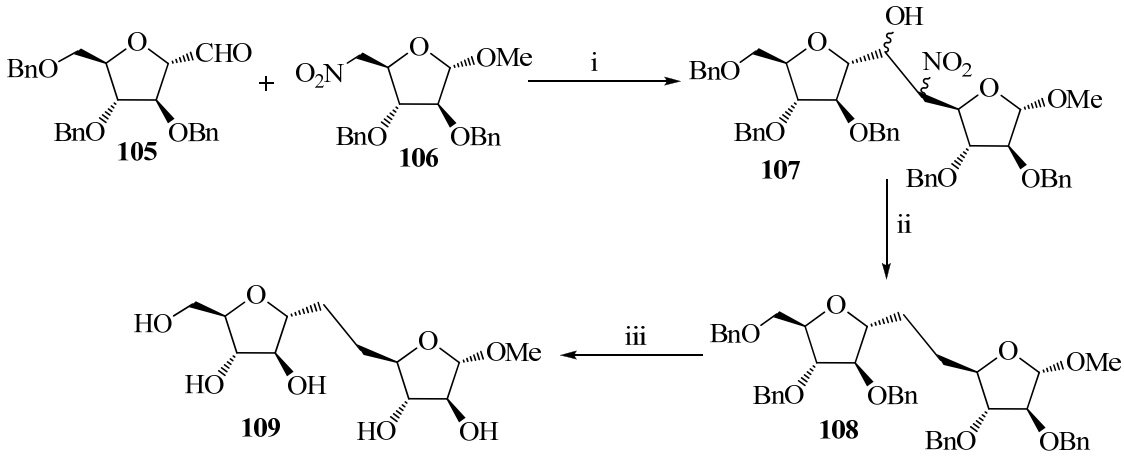


***Reagents and conditions*:** (i) (a). DMSO, $(COCl)_2$, DCM, –78 °C, then Et_3N; (b). CBr_4, Ph_3P, DCM, 0 °C; (ii) *n*-BuLi, THF, –78 to 0 °C; (iii) *n*-BuLi, THF, –78 °C, then **100**; (iv) $BF_3{\cdot}Et_2O$, Et_3SiH, DCM, –78 °C; (v) $Pd(OH)_2/C$, H_2 (1 atm), MeOH; (vi) dipotassium azodicarboxylate, MeOH–pyridine, then HOAc.

(b) Using nitro-aldol condensation[52]

The coupling reaction between **105** and **106** occured in the presence of catalytic KF in CH_3CN to give a diastereomeric mixture of **107** which was subjected to three successive steps, i.e. dehydration, selective reduction of conjugated olefin and denitration with *n*-Bu_3SnH to give the penta-*O*-benzyl *C*-disaccharide **108** and hydrogenolysis of **108** in presence of $Pd(OH)_2$ at normal temperature and pressure gave the *C*-disaccharide **109** (Scheme 15).

Scheme 15

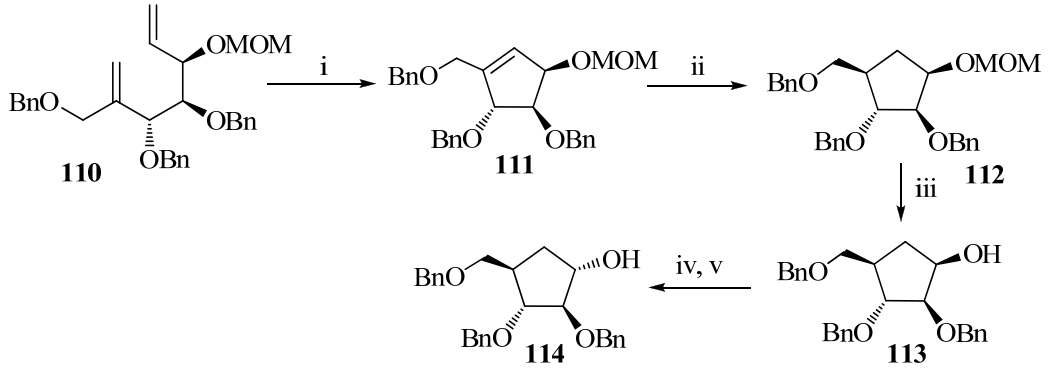


***Reagents and conditions*:** (i) KF, 18-C-6, MeCN, rt, 3.5 h (48%); (ii) (a). Ac_2O, Py, $CHCl_3$, 12 h; (b). $NaBH_4$, EtOH, CH_2Cl_2, rt, 2.5 h; (c). Bu_3SnH, AIBN, $C_6H_5CH_3$, Δ, 1 h (44% in three steps); (iii) $Pd(OH)_2$, H_2, rt, 1 atm, 24 h (74%).

(c) Using olefin metathesis and alkylation condition[53]

Diene **110** with olefin metathesis conditions gave **111** and subsequently stereoselectivly reduced by hydrogenation with Wilkinson's catalyst under an atmosphere of hydrogen to yield **112**. The removal of the MOM ether in **112** with trace hydrochloric acid in methanol gave alcohol **113**.

Scheme 16

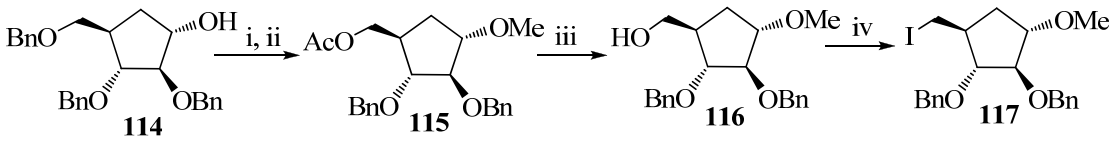


***Reagents and Conditions*:** (i) Grubb's Catalyst (10 mol%), CH_2Cl_2, 40 °C, 84%; (ii) $(Ph_3P)_3RhCl$, (30 mol%), H_2, toluene, rt, 88%; (iii) trace conc. HCl, CH_3OH, rt, 95%; (iv) DEAD, PPh_3, *p*-$O_2NC_6H_4CO_2H$, toluene, rt; (v) $NaOCH_3$, CH_3OH, rt, 84%.

The hydroxyl group in **113** was reacted with *p*-nitrobenzoic acid, triphenylphosphine, and DEAD, followed by deacylation with sodium methoxide in methanol provided the C_1 inverted alcohol **114** in 84% yield (two steps) (Scheme 16).

In order to prepare the other building block, **114** was subjected to methylation conditions and selectively deprotected at O-5 by exposure to acetolysis conditions of $AcOH/H_2SO_4/Ac_2O$. The reaction provided the 5-*O*-acetyl carbasugar **115** and deprotected with sodium methoxide in methanol to provide 5-OH compound **116**. The free hydroxyl group in **116** was transformed into the iodide **117** by exposure to PPh_3 and I_2 in 91% yield (Scheme 17).

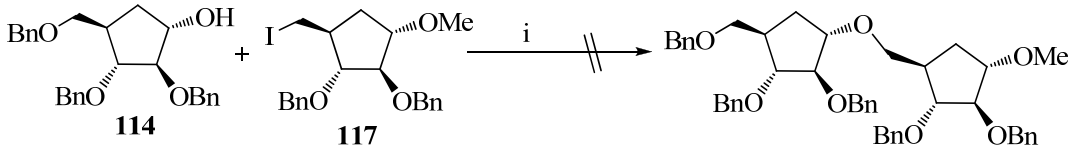
Scheme 17



***Reagents and Conditions*:** (i) CH_3I, NaH, THF, rt , 93%; (ii) AcOH, Ac_2O, H_2SO_4, rt, 91%; (iii) $NaOCH_3$, CH_3OH, CH_2Cl_2, rt, 99%; (iv) I_2, PPh_3, THF, rt, 87%.

114 was dissolved in a THF/DMF (1:1) and NaH was added at 0 ^oC, to this solution was added a solution of **117** dissolved in THF. Reaction only resulted in massive decomposition of the electrophile and recovered alcohol **114** (Scheme 18).

Scheme 18



***Reagents and Conditions*:** (i) NaH, DMF:THF (1:1), 0 °C.

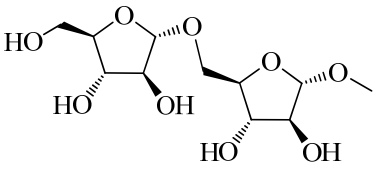
Present Work

The mycolic arabinogalactan (AG) complex present on the cell wall surface of *Mycobacterium tuberculosis* has unique structural features unknown in actinomycetes. The furanoside rings of AG complex are conformationally more mobile (than pyranosides) and are largely linked through primary hydroxyl groups. These characteristics enable the crowded AG complex to adopt a structure in which mycolic acids are closely arranged in parallel arrays.[54] The AG complex is critical for the survival of *M. tuberculosis*. The hydrophobic AG complex acts as a strong barrier for the passage of antibiotics into the cell and therefore, plays an important role in developing the resistance of mycobacteria to many antibiotics. The drug ethambutol blocks the biosynthetic pathway of arabinose. The inhibition of biosynthetic pathway, involved in displacement of *M. tuberculosis* cells, is considered as an attractive strategy for drug development against *M. tuberculosis*. The oligosaccharides present on various motifs of AG complex are structurally elucidated and their synthesis has dominated the area in recent times.

There has been increasing interest in the synthesis of "glycoconjugates" containing carbasugar residues for use as potential therapeutic agents. It is believed that such species will be more efficacious than their glycoside counterparts due to increased acidic and metabolic stability. The approach has already been validated in that many carbasugar-containing nucleoside analogues have been demonstrated to possess antiviral activity.[55] Given that oligosaccharide analogues containing carbasugar residues have been shown to be competent glycosyltranferases, we postulated that arabinosyltransferase inhibitors containing carbasugar residues would be attractive synthetic targets.[56]

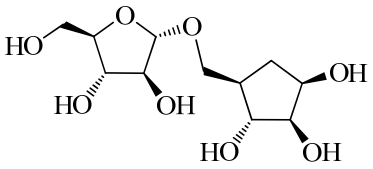
The logical extension of work was to develop a synthetic strategy to assemble carba analogue of disaccharide of motif C. The synthetic target of interest is 5-O-(4a-carba-β-D-arabinofuranosyl)-α-D-arabinofuranoside (**118**) as shown in Figure 7.

Figure 7: Motif C of *M. tuberculosis* and its carba analogue



Motif C

3

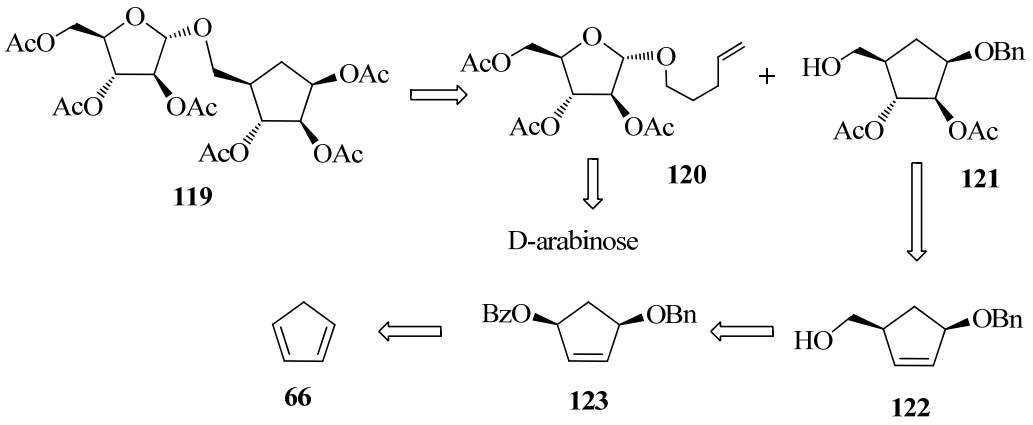


5-O-(4a-carba-β -D-arabinofuranosyl)-
α -D-arabinofuranoside

118

As depicted in the retrosynthetic plan (Scheme 19), the acylated disaccharide **119** can be obtained by *O*-glycosidatoin between glycosyl donor **120** and glycosyl acceptor **121** by using Fraser Reid glycosidation protocol. The pentenyl glycoside donor **120** could be obtained from D-arabinose. The carba sugar derivative **121** can be obtained from **122** through *m*-CPBA epoxidation followed by acid catalysed regioselective epoxide opening.

Scheme 19: Retrosynthetic plan

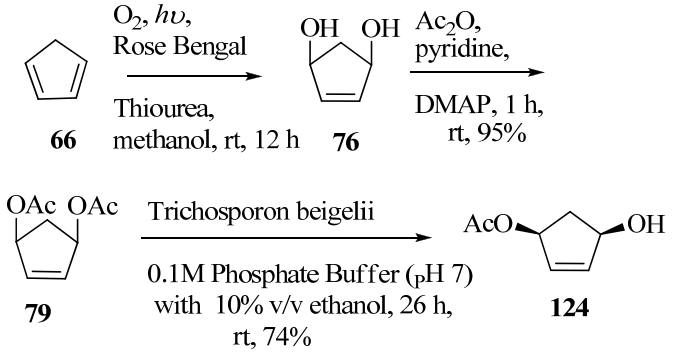


The synthesis of homoallylic alcohol **122** was planned from **123** using a Pd(0) mediated allylic alkylation with phenyl sulfonyl nitromethane. Cyclopentadiene **66** was chosen as starting point for the synthesis of **123** through enzymatic desymmetrization and protecting group manipulations.

The synthetic sequences started with cyclopentadiene (**66**) to obtain known *cis*-2-cyclopentene-1,4-diol (**76**) as reported by Kaneko et al.[57] Cyclopentadiene (**66**) was treated with molecular oxygen in the presence of thiourea and Rose Bengal in methanol

and irradiated with a 450 W high pressure mercury immersion lamp to give *cis*-2-cyclopentene-1,4-diol (**76**) in quantitative yield. Diol **76** was acetylated with acetic anhydride in neat pyridine using catalytic amount of DMAP to give *cis*-2-cyclopentene-1,4-diacetate (**79**). The *meso*-di-acetate **79** was enzymatically hydrolysed with *Trichosporone beigelii* (NCIM 3326) in 0.1M sodium phosphate buffer (pH 7) with 10% v/v ethanol to give enantiomerically pure 4-*R*-Hydroxy cyclopent-2-en-1-*S*-acetate (**124**) (Scheme 20).[58] The assigned structure of **124** was confirmed by its spectral and analytical data.

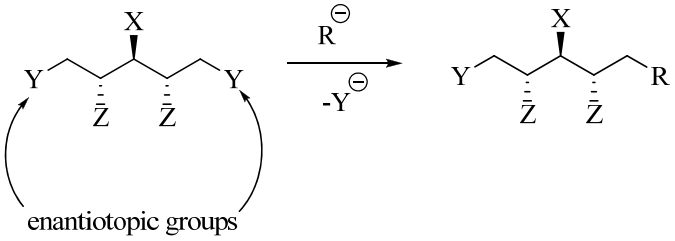
Scheme 20: Enzymatic hydrolysis of *meso*-diacetate



A Short account of desymmetrization

The modification of a molecule which results in the loss of one or more symmetry elements, such as those which preclude chirality (mirror plane, centre of inversion, rotation-reflection axis), as in the conversion of a prochiral molecular entity into a chiral one is referred to as ***desymmetrization****.*

Scheme 21*: *Desymmetrization of a meso compound



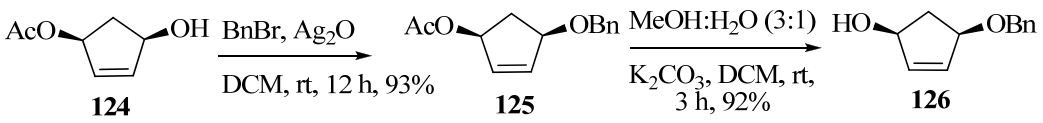
A Short account of Lipases

*A **lipase** is a water-soluble enzyme that catalyzes the hydrolysis of ester in water–insoluble, lipid substrates. Lipases thus comprise a subclass of the esterases. Lipases are ubiquitous throughout living organisms, and genes encoding lipases are even present in certain viruses. Most lipases act a specific position on the glycerol backbone of a lipid substrate. In the example of human pancreatic lipase (HPL), which is the main enzyme responsible for breaking down fats in the human digestive system, a lipase converts triglyceride substrates found in oils from food to monoglycerides and free fatty acids. Myriad of other lipase activities exist in nature, especially when the phospholipases and sphingomyelinases are considered. While a diverse array of genetically distinct lipase enzymes are found in nature, and represent several types of protein folds and catalytic mechanisms, most are built on an alpha/beta hydrolase fold and employ a chymotrypsin-like hydrolysis mechanism involving a serine nucleophile, an acid residue (usually aspartic acid), and a histidine. Some lipases work within the interior spaces of living cells to degrade lipids. In the example of lysosomal lipase, the enzyme is confined within an organelle called the lysosome. Other lipase enzymes, such as pancreatic lipases, are found in the spaces outside the cells and have roles in the metabolism, absorption and transport of lipids throughout the body. As biological membranes are integral to living cells and are largely composed of phospholipids, lipases play important roles in cell biology. Furthermore, lipases are involved in diverse biological processes ranging from routine metabolism of dietary triglycerides to cell signaling and inflammation. The main lipases in the human digestive system are human pancreatic lipase (HPL) and pancreatic lipase related protein 2 (PLRP2), which are secreted by the pancreas. Humans also have several other related enzymes, including hepatic lipase (HL), endothelial lipase, and lipoprotein lipase.*

Once the enzymatic hydrolysis of *meso*-diacetate **79** was successful, we then proceeded towards the synthesis of glycosyl acceptor **121**. The hydroxyl acetate **124** was treated with BnBr and Ag_2O in dry CH_2Cl_2 to afford benzylic derivative **125** (Scheme 22). The ^{1}H NMR spectrum and ^{13}C NMR were in full agreement with assigned structure.

In ^{1}H NMR spectrum the benzylic protons were observed at δ 4.52-4.59 as quartet and in ^{13}C NMR the carbonyl carbon was observed at δ 170.5. The benzylic derivative **125** was subjected to deacetylation by using K_2CO_3 in Methanol–H_2O (3:1) to furnish **126**. In the ^{1}H NMR spectrum of **126**, the olefinic protons were observed at δ 6.02 and in the ^{13}C NMR spectrum, the benzylic carbon resonated at δ 70.8.

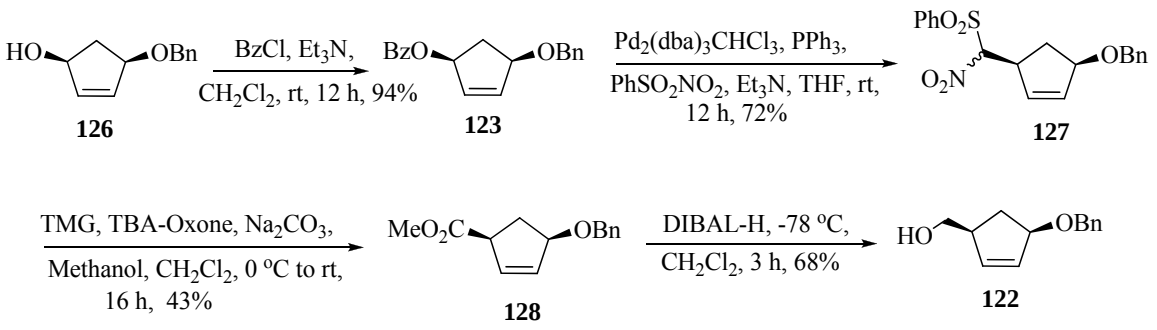
Scheme 22



124 **125** **126**

The free hydroxyl group in **126** was protected as its benzoate by using benzoyl chloride in the presence of Et_3N in CH_2Cl_2 to afford **123** in 94% yield (Scheme 23). The introduction of hydroxymethyl functionality at the benzoate position was accomplished in a highly stereospecific manner by using palladium (0) catalyzed allylic alkylation.[59] The Pd(0)-catalyzed alkylation with the anion of phenylsulfonyl-(nitro)methane introduces a one-carbon side chain which can be converted into the hydroxymethyl group. Thus the benzoate **123** was subjected to a palladium (0) catalyzed cross-coupling reaction with a phenylsulfonyl nitromethane anion to afford **127** as a 1:1 diastereomeric mixture almost quantitatively. The NMR analysis and other analytical data were in full agreement with the assigned structure. Further, in the IR spectrum of compound **127**, the characteristic absorption for NO_2 group was observed at 1560 and 1345 cm^{-1}. Treatment of **127** with tetramethylguanidine salt and tetrabutyl ammonium oxone (TBA-Oxone)[60] in methanol/CH_2Cl_2 buffered with sodium carbonate gave the methyl ester **128** in 43% yield. The structure was fully confirmed by ^{1}H and ^{13}C NMR analyses. In the ^{1}H NMR spectrum, the methyl group resonated at δ 3.71 ppm and in ^{13}C NMR analysis showed signal corresponding to carbonyl carbon at δ 173.5. The methyl ester **128** was treated with DIBAL-H in CH_2Cl_2 at –78 ^{o}C to procure the hydroxymethyl derivative **122** in 68% yield. In the ^{1}H NMR spectrum, the methyl ester peak disappeared and two methylene protons were observed at δ 3.62 as a doublet. Further ^{13}C NMR spectrum showed the absence of carbonyl peak and showing a triplet carbon at δ 65.0.

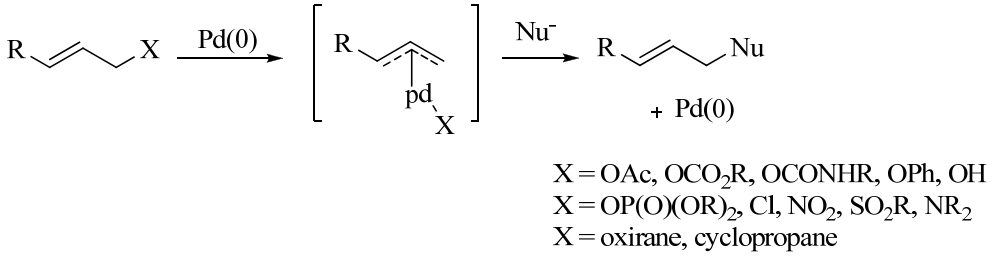
Scheme 23



A Short Account of palladium(0)-catalyzed allylic alkylation

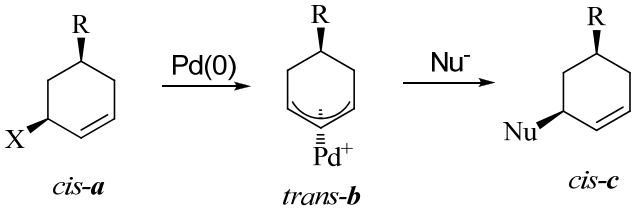
The palladium(0)-catalyzed allylic alkylation is a powerful method which has gained recognition due to its regio- and stereoselectivity and broad scope. The area is developing rapidly and has been widely used in nucleoside chemistry, both for the introduction of the heterocycle into the sugar moiety and for the introduction of the 5[1]-hydroxyl precursor group of the sugar itself. The catalytic cycle requires the initial formation of a cationic η^3-allylpalladium(II) complex, which can be attacked by nucleophiles (soft and hard) at its less hindered site. Allylic esters and carbonates have been employed mainly as substrates for the catalytic reaction, but many other types of allylic compound (embracing carbamate, oxirane, phenyl ether, alcohol, chloride, nitro, sulfone, phosphate, amine, ammonium salt, vinylcyclopropane) are known to react with Pd(0) and to form the cationic η^3-allylpalladium(II) complex (Scheme 24).

Scheme 24*: *Pd(0) catalyzed allylic alkylation



*The oxidative addition of allylic acetates to Pd(0) is reversible and must be carried out in the presence of base, but neutral conditions are required for allylic carbonates, carbamates, aryl ethers, and vinyl epoxides. The stereochemistry of the Pd-catalyzed allylation of nucleophiles has been widely studied and seems to depend on the nucleophile used. The first step is the formation of the cationic η^3-allyl palladium(II) complex, which occurs with inversion of configuration (from cis-**a** to trans-**b**).Many common soft nucleophiles (e.g., malonates, β–ketoesters, amines) then attack the cationic palladium intermediate with a second inversion of configuration, affording the final compound (from trans-**b** to cis-**c** with overall retention of configuration (Scheme 25).*

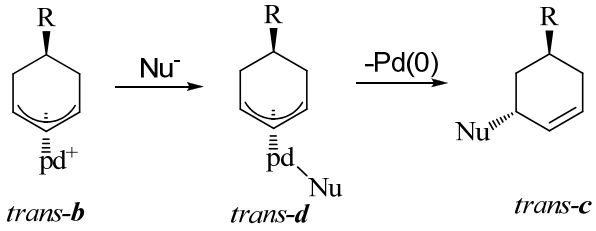
Scheme 25



*cis-**a*** *trans-**b*** *cis-**c***

*In the case of hard nucleophiles (such as organometallic derivatives of Mg, Al, Zr, Sn, and B), a transmetallation step (from trans-**b** to trans-**c)** occurs, followed by intramolecular delivery or reductive elimination with retention of configuration (from trans-**d** to trans-**c** (Scheme 26).*

Scheme 26

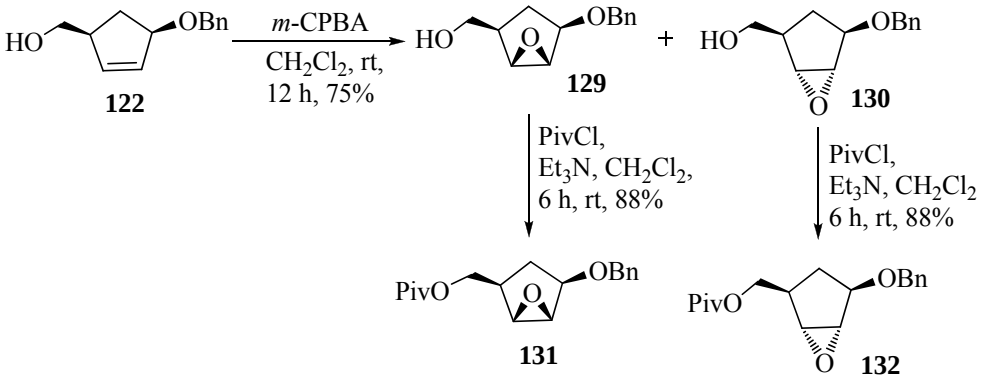


*trans-**b*** *trans-**d*** *trans-**c***

After having synthesized the hydroxymethyl derivative **122**, our next objective was to introduce the *trans* diol originating from the ring olefin of **122**. In that direction,

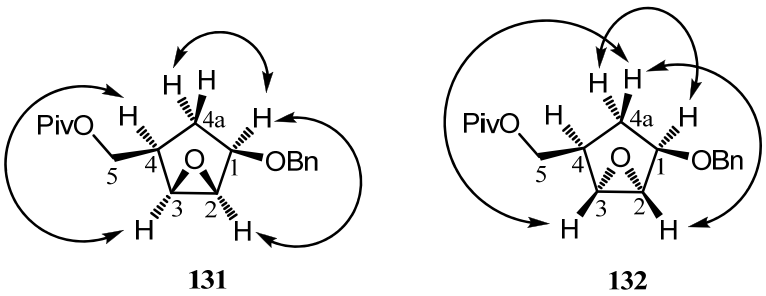
treatment of **122** with *m*-CPBA gave a diastereomeric mixture of epoxides (α- and β-epoxides) in 3:7 ratio, which were separated by silica gel column chromatography (Scheme 27). The NMR analysis and other analytical data were in full agreement with the assigned structure of epoxides **129** and **130**.

Scheme 27: Synthesis of epoxides



In ^{1}H NMR spectrum of **129** the epoxide protons were observed as a doublet at δ 3.49 and the same for **130** was observed at δ 3.53 as a singlet. To determine the relative configuration of epoxides **129** and **130**, both the epoxides were independently treated with PivCl and Et_3N in CH_2Cl_2 to furnish the corresponding pivolate ester derivatives **131** and **132**. The assigned structures of pivolate derivatives **131** and **132** were ascertained by its spectral and analytical data. Further, COSY/NOESY experiments were carried out on epoxides **131** & **132** and the relative stereochemistry was assigned based on observed spatial interactions (Figure 8).

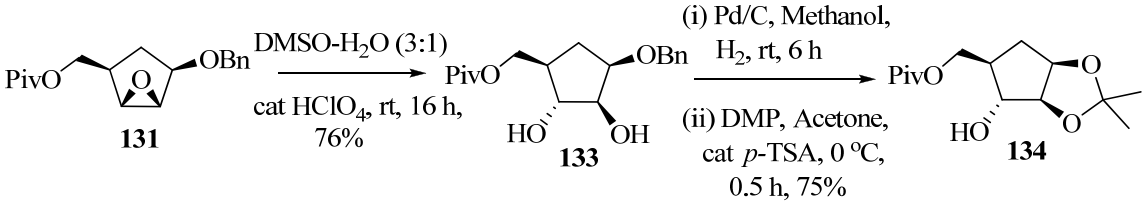
Figure 8: NOESY correlations



In the NOESY spectrum of **131**, the observed spatial interactions between H-C(1) and H-C(2), H-C(1) and H_α-C(4a), H-C(3) and H-C(4) established the assigned structure. In similar lines, the observed correlations for **132**, i e. H-C(1) and H_α-C(4a), H-C(2) and H_β-C(4a), H-C(3) and H_β-C(4a) supported the assigned structure.

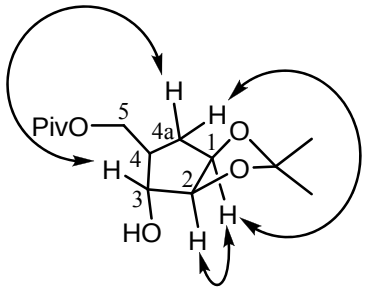
We proceeded with β-epoxide **131** for regioselctive epoxide opening.[61] Epoxide **131** was treated with catalytic amount of $HClO_4$ in DMSO-H_2O (3:1) solvent mixture to afford the diol **133** quantitatively. The structure of **133** was fully confirmed by ^1H and ^{13}C NMR spectral analysis. Further, the IR spectrum of **133** revealed the presence of –OH group with absorption at 3432 cm^{-1}. To confirm whether the epoxide opening took place at C2 or C3 position, **133** was subjected to debenzylation using Pd/C (catalytic amount) in methanol under H_2 pressure to give intermediate triol (Scheme 28). The *syn*-diol functionality of triol was protected as its acetonide using 2,2-dimethoxypropane in acetone with catalytic amount of *p*-TSA to give acetonide **134**. In the ^1H NMR spectrum, the two isopropylidene methyl groups were observed at δ 1.29 and 1.48 as two distinct singlets. Further, in ^{13}C NMR spectrum, the quaternary isopropylidene carbon was observed at δ 111.8. Rest of the spectral and analytical data are in well supportive with the assigned structure.

Scheme 28



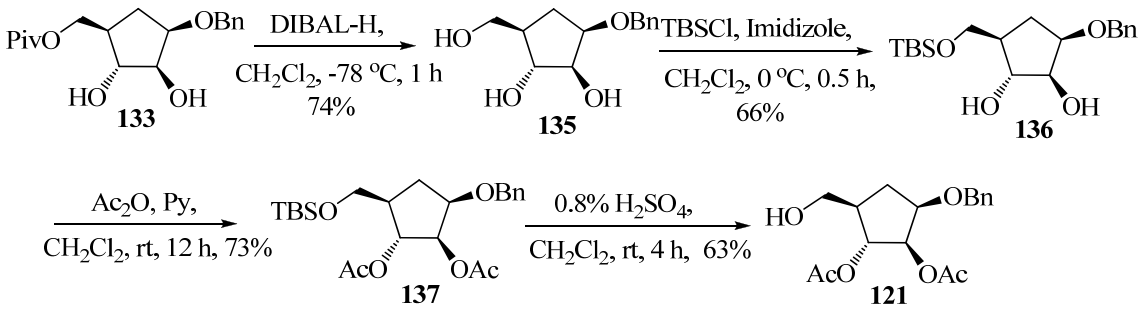
The stereochemistry of **134** was unambiguously confirmed by its COSY/NOESY spectral analysis (Figure 9). The observed spatial interaction between H-C(1) and H-C(2), H-C(1) and H_α-C(4a), H_β-C(3) and H_β-C(4a) established the assigned structure of **134**. Rest of the correlations are in well accordance with the given structure of **134**, which also unambiguously confirms the stereochemistry of epoxide **131**.

Figure 9: NOESY correlations for **134**



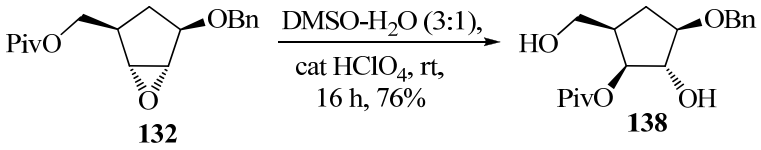
Once we are through with the stereochemistry of the **133**, we proceeded towards the target **121**. The pivolate **133** was subjected to DIBAL-H reduction in CH_2Cl_2 at −78 ^oC to give triol **135** in 74% yield. The structure **135** was confirmed by its ^1H and ^{13}C NMR spectral analysis. Further, in the IR spectra the characteristic –OH stretch was observed at 3369 cm^{-1}. Primary hydroxyl functionality of triol **135** was protected as its TBS ether using TBS-Cl and imidazole in CH_2Cl_2 to obtain diol **136** quantitatively (Scheme 29). In the ^1H NMR spectrum, the TBS group was observed at δ 0.06 (6H) as a doublet and δ 0.90 (9H) as a singlet. Further, in the ^{13}C NMR spectrum, the *t*-butyl group was observed at δ 25.9 and the two methyl groups attached to silicon resonated at δ –5.5. Rest of the spectral and analytical data are in well accordance with the structure **136**. The diol **136** was acetylated using Ac_2O and pyridine in CH_2Cl_2 to procure the diacetate **137**. In the ^1H NMR spectrum the two methyl groups of acetate were observed at δ 2.00 and δ 2.06 as singlets. Further, in the ^{13}C NMR spectrum the carbonyl carbons resonated at δ 170.0 and 170.3. Diacetate **137** was subjected to TBS deprotection using catalytic 0.8% H_2SO_4 to afford the glycosyl acceptor **121** in 63% yield. Spectral and analytical data for **121** are well supportive to the assigned structure.

Scheme 29: Preparation of glycosyl acceptor



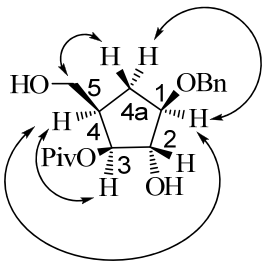
In similar lines, the α-epoxide **132** was opened with the same reaction conditions as described for epoxide **131**. Surprisingly, it gave the epoxide opened product with pivoloyl group migration from primary to secondary hydroxyl group. This was confirmed by extensive spectral studies of **138** (Scheme 30).

Scheme 30



COSY/NOESY experiments were performed on diol **138** and the observed correlations were shown in figure10.

Figure 10: NOESY correlations for **138**

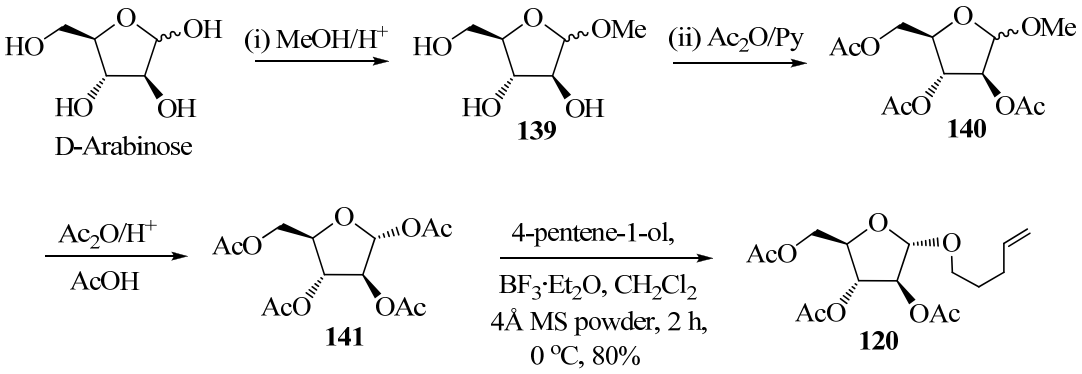


The observed spatial interaction between H-C(1) and H-C(4), H-C(1) and H_α-C(4a), H-C(3) and H-C(4), H_β-C(4a) and H-C(5) established the assigned structure of

138. Rest of the correlations are in well accordance with the structure**,** which unambiguously confirms the stereochemistry of epoxide **138**.

Our next endeavor was to synthesize the *n*-pentenyl glycosyl donor **120** starting from D-arabinose. Methyl D-arabinofuranoside (**139**) was prepared from D-arabinose using methanolic HCl at room temperature, which was subsequently treated with Ac_2O, pyridine to afford methyl 2,3,5-tri-*O*-acetyl-D-arabinofuranoside (**140**). The per-*O*-acetyl D-arabinose (**141**) was prepared from **140** using $Ac_2O/AcOH/H_2SO_4$ in quantitative yield. Following Fischer's glycosidation of **141** with 4-penten-1-ol with a catalytic amount of $BF_3{\cdot}OEt_2$ and 4Å MS powder in CH_2Cl_2 at room temperature furnished pentenyl glycosyl donor **120** (Scheme 31). The ^1H and ^{13}C NMR spectral analysis are in full agreement with the structure **120.** In the ^1H NMR the olefinic protons are resonated at δ 5.82 and δ 5.08. Further, in the ^{13}C NMR spectrum the carbonyl carbons resonated at δ 169.3, 169.8, and 170.2.

Scheme 31: Preparation of glycosyl donor

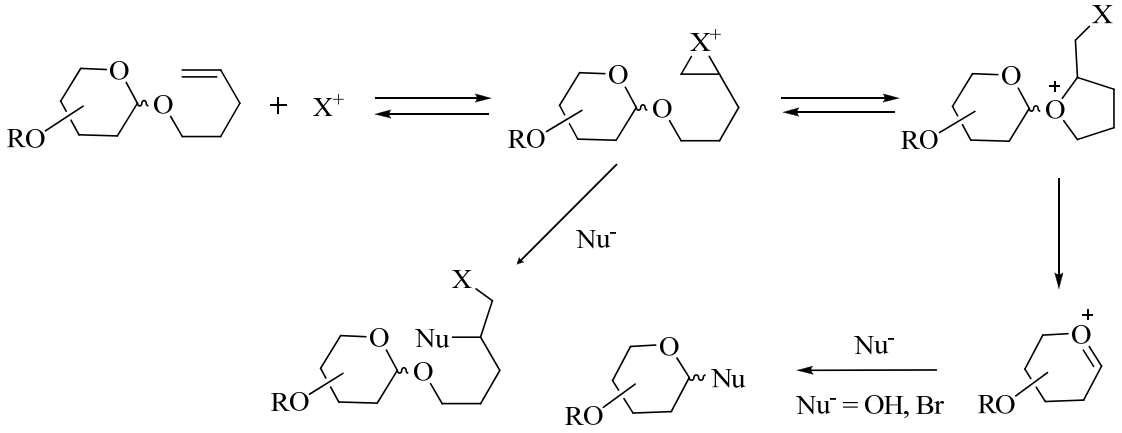


Once we have both glycosyl donor (**120**) and glycosyl acceptor (**121**) in hand we planned for the crucial *O*-glycosylation. Before we discuss the approach it is pertinent to mention the concepts of *n*-pentenyl mediated *O*-glycosylation reaction as it is first disclosed by Fraser- Reid.[62]

Salient Features of Fraser-Reid's Glycosylation Method

The serendipitous discovery of n-pentenyl leaving group strategy by Fraser-Reid's group opened a new era in the art of oligosaccharide synthesis. n-Pentenyl glycosides (NPGs) are readily obtained by standard glycosidations including Fischer's direct method and although they are stable to a wide range of reagents, they are easily activated by treatment with a halonium ion (scheme 32). The effect of some of the commonly used protecting groups upon glycoside reactivity has been probed with these substrates, and the "armed/disarmed" strategy for oligosaccharide assembly emanated directly from these investigations. Thus esters disarm electronically, while benzylidene and isopropylidene groups disarm by torsional strain.

Scheme 32: *n-Pentenyl mediated Glycosylation method*

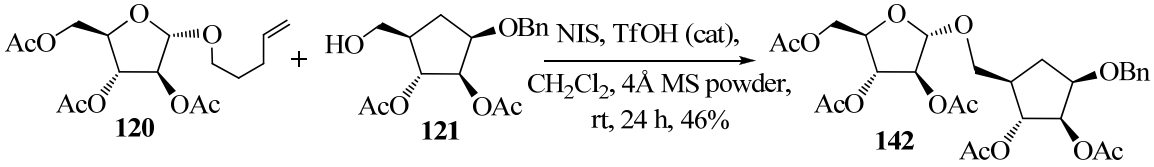


Most commonly used activators for NPGs are NBS, IDCP (Iodonium dicollidine perchlorate). However, IDCP is not commercially available, a circumstance which compromised its attractiveness. Later on alternative promoters were sought that would, among other things not require laboratory preparation. A non-nucleophilic counter anion was essential, and trifluoro methanesulfonate (triflate) was preferred and it was found that NIS reacted with TfOH to generate a ready source of iodonium ion solved the problem, as both NIS and TfOH are commercially available. A general drawback of this

protocol is the use of strong acid and thus care should be taken while planning and executing the glycosylation reaction.

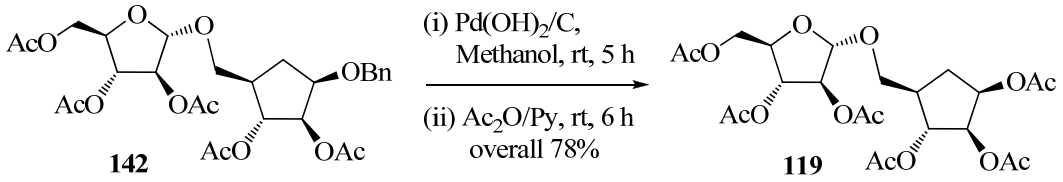
The Fraser-Reid glycosidation reaction between glycosyl donor **120** and glycosyl acceptor **121** in the presence of NIS, TfOH (catalytic) and 4Å MS powder in CH_2Cl_2 at room temperature gave the disaccaharide **142** in 46% yield (Scheme 33).

Scheme 33: Glycosidation reaction



The 1,2-*trans* configuration of disaccharide of **142** was apparent from its ^1H and ^{13}C NMR spectra studies. In the ^1H NMR spectrum of **142**, the anomeric proton was observed at δ 5.01 as a characteristic singlet. Further, the location of the signal due to C-1' at 105.3 ppm in the ^{13}C NMR spectrum confirmed the α-linkage at the newly formed glycosidic bond and satisfactory elemental analysis supported the structure of **142**. Finally the disaccharide **142** was subjected to benzyl deprotection using $Pd(OH)_2/C$ in MeOH at room temperature to give the alcohol which was subsequently acetylated using Ac_2O and pyridine to give hexa-acetyl disaccharide **119** in 78% overall yield (Scheme 34).

Scheme 34



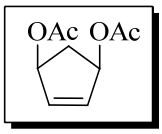
The structure of **119** was unequivocally confirmed by its spectral and analytical data. In the ^1H NMR spectrum, the anomeric proton was observed at δ 4.94 as a singlet and rest of the spectrum was in full accordance with the structure. In the ^{13}C NMR

spectrum the characteristic C-1 carbon resonated at δ 105.23. The six carbonyl carbons were observed at δ 169.6, 170.0, 170.0, 170.2, 170.3, 170.6.

Conclusion: Herein we describe the first synthesis of carba analogue of motif C of arabinogalactan complex present in *M. tuberculosis* cell wall. The Pd(0) catalyzed allylic alkylation and Fraser-Reid's glycosidation are the two key reaction thats were employed for the synthesis of central glycosyl accepter unit and the glycosylation respectively.

Experimental

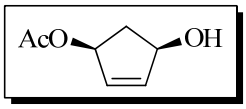
(1*R*,3*S*)-Cyclopent-4-ene-1,3-diyl diacetate (79)



To a solution of diol **76** (5 g, 50 mmol) in pyridine (80 mL) was added acetic anhydride (15.3 g, 150 mmol) slowly dropwise at 0 ^{o}C and add catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, pyridine was removed under reduced pressure. The crude obtained was purified by column chromatography (20% ethyl acetate in petroleum ether) to procure **79** (8.7 g, 95%) as colorless oil.

Mol. Formula	: $C_9H_{12}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 3455, 2950, 1737, 1366, 1233, 1077, 1022, 608 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.74 (dt, *J* = 4.0, 15.0 Hz, 1H), 2.0 (s, 6H), 2.89 (dt, *J* = 7.5, 15.0 Hz, 1H), 5.55 (dd, *J* = 4, 7.5 Hz, 2H), 6.10 (s, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.8 (q), 36.8 (t), 76.3 (d), 134.3 (d), 170.3 (s) ppm.
Elemental Analysis	Calcd.: C, 58.69; H, 6.57. Found: C, 58.65; H, 6.52.

(1*S*,4*R*)-4-Hydroxycyclopent-2-enyl acetate (124)

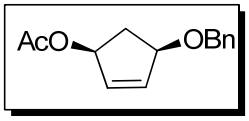


meso-Diacetate (**79**) (100 g, 0.543 mol) was dissolved in ethanol (300 mL) in a 5L three–necked round bottomed flask equipped with an overhead stirrer, pH electrode and a dropping funnel. Sodium phosphate buffer (0.1 M, pH 7, 2.7 L) was added and the mixture was stirred vigorously using a overhead stirrer. To the stirred reaction mixture, wet biomass (50 g) of *Trichosporon beigelii* (NCIM 3326) was added with a small amount of buffer. The whole mixture was stirred vigorously to yield uniform emulsion.

The pH of the reaction was monitored regularly and was maintained at 7 by adding 1 M aqueous sodium hydroxide solution through a dropping funnel. Progress of the reaction was monitored by TLC (30% ethyl acetate in pet ether). Reaction was continued for 26 h and was then filtered through a *Celite* bed and the filtrate was extracted with ethyl acetate (3 X 2 L). The organic extracts were combined and washed with brine. The aqueous layer was separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to get the product as white crystalline needles. It was melted on a water bath and was stirred vigorously with pet ether. The mixture was allowed to stand at room temperature for few hours. Product **124** separated as fine crystalline needles. Pet ether was decanted off and washing with pet ether was repeated once again. These washings removed any unreacted diacetate (**79**) and other non-polar impurities to yield **124** (57.4 g, 74%) as colorless needles.

Mol. Formula	: $C_7H_{10}O_3$
$[\alpha]_D$	: –67.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3409, 2943, 1734, 1363, 1247, 1019, 981, 772 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.64 (dt, *J* = 3.9, 14.7 Hz, 1H), 2.05 (s, 3H), 2.80 (dt, *J* = 7.3, 14.7 Hz, 1H), 3.42 (br s, 1H), 4.60–4.74 (m, 1H), 5.45–5.52 (m, 1H), 5.94–6.12 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.9 (q), 40.3 (t), 74.4 (d), 76.9 (d), 132.1 (d), 138.5 (d), 170.7 (s) ppm.
Elemental Analysis	Calcd.: C, 59.14; H, 7.09. Found: C, 59.12; H, 7.67.

(1*S*,4*R*)-4-(Benzyloxy)cyclopent-2-enyl acetate (125)

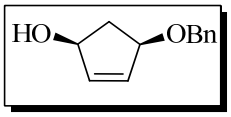


To a solution of **124** (6 g, 45.3 mmol) in DCM (720 mL), silver oxide (29.4 g, 126.8 mmol) was added followed by benzyl bromide (10.8 g, 63.4 mmol) and the reaction mixture was stirred at room temperature for 12 h. The mixture was filtered through a *Celite* bed. The filtrate was dried over anhydrous Na_2SO_4, concentrated and the

crude was purified by column chromatography (10% ethyl acetate in petroleum ether) to yield **125** (9.2 g, 93%) as colorless oil.

Mol. Formula	: $C_{14}H_{16}O_3$
$[\alpha]_D$	: –12.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3064, 2860, 1735, 1454, 1364, 1240, 1026, 909, 738, 698, 608 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.75 (dt, *J* = 4.6, 14.2 Hz, 1H), 2.05 (s, 3H), 2.76 (dt, *J* = 7.3, 14.7 Hz, 1H), 4.48–4.50 (m, 1H), 4.55 (qt, *J* = 11.7 Hz, *J* = 22.0 Hz, 2H), 5.48–5.50 (m, 1H), 5.98–5.99 (m, 1H), 6.11–6.12 (m, 1H), 7.25–7.33 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 21.1 (q), 37.5 (t), 70.9 (t), 76.8 (d), 81.1 (d), 127.5 (d), 127.6 (d), 128.3 (d), 132.8 (d), 136.1 (d), 138.2 (s), 170.6 (s) ppm.
Elemental Analysis	Calcd.: C, 72.39; H, 6.94. Found: C, 72.25; H, 7.20.

(1*S*, 4*R*)-4-(Benzyloxy)cyclopent-2-enol (126)

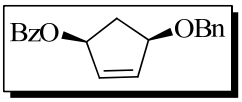


A suspension of **125** (4 g, 17.2 mmol), K_2CO_3 (3.65 g, 34.5 mmol) in MeOH: H_2O (50 mL, 3:1) was stirred at room temperature for 3 h. The mixture was concentrated, extracted with DCM (60 mL). The aqueous layer inturn extracted with DCM (100 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, concentrated. The crude produce was purified by column chromatography (20% ethyl acetate in petroleum ether) to give **126** (3 g, 92%) as colorless oil.

Mol. Formula	: $C_{12}H_{14}O_2$
$[\alpha]_D$	: +21.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3387, 2862, 1454, 1359, 1072, 750, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.65 (dt, *J* = 3.9, 14.1 Hz, 1H), 2.23 (br s, 1H), 2.64 (dt, *J* = 7.1, 14.2 Hz, 1H), 4.39–4.64 (m, 4H), 6.02 (s, 2H),

	7.25–7.35 (m, 5H) ppm.
^{13}C NMR	: δ 40.6 (t), 70.9 (t), 74.4 (d), 81.5 (d), 127.5 (d), 127.7 (d),
($CDCl_3$, 50 MHz)	128.3 (d), 133.4 (d), 137.3 (d), 138.0 (s) ppm.
Elemental Analysis	Calcd.: C, 75.76; H, 7.42.
	Found: C, 75.74; H, 7.39.

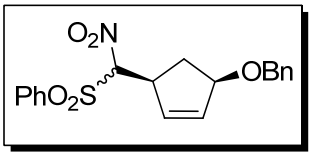
(1*S*,4*R*)-4-(Benzyloxy)cyclopent-2-enyl benzoate (123)



To a solution of **126** (5 g, 26.3 mmol) in DCM (100 mL), triethyl amine (5.3 g, 52.6 mmol) was added and stirred for 10 minutes. To this benzoyl chloride (5.5 g, 39.5 mmol) was added slowly dropwise and the reaction mixture was stirred at room temperature for 12 h. The mixture was extracted with DCM (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (10% ethyl acetate in petroleum ether) to procure **123** (7.2 g, 94%) as colorless oil.

Mol. Formula	: $C_{19}H_{18}O_3$
$[\alpha]_D$	: –45.5 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 1713, 1274, 1215, 756, 668 cm^{-1}.
^{1}H NMR	: δ 1.91 (dt, *J* = 4.3, 14.2 Hz, 1H), 2.9 (dt, *J* = 7.3, 14.2 Hz,
($CDCl_3$, 500 MHz)	1H), 4.55–4.62 (m, 3H), 5.75–5.77 (m, 1H), 6.10–6.18 (m, 2H) 7.26–7.35 (m, 4H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.53 (q, *J* = 7.3, 13.7 Hz, 2H), 8.04 (d, *J* = 7.3 Hz, 2H) ppm.
^{13}C NMR	: δ 37.7 (t), 70.9 (t), 77.3 (d), 81.2 (d), 127.5 (d), 127.6 (d),
($CDCl_3$, 125 MHz)	128.2 (d), 128.3 (d), 128.8 (d), 129.6 (d), 132.8 (s), 134.3 (d), 134.4 (d), 136.3 (d), 138.8 (d), 162.1 (s), 166.0 (s) ppm.
Elemental Analysis	Calcd.: C, 77.53; H, 6.16.
	Found: C, 77.48; H, 6.57.

(((1*S*,4*R*)-4-(Benzyloxy)cyclopent-2-enyl)(nitro)methylsulfonyl)benzene (127)



To a deoxygenated solution of triphenyl phosphine (89 mg, 0.34 mmol) in THF (20 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (35 mg, 0.034 mmol), was added and the mixture was stirred for 20 min. It was then added to a deoxygenated solution of mono benzoate **123** (1 g, 3.4 mmol), phenyl sulfonyl (nitro) methane (821 mg, 4.1 mmol) and triethyl amine (860 mg, 8.5 mmol) in THF (20 mL). After being stirred for 12 h the reaction mixture was diluted with chloroform (25 mL) and washed with water (100 mL). The aqueous phase was extracted with chloroform (250 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (6% ethyl acetate in petroleum ether) to give **127** (0.9 g, 72%) as 1:1 diastereomeric mixture.

Mol. Formula : $C_{19}H_{19}NO_5S$

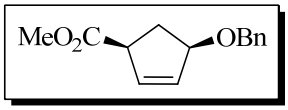
IR ($CHCl_3$) $\tilde{\nu}$: 3030, 2864, 1560, 1449, 1345, 1082, 755, 686 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.62 (dt, *J* = 4.1, 13.7 Hz, 1H), 2.27 (dt, *J* = 3.6, 14.2 Hz, 1H), 2.36 (dt, *J* = 6.8, 14.2 Hz, 1H), 2.50 (dt, *J* = 7.3, 14.6 Hz, 1H), 3.50–3.61 (m, 2H), 4.45–4.53 (m, 4H), 4.57–4.60 (m, 2H), 5.47 (qt, *J* = 10.5, 16.9 Hz, 2H), 5.63–5.64 (m, 1H), 6.13–6.16 (m, 2H), 6.30–6.31 (m, 1H), 7.26–7.36 (m, 9H), 7.60 (t, *J* = 7.5, 4H), 7.75 (t, *J* = 7.3 Hz, 2H), 7.89–7.91 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 33.6 (d), 34.6 (d), 43.2 (d), 43.51 (d), 71.38 (d), 81.5 (d), 82.8 (d), 96.2 (d), 105.3 (s), 105.6 (s), 127.8 (d), 128.4 (d), 129.4 (d), 129.96 (d), 129.99 (d), 131.6 (d), 131.9 (d),135.3 (s), 135.9 (s), 137.06 (s) ppm.

Elemental Analysis Calcd.: C, 61.11; H, 5.13; N, 3.75; S, 8.59.
Found: C, 61.14; H, 5.09; N, 3.71; S, 8.60.

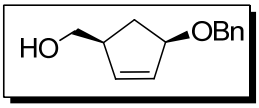
(1*S*,4*R*)-Methyl 4-(benzyloxy)cyclopent-2-enecarboxylate (128)



To an ice cold solution of nitrosulfone **127** (2 g, 5.36 mmol) in methanol (40 mL) tetra methyl guanidine (0.93 g, 8.1 mmol) was added and the mixture was stirred at 0 ^{o}C for 15 min followed by addition of TBA-Oxone (22.98 g, 26.8 mmol), sodium carbonate (2.84 g, 26.8 mmol) and DCM (50 mL). The solution was stirred at room temperature for an additional 16 h. It was then diluted with chloroform and washed with water (100 mL). The aqueous layer was extracted with chloroform (200 mL), and the chloroform layer was dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (6% ethyl acetate in petroleum ether) to give **128** (0.53 g, 43%) as colorless oil.

Mol. Formula	: $C_{14}H_{16}O_3$
$[\alpha]_D$	: –46.8 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2863, 1733, 1360, 1216, 1068, 756, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 2.13 (dt, *J* = 6.4, 13.7 Hz, 1H), 2.51 (dt, *J* = 8.7, 13.7 Hz, 1H), 3.43–3.46 (m, 1H), 3.71 (s, 3H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.64 (t, *J* = 6.4 Hz, 1H), 5.96–5.99 (m, 2H), 7.24–7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 33.3 (t), 48.9 (q), 51.9 (d), 70.8 (t), 83.3 (d), 127.5 (d), 127.8 (d), 128.4 (d), 132.0 (d), 133.9 (d), 138.7 (s), 173.5 (s) ppm.
Elemental Analysis	Calcd.: C, 72.39; H, 6.94. Found: C, 72.34; H, 6.92.

((1*S*,4*R*)-4-(Benzyloxy)cyclopent-2-enyl)methanol (122)

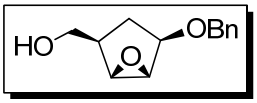


At –78 ^{o}C a solution of ester **128** (1 g, 4.31 mmol) in DCM (20 mL) was treated with DIBAL-H (1.53 g, 10.77 mmol) and the reaction mixture was stirred at –78 ^{o}C for 1 h and quenched with saturated solution of sodium potassium tartarate (2 mL) at the same

temperature. The mixture was warmed to room temperature and stirred for 3 h. The organic phase was separated and the aqueous phase was extracted with DCM. The combined extracts were dried over Na_2SO_4, concentrated the crude product was purified by column chromatography (15% ethyl acetate in petroleum ether) to yield **122** (0.6 g, 68%) as colorless oil.

Mol. Formula	: $C_{13}H_{16}O_2$
$[\alpha]_D$	: +21.9 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3400, 2865, 1364, 1091, 1043, 736, 697 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.57 (br s, 1H), 1.68 (dt, *J* = 3.2, 13.7 Hz, 1H), 2.28 (dt, *J* = 7.3, 14.2 Hz, 1H), 2.86 (br s, 1H), 3.62 (d, *J* = 4.6 Hz, 2H), 4.52–4.58 (m, 3H), 5.95–6.02 (m, 2H), 7.24–7.32 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 33.9 (t), 46.8 (d), 65.0 (t), 70.9 (t), 82.9 (d), 127.6 (d), 127.7 (d), 128.4 (d), 132.6 (d), 136.8 (d), 138.4 (s) ppm.
Elemental Analysis	Calcd.: C, 76.44; H, 7.90. Found: C, 75.47; H, 7.84.

((1*S*,2*R*,4*R*,5*R*)-4-(Benzyloxy)-6-oxabicyclo[3.1.0]hexan-2-yl)methanol (129)



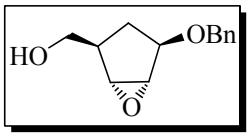
Epoxidation of cyclopentene 122

To a solution of **122** (1 g, 4.9 mmol) in DCM (16 mL), *m*-CPBA (2.11 g, 12.25 mmol) was added at 0 ^oC and the mixture was stirred at rt for 12 h. Precipitated *m*-chloro benzoicacid was filtered off. The filtrate was concentrated and the residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to obtain **129** (570 mg, 52.5%) and **130** (240 g, 22.5%) as colorless liquids.

Mol. Formula	: $C_{13}H_{16}O_3$
$[\alpha]_D$	: –10.1 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3412, 3019, 1716, 1215, 757, 669 cm^{-1}.
^{1}H NMR	: δ 1.17–1.23 (m, 1H), 1.86–1.91 (m, 1H), 2.11–2.16 (m,

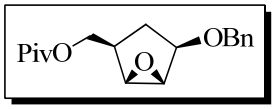
($CDCl_3$, 500 MHz)	1H), 3.49 (d, *J* = 15.6 Hz, 2H), 3.75 (d, *J* = 6.4, 2H), 4.05 (t, *J* = 7.8 Hz, 1H), 4.61 (dt, *J* = 12.4, 16.0 Hz, 2H), 7.27–7.36 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.5 (t), 40.2 (d), 55.8 (d), 56.5 (d), 62.8 (t), 71.6 (t), 78.8 (d), 127.7 (d), 128.4 (d), 138.0 (s) ppm.
Elemental Analysis	Calcd.: C, 70.89; H, 7.32. Found: C, 70.87; H, 7.29.

((1*S*,2*R*,4*R*,5*R*)-4-(Benzyloxy)-6-oxabicyclo[3.1.0]hexan-2-yl)methanol (130)



Mol. Formula	: $C_{13}H_{16}O_3$
$[\alpha]_D$	: –16.3 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3426, 3032, 2973, 2873, 1729, 1480, 1153, 840 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.57 (d, *J* = 14.8 Hz, 1H), 1.80–1.94 (m, 1H), 2.43–2.51 (m, 1H), 2.90 (br s, 1H), 3.53 (s, 2H), 3.70 (dd, *J* = 4.30, 7.83 Hz, 2H), 4.09 (d, *J* = 5.5 Hz, 1H), 4.61 (d, *J* = 3.1 Hz, 2H), 7.31 (s, 5H) ppm.
Elemental Analysis	Calcd.: C, 70.89; H, 7.32. Found: C, 70.79; H, 7.12.

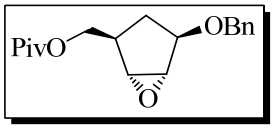
((1*S*,2*R*,4*R*,5*R*)-4-(Benzyloxy)-6-oxabicyclo[3.1.0]hexan-2-yl)methyl pivalate (131)



To a solution of **129** (500 mg, 2.27 mmol) in DCM (12 mL) at 0 ^oC, pyridine (530 mg, 4.54 mmol) was added followed by pivaloyl chloride (550 mg, 4.54 mmol). The reaction mixture was stirred at room temperature for 6 h. Reaction mixture was concentrated and the crude was purified by column chromatography (10% ethyl acetate in petroleum ether) to yield **131** (640 mg, 88%) as colorless oil.

Mol. Formula	: $C_{18}H_{24}O_4$
$[\alpha]_D$	: –17.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3028, 2974, 1725, 1480, 1273, 1158, 754, 715 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.21 (s, 10H), 1.88 (dt, *J* = 7.3, 12.8 Hz, 1H), 2.20–2.26 (m, 1H), 3.30 (d, *J* = 2.7 Hz, 1H), 3.50 (d, *J* = 2.7 Hz, 1H), 4.03 (t, *J* = 8.5 Hz, 1H), 4.07–4.10 (q, *J* = 8.2 Hz, 1H), 4.17–4.22 (m, 1H), 4.61 (s, 2H), 7.26–7.45 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.9 (t), 27.2 (q), 37.4 (d), 38.8 (s), 55.2 (d), 56.4 (d), 64.0 (t), 71.6 (t), 78.6 (d), 127.8 (d), 128.4 (d), 138.0 (s), 178.3 (s) ppm.
Elemental Analysis	Calcd.: C, 71.05; H, 7.89. Found: C, 71.09; H, 7.85.

((1*R*,2*R*,4*R*,5*S*)-4-(Benzyloxy)-6-oxabicyclo[3.1.0]hexan-2-yl)methyl pivalate (132)

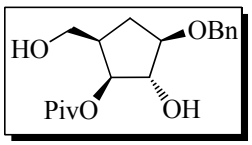


To a solution of **130** (500 mg, 2.27 mmol) in DCM (12 mL) at 0 ^oC, pyridine (530 mg, 4.54 mmol) was added followed by pivaloyl chloride (550 mg, 4.54 mmol). The reaction mixture was stirred at room temperature for 6 h. Reaction mixture was concentrated and the crude was purified by column chromatography (10% ethyl acetate in petroleum ether) to yield **132** (640 mg, 88%) as colorless oil.

Mol. Formula	: $C_{18}H_{24}O_4$
$[\alpha]_D$	: –15.0 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3032, 2973, 2873, 1729, 1480, 1282, 1153, 1094, 840, 697 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.15 (s, 9H), 1.48 (d, *J* = 14.6 Hz, 1H), 1.62–1.68 (m, 1H), 2.50 (q, *J* = 7.8 Hz, 1H), 3.43 (d, *J* = 6.9 Hz, 2H), 3.95–4.03 (m, 2H), 4.05–4.12 (m, 1H), 4.42 (d, *J* = 11.9 Hz, H), 4.51 (d, *J* = 11.5 Hz, 1H), 7.19–7.27 (m, 5H) ppm.
^{13}C NMR	: δ 27.3 (q), 30.1 (t), 38.4 (s), 56.9 (d), 58.5 (d), 64.9 (d),

($CDCl_3$, 125 MHz)	71.7 (t), 78.3 (d), 127.6 (d), 127.8 (d), 128.5 (d), 128.5 (s), 129.7 (s), 133.3 (s), 138.0 (s), 177.9 (s) ppm.
Elemental Analysis	Calcd.: C, 71.03; H, 7.95.
	Found: C, 70.83; H, 7.75.

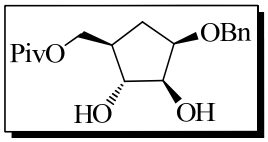
(1*S*,2*S*,3*R*,5*R*)-3-(Benzyloxy)-2-hydroxy-5-(hydroxymethyl)cyclopentyl pivalate (138)



To a solution of **132** (500 g, 1.54 mmol) in 3:1 of DMSO:H_2O (10 mL), catalytic amount of perchloric acid (70%) was added at 0 ^oC. The reaction mixture was stirred at rt for 16 h. The mixture was extracted with ethyl acetate (3 X 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (6% ethyl acetate in petroleum ether) to give **138** (370 mg, 76%) as colorless oil.

Mol. Formula	: $C_{18}H_{26}O_5$
$[\alpha]_D$	: –24.5 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3416, 3021, 1740, 1115, 736, 643 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.23 (s, 9H), 1.62–1.70 (m, 1H), 2.16 (dt, *J* = 6.9, 13.1 Hz, 1H), 2.38–2.52 (m, 1H), 3.16 (br s, 1H), 3.63–3.66 (m, 2H), 3.81–3.90 (m, 1H), 4.05 (t, *J* = 3.9 Hz, 1H), 4.59 (d, *J* = 5.3 Hz, 2H), 4.77–4.82 (q, *J* = 3.3, 6.7 Hz, 1H), 7.28–7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 27.2 (q), 31.9 (t), 41.3 (d), 61.5 (t), 71.7 (t), 76.8 (d), 81.9 (d), 83.0 (d), 83.6 (d), 127.7 (d), 127.8 (d), 128.4 (d), 128.5 (d), 129.8 (s), 138.1 (s), 179.8 (s) ppm.
Elemental Analysis	Calcd.: C, 67.06; H, 8.13.
	Found: C, 66.98; H, 8.03.

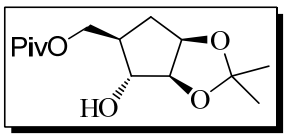
((1*R*,2*R*,3*S*,4*R*)-4-(Benzyloxy)-2,3-dihydroxycyclopentyl)methyl pivalate (133)



To a solution of **131** (500 mg, 1.54 mmol) in 10 mL of DMSO:H_2O (3:1), catalytic amount of perchloric acid (70%) was added at 0 ^oC. The reaction mixture was stirred at rt for 16 h. The mixture was extracted with ethyl acetate (3 X 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (6% ethyl acetate in petroleum ether) to give **133** (370 mg, 76%) as colorless oil.

Mol. Formula	: $C_{18}H_{26}O_5$
$[\alpha]_D$	: –35.5 (*c* 0.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3432, 3019, 1720, 1215, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.13 (s, 9H), 1.45–1.59 (m, 1H), 1.76 (br s, 1H), 1.95–2.15 (m, 2H), 3.77–3.88 (m, 2H), 4.00–4.13 (m, 2H), 4.4 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 7.23–7.29 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 27.1 (q), 29.8 (t), 38.8 (s), 40.7 (d), 65.5 (t), 71.4 (t), 76.7 (d), 78.4 (d), 78.5 (d), 127.7 (d), 127.9 (d), 128.4 (d), 137.5 (s), 178.6 (s) ppm.
Elemental Analysis	Calcd.: C, 67.08; H, 8.13. Found: C, 66.89; H, 7.15.

((3a*S*,4*R*,5*R*,6a*R*)-4-Hydroxy-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-yl)methyl pivalate (134)

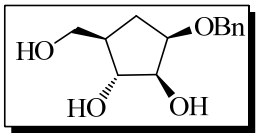


To a solution of **133** (100 mg) in methanol (5 mL), Pd/C (10%, 50 mg) was added and stirred at rt under balloon H_2 pressure for 6 h. The mixture was filtered through a celite bed and the filtrate was concentrated. The crude triol was used directly for the next reaction. To a solution of triol (80 mg, 0.34 mmol) in acetone (6 mL), DMP (530 mg, 0.5 mmol) was added followed by catalytic amount of *p*-TSA (5 mg) and stirred at 0 ^oC for

0.5 h. The mixture was quenched with solid $NaHCO_3$ and the neutral reaction mixture was concentrated in *vacuo.* The residue obtained was purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain **134** (60 mg, 75%) as colorless oil.

Mol. Formula	: $C_{14}H_{24}O_5$
$[\alpha]_D$	: –26.4 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3435, 1721, 1480, 1215, 928, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.22 (s, 9H), 1.29 (s, 3H), 1.48 (s, 3H), 1.63 (br s, 1H), 1.70–1.14 (m, 1H), 2.16–2.24 (m, 2H), 3.96 (dd, *J* = 3.21, 5.04 Hz, 1H), 4.16 (dddd, *J* = 5.5, 11.0, 16.9 Hz, 2H), 4.39 (dd, *J* = 3.2, 6.9 Hz, 1H), 4.67–4.70 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.4 (q), 26.8 (q), 27.3 (q), 32.5 (t), 46.1 (d), 64.3 (t), 78.5 (d), 78.7 (d), 87.0 (d), 111.77 (d), 178.4 (s), 178.8 (s) ppm.
Elemental Analysis	Calcd.: C, 61.74; H, 8.88. Found: C, 61.78; H, 8.85.

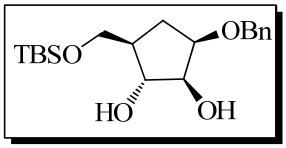
(1*R*,2*S*,3*R*,5*R*)-3-(Benzyloxy)-5-(hydroxymethyl)cyclopentane-1,2-diol (135)



A solution of **133** (400 mg, 1.24 mmol) in DCM (15 mL) was cooled to –78 ^oC. DIBAL-H (440 mg, 3.1 mmol) was added slowly dropwise and the mixture was stirred at –78 ^oC for 1 h. The reaction mixture was quenched with saturated solution of sodium potassium tartarate (5 mL), warmed to room temperature and stirred for additional 3 h. Organic phase was separated and the aqueous phase was extracted with DCM. The combined organic extracts were dried over (Na_2SO_4), concentrated and the crude residue was purified by column chromatography (80% ethyl acetate in petroleum ether) to afford **135** (220 mg, 74.5%) as colorless oil.

Mol. Formula	: $C_{13}H_{18}O_4$
$[\alpha]_D$	: –2.9 (*c* 1, MeOH).
IR (Neat) $\tilde{\nu}$	: 3369, 2930, 1454, 1046, 753, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.44 (br s, 1H), 1.87 (br s, 1H), 1.96–2.03 (m, 1H), 3.53 (t, *J* = 7.3 Hz, 1H), 3.62 (br s, 1H), 3.81 (br s, 2H), 3.82–3.96 (br s, 4H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 7.22–7.31 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 29.4 (t), 43.4 (d), 65.0 (t), 71.6 (t), 77.5 (d), 78.6(d), 79.2 (d), 127.9 (d), 128.5 (d), 137.9 (s) ppm.
Elemental Analysis	Calcd.: C, 65.53; H, 7.61. Found: C, 65.37; H, 7.26.

(1*R*,2*S*,3*R*,5*R*)-3-(Benzyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)cyclopentane-1,2-diol (136)



To a solution of **135** (500 mg, 2.1 mmol) in DCM (12 mL), imidazole (420 mg, 6.3 mmol) was added and stirred at 0 ^oC for 10 minutes. TBDMS-Cl (340 mg, 2.31 mmol) was added and the reaction mixture was stirred for 0.5 h. The reaction mixuture was directly concentrated and purified by column chromatography (40% ethyl acetate in petroleum ether) to yield **136** (490 mg, 66%) as colorless oil.

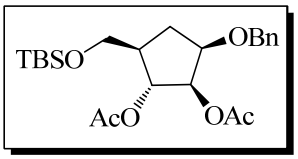
Mol. Formula	: $C_{19}H_{32}O_4Si$
$[\alpha]_D$	: –18.9 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3424, 2929, 1255, 1216, 1067, 837, 758, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 0.06 (d, *J* = 1.9 Hz, 6H), 0.90 (s, 9H), 1.50 (dddd, *J* = 4.4, 8.8, 13.2, 18.1 Hz, 1H), 1.62 (br s, 1H), 1.9 (dt, *J* = 7.8, 16.6 Hz, 1H), 2.6 (dq, *J* = 6.3, 8.8, 15.1Hz, 1H), 2.69–2.71 (d, *J* = 5.8, 1H), 3.60 (t, *J* = 7.83 Hz, 1H), 3.74 (qt, *J* = 5.4, 9.8 Hz, 1H), 3.85 (br s, 1H), 3.89–3.94 (m, 2H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H),

7.30–7.37 (m, 5H) ppm.

^{13}C NMR (CDCl$_3$, 125 MHz): δ –5.4 (q), 18.2 (s), 25.9 (q), 29.4 (t), 43.2 (d), 66.0 (t), 71.4 (t), 77.0 (d), 78.3 (d), 80.5 (d), 127.7 (d), 127.8 (d), 128.5 (d), 137.9 (s) ppm.

Elemental Analysis Calcd.: C, 64.73; H, 9.15.
Found: C, 64.66; H, 9.12.

(1*R*,2*R*,3*R*,5*R*)-3-(Benzyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)cyclopentane-1,2-diyl diacetate (137)



To a solution of **136** (400 mg, 1.13 mmol) in pyridine (8 mL), acetic anhydride (460 mg, 4.54 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated and the residue obtained was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **137** (340 mg, 73%) as colorless oil.

Mol. Formula : $C_{23}H_{36}O_6Si$

$[\alpha]_D$: –8.6 (*c* 1.7, MeOH).

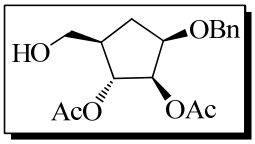
IR (CHCl$_3$) $\tilde{\nu}$: 3019, 2929, 1737, 1216, 1108, 838, 758, 668 cm^{-1}.

^{1}H NMR (CDCl$_3$, 200 MHz): δ 0.02 (d, *J* = 1.3 Hz, 6H), 0.87 (s, 9H), 1.73–1.81 (m, 1H), 2.02–2.08 (m, 8H), 3.56–3.76 (m, 2H), 3.96–4.05 (m, 1H), 4.50–4.51 (m, 2H), 5.10 (qt, *J* = 4.4, 3.8 Hz, 2H), 7.26–7.34 (m, 5H) ppm.

^{13}C NMR (CDCl$_3$, 50 MHz): δ –5.53 (q), –5.44 (q), 18.2 (s), 20.9 (q), 21.02 (q), 25.9 (q), 30.8 (t), 42.9 (d), 64.4 (t), 71.9 (t), 78.0 (d), 127.5 (d), 128.4 (d), 138.2 (s), 170.1 (s), 170.4 (s) ppm.

Elemental Analysis Calcd.: C, 63.27; H, 8.31.
Found: C, 63.54; H, 8.26.

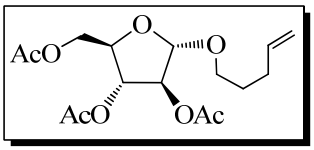
(1*R*,2*R*,3*R*,5*R*)-3-(Benzyloxy)-5-(hydroxymethyl)cyclopentane-1,2-diyl diacetate (121)



To a solution of **137** (300 mg) in ethanol (8 mL), 0.8% H_2SO_4 (Catalytic amount) was added at 0 ^oC and then stirred at rt for 4 h. The reaction mixture was concentrated and the crude was purified by column chromatography (15% ethyl acetate in petroleum ether) to obtain **121** (150 mg, 63%) as colorless oil.

Mol. Formula	: $C_{17}H_{22}O_6$
$[\alpha]_D$	: –9.1 (*c* 1.5, MeOH).
IR (Neat) $\tilde{\nu}$	: 3392, 1737, 1373, 908, 733, 650 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.62–1.74 (m, 1H), 2.09–2.10 (d, *J* = 1.5 Hz, 6H), 2.14–2.24 (m, 1H), 2.81 (br s, 1H), 3.58–3.71 (m, 2H), 4.04–4.14 (m, 1H), 4.52 (s, 2H), 5.08–5.13 (m, 2H), 7.29 –7.38 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.9 (q), 21.1 (q), 30.9 (t), 43.5 (d), 64.7 (t), 71.93 (t), 76.2 (d), 77.4 (d), 78.7 (d), 127.5 (d), 127.7 (d), 128.4 (d), 137.9 (s), 170.4 (s), 171.7 (s) ppm.
Elemental Analysis	Calcd.: C, 63.34; H, 6.88. Found: C, 63.23; H, 7.84.

(2*R*,3*R*,4*S*)-2-(Acetoxymethyl)-5-(pent-4-enyloxy)tetrahydrofuran-3,4-diyl diacetate (120)

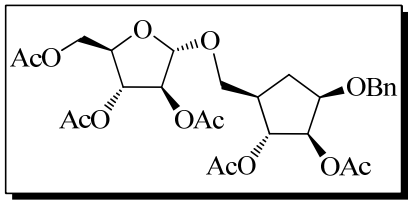


A solution of per-O-acetyl-D-arabinofuranose (**141**) (1 g, 3.14 mmol), 4-pentene-1-ol (400 mg, 4.71 mmol), and 4Å MS powder (100 mg) in DCM (25 mL) under nitrogen, $BF_3{\cdot}Et_2O$ (0.1 mL) was added at 0 ^oC. After 2 h, solid $NaHCO_3$ was added and filtered through celite. The filtrate was washed with brine, dried (Na_2SO_4) and

concentrated. The residual syrup was purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain **120** (870 mg, 80%) as colorless oil.

Mol. Formula	: $C_{16}H_{24}O_8$
IR ($CHCl_3$) $\tilde{\nu}$	: 3024, 2940, 1745, 1371, 1230, 1047, 913, 667 cm^{-1}.
$[\alpha]_D$	: +65.9 (*c* 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.63–1.78 (m, 3H), 2.11 (s, 10H), 3.46 (qt, *J* = 6.3, 12.5 Hz, 1H), 3.72 (dt, *J* = 6.7, 9.6 Hz, 1H), 4.17–4.28 (m, 2H), 4.39–4.48 (m, 1H), 4.94–5.08 (m, 5H), 5.72–5.92 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.6 (q), 28.4 (t), 30.0 (t), 63.1 (t), 66.6 (t), 76.9 (d), 80.0 (d), 81.1 (d), 95.9 (s), 105.3 (d), 114.8 (t), 137.8 (d), 169.3 (s), 169.9 (s), 170.3 (s) ppm.
Elemental Analysis	Calcd.: C, 55.81; H, 7.02. Found: C, 56.79; H, 7.36.

The compound (142)

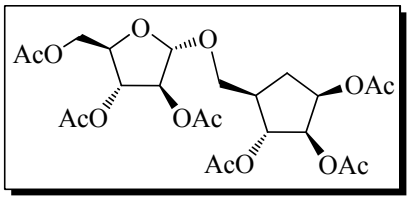


To a stirred suspension of **120** (160 mg, 0.62 mmol) and **121** (100 mg, 0.31 mmol) and 4Å MS powder in dry DCM (5 mL), NIS (130 mg, 0.62 mmol) was added followed by TfOH (catalytic). The reaction mixture was stirred under dark at room temperature for 24 h and filtered through a *celite* bed. The filtrate was washed with saturated solution of $NaHSO_3$ and $NaHCO_3$ followed by brine solution. The organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain **142** (40 mg, 45%) as colorless oil.

Mol. Formula	: $C_{28}H_{36}O_{13}$
$[\alpha]_D$	: +30.9 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2927, 1742, 1372, 1216, 1083, 758, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.77–1.84 (m, 1H), 2.05 (s, 3H), 2.07 (s, 3H), 2.08 (s, 6H), 2.11 (s, 3H), 2.13–2.18 (m, 2H), 3.57 (dd, *J* = 5.0, 9.6 Hz, 1H), 3.73 (dd, *J* = 6.9, 9.6 Hz, 1H), 4.04 (qt, *J* = 5.5, 10.5 Hz, 1H), 4.16–4.24 (m, 3H), 4.38 (dd, *J* = 3.2 Hz, 11.5 Hz, 1H), 4.50 (s, 2H), 4.93 (dd, *J* = 1.4, 4.6 Hz, 1H), 5.01 (s, 1H), 5.04–5.12 (m, 2H), 5.17 (t, *J* = 5.9 Hz, 1H), 7.27–7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 20.6 (q), 20.7 (q), 20.8 (q), 20.9 (q), 30.9 (t), 40.0 (d), 63.2 (t), 68.2 (t), 71.9 (t), 76.4 (d), 77.11 (d), 77.14 (d), 77.3 (d), 80.4 (d), 81.0 (d), 105.3 (d), 127.5 (d), 127.7 (d), 128.4 (d), 128.6 (d), 138.1 (s), 169.5 (s), 169.9 (s), 170.1 (s), 170.2 (s), 170.4 (s) ppm.
Elemental Analysis	Calcd.: C, 57.93; H, 6.25. Found: C, 59.86; H, 6.22.

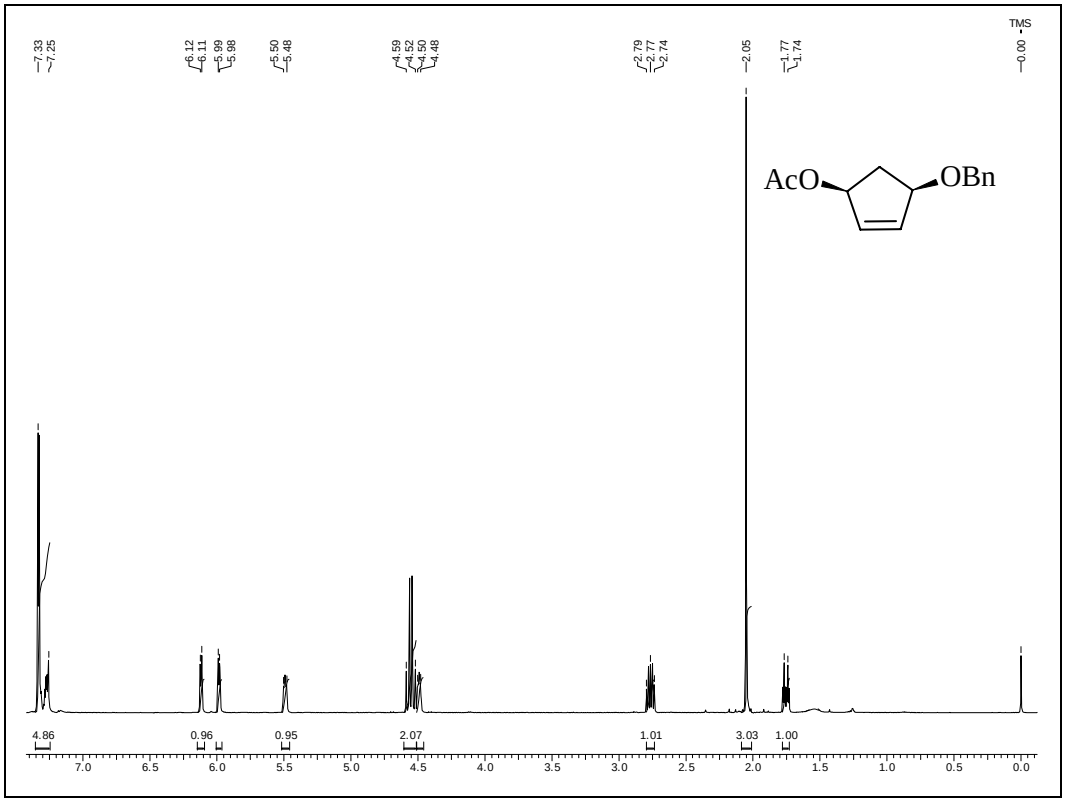
The compound (119)



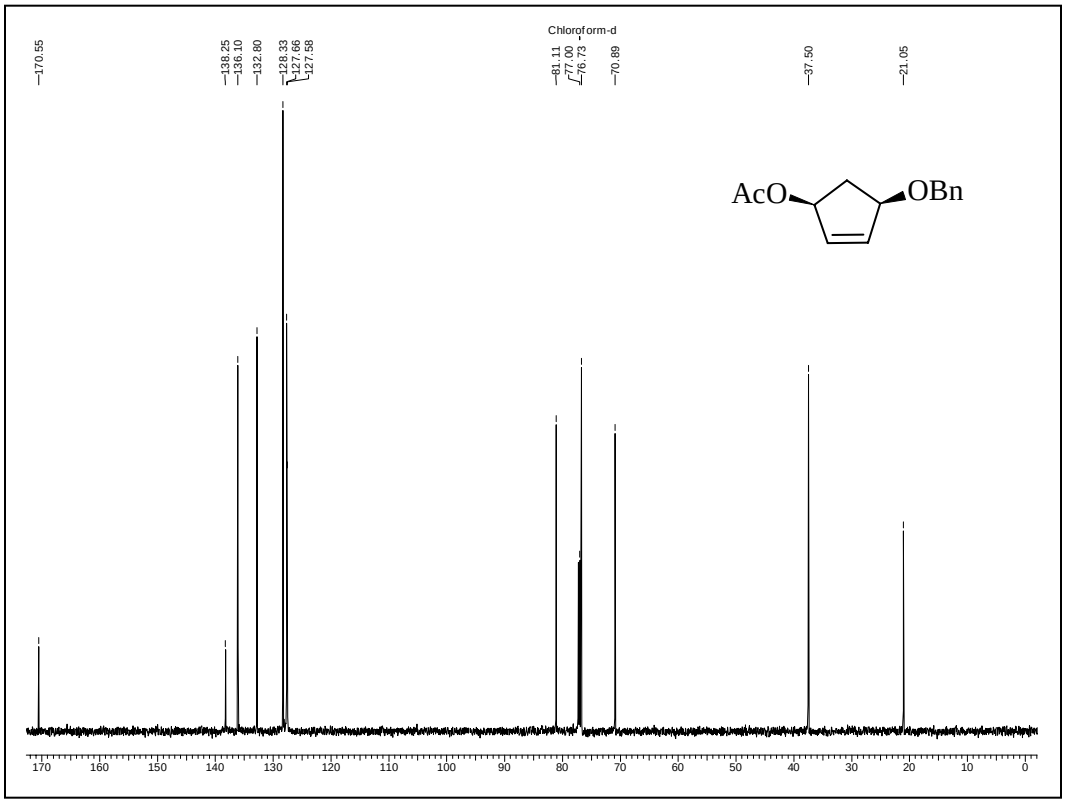
To solution of **142** (40 mg) in ethyl acetate (3 mL), $Pd(OH)_2/C$ (20%, 20 mg) was added at rt and stirred for 5 h. After completion of reaction, the mixture was filtered on a *celite* bed and the filtrate was concentrated. The crude alcohol was directly taken for the next reaction. To a solution of crude alcohol (35 mg, 0.071 mmol) in pyridine (2 mL), acetic anhydride (140 mg, 0.14 mmol) was added at rt and stirred for 6 h. Pyridine and acetic anhydride were removed under reduced pressure. Purification of crude by column chromatography (30% ethyl acetate in petroleum ether) afforded **119** (25 mg, 78%) as colorless oil.

Mol. Formula	: $C_{23}H_{32}O_{14}$
$[\alpha]_D$	: +36.6 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2927, 2400, 1743, 1371, 1215, 1052, 758, 669, 529 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.76–1.82 (m, 1H), 2.04 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.11 (d, *J* = 2.0 Hz, 9H), 2.22–2.39 (m, 2H), 3.55 (dd, *J* = 4.9, 9.5 Hz, 1H), 3.75 (dd, *J* = 6.7, 6.4 Hz, 1H), 4.18–4.29 (m, 2H), 4.39–4.49 (m, 1H), 4.96 (dd, *J* = 1.0, 4.2 Hz, 1H), 5.04 (s, 1H), 5.07 (d, *J* = 1.5 Hz, 1H), 5.12–5.18 (m, 1H), 5.21–5.30 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 20.6 (q), 20.76 (q), 20.79 (q), 20.8 (q), 20.9 (q), 30.2 (t), 39.6 (d), 63.3 (t), 67.6 (t), 71.0 (d), 76.18 (d), 76.2 (d), 77.1 (d), 77.2 (d), 80.6 (d), 80.9 (d), 105.2 (d), 169.6 (s), 170.0 (s), 170.1 (s), 170.2 (s), 170.3 (s), 170.6 (s) ppm.
Elemental Analysis	Calcd.: C, 51.87; H, 6.06. Found: C, 51.84; H, 6.10.

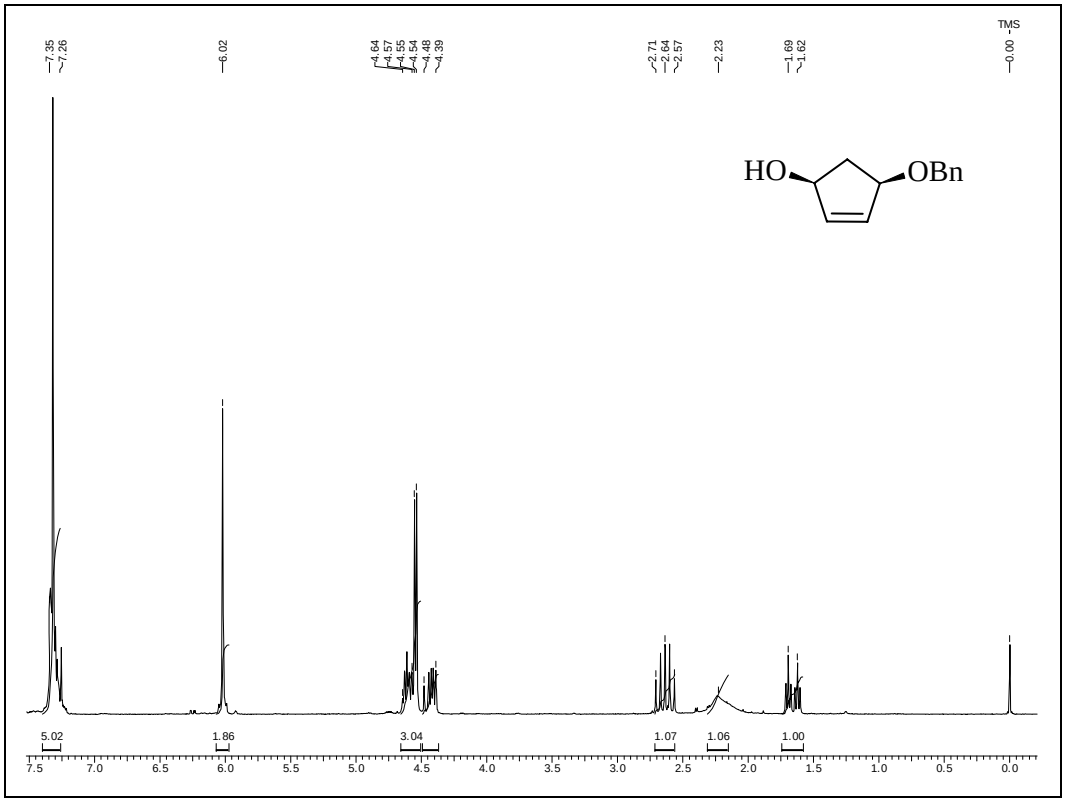
Spectra



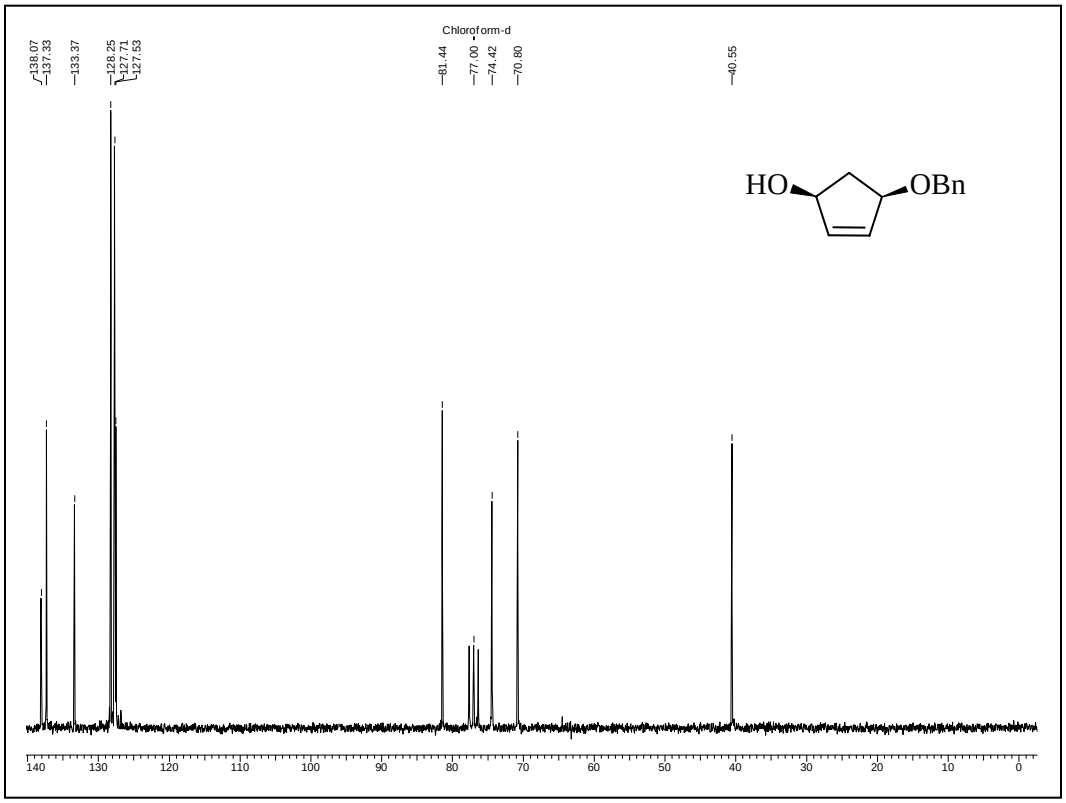
^{1}H NMR Spectrum of 125 in $CDCl_3$



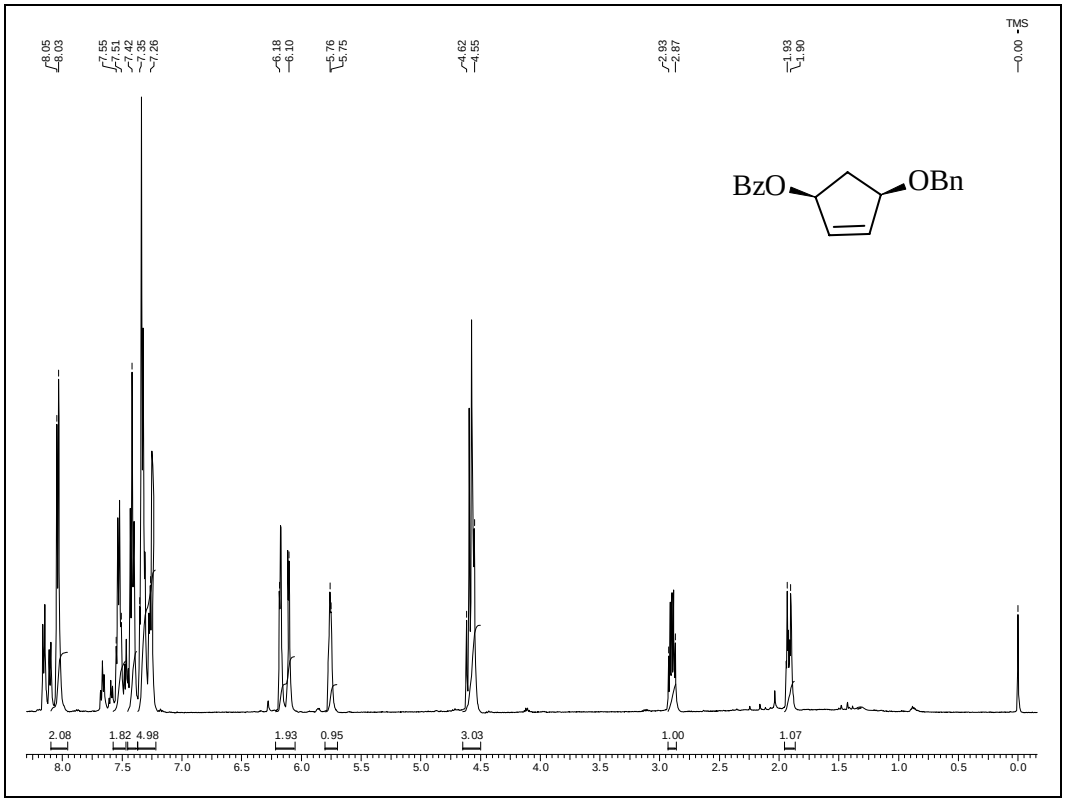
^{13}C NMR Spectrum of 125 in $CDCl_3$



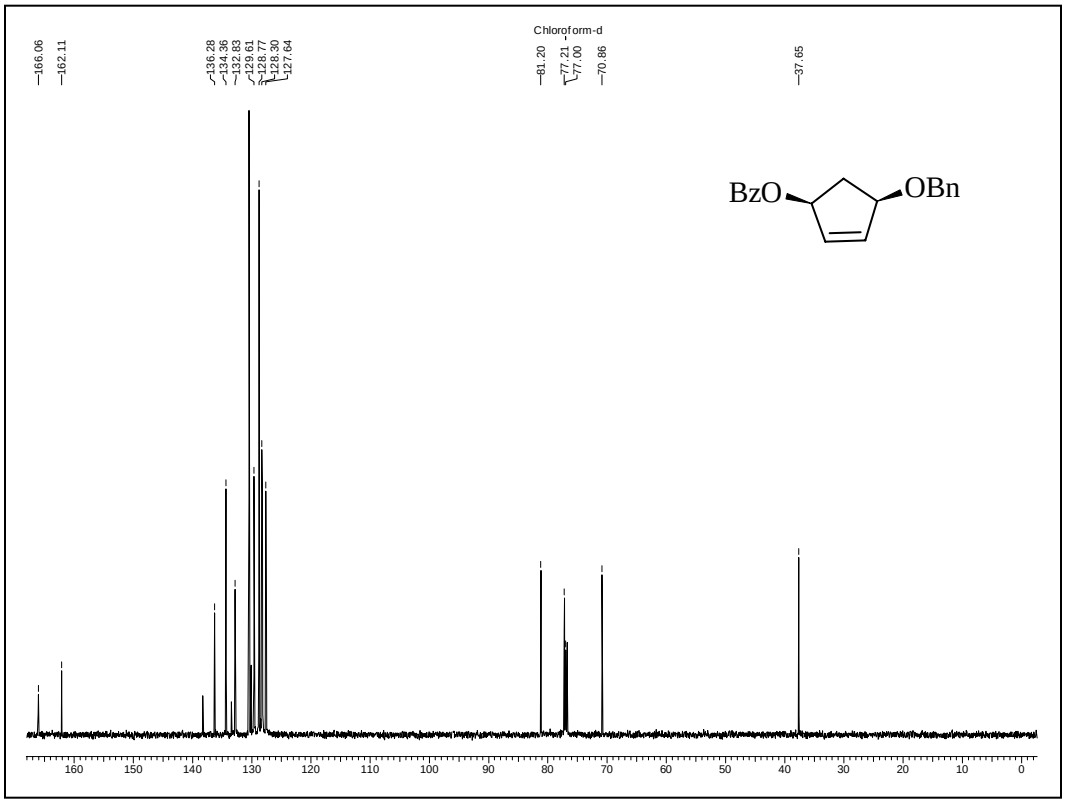
^{1}H NMR Spectrum of 126 in $CDCl_3$



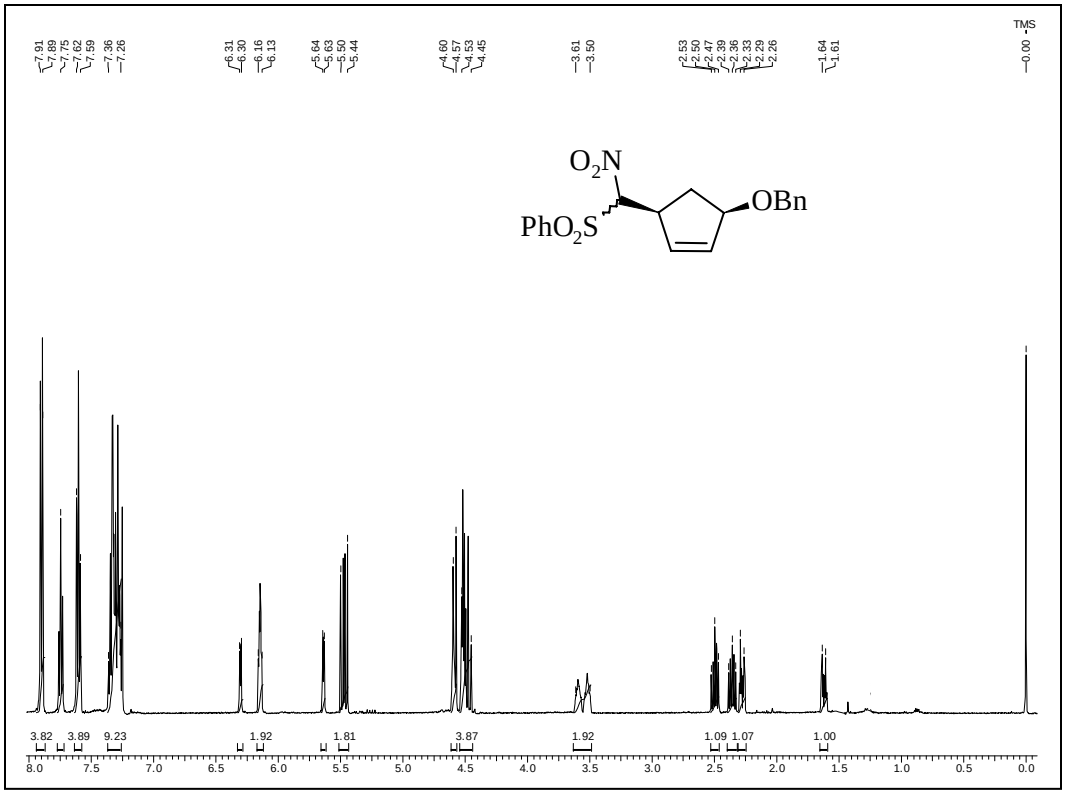
^{13}C NMR Spectrum of 126 in $CDCl_3$



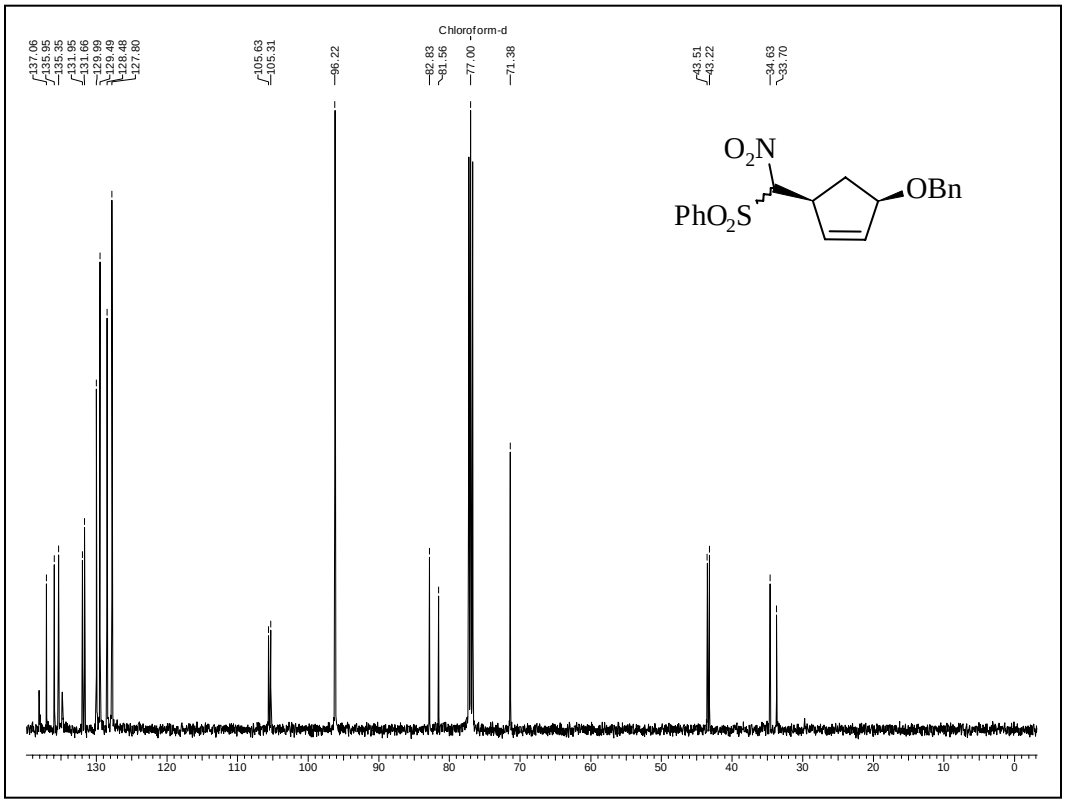
^{1}H NMR Spectrum of 123 in $CDCl_3$



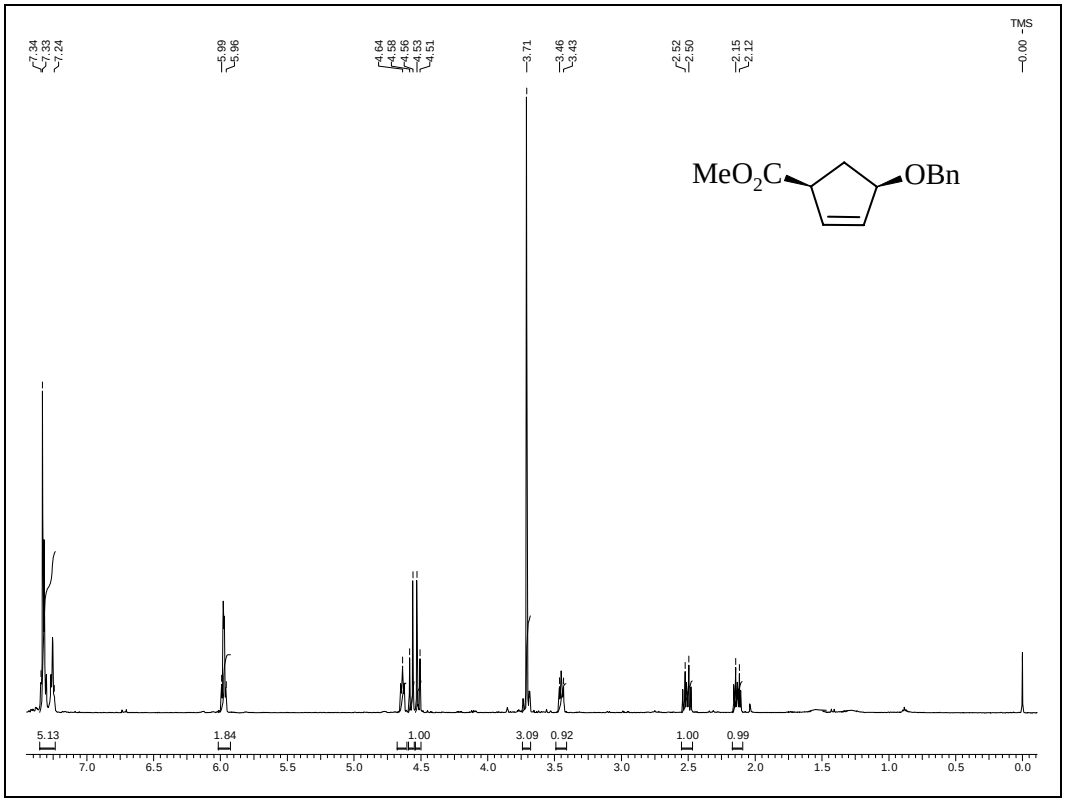
^{13}C NMR Spectrum of 123 in $CDCl_3$



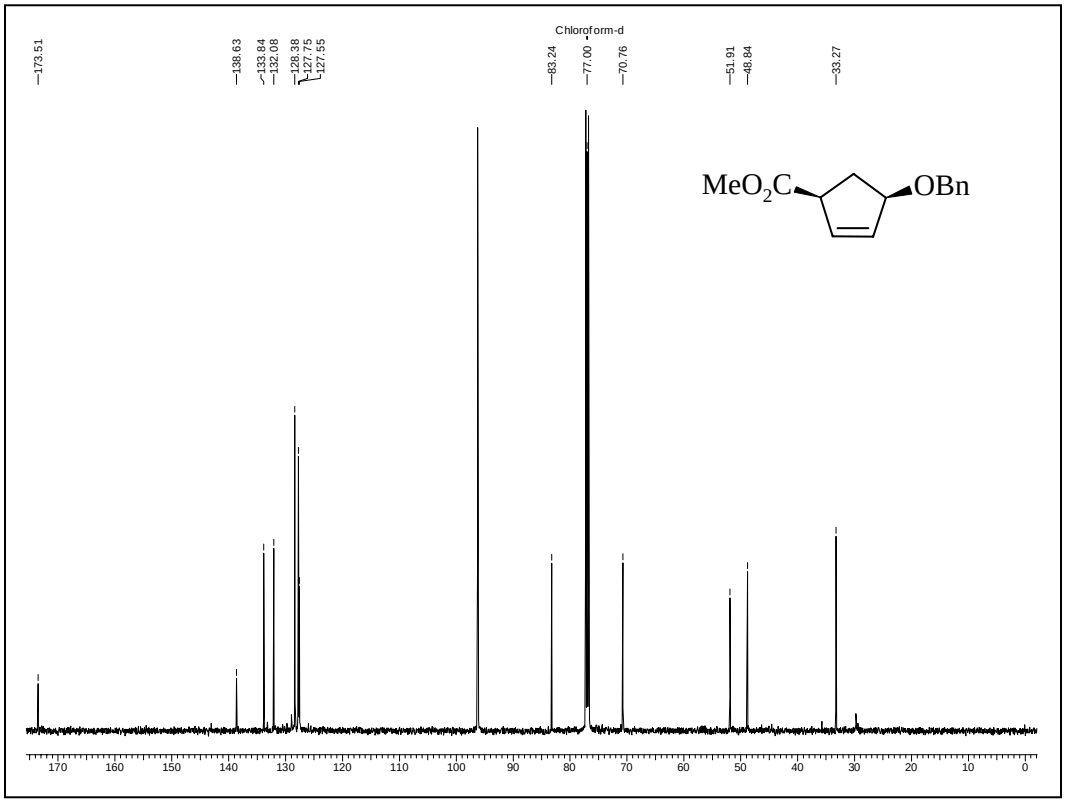
^{1}H NMR Spectrum of 127 in $CDCl_3$



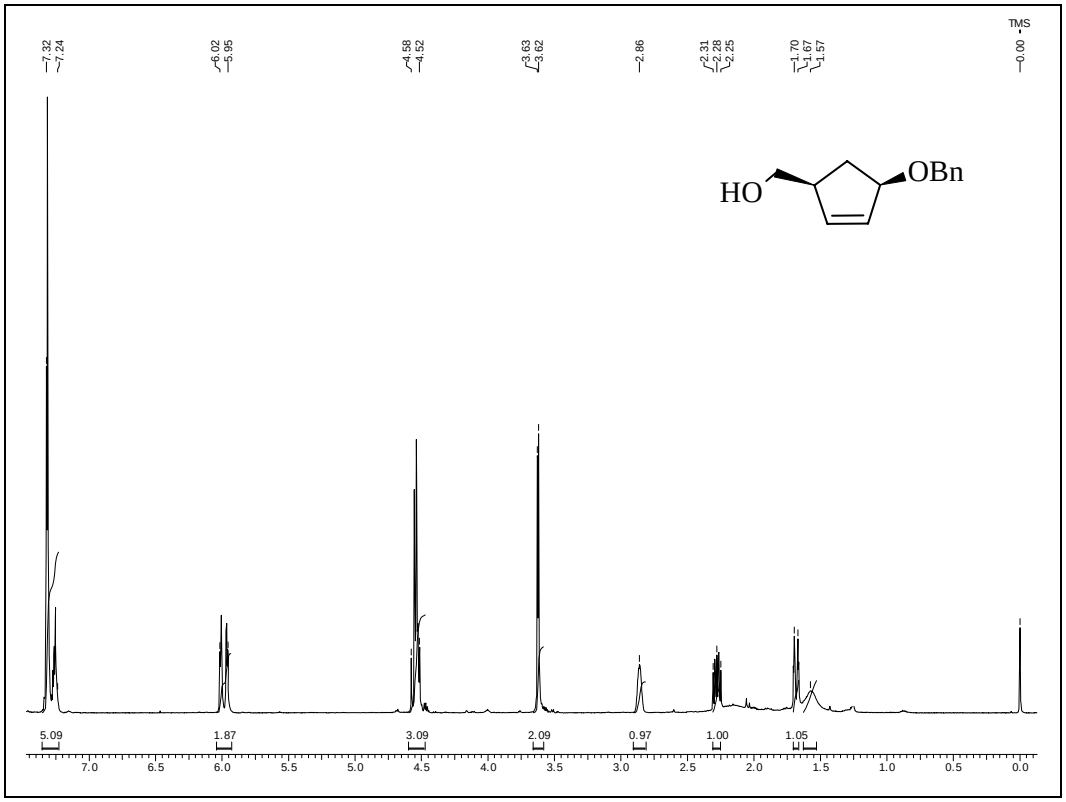
^{13}C NMR Spectrum of 127 in $CDCl_3$



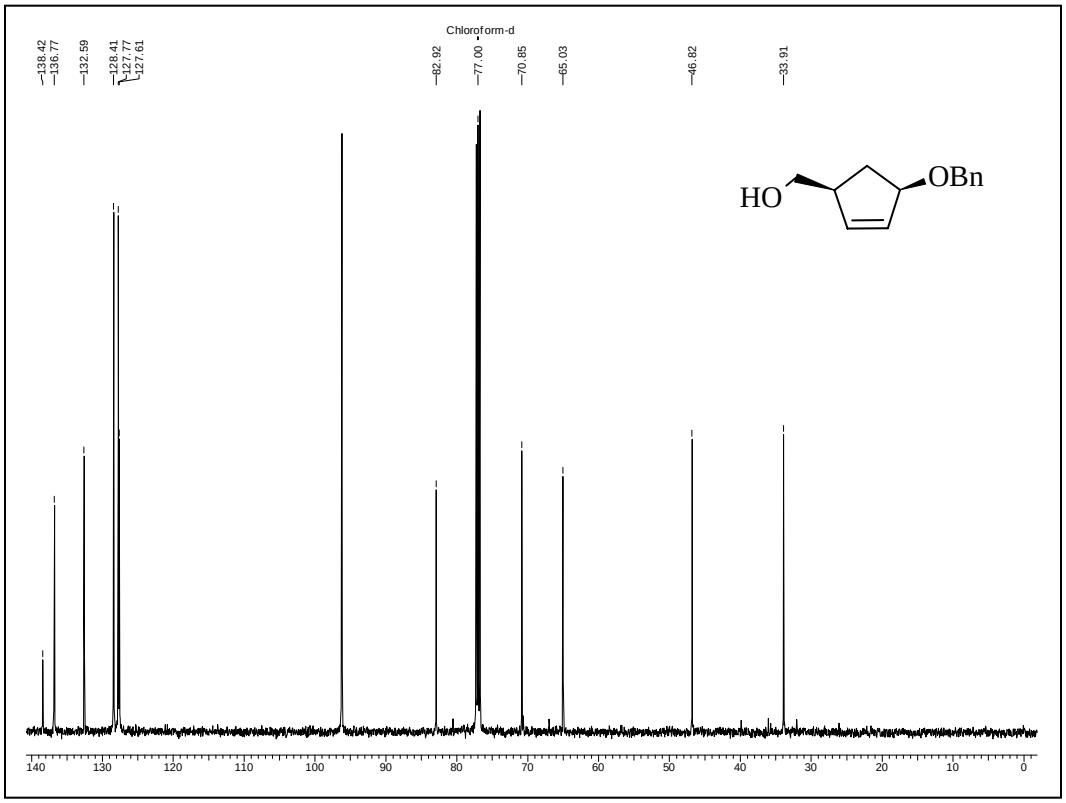
^{1}H NMR Spectrum of 128 in $CDCl_3$



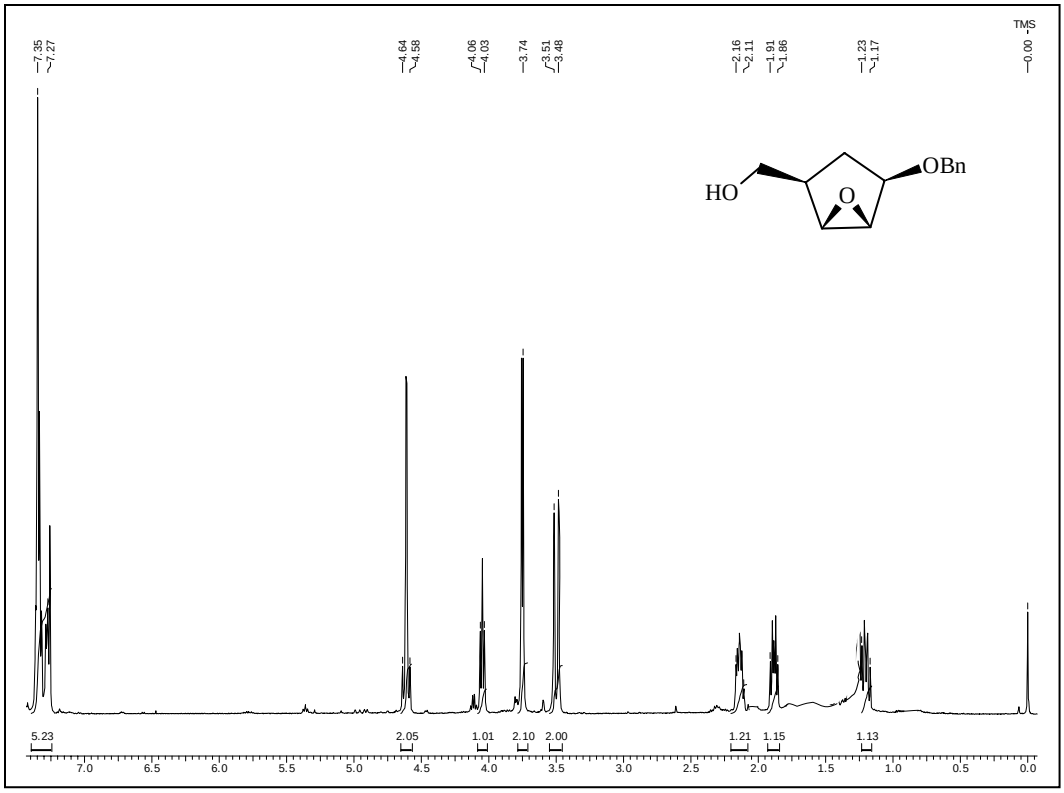
^{13}C NMR Spectrum of 128 in $CDCl_3$



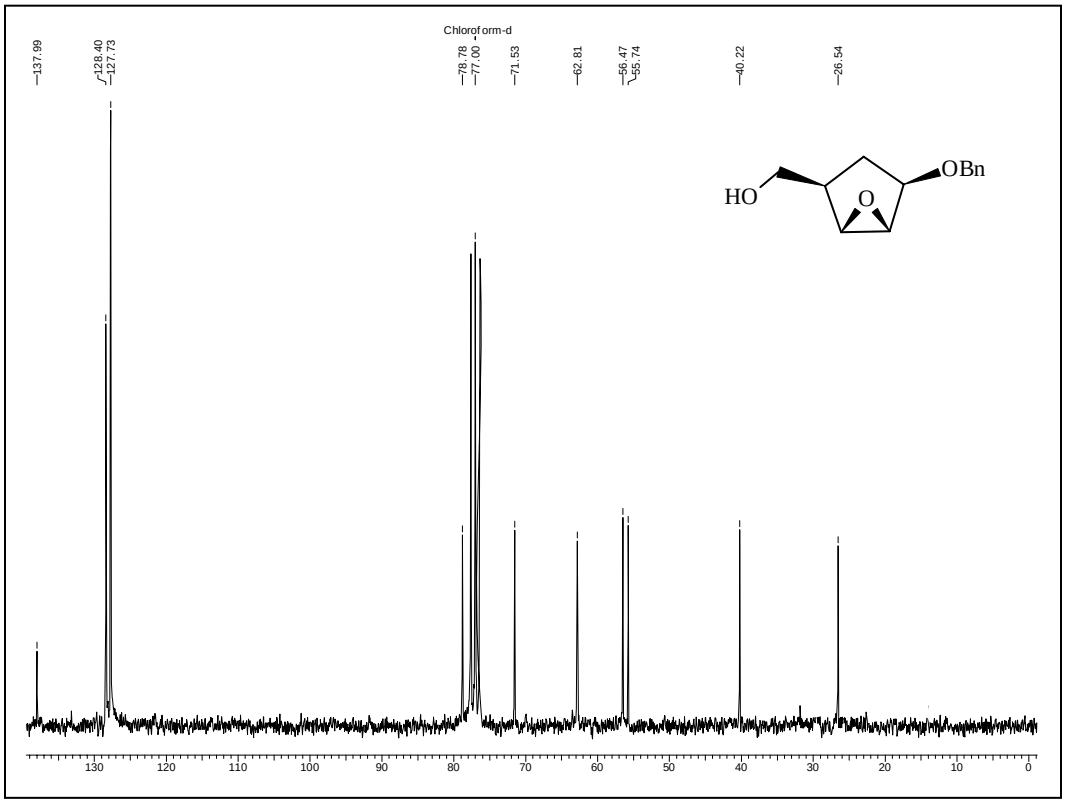
^{1}H NMR Spectrum of 122 in $CDCl_3$



^{13}C NMR Spectrum of 122 in $CDCl_3$

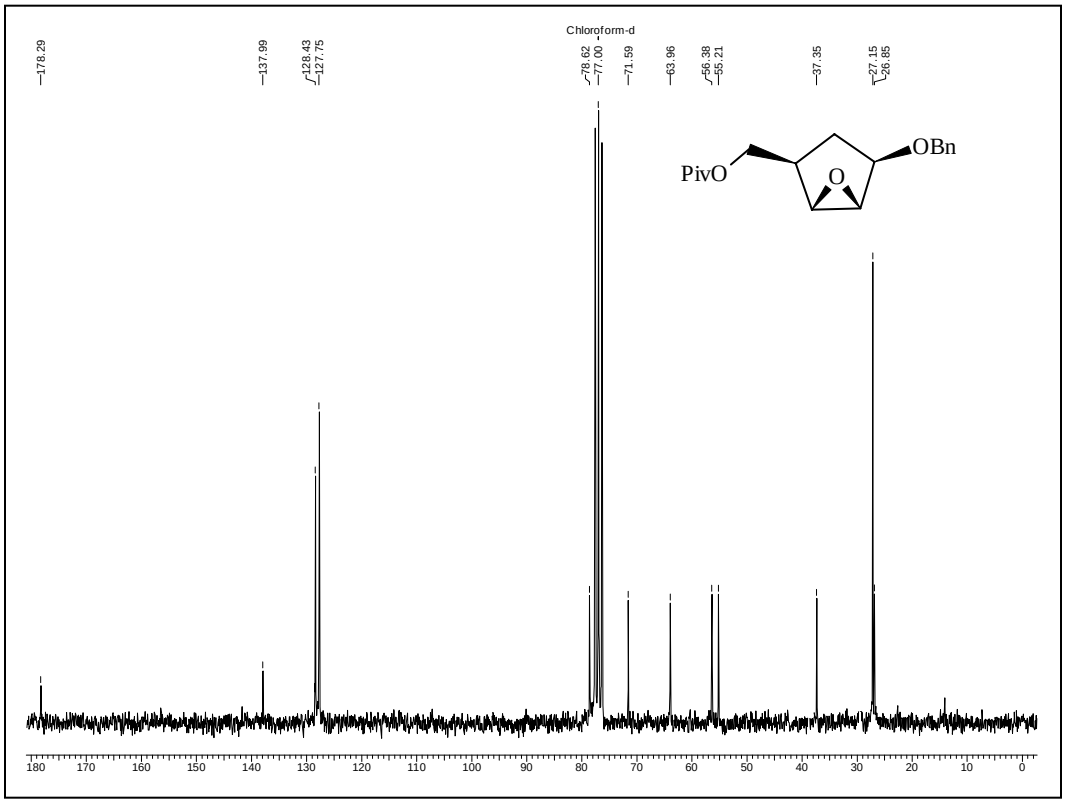


^{1}H NMR Spectrum of 129 in $CDCl_3$

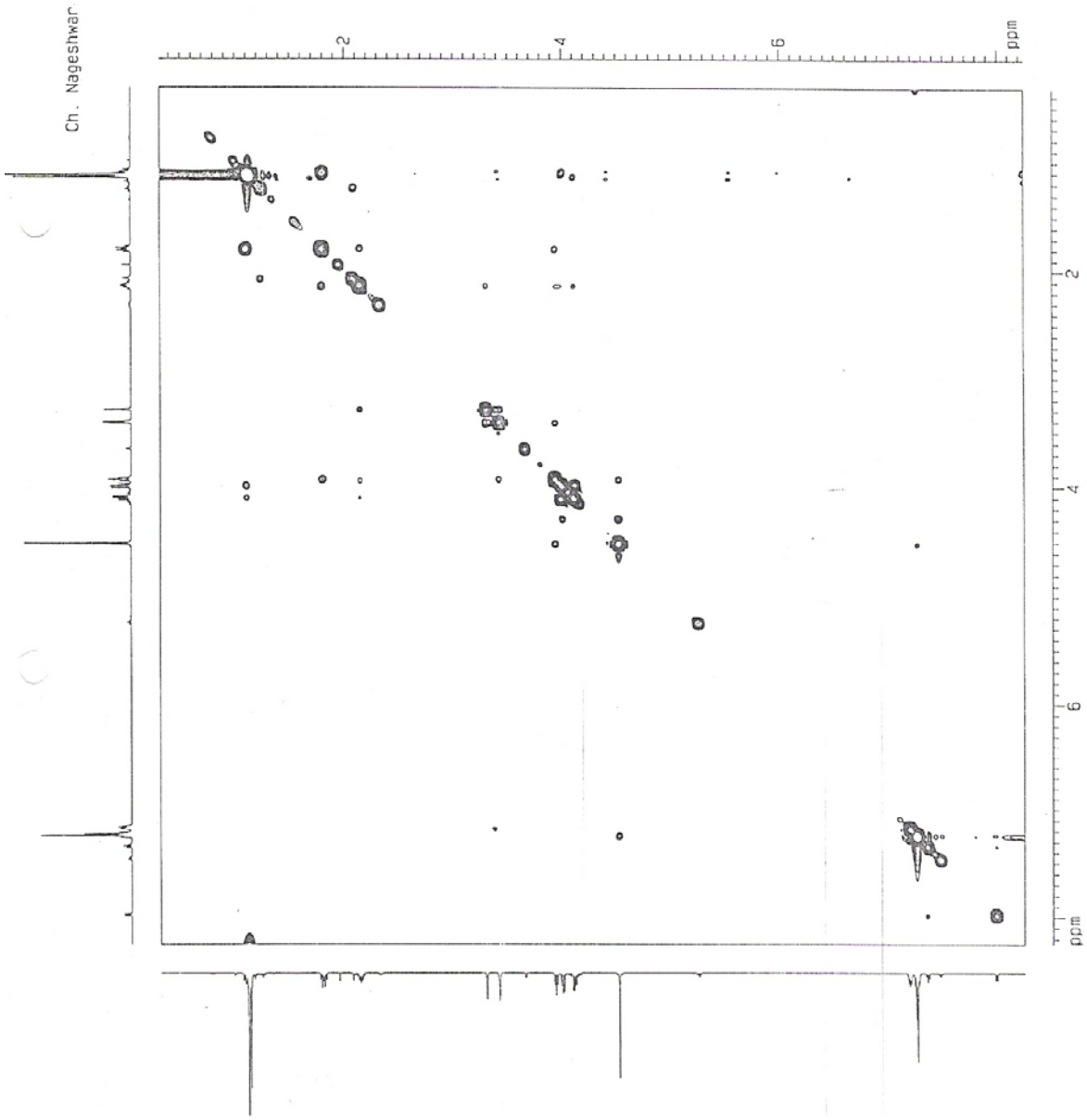


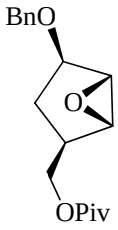
^{13}C NMR Spectrum of 129 in $CDCl_3$

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

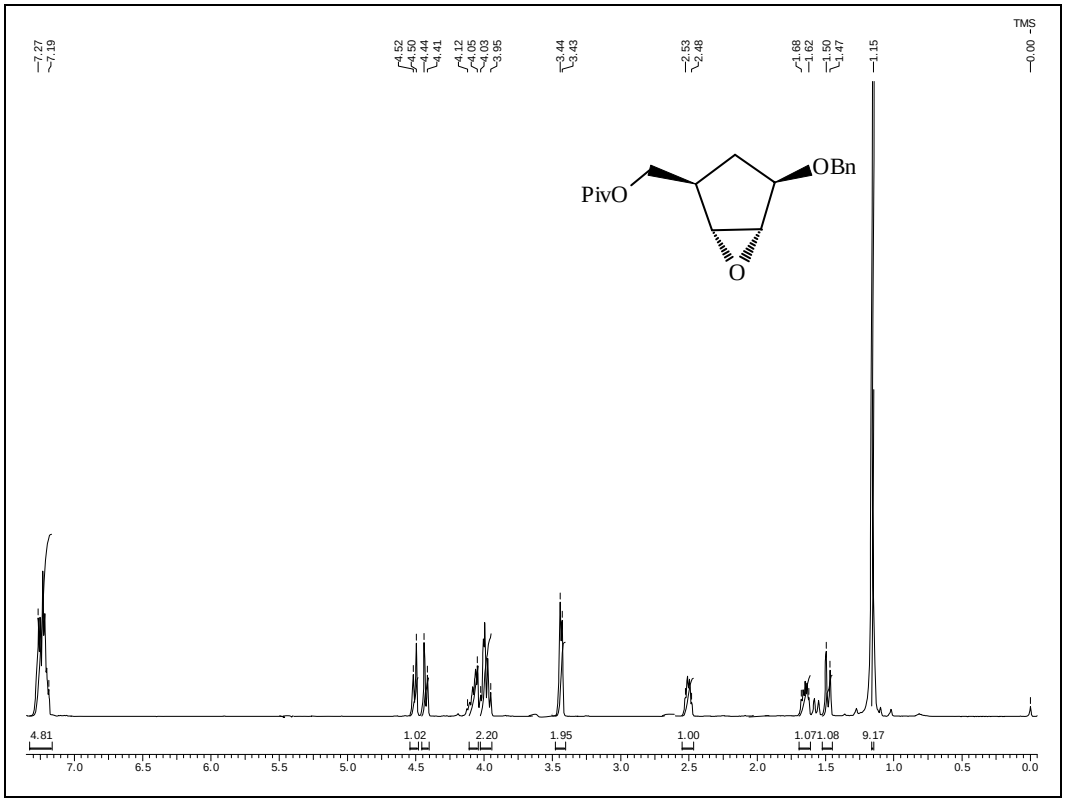


^{13}C NMR Spectrum of 131 in $CDCl_3$

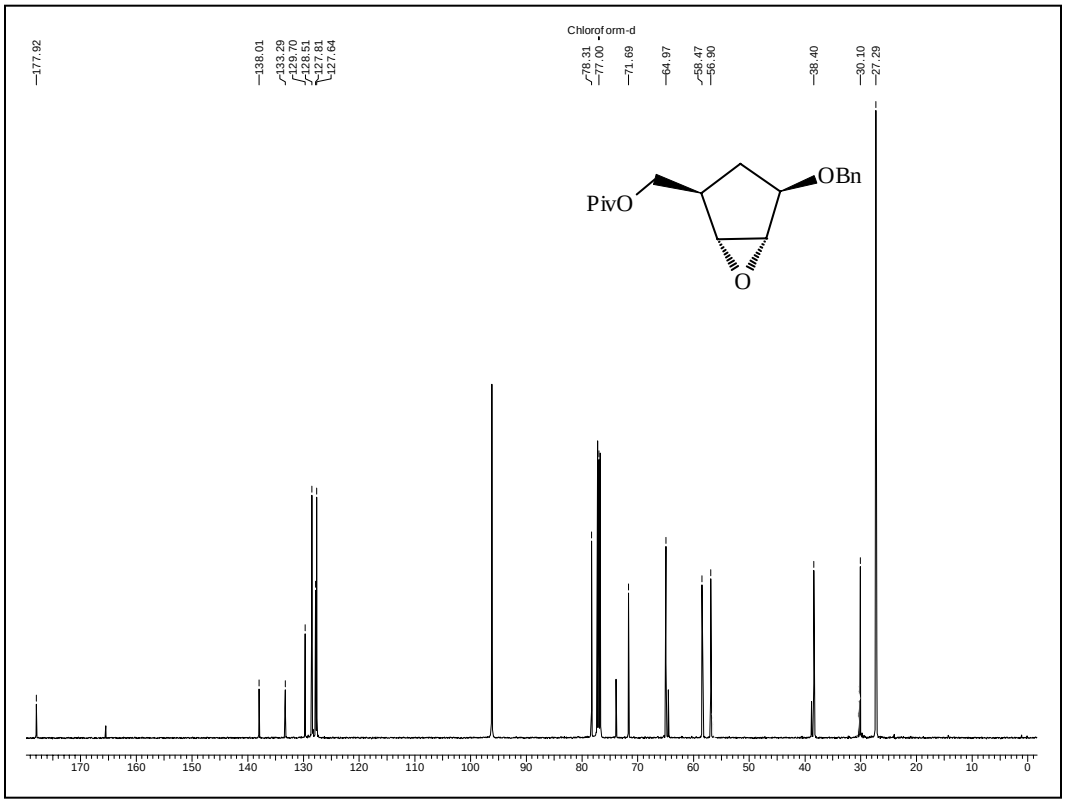




NOESY of compound 131

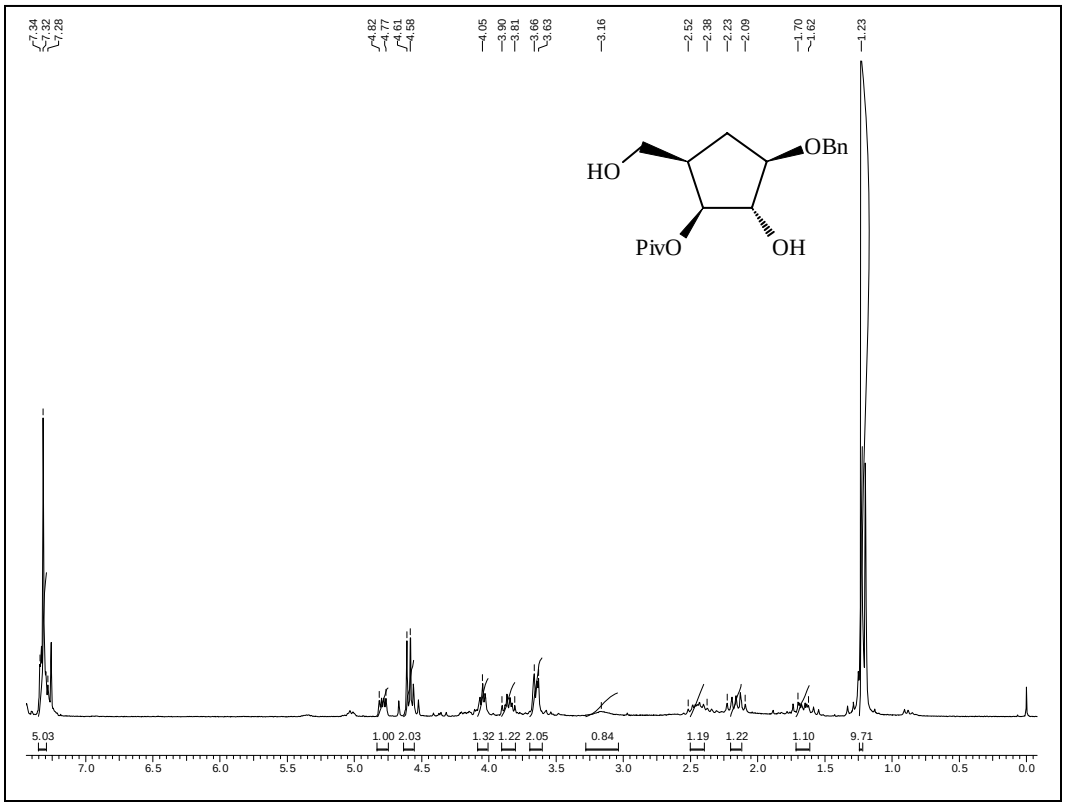


^{1}H NMR Spectrum of 132 in $CDCl_3$

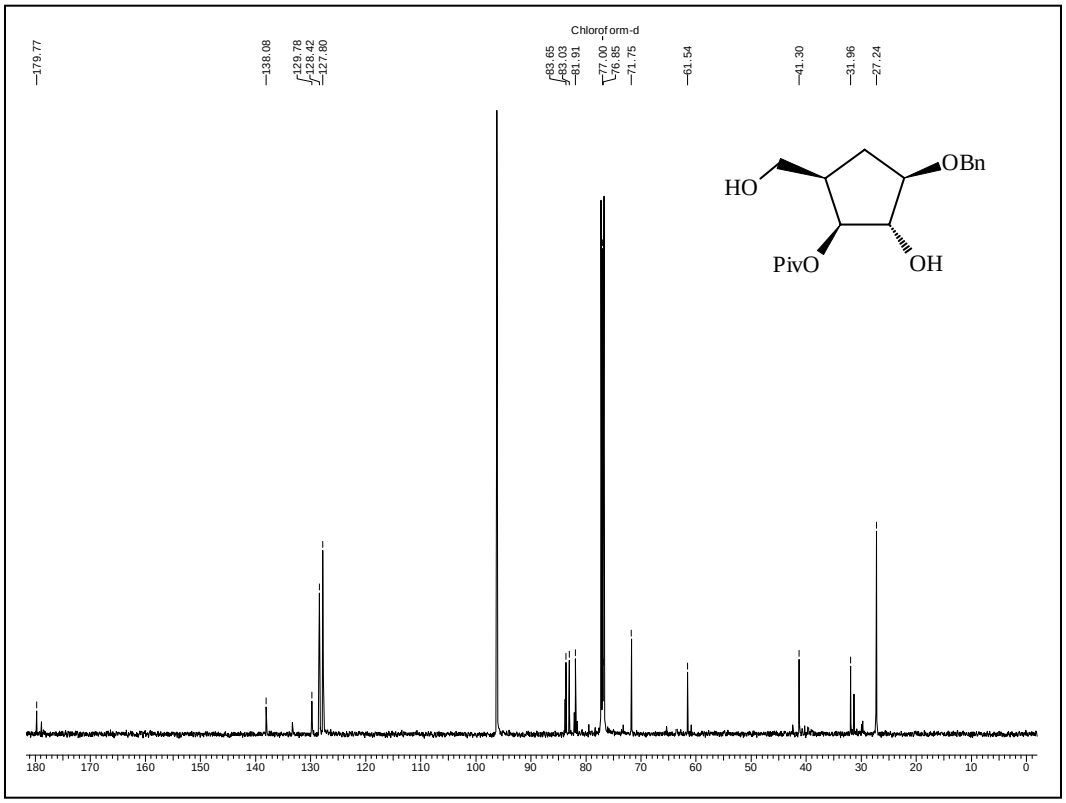


^{13}C NMR Spectrum of 132 in $CDCl_3$

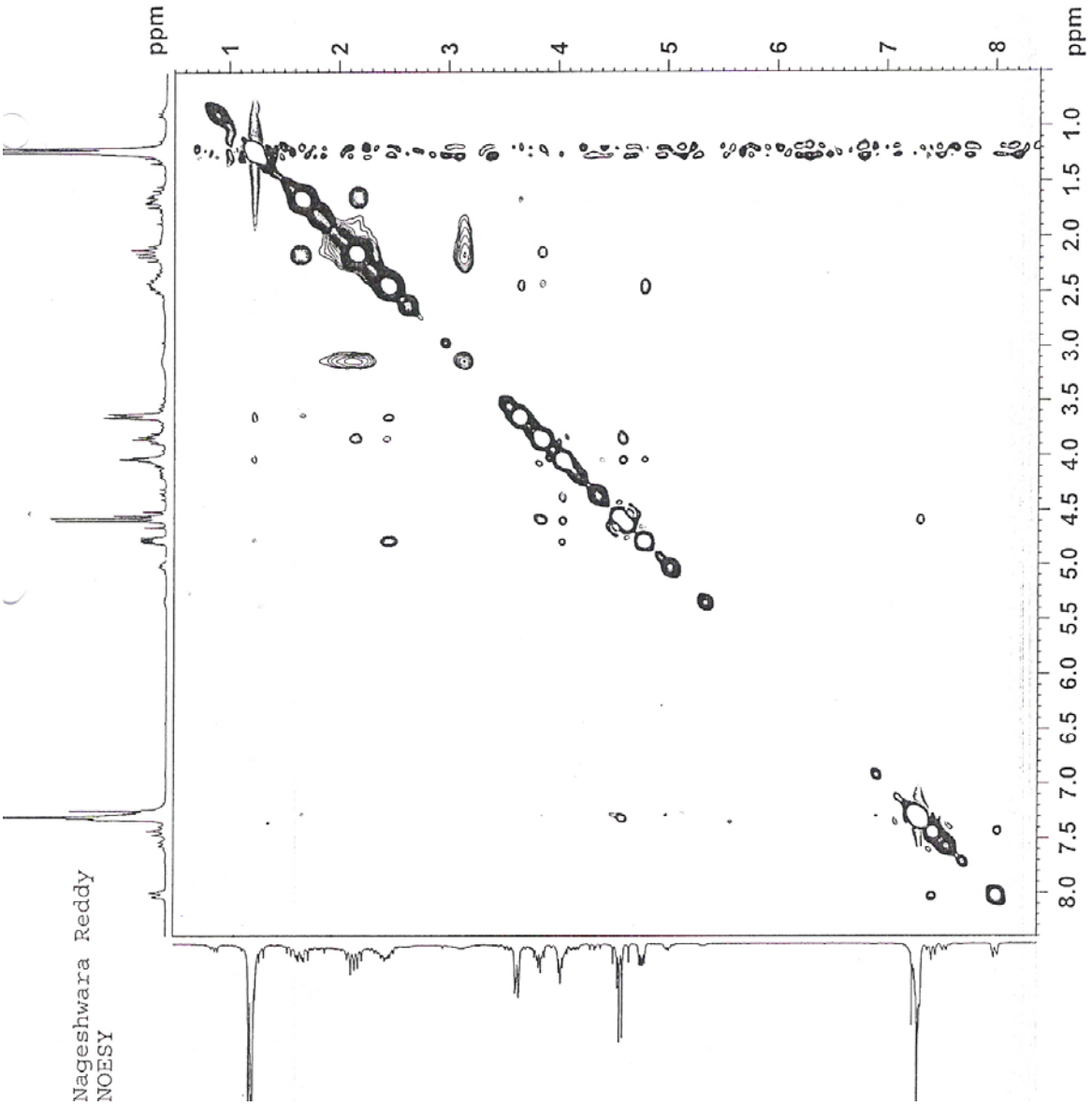
NOESY of compound 132

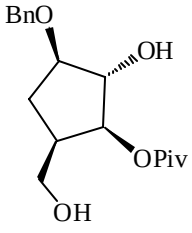


^{1}H NMR Spectrum of 138 in $CDCl_3$

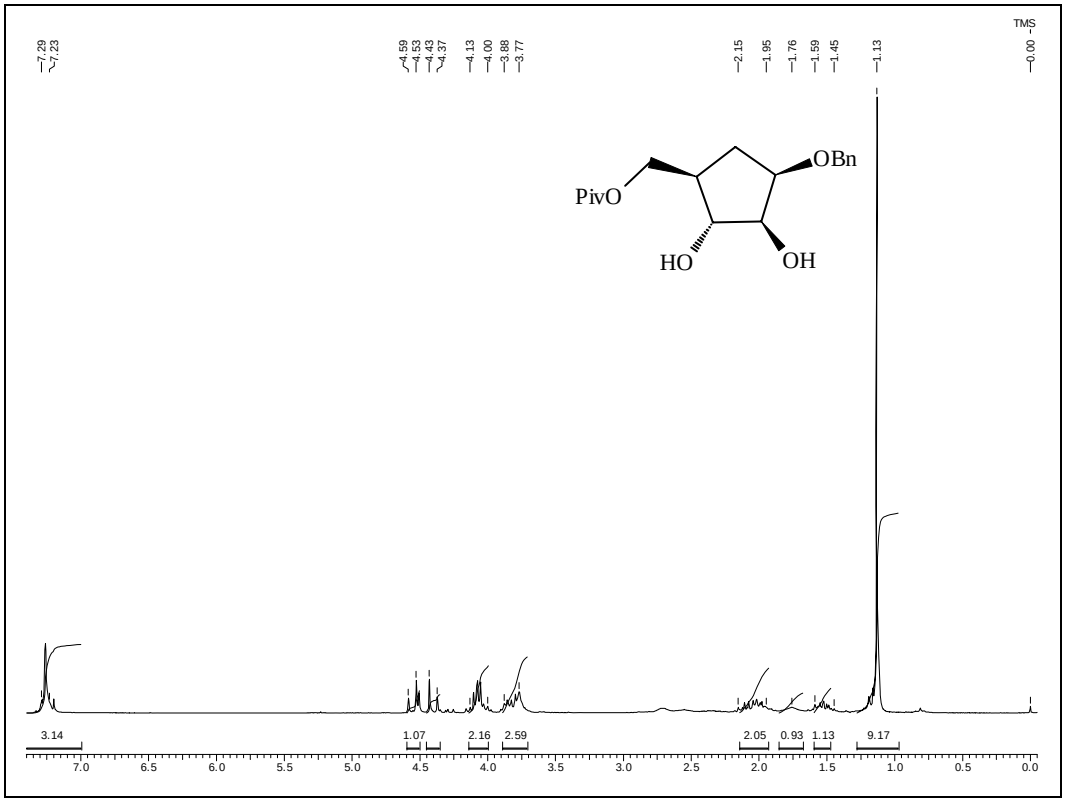


^{13}C NMR Spectrum of 138 in $CDCl_3$

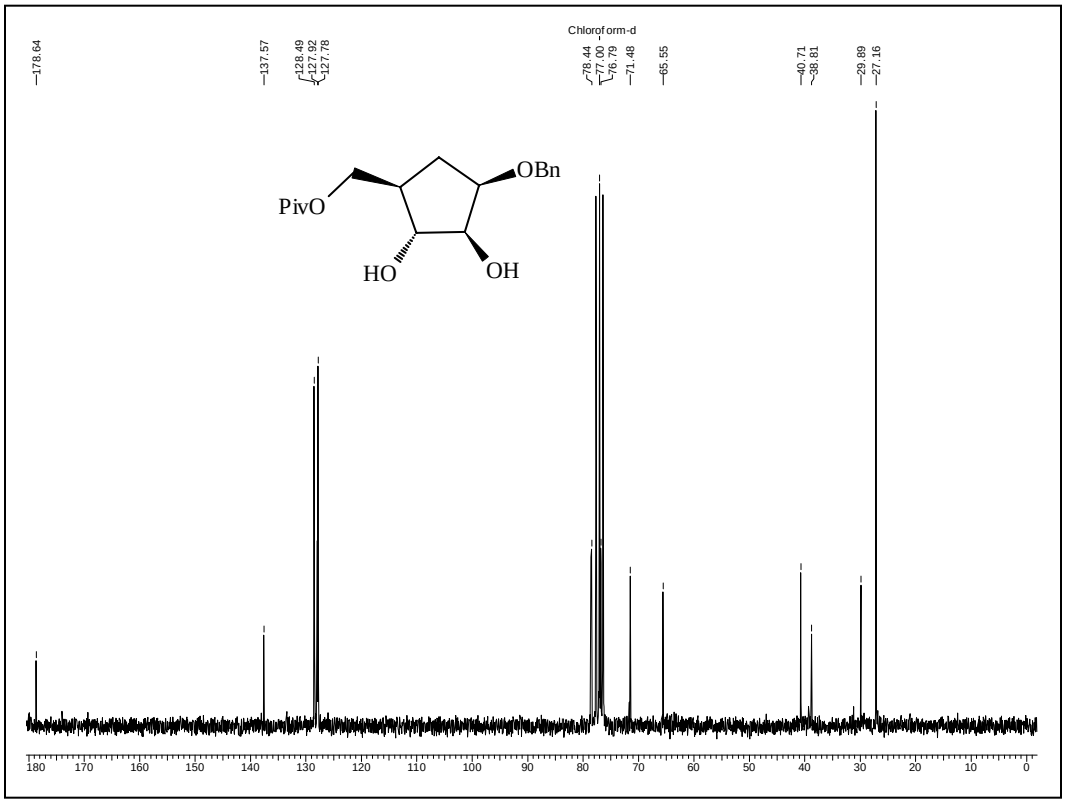




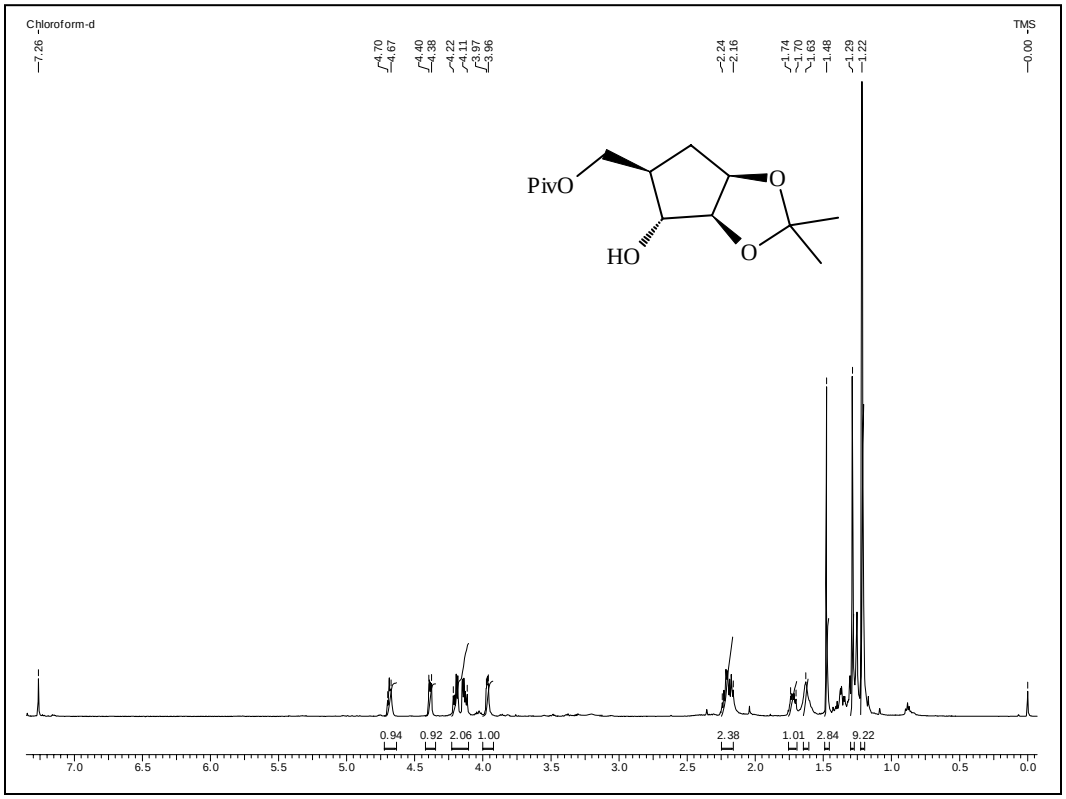
NOESY of compound 138



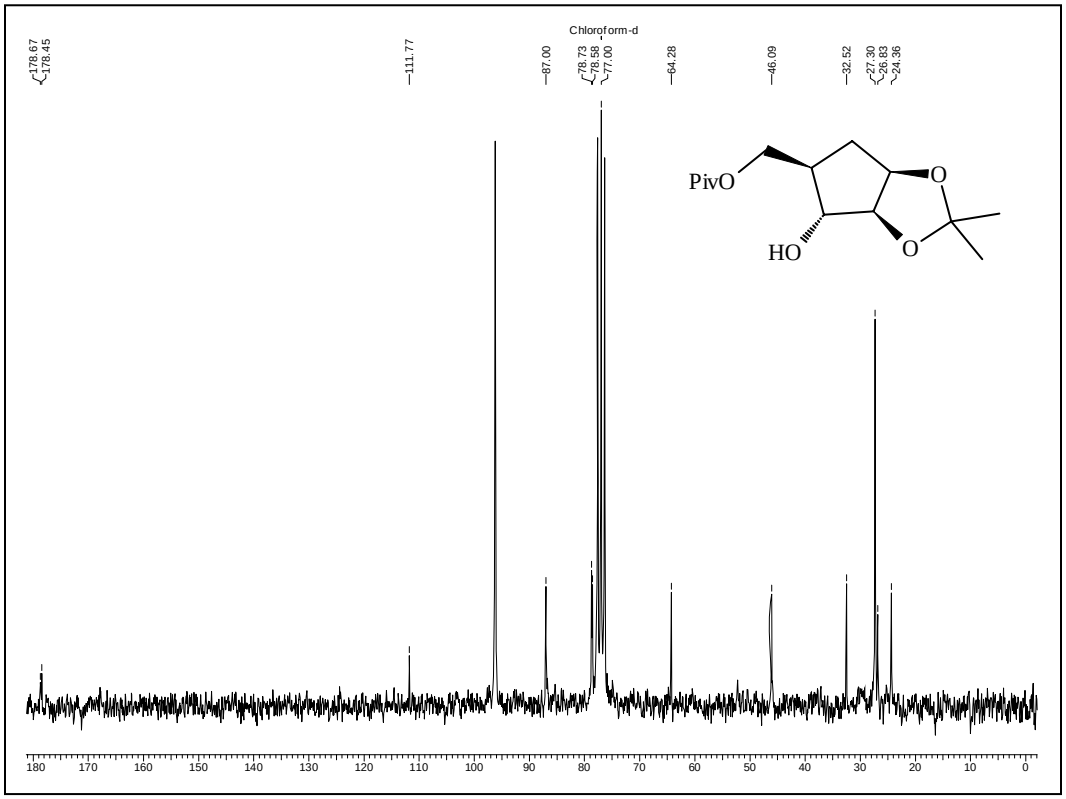
^{1}H NMR Spectrum of 133 in $CDCl_3$



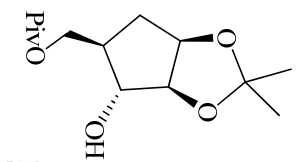
^{13}C NMR Spectrum of 133 in $CDCl_3$



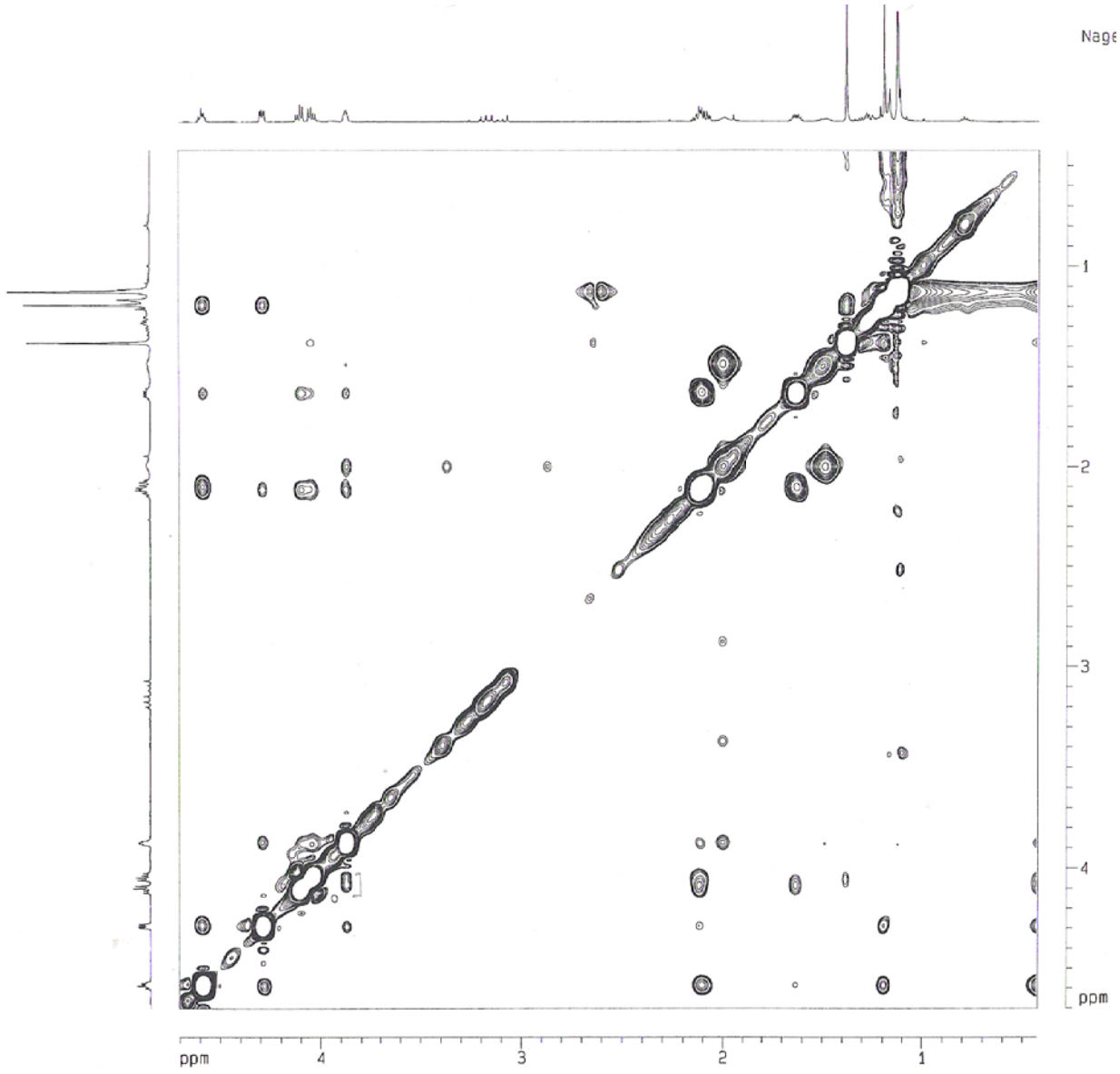
^{1}H NMR Spectrum of 134 in $CDCl_3$

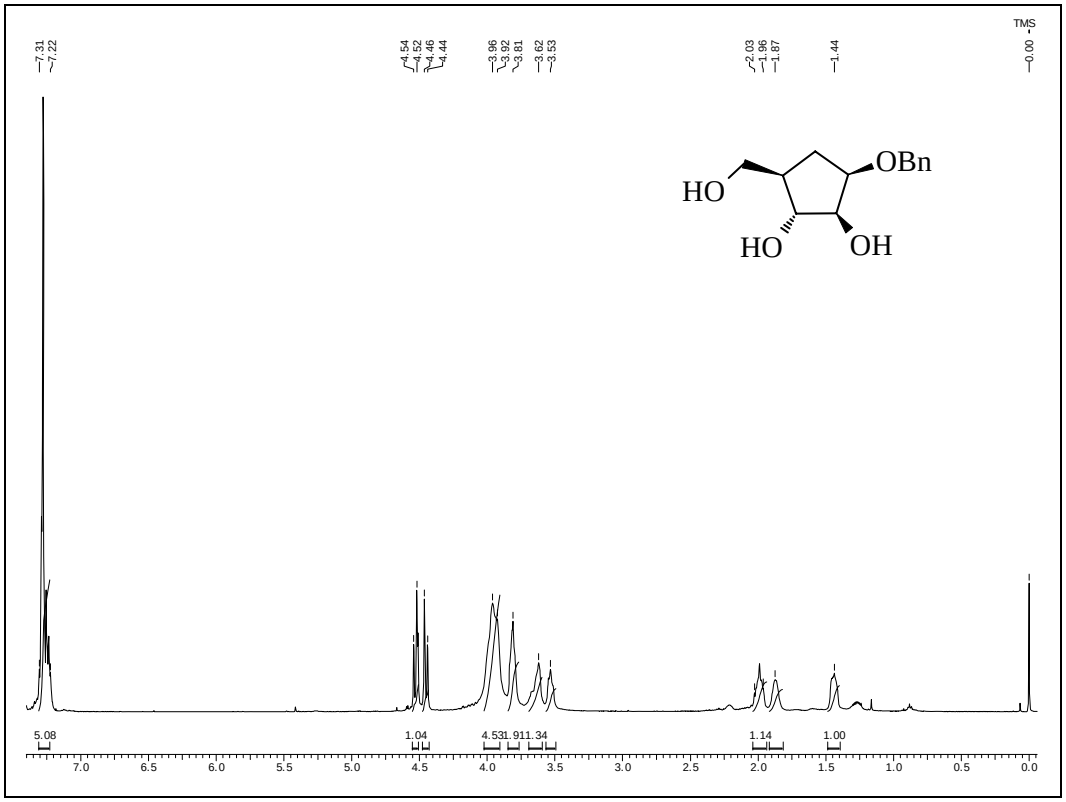


^{13}C NMR Spectrum of 134 in $CDCl_3$

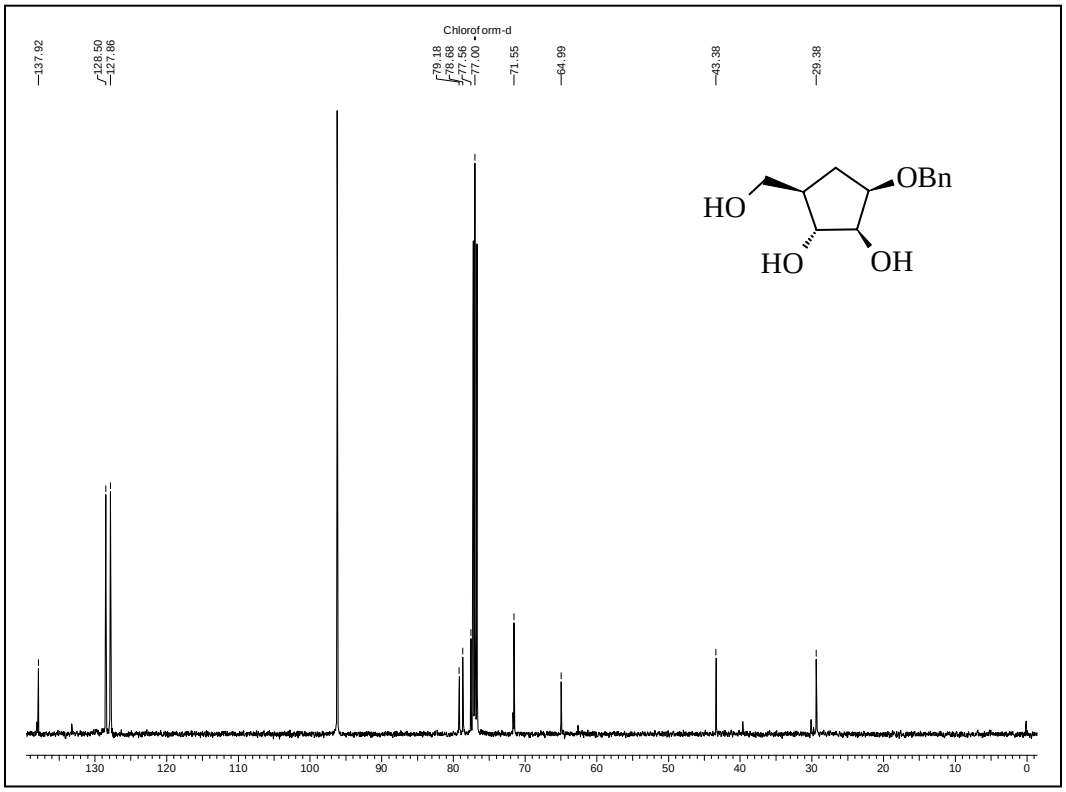


NOESY of compound 134

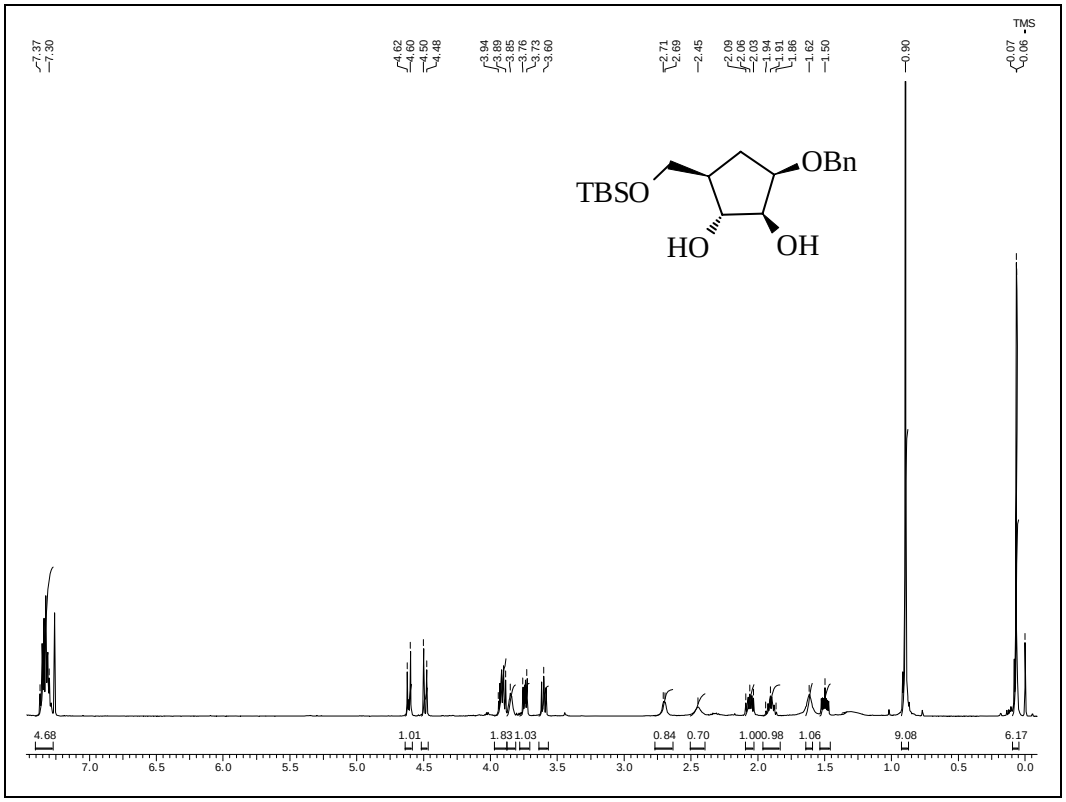




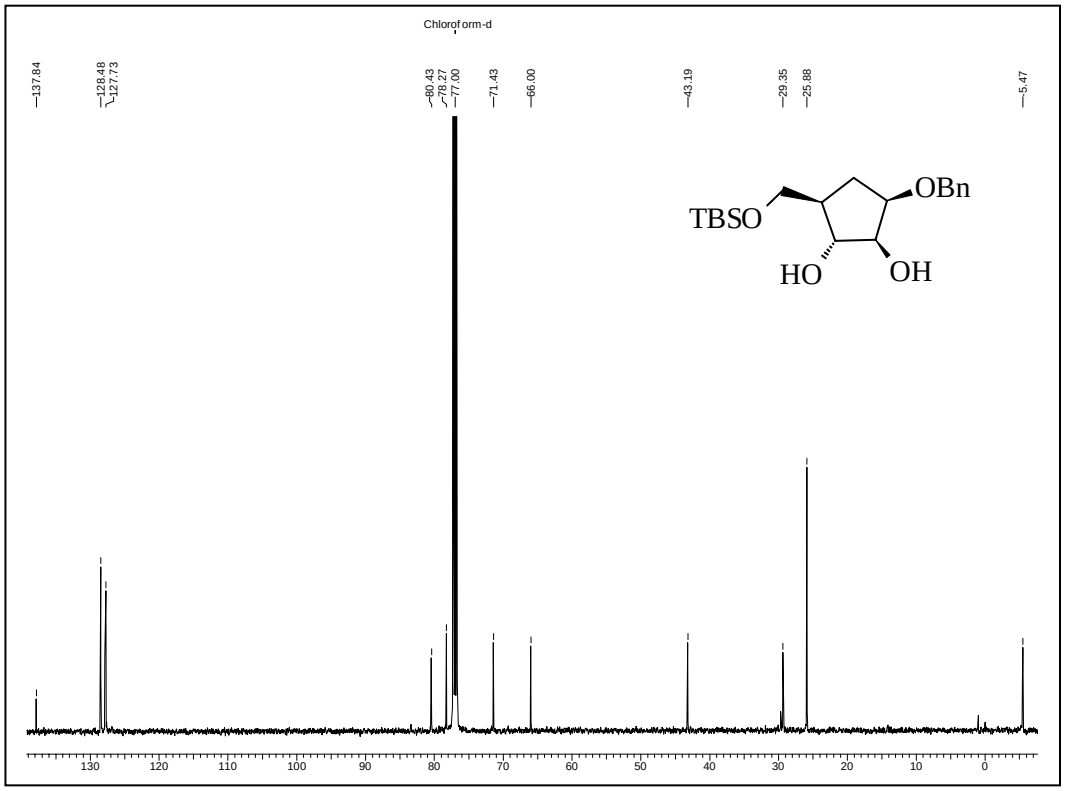
^{1}H NMR Spectrum of 135 in $CDCl_3$



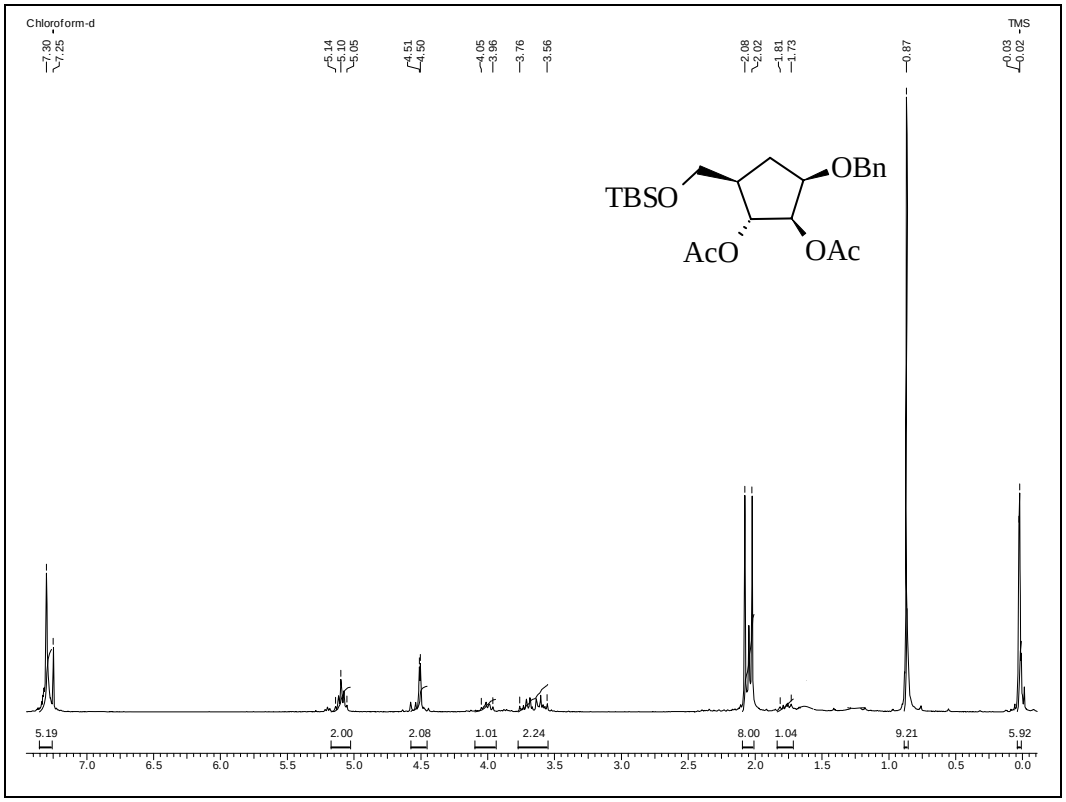
^{13}C NMR Spectrum of 135 in $CDCl_3$



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



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



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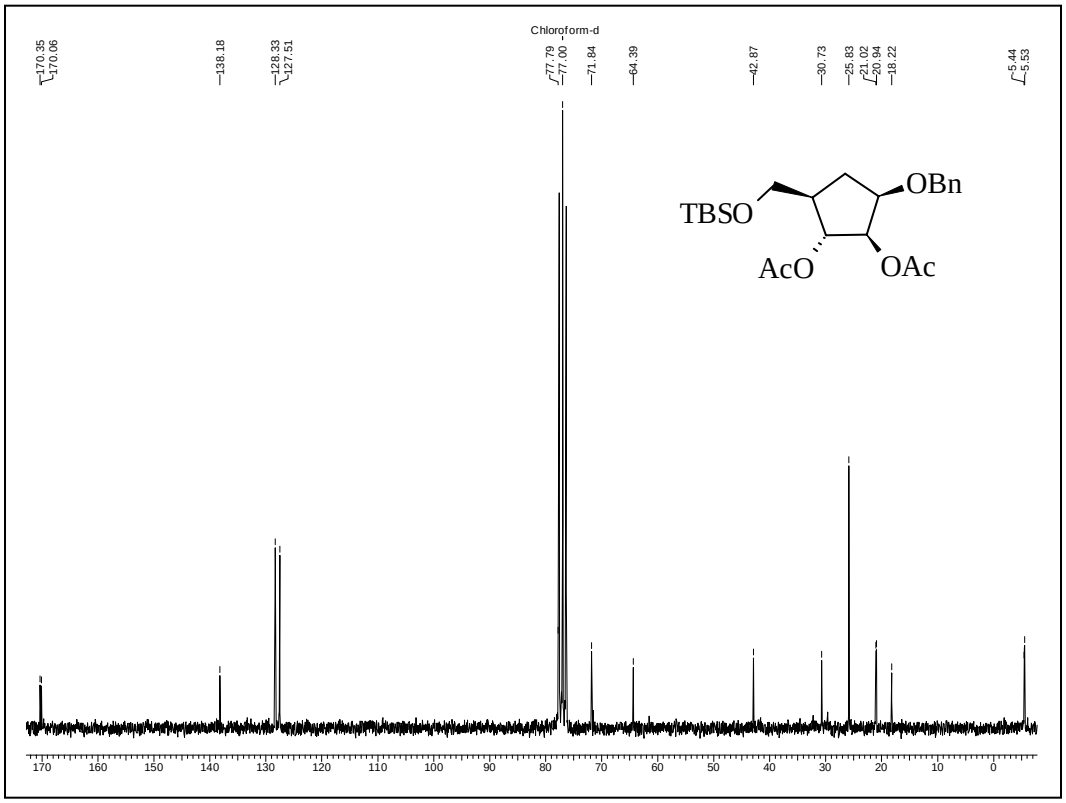

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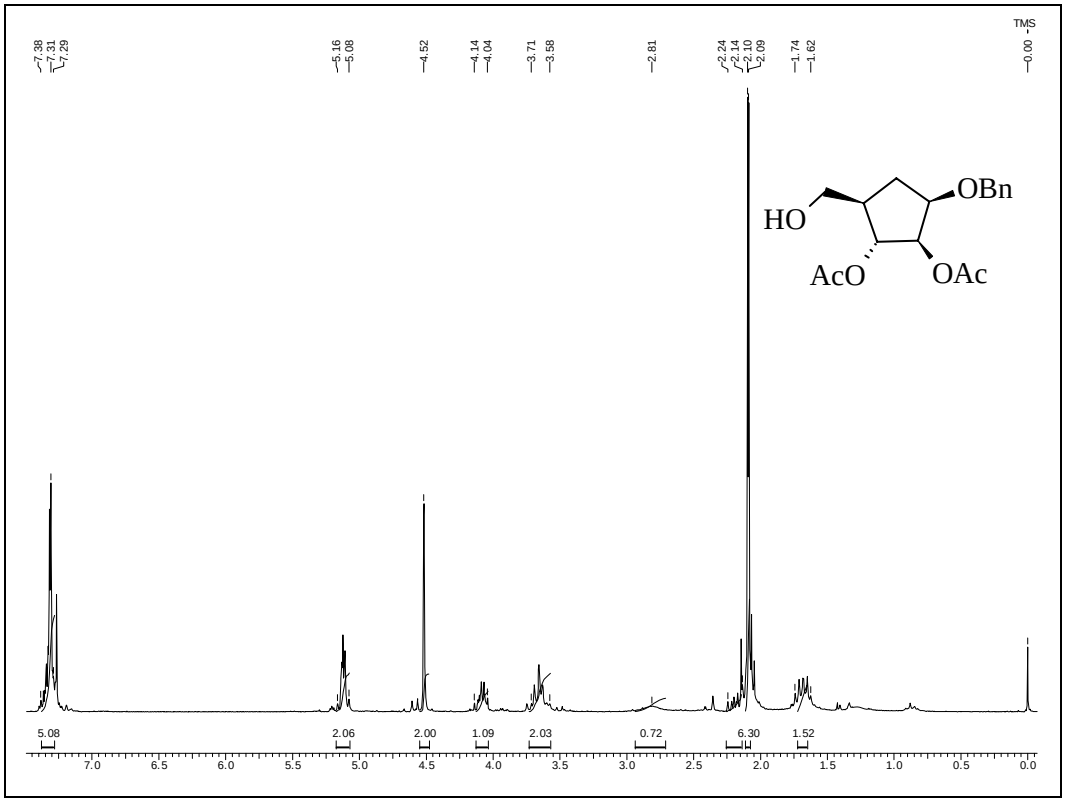

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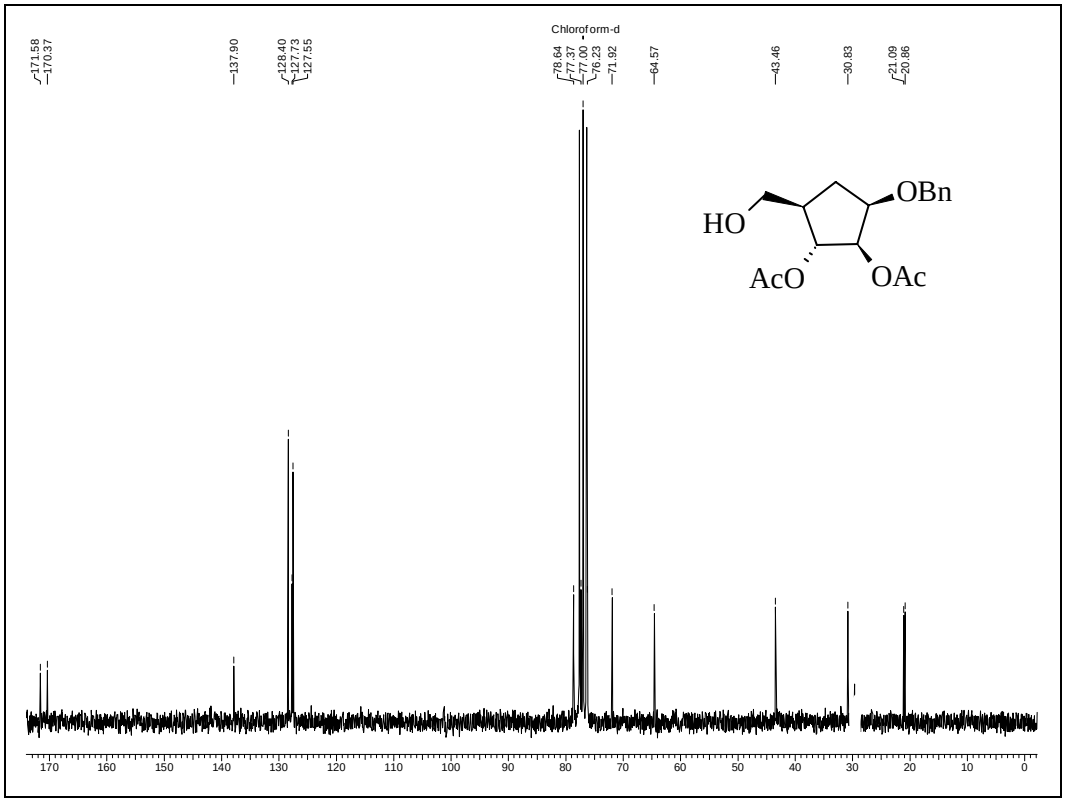
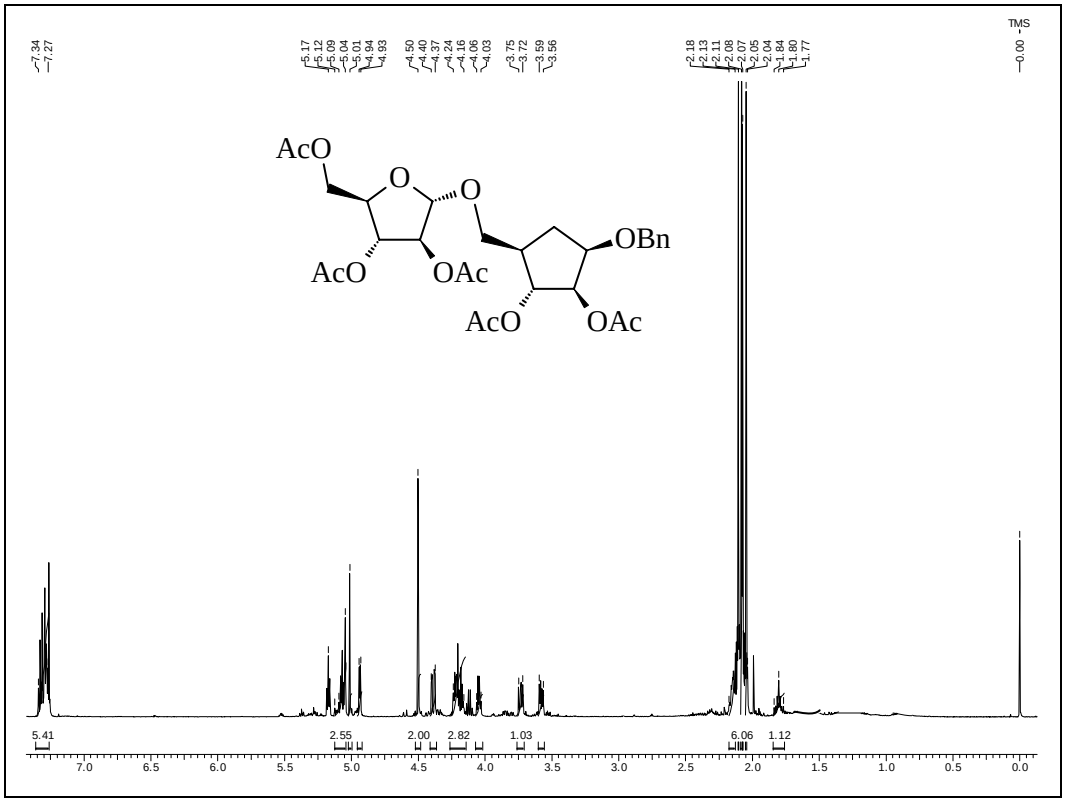


^{13}C NMR Spectrum of 121 in $CDCl_3$



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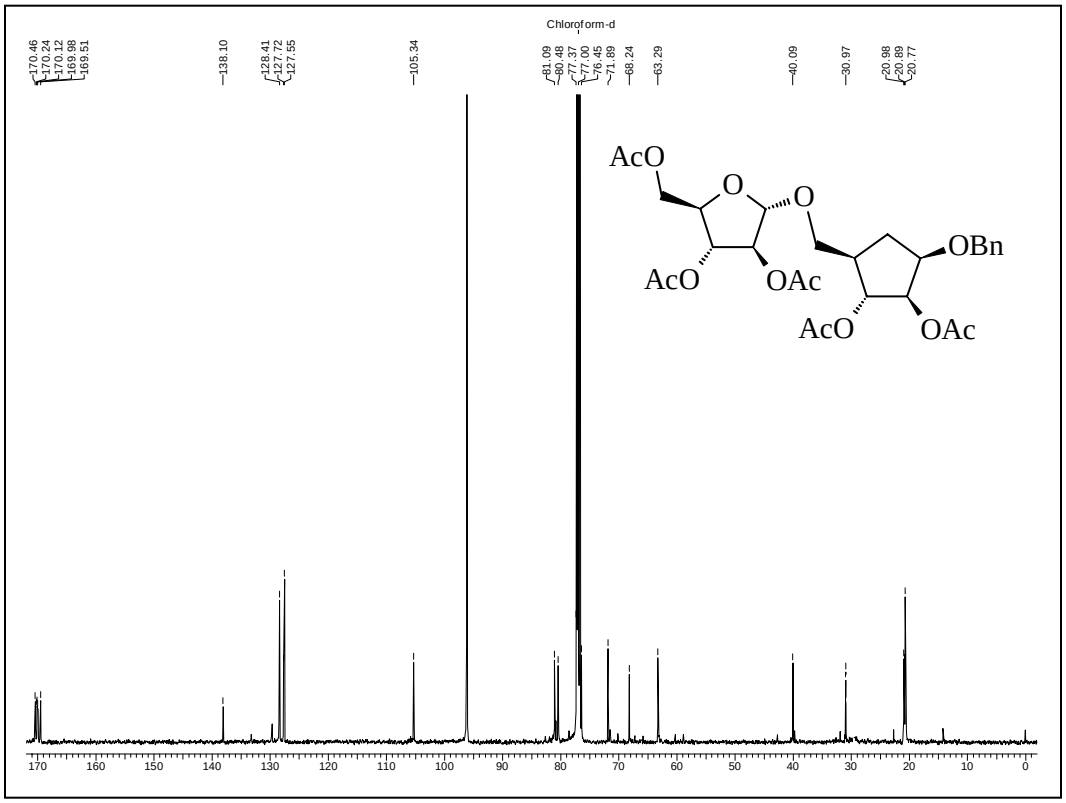
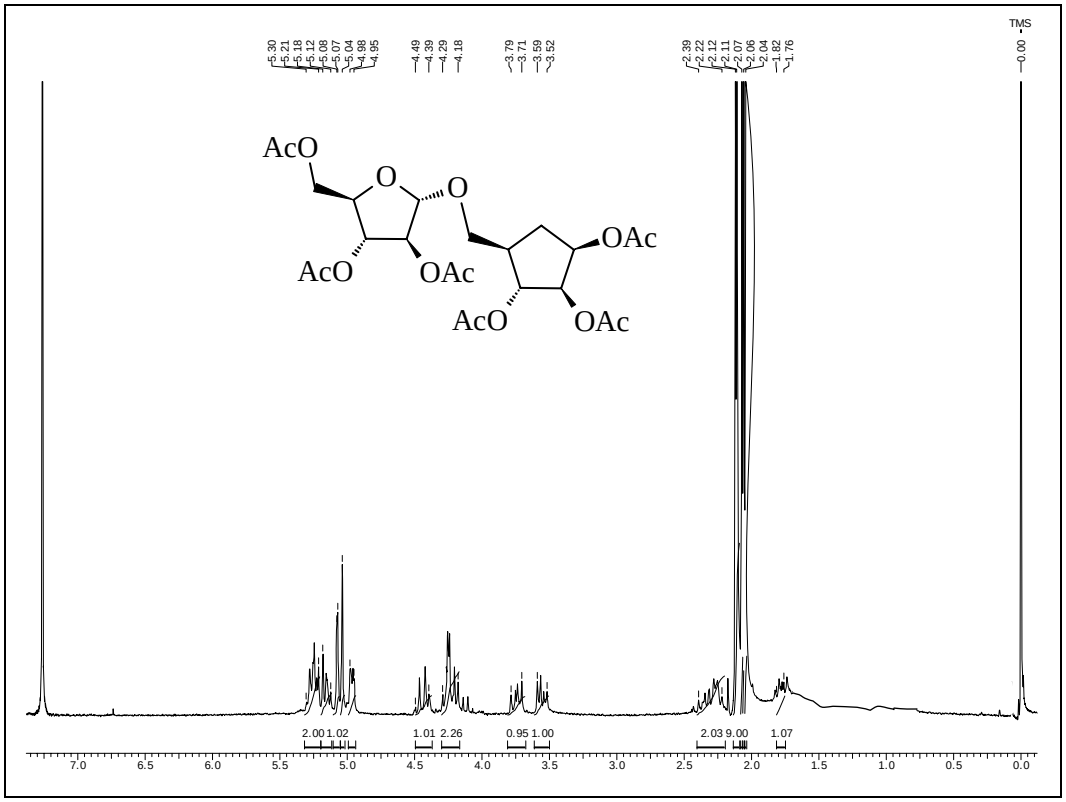
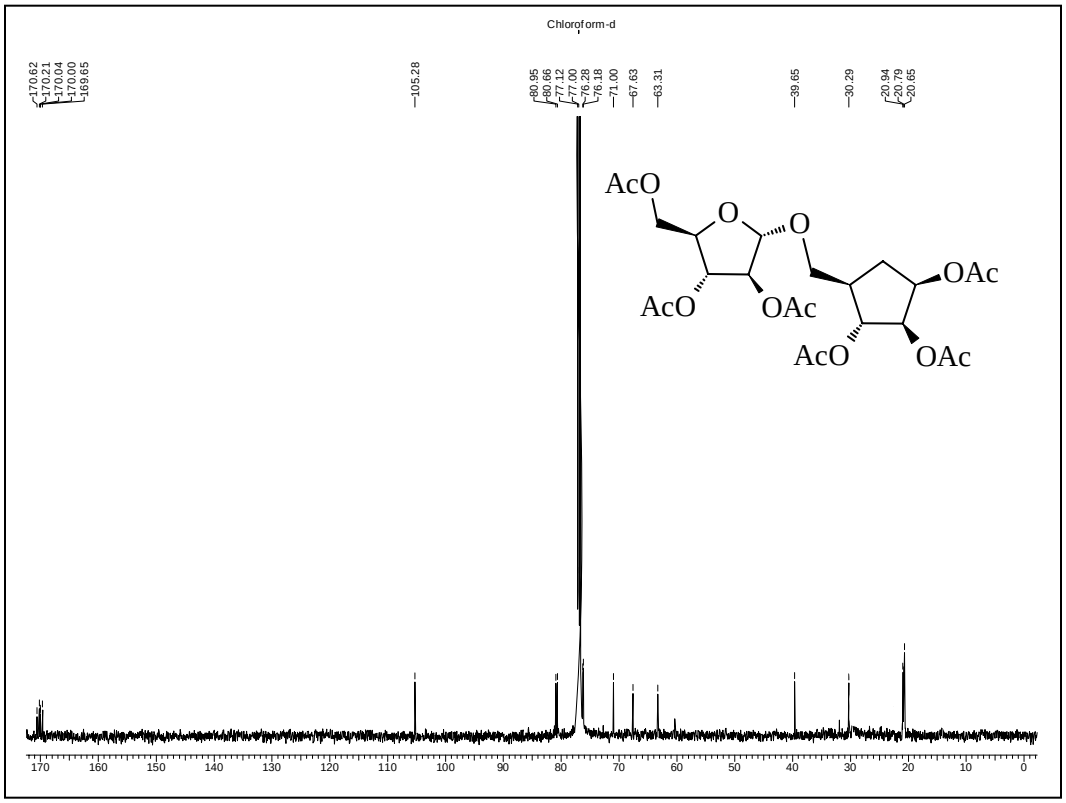


^{13}C NMR Spectrum of 142 in $CDCl_3$



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



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

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Chapter II

An expeditious one-step entry to the central core of integrastatins

Introduction

Epidemiology of HIV/AIDS

Although there are several health related problems facing the world, acquired immuno deficiency syndrome (AIDS) and its causative agent, human immunodeficiency virus (HIV), poses the major global health concern. HIV/AIDS is currently the leading cause of death in Sub-Saharan Africa and the fourth leading cause of death worldwide.[1] In the year 2003 alone, there were 3 million AIDS related deaths, 5 million people were newly infected with HIV and about 40 million people were living with HIV/AIDS.[2]

Since the beginning of the HIV/AIDS epidemic, it is estimated that 60 million people have become infected and more than 20 million people have died of HIV/AIDS. It is projected that 45 million people will be newly infected with HIV by the year 2010 unless a comprehensive set of interventions is implemented. The effects of HIV/AIDS epidemics are broad and include: millions of children orphaned, disruption of village and community life, erosion of civil order and economic growth.[3] A viral infection of this magnitude clearly needs immediate attention.

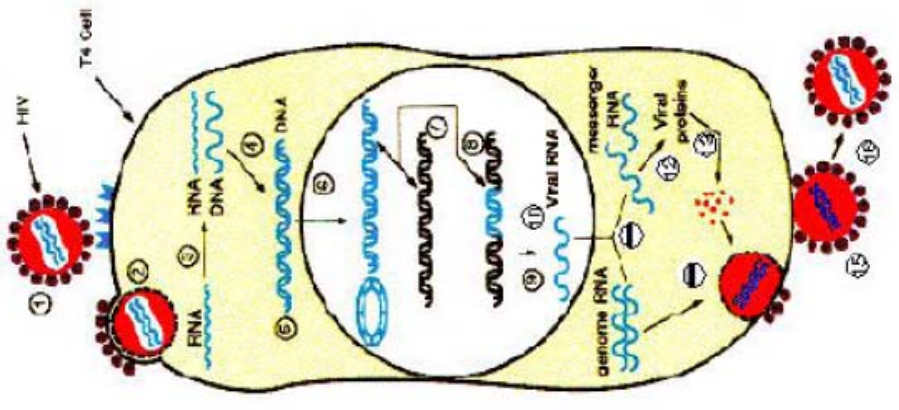
Several approaches (e.g. antiviral chemotherapy and antiviral vaccination) are being explored to completely eradicate, contain or reduce the HIV/AIDS pandemic. There are considerable research advancements that have been made on HIV/AIDS chemotherapy since its discovery two decades ago. However, a complete treatment still remains a challenge.

HIV Life Cycle and Potential Targets of Inhibition

The HIV life cycle can be divided into five major steps; fusion/uncoating, reverse transcription, integration, transcription/translation and viral assembly (Figure 1).[4, 5, 6] The enzymes catalyzing these steps can serve as potential targets for antiretroviral inhibition. The HIV virus infects the host cell by binding to CD4 receptors of T4- lymphocytes (also known as T-helper cells).[4] A recent study has shown that a co-receptor is needed for HIV to enter into the host cell.[6] The binding of HIV to CD4 receptors activates other cell proteins, allowing the HIV envelope to fuse to the outside of the cell. New drug

candidates are being designed to prevent HIV infection by blocking the fusion of HIV with its host cell.[5]

Figure 1: HIV Life Cycle[6]



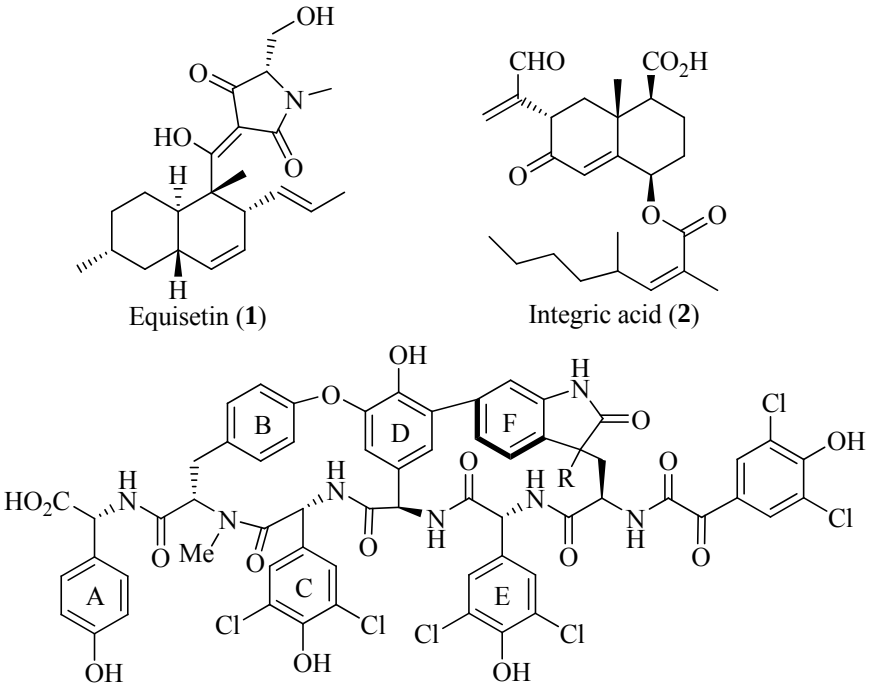
Potential targets: Step 2 – fusion and uncoating; Step 3 – reverse transcripition; Step 7 – integration; Steps 9 and 12 – transcription and translation; Step 14 – viral assembly

Integration is an essential event in the life cycle of retroviruses including HIV and is a three-step process that includes assembly of a proviral DNA on integrase, endonucleolytic processing of the proviral DNA, and strand transfer of the proviral DNA into the host cell DNA.[7] This is a unique process by which the virus proliferates and the entire event is catalyzed by a single viral enzyme, HIV-1 integrase. This process as well as the enzyme is absent in the host, therefore, its intervention presents a safe target for development of a novel anti-HIV therapy that can be used in combination with existing (protease and reverse transcriptase inhibitor) therapies. The recent discovery of diketo acid (DKA) based inhibitors of integrase that showed anti-viral inhibitory potency comparable to clinically effective HIV protease inhibitors has validated the approach and the likelihood of developing integrase inhibitors as useful therapeutic agents.[8] Even though DKAs are valid small molecule chemical leads, which could potentially be refined into clinical agents, the unpredictable nature of the drug development process makes it important to identify alternative structures and provide structurally diverse scaffolds.

Natural product extracts have historically been used for the discovery of leads for a variety of biological targets. Screening of such extracts against recombinant HIV-1

integrase led us to the discovery of several novel natural product inhibitors including equisetin(**1**),[9] integric acid(**2**)[10] and complestatins (**3**) and (**4**).[11]

Figure 2: Natural inhibitors of HIV-1



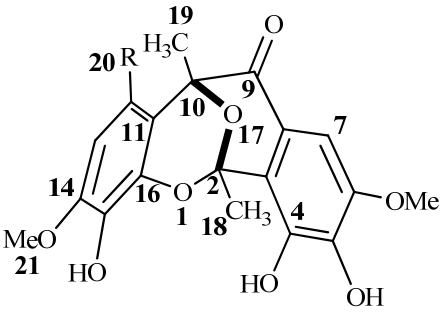
Equisetin (**1**)

Integric acid (**2**)

Complestatin A, R = H (**3**)
Complestatin B, R = OH (**4**)

Continued screening of fungal extracts has more recently led to the discovery of two racemic compounds named herein Integrastatin A (**5**) and B (**6**).

Figure 3: Integrastatins A and B



(Integrastatin A) R = CH_2OH (**5**)
(Integrastatin B) R = CHO (**6**)

These tetracyclic aromatic [6/6/6/6/]- heterocycles of polyketide origin inhibit the strand transfer reaction of recombinant HIV-1 integrase with an IC_{50} value of 1.1 and 2.5 μM, respectively. The bioassay guided isolation, structure elucidation, and the biological activities of integrastatins A (**5**) and B (**6**) are herein described.

Isolation

A sterile unidentified fungus (ATCC74478) isolated from herbivore dung collected in New Mexico was grown on a brown rice-based liquid medium and was extracted with 1.2 volumes of methyl ethyl ketone which was concentrated and dissolved in a 1:6 ratio of methanol–water that was washed with hexane and the activity extracted with ethyl acetate. Size exclusion (Sephadex LH 20) chromatography of the latter extract followed by reversed-phase HPLC (Zorbax RX C-**8**) afforded integrastatin A (**5**, 40 mg/L) and B (**6**, 70 mg/L) as brown powders. Integrastatin B (**6**) was also isolated from an endophytic *Ascochyta* sp. (ATCC74477) isolated from leaves of *Urtica urens* collected in Ontigola, near Madrid, Spain. Both of these compounds were optically inactive and likewise did not exhibit absorption bands in CD spectra.

Integrastatin A[12] (**5**): High-resolution EIMS analysis of integrastatin A (**5**) provided a molecular formula of $C_{20}H_{20}O_9$ (found *m*/*z* 404.1110, calcd *m*/*z* 404.1107) that was corroborated by the ^{13}C NMR spectrum (Table 1) and indicated that it has 11 degrees of unsaturation. The ^{13}C NMR spectrum of (**5)** revealed the presence of two methyls, two aromatic methoxy groups, an oxy-methylene, two aromatic methines, two quaternary carbons each connected with one or two oxygen atoms, 10 non-protonated aromatic carbons including six attached to oxygen atoms, and a conjugated keto group. The UV spectrum showed absorption bands at λ_{max} 212 (log ϵ=4.4), 262 (3.83) and 310 (sh) nm. The IR spectrum of **5** showed absorption bands characteristic of hydroxyl (3394 cm^{-1}), conjugated ketone (1776 cm^{-1}) and aromatic (1610 cm^{-1}) groups. The ^1H NMR spectrum of **5** was rather simple and showed two shielded singlets for aromatic protons (δ 6.70 and 7.03), singlets for two methoxy groups (δ 3.75 and 3.85), two downfield shifted singlets for methyl groups (δ 2.09 and 1.76) and an AB doublet (*J* = 12.8 Hz) of an oxy-methylene group (δ 4.40 and 4.58). The ^1H NMR shifts were assigned to respective ^{13}C

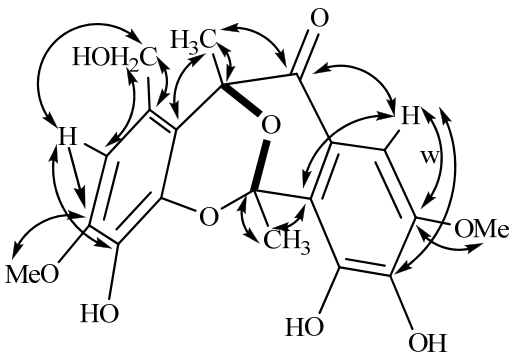
NMR shifts by an HMQC experiment. The elucidation of the structure of integrastatin A was severely hampered by the presence of a disproportionally high numbers of oxygen atoms, 13 of 20 quaternary carbons, and only a limited number of proton bearing carbons. However, HMBC experiments were very helpful in defining the substitution pattern of the two aromatic rings and deducing the structure as **5**. The aromatic singlet H-13 (δ 6.70) produced strong three-bond HMBC correlations (Fig. 4) to C-11, C-15, C-20 and a weak two-bond correlation to C-14, which showed an HMBC correlation with one of the methoxy groups (δ 3.75). The methylene protons H-20 displayed HMBC correlations to C-12 and C-13. The substitution pattern in the left aromatic ring was deduced on the basis of these correlations, and, strongly supported by the calculated ^{13}C chemical shifts of the respective carbons.

Table 1: ^{1}H and ^{13}C NMR spectral assignments of integrastatin A (**5** in CD_3CN) and B (**6** in 1:1 CD_3CN+ $CDCl_3$

Position	δ C (**5**)	δ H (**5**)	δ C (**6**)	δ H (**6**)
2	97.8		97.8	
3	121.3		120.7	
4	140.1		140.1	
5	140.4		142.2	
6	148.6		148.7	
7	101.4	7.03, s	101.8	7.06, s
8	121.1		120.4	
9	193.8		193.7	
10	77.4		77.1	
11	114.1		121.3	
12	130.5		126.0	
13	107.5	6.70, s	105.7	7.14, s
14			147.8	
15	134.4		140.9	
16	142.0		140.8	

18	26.4	2.09, s	26.5	2.15, s
19	22.2	1.76, s	25.8	1.87, s
20	60.9	4.58, d, 12.8	190.6	10.21, s
		4.40, d, 12.8		
21	56.4	3.75, s	56.6	3.75, s
22	56.6	3.83, s	56.7	3.85, s

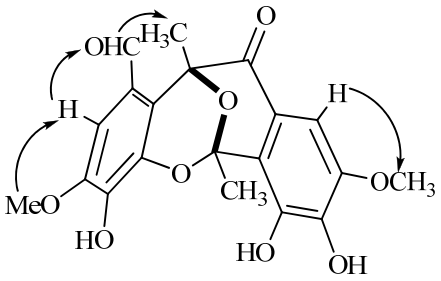
Figure 4: HMBC ($^{n}J_{CH}$ = 7 Hz) correlations of **5** in CD_3CN



Similar two and three-bond HMBC correlations from the other aromatic proton H-7 (δ 7.03) to C-3, C-5, C-6 and from methoxy group (δ 3.83) to C-6 established the substitution pattern of the other aromatic ring, and was supported by NOEDS experiments of congener **6** (*vide infra*). In addition, H-7 showed an HMBC correlation to the C-9 keto group which was also correlated to the methyl group H3-19 (δ 1.76). This methyl group also exhibited HMBC correlations to C-10 and C-11, and enabled connection of C-8 and C-11 of the two aromatic rings through a two-carbon bridge. The remaining methyl group H3-18 showed HMBC correlations to doubly oxygenated carbon C-2 and aromatic carbon C-3 thus placing a phenethyl type substitution at C-3 of the other aromatic ring. The pyranone and the 1,3-dioxane rings were assembled to meet the requirement of the remaining two degrees of unsaturation and to fulfill the ^{13}C chemical shift requirement of C-2. Based on these data, a novel [6/6/6/6]-tetracyclic heterocycle structure **5** was established for integrastatin A.

Integrastatin B (**6**): The high-resolution EIMS of **6** gave a molecular formula of $C_{20}H_{18}O_9$ (found 402.0960, calcd. 402.0950) and indicated that it was a dehydro derivative of **5**. Comparison of the ^{1}H NMR spectrum of **6** with that of **5** (Table 1) showed the absence of the oxy-methylene protons and the presence of an aldehyde group (δ 10.21) which was corroborated by the corresponding signals in the ^{13}C NMR spectrum. The structural assignment was supported by analogous HMBC correlations and by NOEDS experiments (Fig. 5). This was further supported by the bathochromic shift and hyperchromic effect of the second absorbance band that appeared at λ_{max} 315 (log ϵ=4.09) nm in the UV spectrum of **6** due to additional conjugation caused by the aldehyde group.

Figure 5: NOEDS of **6** in $CDCl_3$-CD_3CN



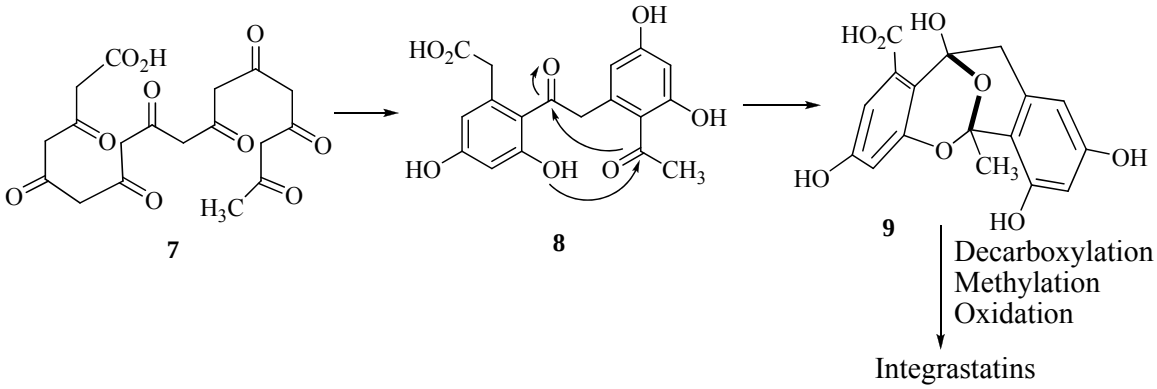
Relative stereochemistry

The relative stereochemistry and conformation of integrastatins **5** and **6** was deduced as *R*,*R* or *S*,*S* by ChemDraw 3D modelling and was supported by the analysis of different possibilities by the Dreiding model. These models indicated that the bridgehead oxygen-17 connected C-2 and C-10 through di-equatorial bonds to attain the lowest energy (12 kcal/mol) conformation and thus leading to the diaxial fusion of the pyranone ring producing a inverted-V-shaped (*R*,*R*) or a V-shaped (*S*,*S*) conformation. This would allow only the equatorial orientations of C-18 and C-19 methyl groups leading to a wing like structures. These structural conformations supported the inter-atomic distance (2.1 Å) and observed NOEs between the aldehyde proton and the H3-19 of **6**.

Biogenesis

Integrastatins are likely produced by traditional polyketide pathway originating from the condensation of nine acetate units as shown in Scheme 1. The aromatization, decarboxylation, methylation and oxidations of the putative intermediate would presumably result in the formation of integrastatins. The introduction of the C-19 methyl at the C-10 keto group could potentially precede the hetero-cyclization, which would result in the elimination of the C-10 *tert*-hydroxy group.

Scheme 1: Proposed biogenesis of integrastatin B (**6**)



Biological activities

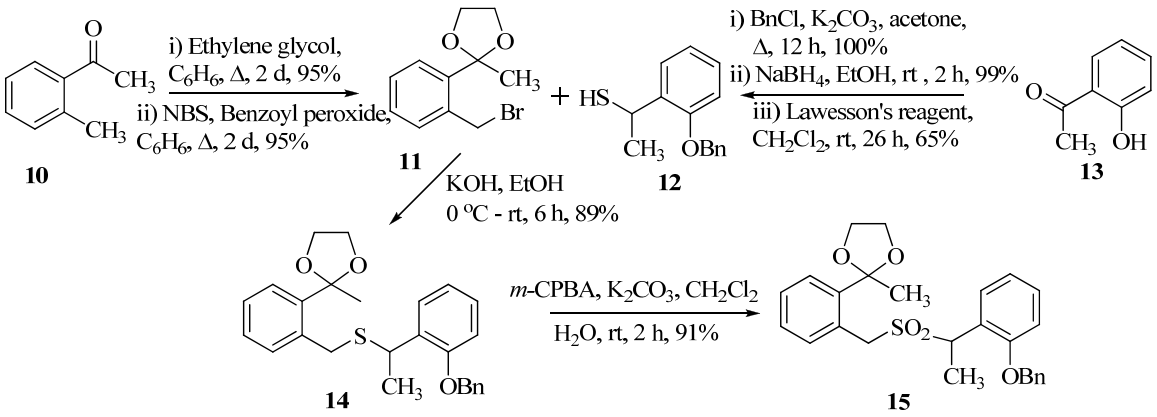
Integrastatins A (**5**) and B (**6**) were evaluated in the coupled and the strand transfer HIV-1 integrase assays using recombinant enzyme.[13] Integrastatin A exhibited IC_{50} values of 0.6 and 1.1 μM in coupled and strand transfer assays, respectively. Integrastatin B (**6**) was two-fold less active and exhibited corresponding IC_{50} values of 1.04 and 2.5 μM. These compounds were about 5- to 10-fold selective for HIV-1 integrase when compared with DNAase (IC_{50}=12 μM).

Past work

Tylor and co workers first synthesized the integrastatin nucleus. The key steps of his synthesis involve a novel *cis*-selective Ramberg-Backlund reaction and an unusual Lewis acid-promoted cyclization.[14]

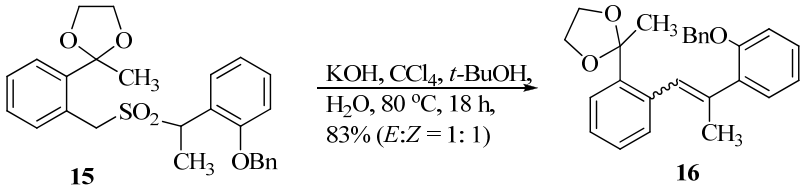
The two coupling partners **11** and **12** (Scheme 2) were synthesized from the commercially available 2-methylacetophenone (**10**) and 2-hydroxyacetophenone (**13**) respectively. Coupling and oxidation of the resultant thioether proceeded smoothly to afford the sulfone **15** in 52% yield overall.

Scheme 2: Formation of sulfone **15**



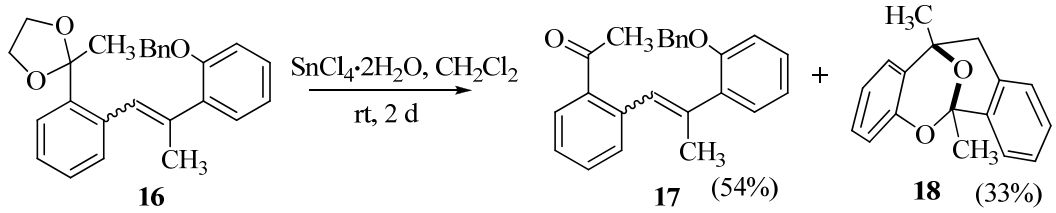
Sulfone **15** was then subjected to *in situ* chlorination-Ramberg-Backlund reaction using the conditions described by Meyers et al. (Scheme 3),[15] to give the corresponding olefin **16** in 83% yield as a (1:1) *E*:*Z* mixture.

Scheme 3: Formation of olefin **16**



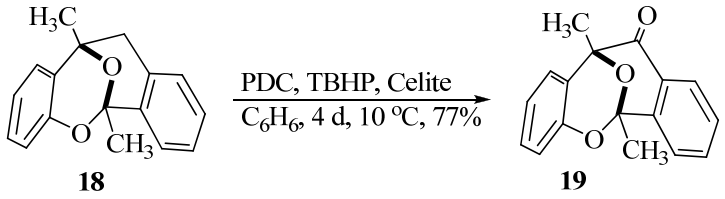
Attempts to transform **16** into **17** through Lewis acid promoted ketal removal, formed the tetracycle compound **18**[16](Scheme 4).

Scheme 4: Formation of Deoxy-nucleus **18**



Direct oxidation of **18** was achieved by using TBHP and PDC supported on Celite (Scheme 5)[17] gave the racemic integrastatin nucleus **19**.

Scheme 5: Formation of the Integrastatin nucleus **19**

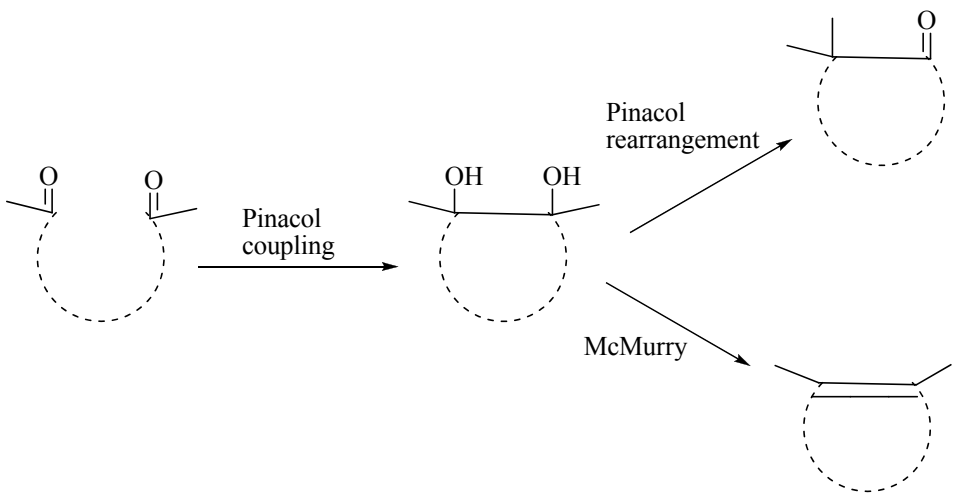


As the key retrosynthetic disconnection for the integrastatins A and B is a pinacol coupling reaction, some important aspects of pinacol reactions are

Pinacol coupling

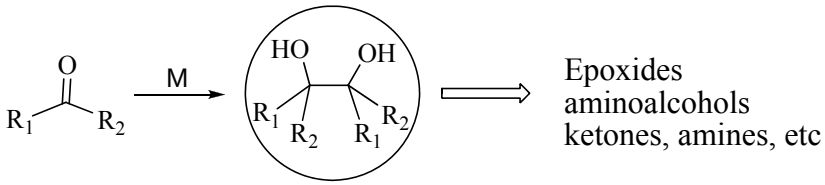
An old-timer in the history of chemistry, the pinacol coupling, was first described over 130 years ago in a publication on the synthesis of pinacols.[18] The intrinsic elegance of the method for the preparation of 1,2-diols (pinacols) by the reductive coupling of carbonyl compounds.[19] Starting with two carbonyl functionalities, a C-C bond is formed and two new adjacent stereocenters created. The most important aspect of this reaction is that it combines two functional groups of same polarity, very rare in organic synthesis. 1,2-Diols are versatile intermediates in synthesis; for example, they can be used for the preparation of ketones by the pinacol rearrangement or alkenes by the McMurry reaction (Scheme 6).

Scheme 6: Pinacol coupling



Whether the reductive coupling of carbonyl compounds leads to 1,2-diols or to the deoxygenated or rearranged products is dependent on the oxygen affinity of the reducing agent employed. The McMurry reaction uses low-valent titanium compounds, which under certain reaction conditions can transform the 1,2-diol intermediates into alkenes by rapid deoxygenation (Scheme 6).

Scheme 7: Pinacol coupling, a versatile reaction

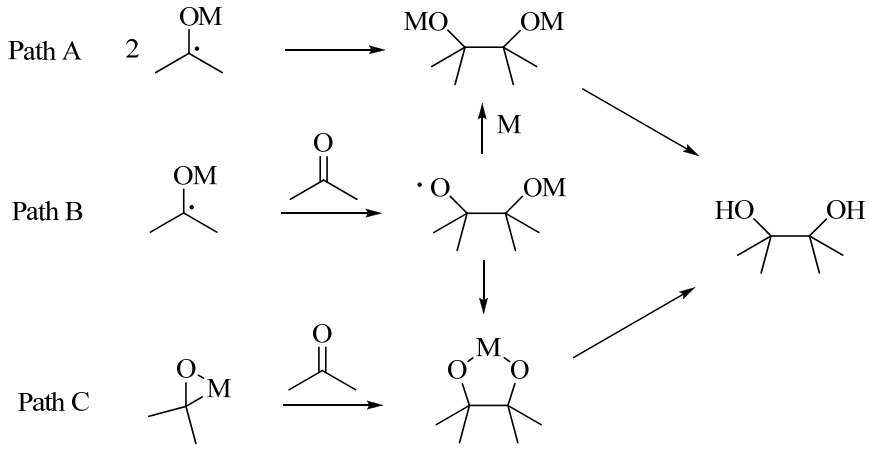


Reducing agents suitable for the synthesis of pinacols must allow the reaction to be stopped at the 1,2-diol stage. One of the first practical reductants for pinacol coupling reactions was the Mg/MgI_2, system reported by Gomberg and Bachmann.[20] More recently these reducing agents have been extended by a magnesium-graphite system, which is competitive with other currently available reductants.[21] Different low-valent titanium compounds have proved to have similar efficiency for pinacol coupling reactions.[22]

Mechanism

The mechanisms for pinacol couplings are shown in Scheme 8. In the first reduction step a ketyl radical is formed, which can dimerize (path A) or add to a second carbonyl group (path B) forming a C-C bond. In path B a second one-electron reduction must then follow. For pinacol coupling reactions mediated by transition metals, the insertion of a carbonyl group into the metal-carbon bond of initially formed metal oxiranes has been proposed (path C).

Scheme 8: Mechanism of pinacol coupling



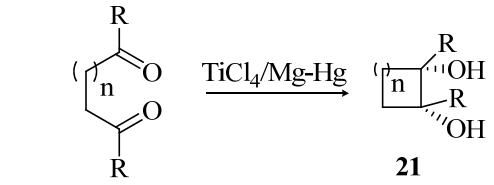
Titanium is the most popular reagent for pinacol coupling. The development of titanium chemistry proliferated in the early 1980s following three independent discoveries by Tyrlik et al.,[23] Mukaiyama et al.,[24] and McMurry and Fleming[25] that described low-valent titanium species for the reductive coupling of ketones/aldehydes. All these investigations unveiled the synthetic utility of low-valent titanium and opened new vistas in organometallic chemistry.

Different Titanium Reagents for pinacol coupling

(i) Ti(II)-based coupling agents were used and these met with moderate success in terms of selectivity.[26] One of the most efficient protocol was developed by Corey et al. using

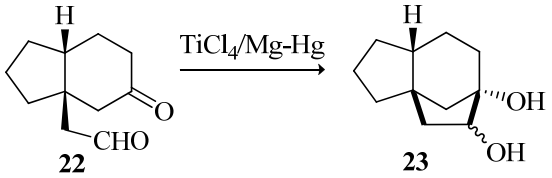
$TiCl_4$ and magnesium amalgam.[27] This was further modified to $CpTiCl_3$–LAH for the cross-coupling of ketones with aldehydes (Scheme 9).[28]

Scheme 9

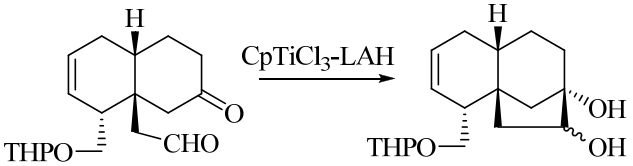


n = 1 or 3, R = Me or H

20 **21**



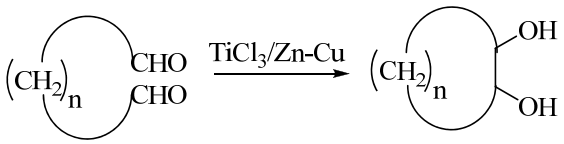
22 **23**



24 **25**

(ii) The combination of $TiCl_3$/Zn–Cu, introduced by McMurry and Rico, was used successfully for the intramolecular coupling of various aldehydes (Scheme 10).[29]

Scheme 10

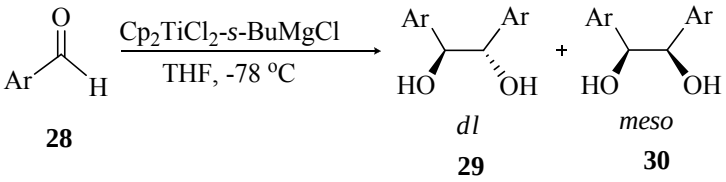


n = 4, 6, 8 etc

26 **27**

(iii) Inanaga in 1987 reported a cyclopentyl-bound Ti^{+3} reagent, generated by the reduction of Cp_2TiCl_2 with *s*-BuMgCl, for the coupling of aromatic aldehydes (Scheme 11).[30]

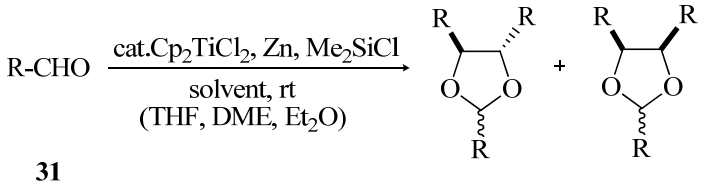
Scheme 11



28 *dl* **29** *meso* **30**

(iv) Hirao et al. reported[31] the new catalytic system for pinacol coupling. They found that Cp_2TiCl_2 acts as a useful catalyst for the reductive coupling of aldehydes and ketones in the presence of zinc and chlorotrimethylsilane (Scheme 12).

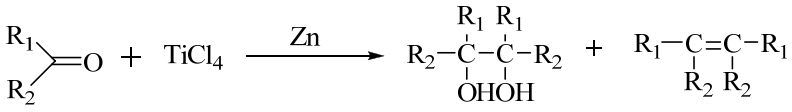
Scheme 12



31 *dl* **32** *meso* **33**

(v) Mukaiyama et al.[32] reported that aldehydes and ketones were reduced by low valent titanium compound, produced from $TiCl_4$ and Zn, to give the corresponding pinacols and olefins in high yields (Scheme 13).

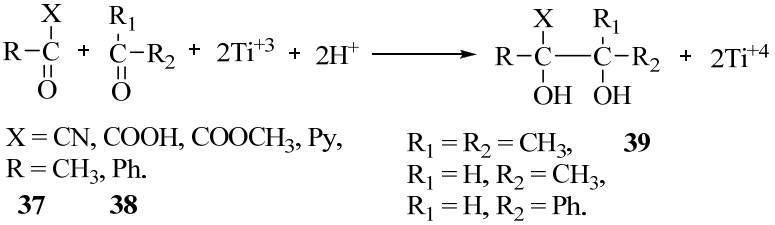
Scheme 13



34 **35** **36**

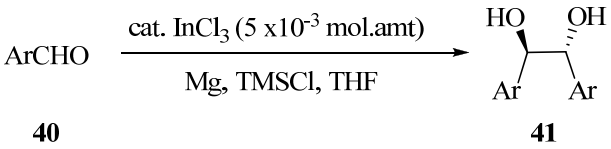
(vi) Clerici et al[33] reported electron withdrawing substituted carbonyl compounds when allowed to react with 2 equiv of aqueous titanium trichloride in the presence of acetone, acetaldehyde, or benzaldehyde afford unsymmetrical 1,2-diols in high yields under very simple experimental conditions (Scheme 14).

Scheme 14



(vii) Mori et al[34] reported the pinacol coupling of aromatic aldehydes and ketones in tetrahydrofuran at room temperature using a catalytic $InCl_3$ (0.005-0.1 molar amount) under nitrogen atmosphere in the presence of both chlorotrimethylsilane and magnesium metal (Mg turnings) to provide the corresponding 1,2-diols in good to moderate yields with a high diastereoselectivity (Scheme 15).

Scheme 15

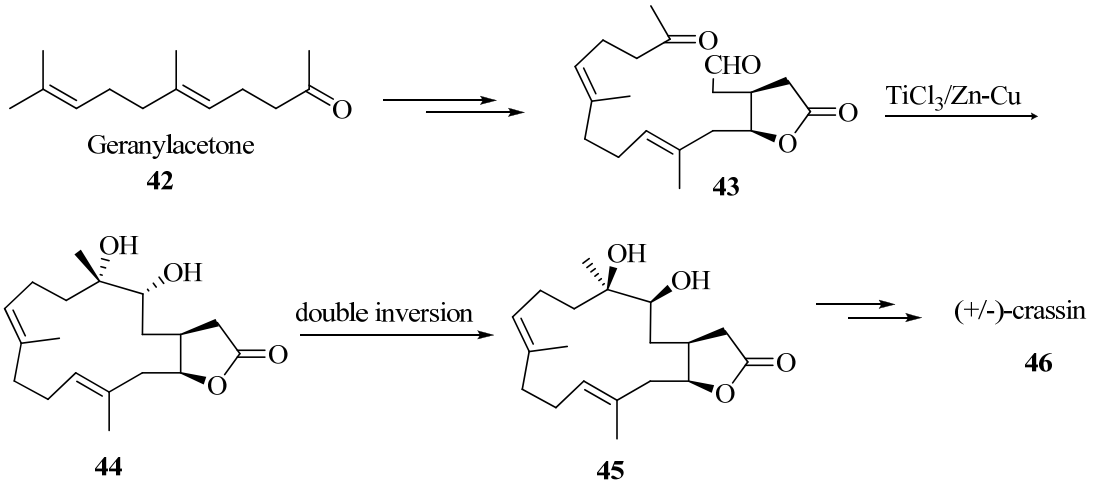


Synthetic applications of pinacol coupling

(i) Terpenes

McMurry and Dushin prepared racemic crassin, a diterpenoid, using $TiCl_3$/Zn–Cu to construct the 14-membered ring.[35] The keto–aldehyde coupling proceeded with 48% yield (including four isomers). As the yield of the desired isomer (**45**) was very low, the major isomer (**44**) was epimerized at the C3, C4 centre through double inversion (Scheme 16).

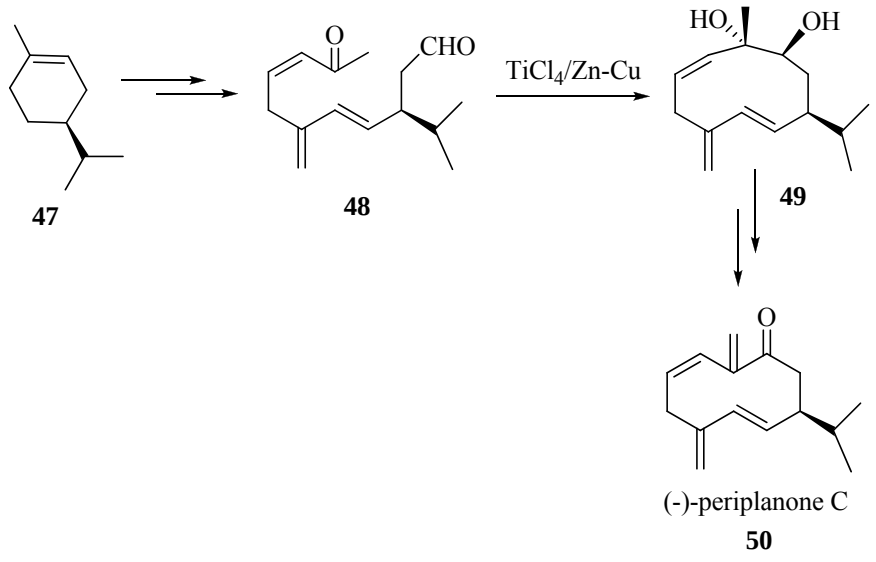
Scheme 16



(ii) Synthesis of (–)-periplanone C

McMurry and Siemers reported the synthesis of (–)-periplanone C, a 10-membered sesquiterpene, which is an insect pheromone.[36] The 10-membered ring was constructed in a similar manner. Unlike the previous example and contrary to mechanistic calculations, the trans diol (**49**) was formed as the major product. Further transformations led to the final product (Scheme 17).

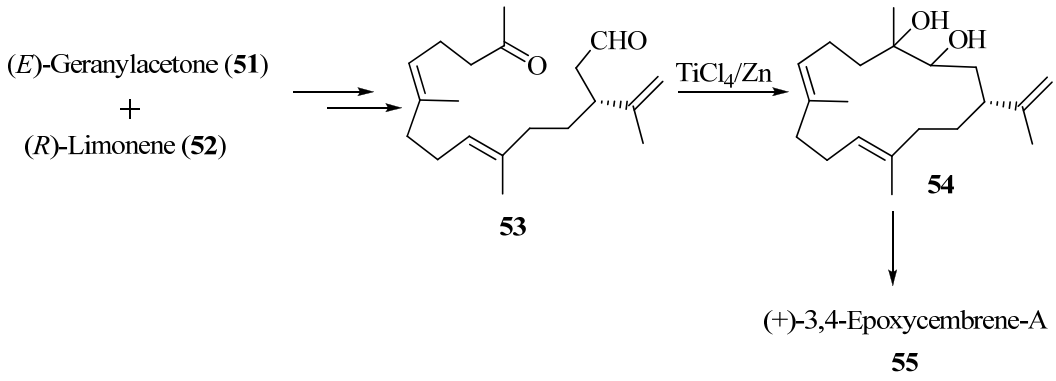
Scheme 17



(iii) Synthesis of (+)-3,4-epoxycembrene-A

Li and Yue constructed the 14-membered ring of the macrocyclic diterpene, (+)-3,4-epoxycembrene-A, using $TiCl_4/Zn$.[37] The final product was obtained as a mixture of four stereoisomers (23:21:15:6), which were separated as epoxides through HPLC (Scheme 18).

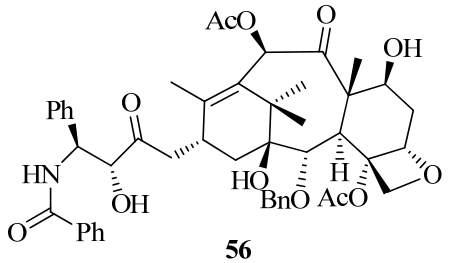
Scheme 18

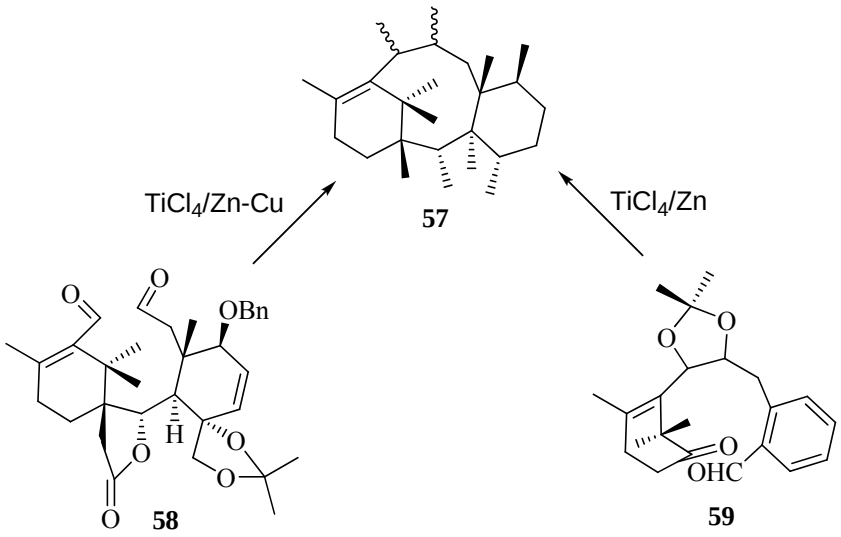


(iv) Taxol

Nicolaou et al. have used pinacol coupling as a key step to link the A-and C-ring by forming the C9–C10 bond using $TiCl_3/Zn–Cu$ with a predominant *syn* stereochemistry (**58**). In a different approach, Swindell and Fan constructed the B-ring (**59**) by forming C1–C2 bond through pinacol coupling using $TiCl_4/Zn$ (Scheme 19).[38]

Scheme 19

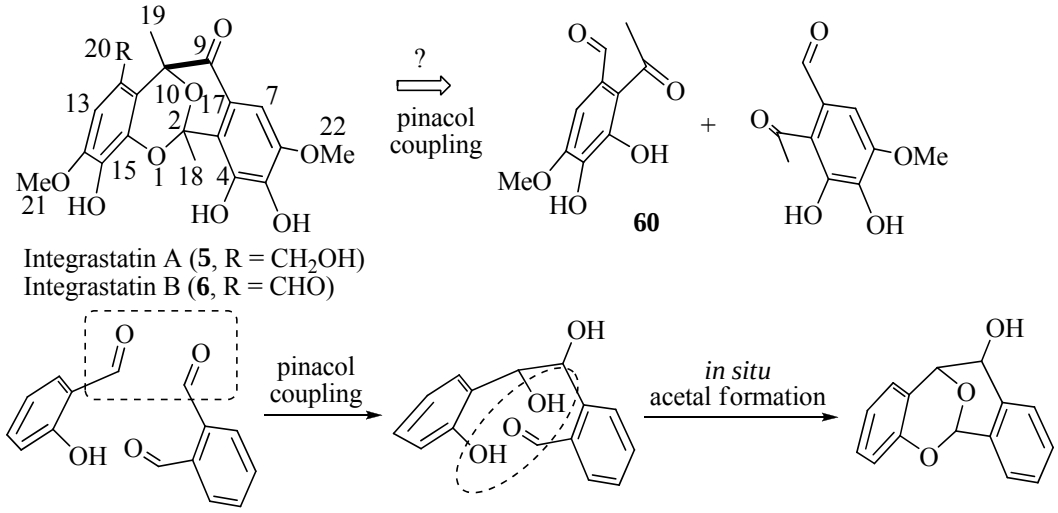



TiCl4/Zn-Cu
57
TiCl4/Zn
OBn
H
O
OHC
58
59

Present Work

Construction of architecturally complex molecules from simple building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity.[39] Accessing distinctive three-dimensional architectures by employing structurally simplifying transforms from simple or commercially available starting compounds remains as a challenging problem especially when the targets are required in a fewer steps.[40] Domino reactions characterized by several bond formations through sequential intramolecular transformations are well outfitted to address the above issues.[41] We illustrate such a domino process comprising a low valent titanium mediated pinacol cross coupling[42] and an intramolecular trapping of the intermediate diol with suitably disposed carbonyl group resulting in a one step assembly of the central core of integrastatins. Integrastatin A (**5**) and B (**6**) are two recently discovered natural products isolated from both an unnamed fungal source (ATCC74478) and from an endophytic *Ascochtya* species (ATCC74477), which have been found to selectively inhibit the strand-transfer reaction of recombinant HIV-1 integrase at micromolar concentrations.[13] They have been been synthesized with a novel [6.6.6.6] tetracycle, although they contain two chiral centers, they exist in nature as a racemic mixture.

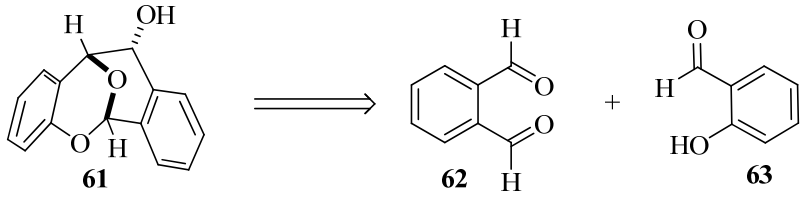
Scheme 20: Integrastatins A (**5**) and B (**6**) and identified pinacol transform for central tetracyclic aromatic [6/6/6/6/]-heterocyclic core



Considering the importance of integrase as an emerging therapeutic target in anti-retroviral drug development programs,[43] a flexible approach in this context will bestow a significant incentive for structure activity studies. As shown in Scheme 18, disconnection of the central core of integrastatin B between C(9)-C(10) after oxidation state adjustment at C(9) revealed a striking feature that **6** is a pinacol cross-dimer of a *o*-ketoaldehyde **60** (Scheme 20).

Inspired by the simplicity of the retrosynthetic strategy, the feasibility of projected transformation was examined by employing commercially available *o*-phthalaldehyde (**62**) and *o*-hydroxy benzaldehyde (**63**).

Scheme 21: Retrosynthetic analysis



According to our retrosynthetic plan we started the coupling with **62** and **63** with some of the available pinocol conditions.[44-48]

Scheme 22: Pinacol coupling of *o*-phthalaldehyde and *o*-hydroxybenzaldehyde

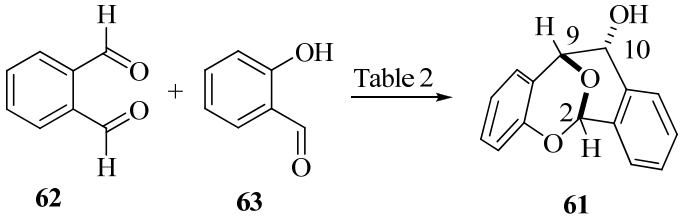


Table 2: Reagents and Conditions

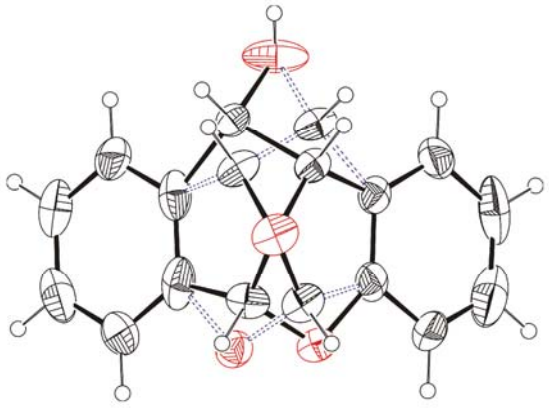
Entry	Conditions	Yield
1	[44]15% aq.solution of $TiCl_3$, Acetone, rt	7%
2	[45]Zn, $TiCl_4$, THF, 0 ^oC	21%

3	[46]Mg(Hg), $TiCl_4$, THF, 0 °C	42%
4	[47]Cat Cp_2TiCl_2, Zn, TMSCl, THF, rt	15%
5	[48]Mg, TMSCl, Cat $InCl_3$, THF, rt	No reaction

As indicated in the table 2, the proposed transformation was found to be feasible with the low valent titanium reagent generated *in situ* by employing Zn-Cu,[44] Zn,[45] or Mg(Hg)[46] the later being yielded better. The reaction in general results in a complex mixture. Repeated column chromatography is required to isolate and the product identification with the help of NMR spectroscopy.

The assigned *threo*-configuration for compound **61** was derived from the NMR studies. For example, in the ^{1}H NMR spectrum of **61**, the bicyclic acetal H-2 was appeared as a singlet at down field compared to the other two benzylic protons H-9 and H-10. H-10 resonated as sharp doublet at δ 5.13 ppm with J = 5.9 Hz characteristic of *axial-equatorial* coupling. Energy minimization calculations for both the possible diastereomers revealed a preference of half conformation for rings B and C, and an axial disposition for the *β*-functional group at C(10). Finally, single crystal X-ray analysis of compound **61** proved the proposed stereochemistry beyond the doubt (Figure 6).

Figure 6: The molecular structure of the bicylic enol ether **61**
Displacement ellipsoids are drawn at the 50% probability level



Considering the moderate yield we obtained, though various possible alternatives for entry 4 like changing the solvent and temperature were attempted, however, the initial conditions are found to be better and were adopted for the generalization of this reaction

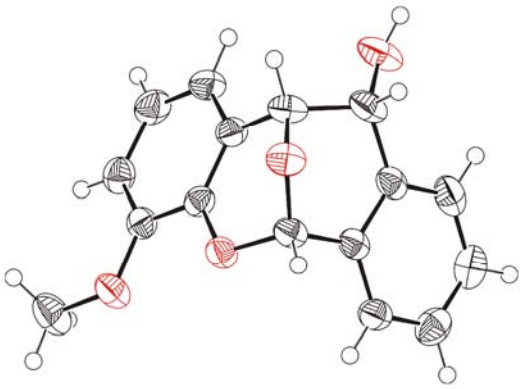
with other commercially available *o*-hydroxy benzaldehydes **64** and **65**. The *threo*-configuration for the resulting products **73** and **74** was assigned by comparing the chemical shifts and coupling constants with that of **61**.[49]

Table 3: ^{1}H and ^{13}C NMR spectral assignments of compound **61**, **73** and **74**

compound	δ H			δ C		
	H2	H9	H10	C2	C9	C10
61	6.30	5.13	5.27	93.0	69.2	70.7
73	6.30	5.24	5.11	93.3	69.3	70.6
74	6.27	5.23	5.08	93.1	69.1	70.7

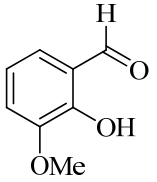
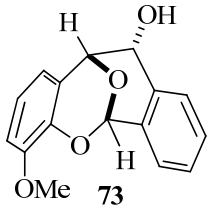
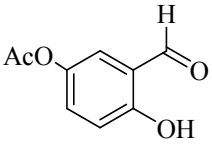
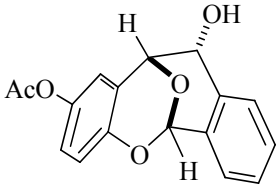
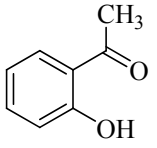
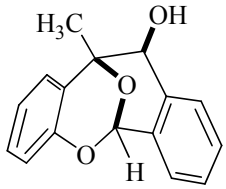
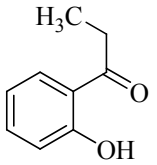
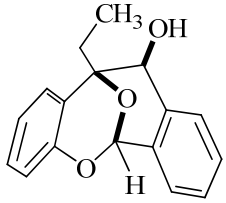
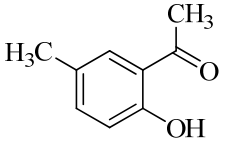
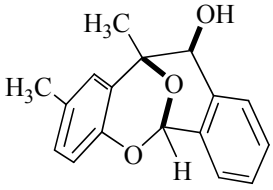
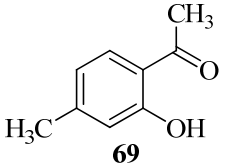
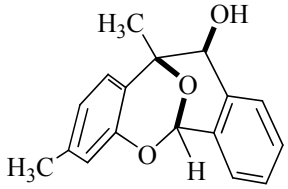
The single crystal X-ray structural analyses of **73** further confirmed the assigned structure (Figure 7).

Figure 7: The molecular structure of the bicylic ketal **73**
Displacement ellipsoids are drawn at the 50% probability level



The generality of this method was further extended by employing diverse aromatic ketones with *o*-hydroxyl group (Table 4, **66**–**72**) and the corresponding tetracyclic derivatives **75**–**78** were obtained in moderate yields and exclusively as a single diastereomers.

Table 4

Entry	Substrate	Product	Yield
1	 **64**	 **73**	47%
2	 **65**	 **74**	57%
3	 **66**	 **75**	49%
4	 **67**	 **76**	37%
5	 **68**	 **77**	43%
6	 **69**	 **78**	41%

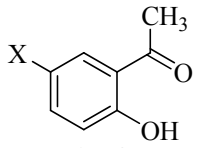
7	 **70 -72** X = F, Cl, Br	----	----

Table 5: ^{1}H and ^{13}C NMR spectral assignments of compound **75**, **76**, **77** and **78**

compound	δ H			δ C			
	H2	H9	H19	C2	C9	C10	C19
75	6.30	4.38	1.77	93.1	72.8	75.7	23.2
76	6.30	4.90	2.08	93.1	73.7	76.8	29.5
77	6.30	4.36	1.75	93.1	72.9	75.6	23.2
78	6.31	4.35	1.75	93.2	72.9	75.5	23.3

Surprisingly, we could not isolate any expected products from the cross pincol coupling reaction of **62** with halogen substituted acetophenones (entry 7). The stereochemistry of the tetracyclic compound **75** obtained from the cross pinacol coupling of *o*-hydroxy acetophenone (**66**) with **62** was established as *erythro* with the help of NOESY studies. For example, a strong nOe noticed between the methyl group and the benzylic-H clearly indicated a close spatial proximity between these groups (Figure 8). More importantly, the benzylic-H showed spatial interaction with *ortho*-proton of both the aromatic rings revealing a *syn*-periplanar arrangement. MM2 caluclations revealed such a close proximity is possible when the benzylic-H is *syn* to the adjacent methyl group.

Figure 8: Observed through space interactions of compound **75**

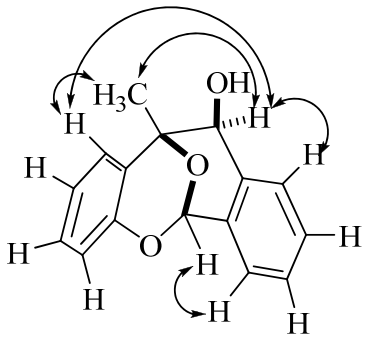
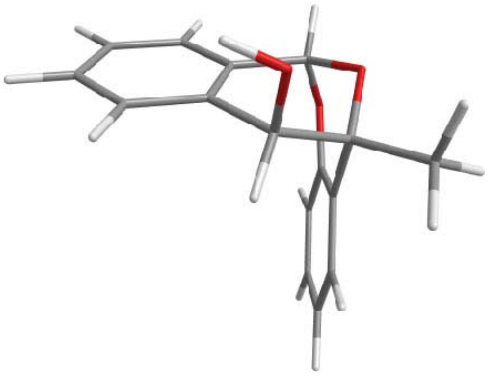
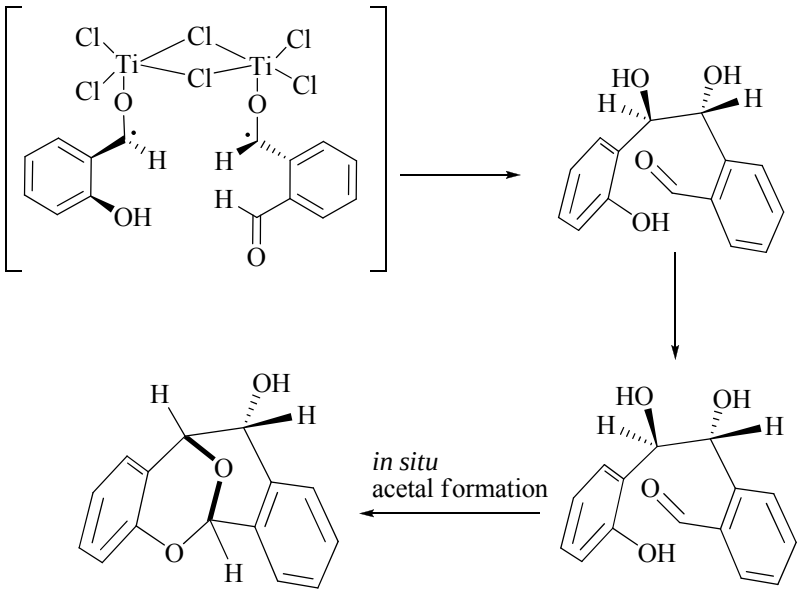


Figure 9: MM2 energy minimized structure for the erythro isomer revealing relative orientation of aromatic protons and the benzylic-H



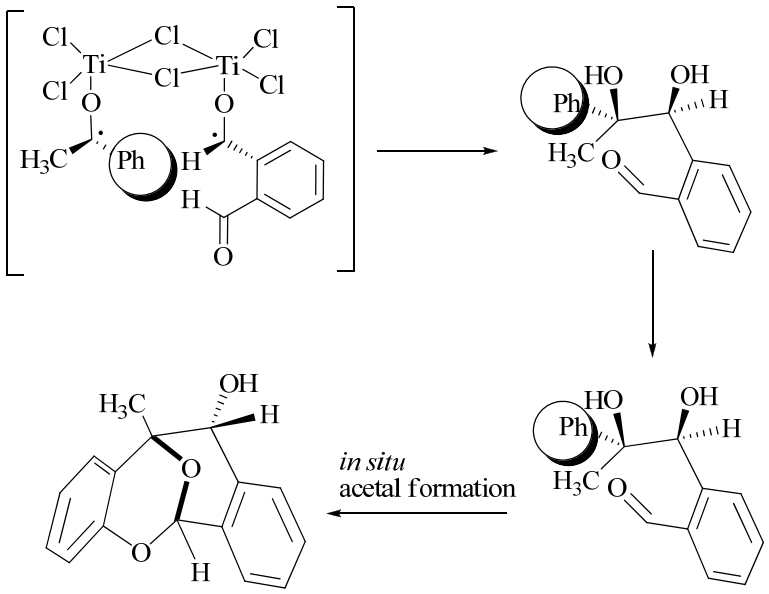
A mechanistic hypothesis for the observed diastereoselectivity is depicted in Figure 9. As suggested in most of the cases, the reductive carbonyl coupling reactions complex both ketyl radicals that dimerise via a sterically less demanding transition state consisting an *anti* orientation of the aryl groups. This metal pinacol upon hydrolysis followed by ketalization provide the bicylic ketal derivative obtained.

Figure 9: A mechanistic hypothesis for the observed *threo* selectivity



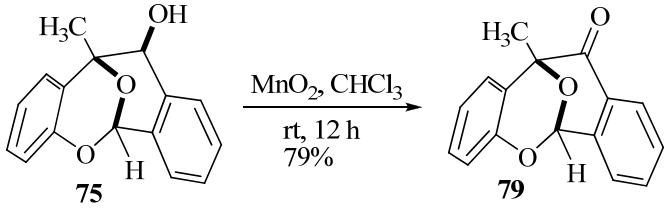
A mechanistic hypothesis for the observed *erythro* stereoselectivity is depicted in Figure 10. The mechanism is similar to that described in Figure 9. The only difference is in the present case the methyl group taken the bulky group position and phenyl group in the H-position.

Figure 10: A mechanistic hypothesis for the observed *erythro* selectivity



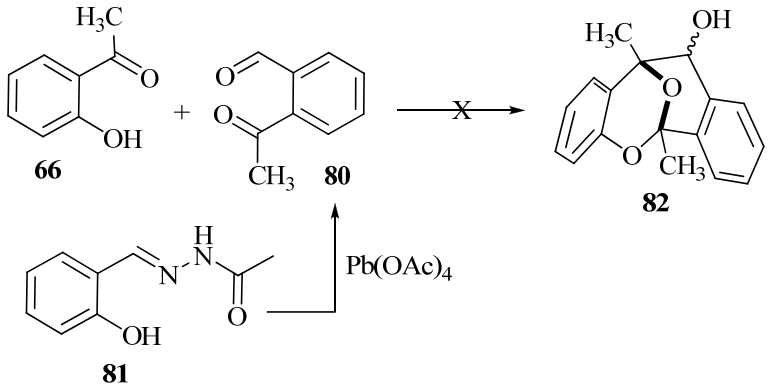
Oxidation of one of the compound **75** was carried out with MnO_2 to show the feasibility of projected benzylic-OH oxidation (Scheme 23) and corresponding keto compound **79** was obtained in 70% yield. The compound was confirmed by its ^{1}H NMR studies. In ^{1}H NMR the methyl protons were resonated at δ 1.87 and acetal proton observed at δ 6.43.

Scheme 23: Benzylic oxidation of compound **75**



Finally, when 2-formylacetophenone (**80**) and *o*-hydroxy acetophenone (**66**), despite being various reagents have been surveyed, the projected pinacol coupling of compound **80** and **66** to afford **82** was found to be a difficult proposition. In all the cases, the reactions afforded complex mixture of products. Though, majority of the products could be separated and checked for expected constitution of compound **82**, none of them are found to be matching. Though we are not sure, one reason for the failure of the pinacol coupling with compound **80** might be the possibility of an intramolecular aldol reaction on one hand and its instability (on standing at rt, formation of a more polar product was noticed) on the other hand.

Scheme 24

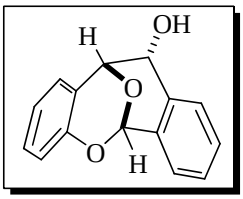


Conclusion:

In summary, inspired with the skeletol complexity and promising antiviral activity of integrastatins, herein we document a facile one-step approach for the central tetracyclic core by employing low valent titanium mediated pinacol cross coupling reaction and intramolecular acetal formation. The present approach characterized by consecutive formation of three bonds affording topologically complex tetracyclic compounds adds another dimension to the pinacol reaction and has the potential to be extended for synthesis of hitherto unknown small molecules with multiple skeletons in fewer steps by judicious juxtaposition of reactive groups.

Experimental

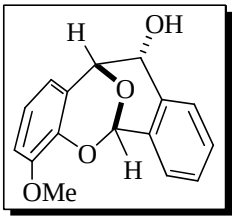
The compound (61)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **62** (510 mg, 3.7 mmol) and **63** (450 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (9:1 petroleum ether/ethyl acetate) to afford **61** (370 mg, 42%) as a colorless solid. The compound **61** was obtained as crystals by slow evaporation of EtOAc/petroleum ether.

Mol. Formula	: $C_{15}H_{12}O_3$
IR ($CHCl_3$) $\tilde{\nu}$	: 3324, 3020, 2964, 1720, 1486, 1215, 1059, 758, 668 cm^{-1}.
M. P.	: 165-166 ^{o}C.
^{1}HNMR ($CDCl_3$, 200 MHz)	: δ 1.72 (br d, *J* = 10.2 Hz, 1H), 5.14 (d, *J* = 5.8 Hz, 1H), 5.27 (br dd, *J* = 5.8, 10.2 Hz, 1H), 6.30 (s, 1H), 6.81 (br dd, *J* = 1.4, 8.3 Hz, 1H), 6.89 (br ddd, *J* = 1.2, 7.1, 7.9 Hz, 1H), 7.12–7.20 (m, 2H), 7.29–7.37 (m, 3H), 7.50–7.55 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 69.2 (d), 70.7 (d), 93.0 (d), 117.2 (d), 118.9 (s), 120.6 (d), 125.4 (d), 126.4 (d), 127.5 (d), 128.0 (d), 129.5 (d), 129.7 (d), 132.3 (s), 136.7 (s), 150.3 (s) ppm.
Elemental Analysis	Calcd.: C, 74.99; H, 5.03. Found: C, 74.75; H, 4.83.

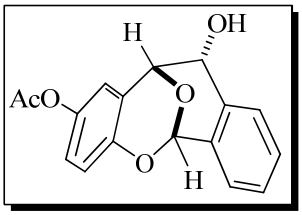
The compound (73)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **62** (510 mg, 3.7 mmol) and **64** (560 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (4:1 petroleum ether/ethyl acetate) to afford **73** (470 mg, 47%) colorless solid. The compound **73** was obtained as crystals by slow evaporation of EtOAc/petroleum ether.

Mol. Formula	: $C_{16}H_{14}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 3422, 3019, 1487, 1215, 1058 cm^{-1}.
M. P.	: 191-192 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.67 (br s, 1H), 3.80 (s, 3H), 5.12 (d, *J* = 5.8 Hz, 1H), 5.24 (br s, 1H), 6.39 (s, 1H), 6.72–6.88 (m, 3H), 7.26–7.31 (m, 1H), 7.35 (dd, *J* = 1.9, 7.4 Hz, 1H), 7.39 (br dd, *J* = 2.2, 6.8 Hz, 1H), 7.50–7.54 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.9 (q), 69.3 (d), 70.6 (d), 93.3 (d), 110.2 (s), 111.5 (d), 119.1 (d), 119.5 (s), 120.4 (d), 125.4 (d), 126.6 (d), 128.1 (d), 129.8 (d), 132.3 (s), 136.8 (s), 148.5 (s) ppm.
ESI-MS (*m/z*)	: 293.2 $[M+Na]^{+}$.
Elemental Analysis	Calcd.: C, 71.10; H, 5.22. Found: C, 70.90; H, 5.01.

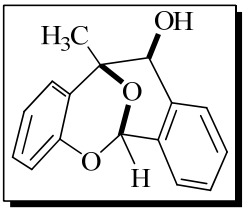
The compound (74)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (150 mg, 0.55 mmol) and Mg (530 mg, 22.2 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.1 g, 11.1 mmol) followed by a solution of **62** (370 mg, 2.7 mmol) and **65** (500 mg, 2.77 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (3:2 petroleum ether/ethyl acetate) to afford **74** (136 mg, 57%) as a colorless oil.

Mol. Formula	: $C_{17}H_{14}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 3435, 2926, 1756, 1492, 1186, 1067 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.24 (s, 3H), 5.09 (d, *J* = 5.9 Hz, 1H), 5.24 (d, *J* = 5.9 Hz, 1H), 6.27 (s, 1H), 6.75–6.93 (m, 3H), 7.27–7.36 (m, 3H), 7.46–7.51 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.9 (q), 69.1 (d), 70.7 (d), 93.1 (d), 117.7 (d), 119.7 (s), 120.7 (d), 122.4 (d), 125.5 (d), 126.3 (d), 128.0 (d), 129.7 (d), 132.0 (s), 136.5 (s), 143.6 (s), 148.0 (s), 169.8 (s) ppm.
ESI-MS (*m/z*)	: 321.4 $[M+Na]^{+}$.
Elemental Analysis	Calcd.: C, 68.45; H, 4.73.
	Found: C, 68.32; H, 4.51.

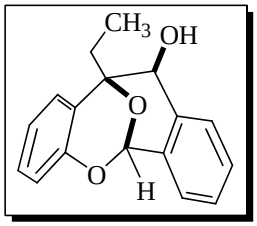
The compound (75)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **62** (510 mg, 3.7 mmol) and **66** (507 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (4:1 petroleum ether/ethyl acetate) to afford **75** (460 mg, 49%) as a pale yellow syrup.

Mol. Formula	: $C_{16}H_{14}O_3$
IR ($CHCl_3$) $\tilde{\nu}$	: 3409, 2987, 2936, 1586, 1487, 1221, 1031, 978 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.77 (s, 3H), 4.38 (s, 1H), 6.30 (s, 1H), 6.71 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.87 (ddd, *J* = 1.6, 7.3, 8.4 Hz, 1H), 7.07 (ddd, *J* = 1.2, 7.3, 7.8 Hz, 1H), 7.08 (dd, *J* = 1.6, 7.8 Hz, 1H), 7.29–7.36 (m, 4H) ppm.
^{13}CNMR ($CDCl_3$, 50 MHz)	: δ 23.3 (q), 72.8 (d), 75.7 (s), 93.1 (d), 117.4 (d), 121.2 (d), 125.0 (d), 126.5 (s), 126.7 (d), 128.9 (d), 129.6 (d), 131.2 (s), 135.2 (s), 149.1 (s) ppm.
ESI-MS (*m/z*)	: 277.28 $[M+Na]^{+}$.
Elemental Analysis	Calcd.: C, 75.57; H, 5.55.
	Found: C, 75.32; H, 5.43.

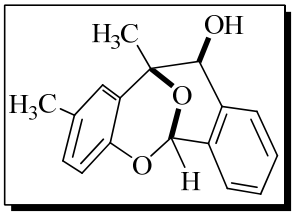
The compound (76)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **62** (510 mg, 3.7 mmol) and **67** (560 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (4:1 petroleum ether/ethyl acetate) to afford **76** (366 mg, 37%) as a yellow colour oil.

Mol. Formula	: $C_{17}H_{16}O_3$
IR ($CHCl_3$) $\tilde{\nu}$	: 3459, 2970, 2925, 1581, 1484, 1230, 789, 753 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.86 (t, *J* = 7.4 Hz, 3H), 2.07 (dq, *J* = 7.3, 14.5 Hz, 1H), 2.40 (dq, *J* = 7.9, 14.9 Hz, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 6.29 (s, 1H), 6.77 (dd, *J* = 1.1, 8.0 Hz, 1H), 6.89 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.12 (dt, *J* = 1.6, 7.8 Hz, 1H), 7.17 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.27–7.35 (m, 3H), 7.46–7.50 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 7.1 (q), 29.4 (t), 73.6 (d), 93.1 (d), 117.4 (d), 120.9 (d), 121.8 (s), 125.3 (d), 126.3 (d), 126.8 (d), 127.8 (d), 128.9 (d), 129.5 (d), 132.6 (s), 137.7 (s), 150.9 (s) ppm.
Elemental Analysis	Calcd.: C, 76.10; H, 6.01. Found: C, 75.90; H, 6.01.

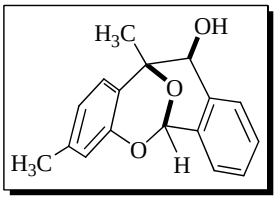
The compound (77)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **62** (510 mg, 3.7 mmol) and **68** (560 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (3:2 petroleum ether/ethyl acetate) to afford **77** (425 mg, 43%) as a colorless syrup.

Mol. Formula	: $C_{17}H_{16}O_3$
IR ($CHCl_3$) $\tilde{\nu}$	: 3422, 3019, 2927, 1497, 1458, 1216, 1033, cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.75 (s, 3H), 2.21 (s, 3H), 4.36 (br s, 1H), 6.30 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.86–6.88 (m, 2H), 7.28–7.34 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 20.8 (q), 23.2 (q), 72.9 (d), 75.6 (s), 93.1 (d), 117.0 (d), 125.3 (d), 126.7 (d), 128.9 (d), 129.5 (d), 129.6 (d), 130.4 (s), 131.3 (s), 135.2 (s), 146.8 (s) ppm.
Elemental Analysis	Calcd.: C, 76.10; H, 6.01. Found: C, 75.80; H, 5.82.

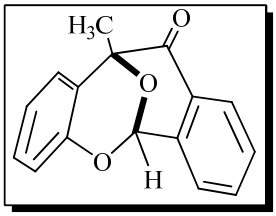
The compound (78)



At –10 ^{o}C, a suspension of Mg(Hg) [preparted from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to the Corey's procedure] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **62** (510 mg, 3.7 mmol) and **69** (560 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 ^{o}C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 ^{o}C for 15 min. Ether (10 ml) was added and the mixture was filtered through *celite*. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude was subjected for flash column chromatography (3:2 petroleum ether/ethyl acetate) to afford **78** (405 mg, 41%) as a yellow color oil.

Mol. Formula	: $C_{17}H_{16}O_3$
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.75 (s, 3H), 2.28 (s, 3H), 4.35 (d, *J* = 7.5 Hz, 1H), 6.32 (s, 1H), 6.52 (s, 1H), 6.66–6.69 (m, 1H), 6.95 (br d, *J* = 7.8 Hz, 1H), 7.28–7.36 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 21.1 (q), 23.3 (q), 72.9 (d), 75.5 (s), 93.2 (d), 117.6 (d), 122.2 (d), 123.5 (s), 124.8 (d), 126.7 (d), 128.9 (d), 129.5 (d), 129.6 (d), 131.3 (s), 135.2 (s), 139.0 (s), 148.9 (s) ppm.
Elemental Analysis	Calcd.: C, 76.10; H, 6.01. Found: C, 75.90; H, 5.81.

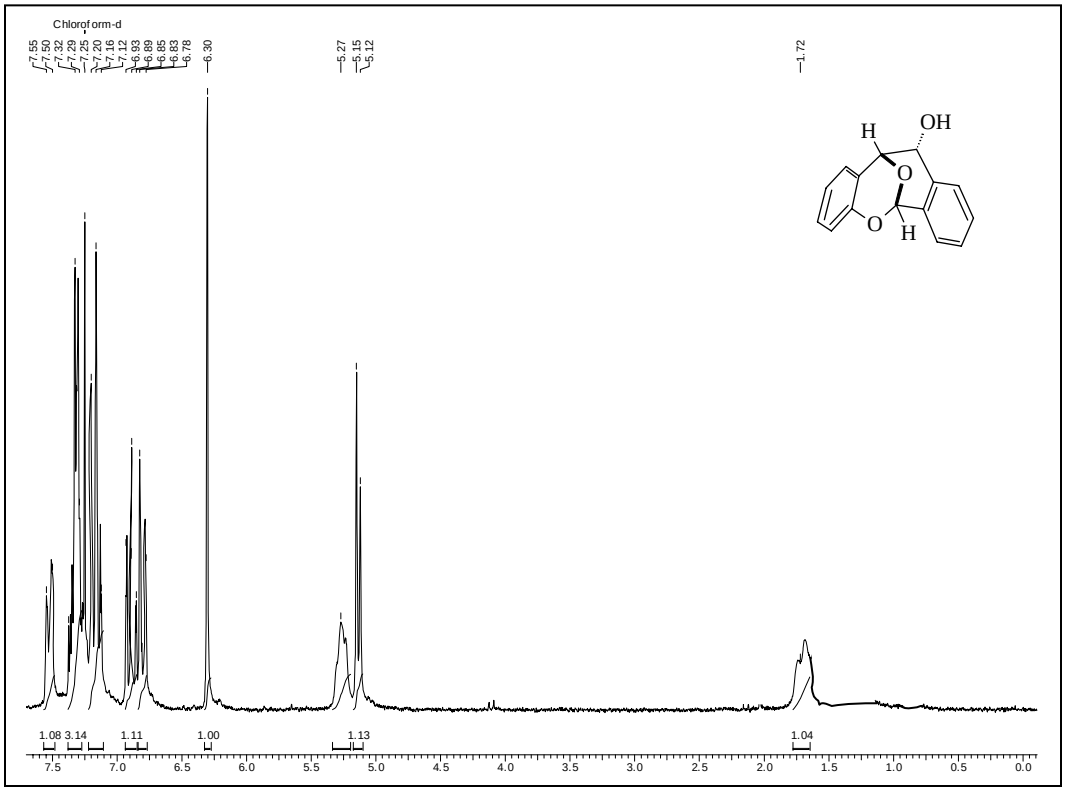
Oxidation of compound 75



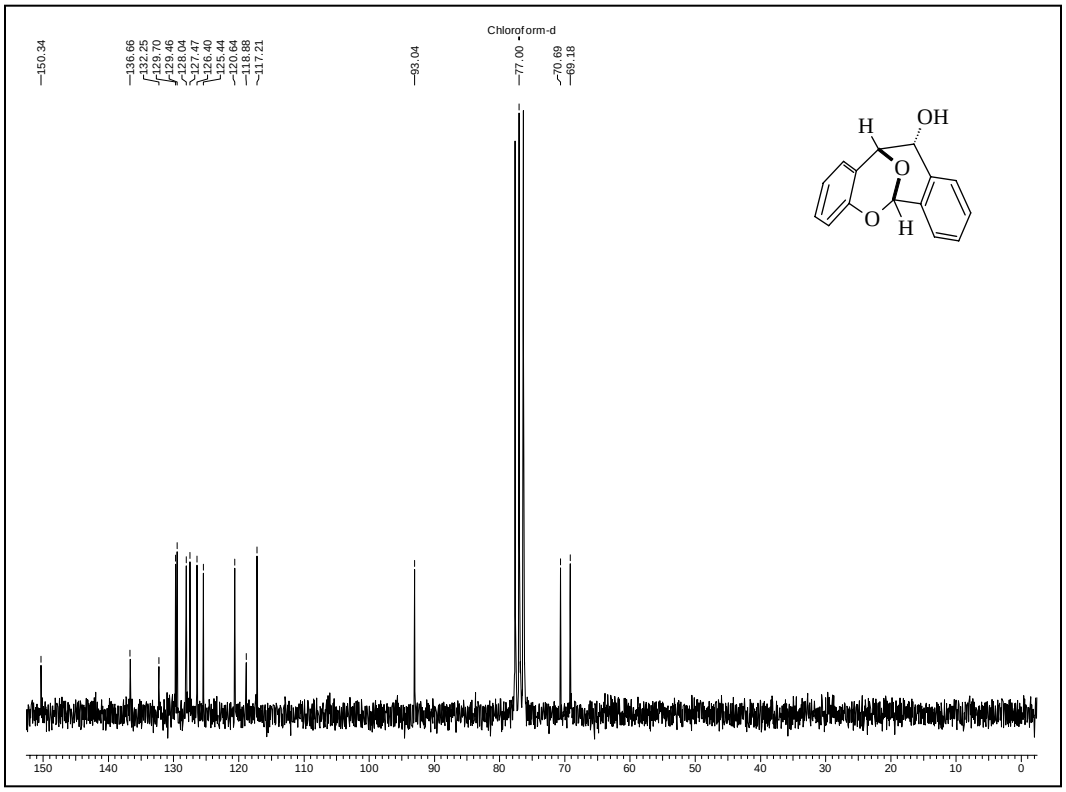
The compound **75** (50 mg, 0.19 mmol) was dissolved in chloroform (3 ml), and added MnO_2 (51 mg, 0.59 mmol) stirred the reaction mixture in room temperature for 12 h. The reaction mixture was diluted with dichloromethane (20ml) and filtered over *celite* pad and concentrated. The crude was subjected for column chromatography (9:1 petroleum ether/ethyl acetate) to afford **79** (38 mg, 79%) as a yellow color oil.

Mol. Formula	: $C_{16}H_{12}O_3$
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.87 (s, 3H), 6.43 (s, 1H), 6.78 (dd, *J* = 1.4, 8.4 Hz, 1H), 6.87–6.95 (m, 1H), 7.12–7.21 (m, 2H), 7.41–7.49 (m, 2H), 7.59–7.69 (m, 1H), 7.94–7.98 (m, 1H) ppm.
Elemental Analysis	Calcd.: C, 76.18; H, 4.79. Found: C, 75.30; H, 4.81.

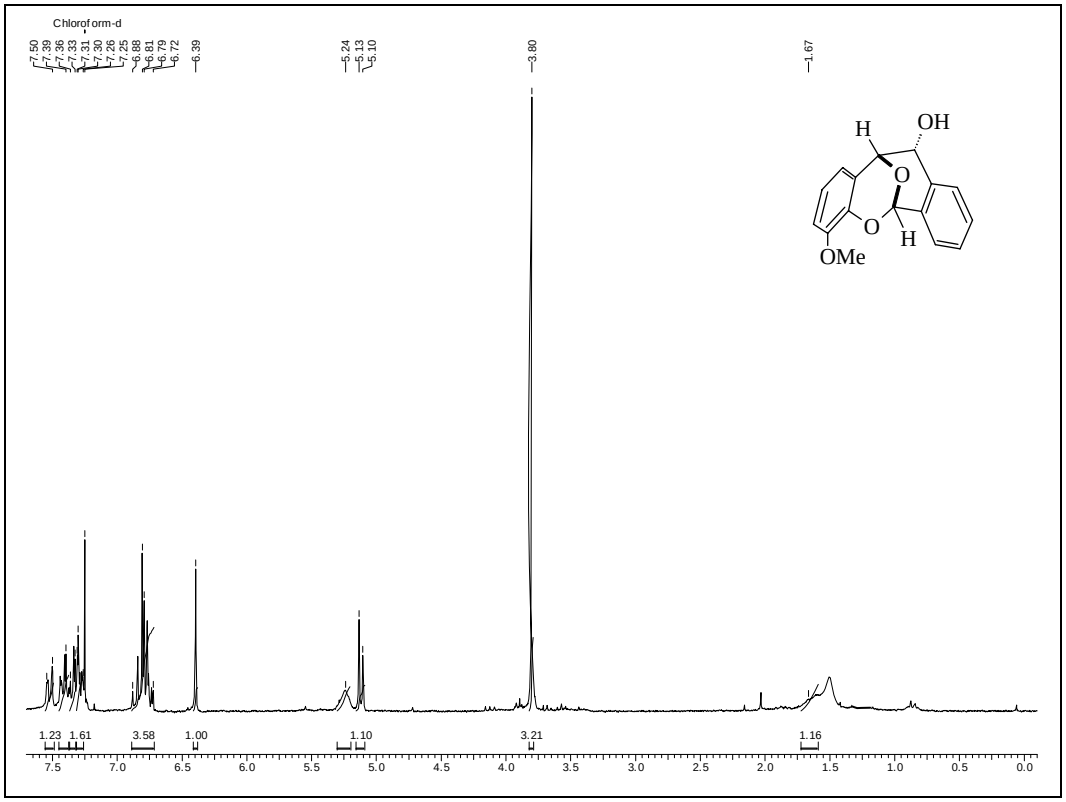
Spectra



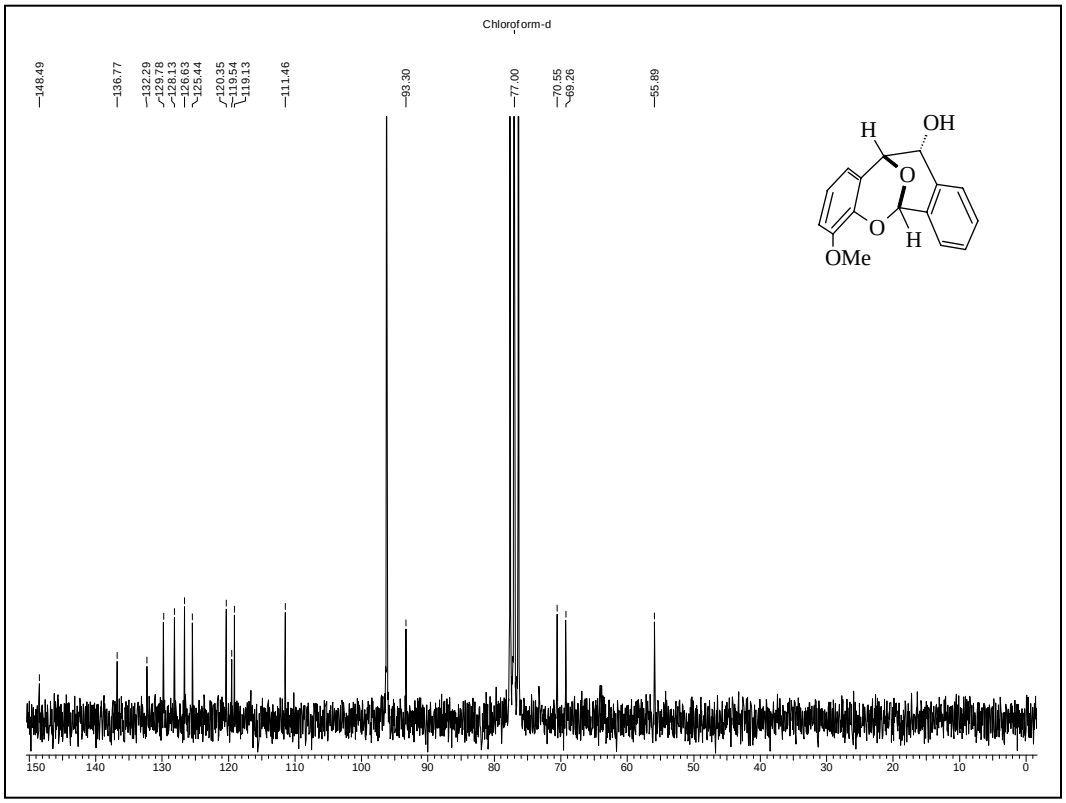
^{1}H NMR Spectrum of 61 in $CDCl_3$



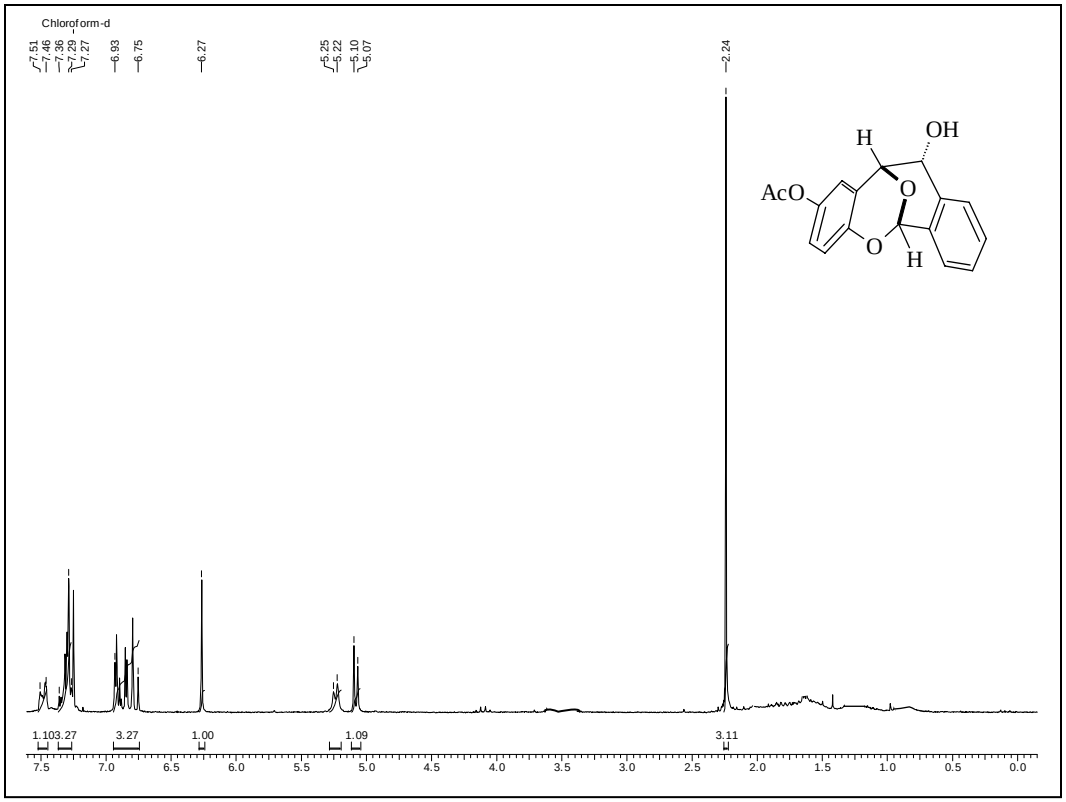
^{13}C NMR Spectrum of 61 in $CDCl_3$



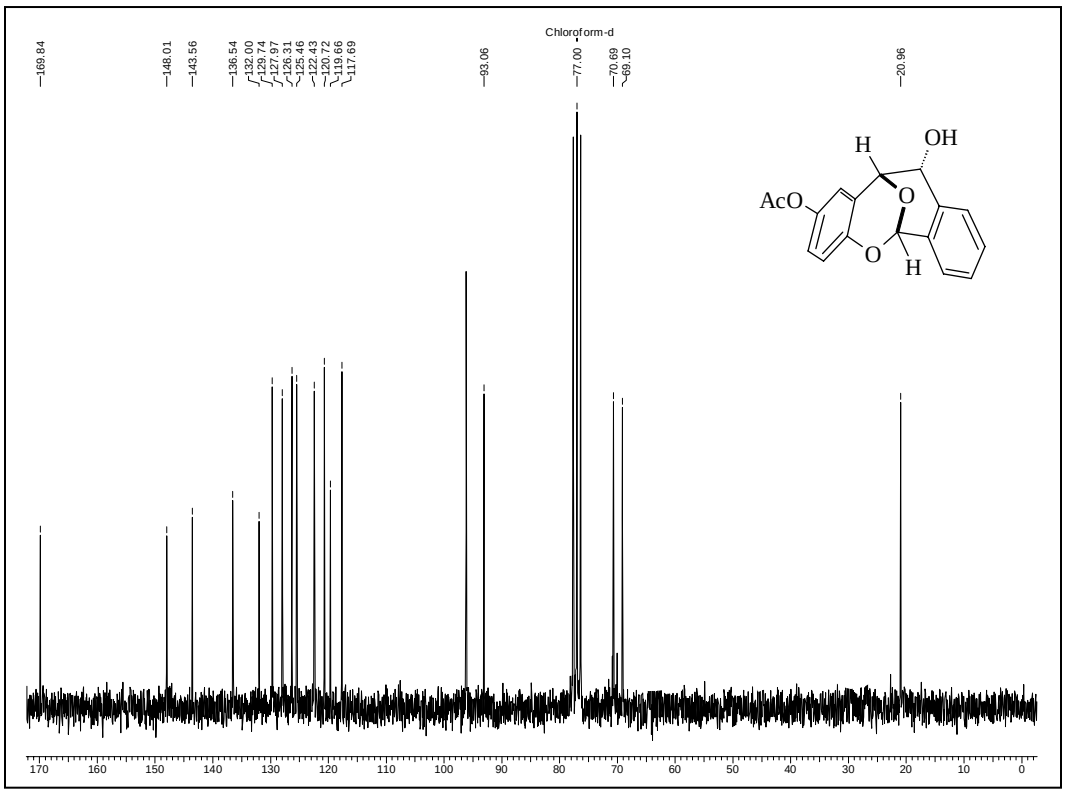
^{1}H NMR Spectrum of 73 in $CDCl_3$



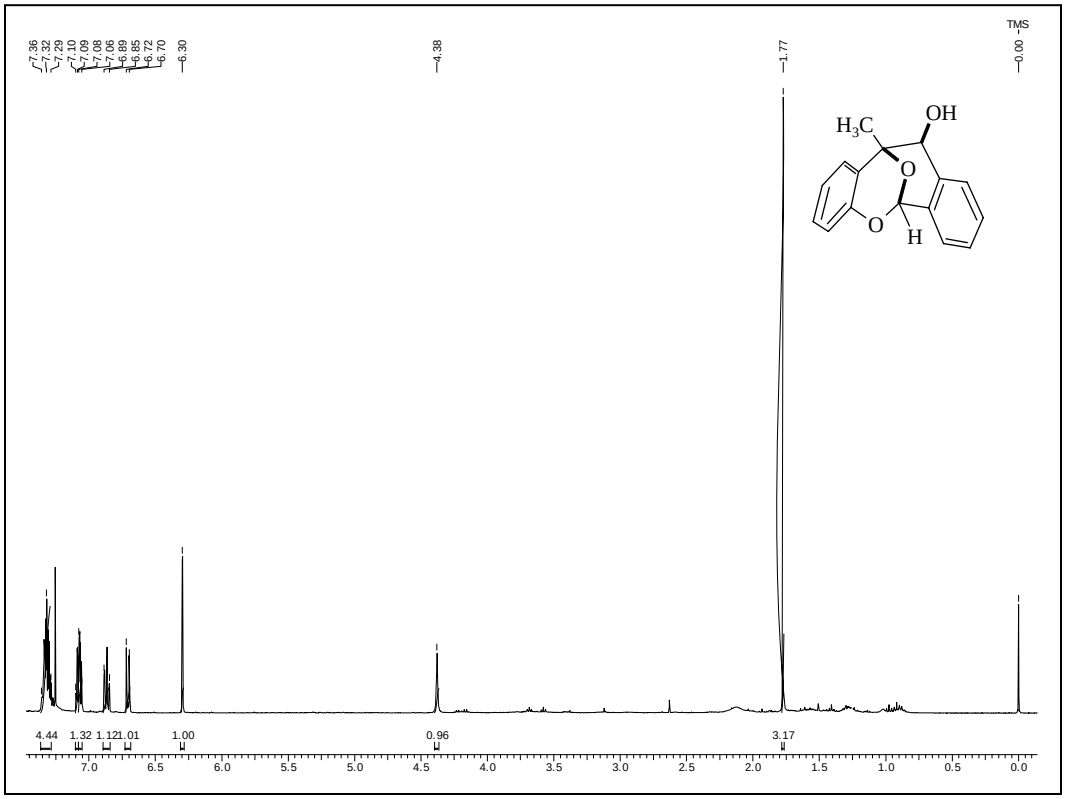
^{13}C NMR Spectrum of 73 in $CDCl_3$



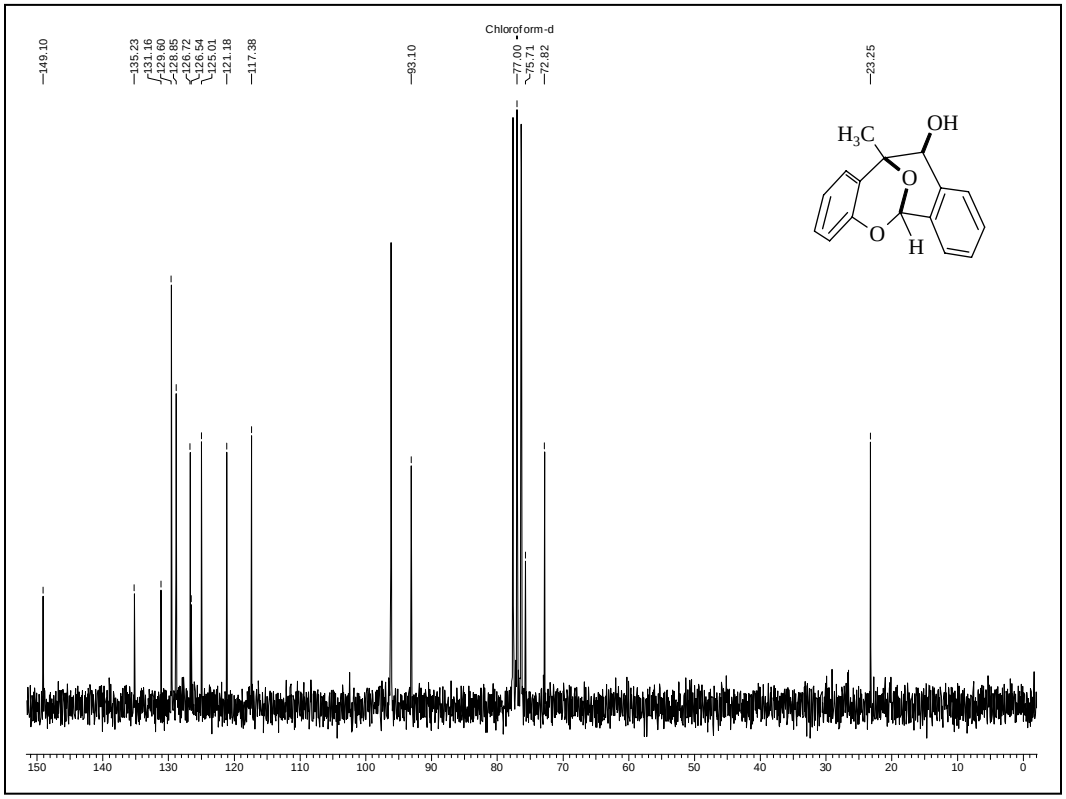
^{1}H NMR Spectrum of 74 in $CDCl_3$



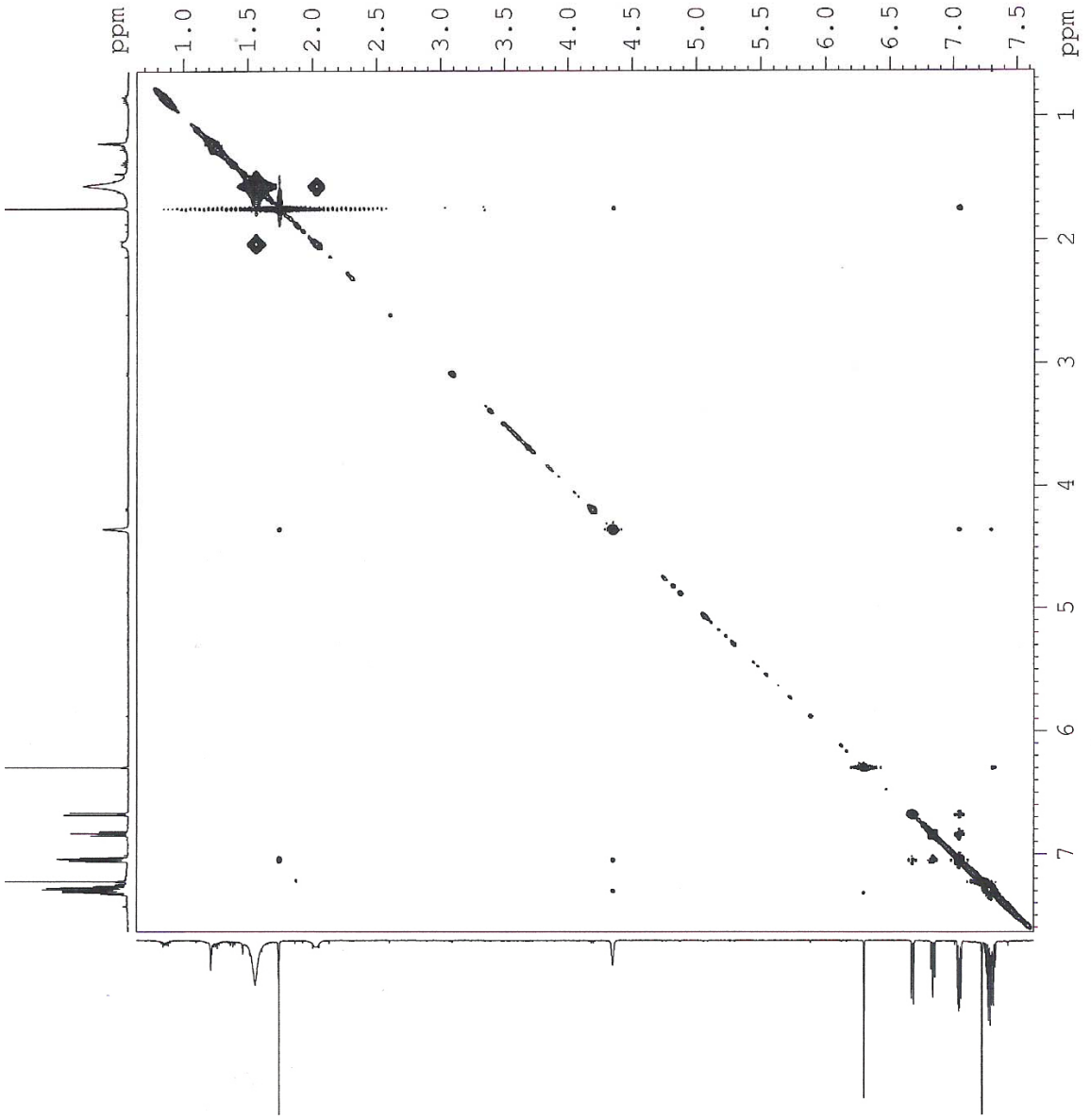
^{13}C NMR Spectrum of 74 in $CDCl_3$

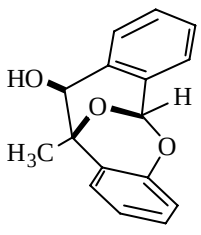


^{1}H NMR Spectrum of 75 in $CDCl_3$



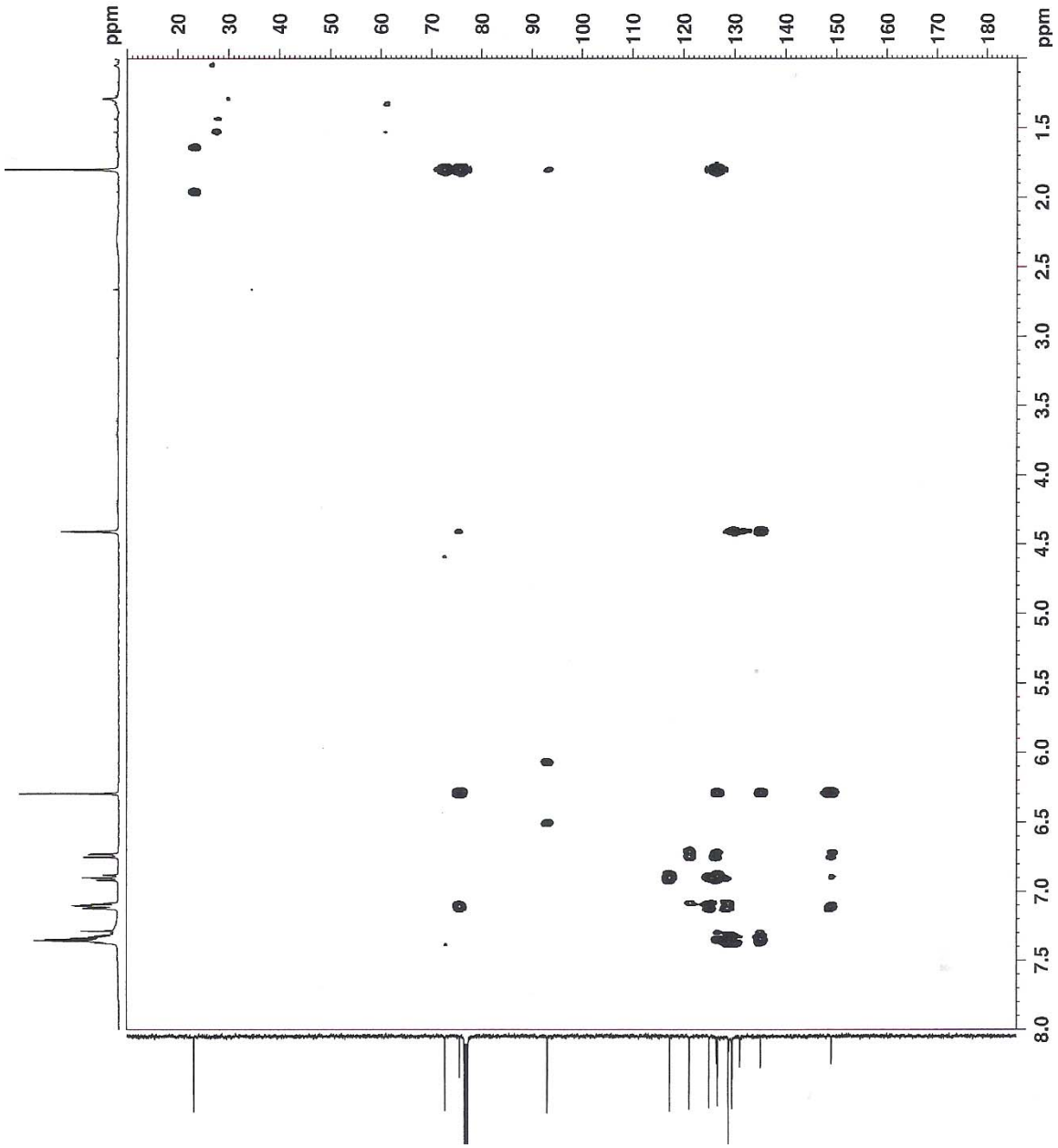
^{13}C NMR Spectrum of 75 in $CDCl_3$

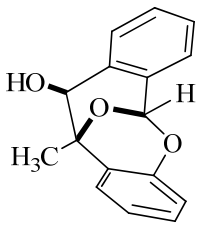




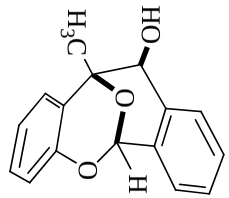
NOESY of compound 75

NOESY of compound 75

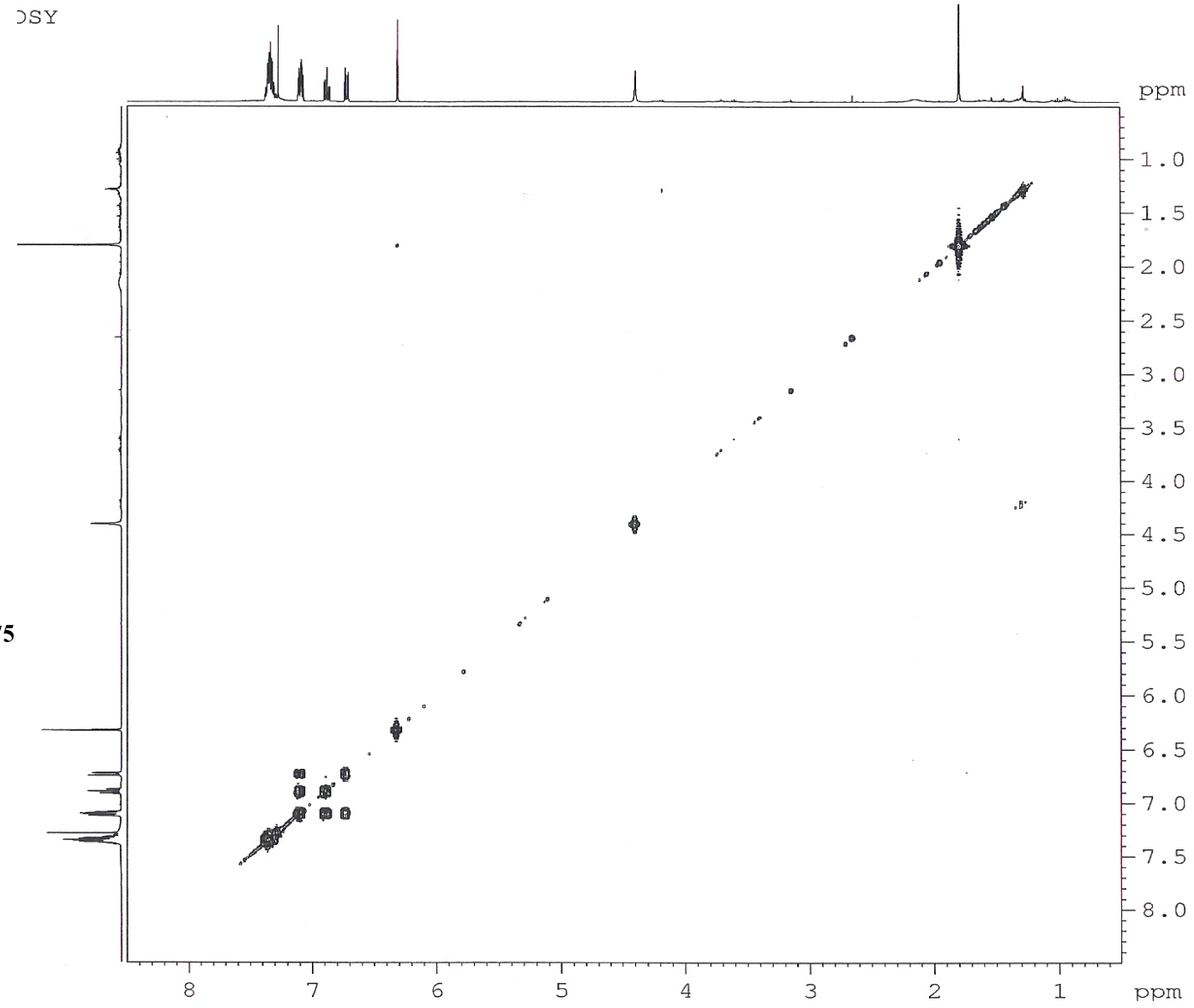


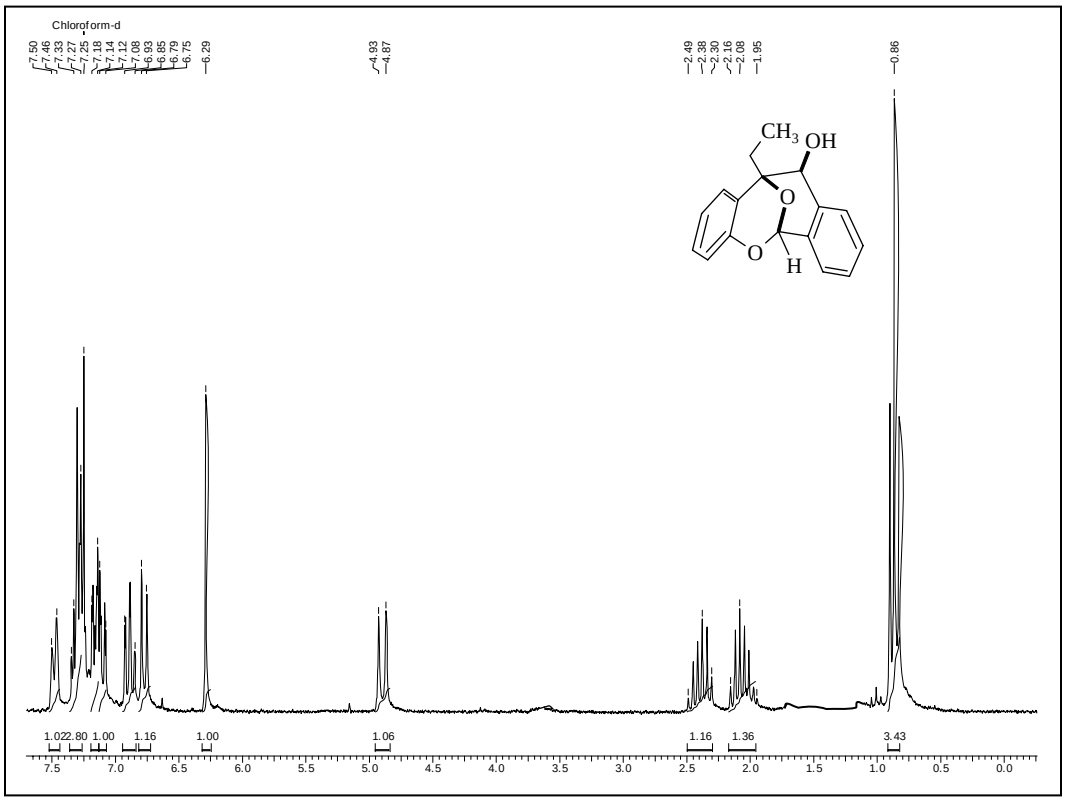


HMBC of compound 75

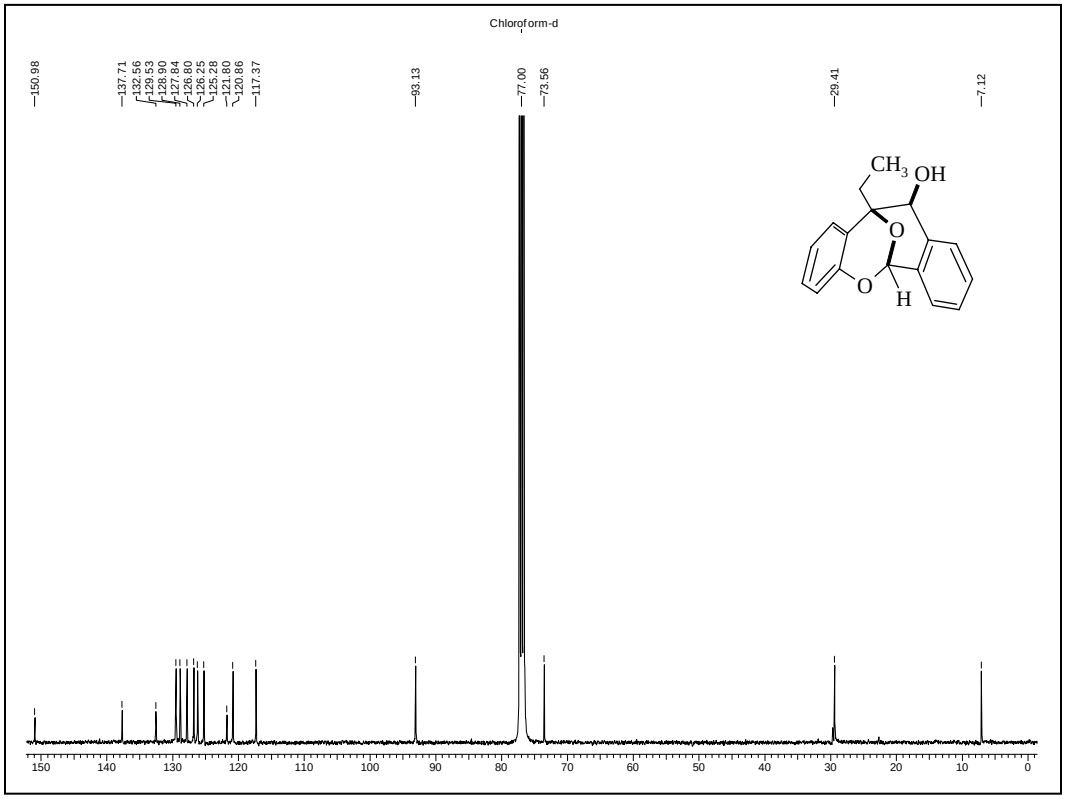


COSY of compound 75

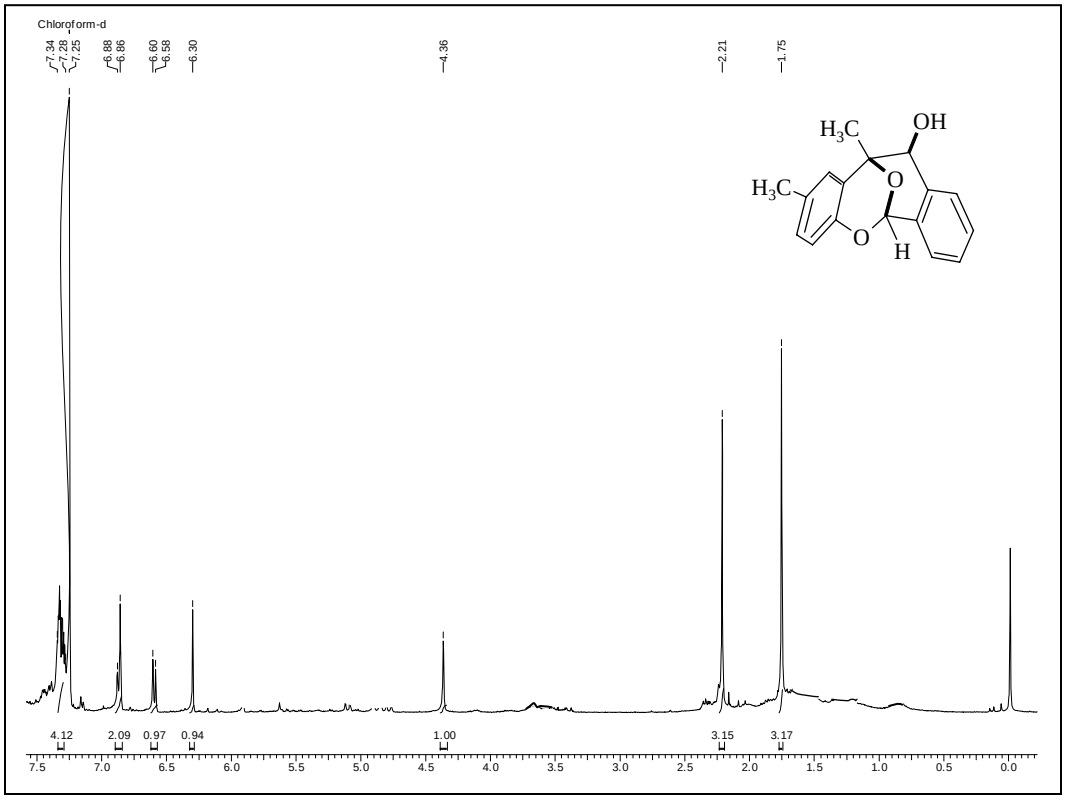




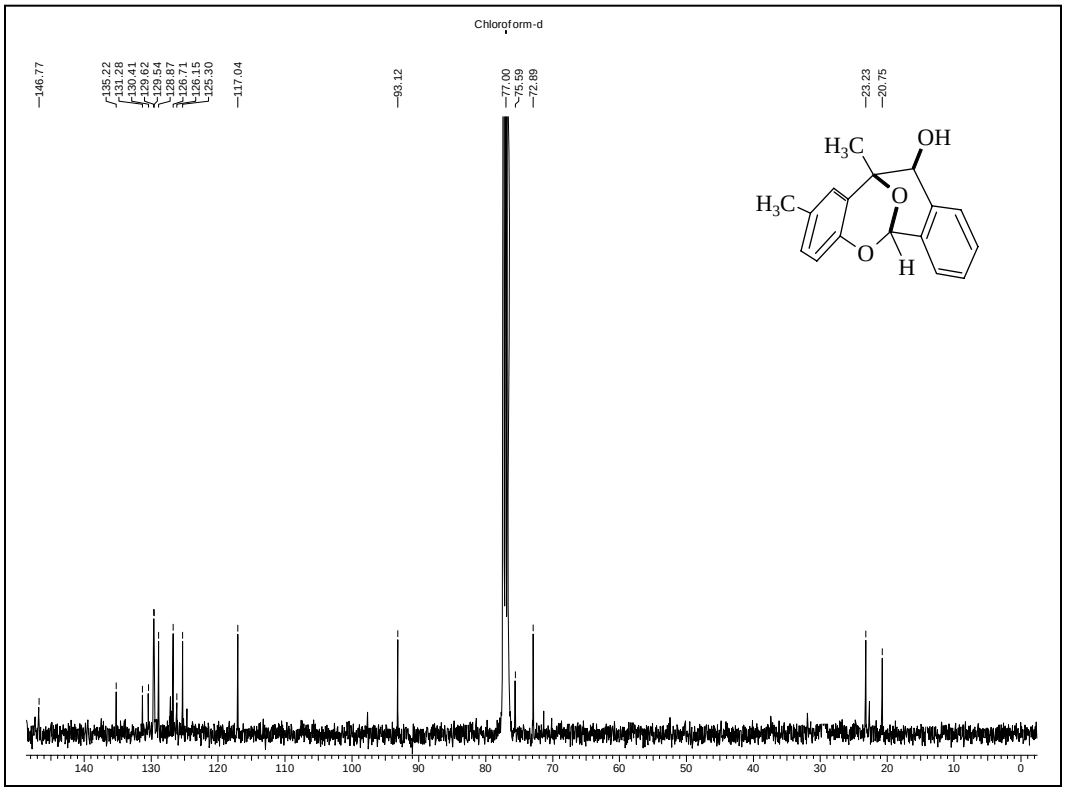
^{1}H NMR Spectrum of 76 in $CDCl_3$



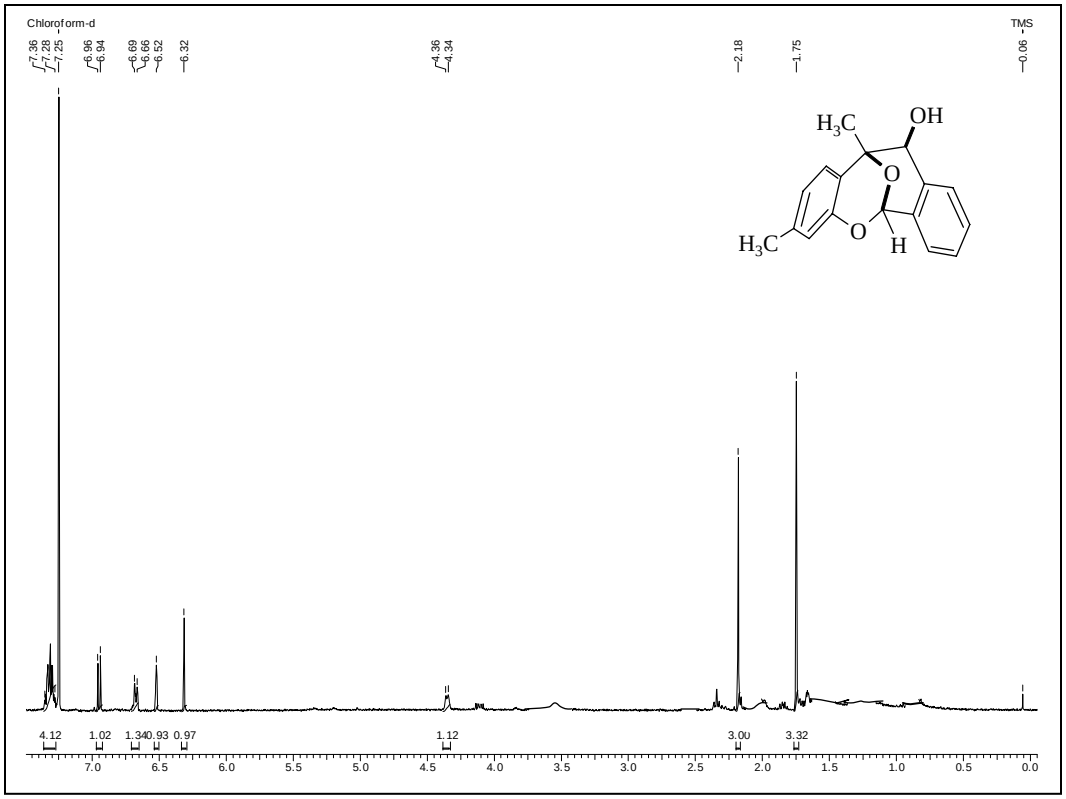
^{13}C NMR Spectrum of 76 in $CDCl_3$



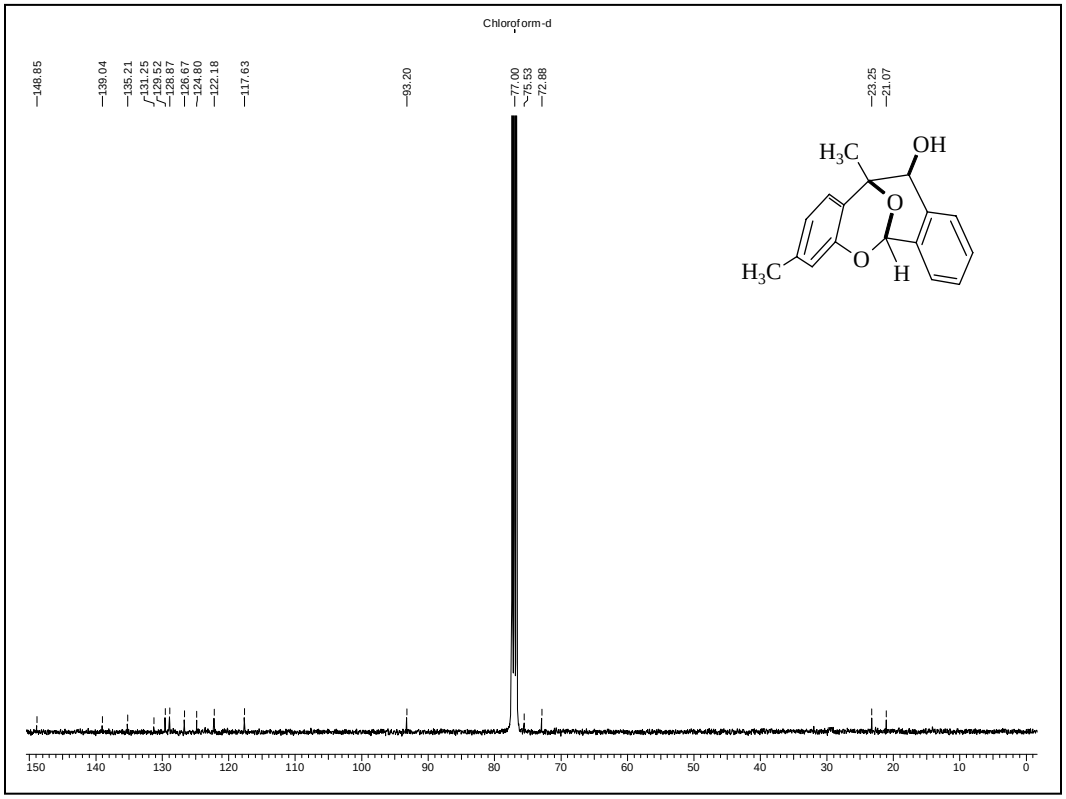
^{1}H NMR Spectrum of 77 in $CDCl_3$



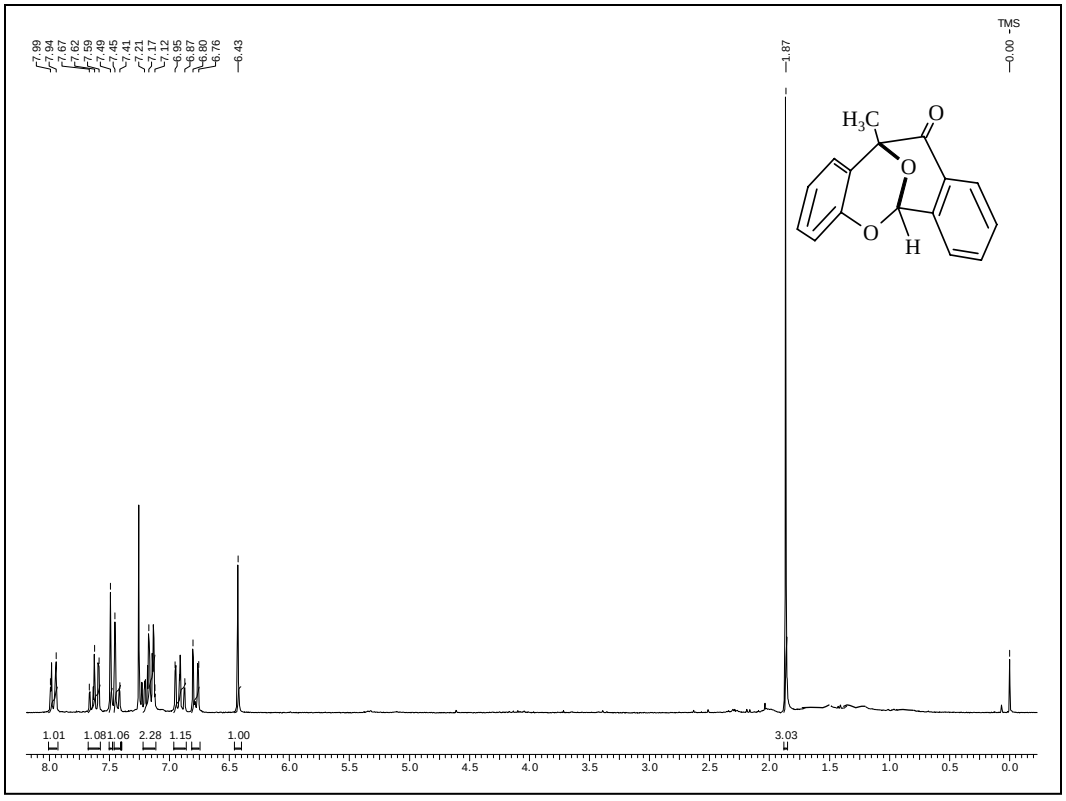
^{13}C NMR Spectrum of 77 in $CDCl_3$



^{1}H NMR Spectrum of 78 in $CDCl_3$



^{13}C NMR Spectrum of 78 in $CDCl_3$



^{1}H NMR Spectrum of 79 in $CDCl_3$

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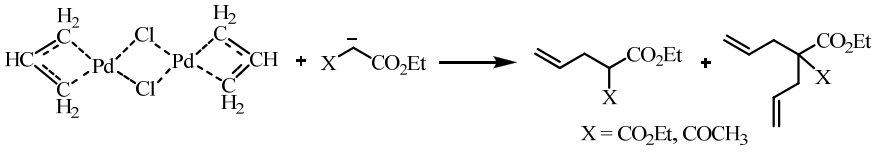
Chapter III

A Double-Suzuki Approach for Synthesis of Substituted Diarylmethylidenefluorenes

Introduction

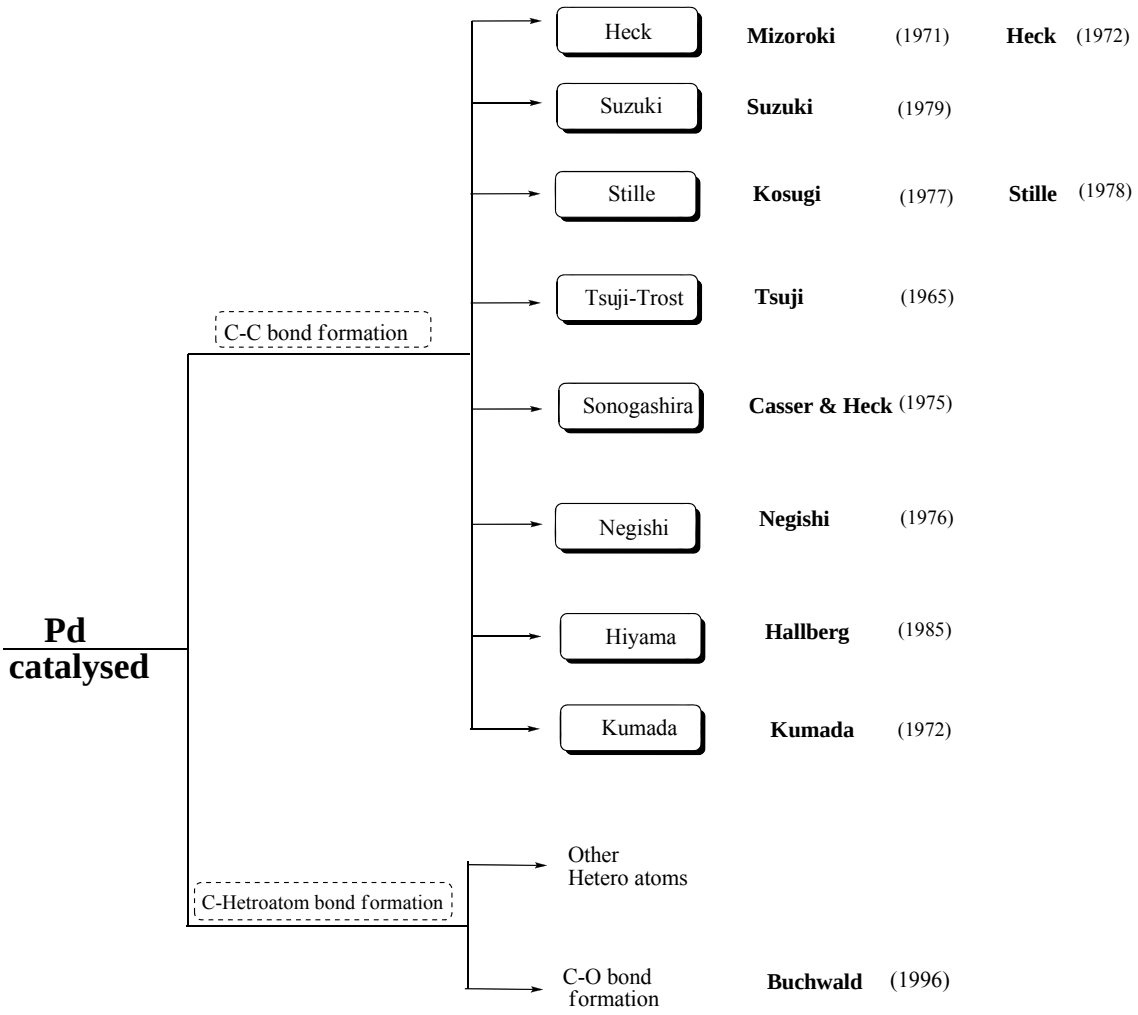
Construction of architecturally complex molecules from simple building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity. Designing effective routes to construct complex cyclic structures through organotransition-metal catalyzed reactions provides many attractive possibilities, which by conventional procedures would need a large number of synthetic transformations. The formation of carbon-carbon and carbon-heteroatom bonds are extremely important for the synthesis of biologically active natural products.[1] The use of transition metals, especially Pd, for the formation of C-C and C-heteroatom bonds have been extensively documented as demonstrated by numerous reviews and books.[2-6] The great interest in palladium catalysis stems from the fact that they often provide greater chemo, regio and enantioselectivity and relatively inexpensive in comparison to the traditional organic synthetic routes. Moreover the ability of palladium to tolerate a wide range of functional groups including carbonyl, hydroxyl, amide, and ester makes the Palladium as one of the most versatile reagent available to organic chemists. The metal catalyzed C-C bond formation reaction particularly attracted much attention including the palladium catalyzed cross coupling reactions. Pd catalyzed reactions were studied and explored in the last 40 years. One of the earliest cross coupling reactions using Pd was reported in 1965 by Tsuji and co-workers[7] for the C-C bond formation on allylic system and using ethyl malonate/acetoacetate as shown in Scheme 1.

Scheme 1



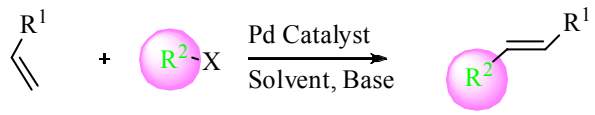
A variety of Pd-mediated transformations involves C-C, C-O bond formations have been developed and disscused with the names of researchers who disclosed (Figure 1).

Figure 1: Pd Catalyzed C-C & C-heteroatom bond formation reaction



Considering the relevance and importance, the salient features of the Heck and Suzuki coupling are discussed in the following pages.

Heck coupling



R^2 = benzyl, aryl, vinyl

X = Cl, Br, I, OTf

The Heck reaction is the carbon-carbon bond forming reaction, coupling the two sp^2-hybridized species by using Palladium catalyst. Mizoroki and co-workers[8] showed that Pd metal can assist the coupling of olefin with aryl halides in 1971 and later the scope of this reaction was increased when Heck improved the generality of this reaction. The inter- and intramolecular versions of the Heck reaction have been widely applied for the total synthesis of myriad of bioactive organic compounds. By applying Heck reaction it is possible to form polyene, to couple fragments and to form cyclic frameworks.The numerous reviews[9] covering the utility of the Heck reaction attest to it being one of the most widely utilized methodologies for the formation of C-C bonds. In view of large number of excellent reviews we want to discuss the mechanistic pathway, which impart the regio- and enantio control necessary for Heck reaction. The regioselectivity of the Heck reaction depends upon the following major factors;

1. The regioselectivity in case of unsymmetrical alkenes depends on the electronic and steric environment.
2. In case of availability of both the β and β′ hydrogen, there is possibility of competition for the hydrogen elimination.

Substrates: A traditional Heck reaction requires one electrophilic partner and one nucleophilic partner. Aryl/benzyl/vinyl halides as well as aryl/benzyl/vinyl triflates can acts as the electrophilic partner and alkenes as the nucleophilic partner. The rate of reaction is high for olefins containing electron withdrawing groups. The most widely used halide partners (electrophilic) for the coupling reactions are aryl halides. Reactivity of aryl halides toward the coupling reaction depends on the bond dissociation energy of the C-X bond. In the Halogen family of the periodic table, the bond dissociation energy decreases from top to bottom and hence the reactivity order of these aryl halides increases in the same order accordingly.

Catalytic system: Various catalytic systems have been developed for Pd catalyzed Heck reactions including homogenous as well as heterogeneous catalysts, ligands as well as ligand free system, stable colloids, nanoparticles and polymer supported catalyst. For the Heck reactions catalyzed by Pd the turnover number (TON) is good. The TON is a value calculated by the ratio of the amount of product formed and the amount of catalyst

present in the reaction and is used to evaluate the efficiency of the catalyst in a given reaction. A variety of ligands are being developed in order to enhance the reactivity of the catalytic system and to increase the TON. Nitrogen and phosphorous compounds are commonly used ligands in transition metal chemistry. Palladium complexes with various phosphines as ligands have been most commonly used as catalysts for the Mizoroki-Heck reaction. The ligand free catalytic system have been also reported including an automated reactor performing ligand-free Heck reactions in continuous flow mode utilizing a monolithic reactor cartridge with Pd(0) nanoparticles. A ligand free Heck reaction proceeds in the presence of an ionic liquid.

Solvents: Polar solvents (DMF, DMSO, DMA and acetonitrile) are often used. Aqueous methanol also has been successfully used.

Bases and additives: Generally bases like Et_3N, K_2CO_3, $NaHCO_3$, KOAc and NaOAc are most common.

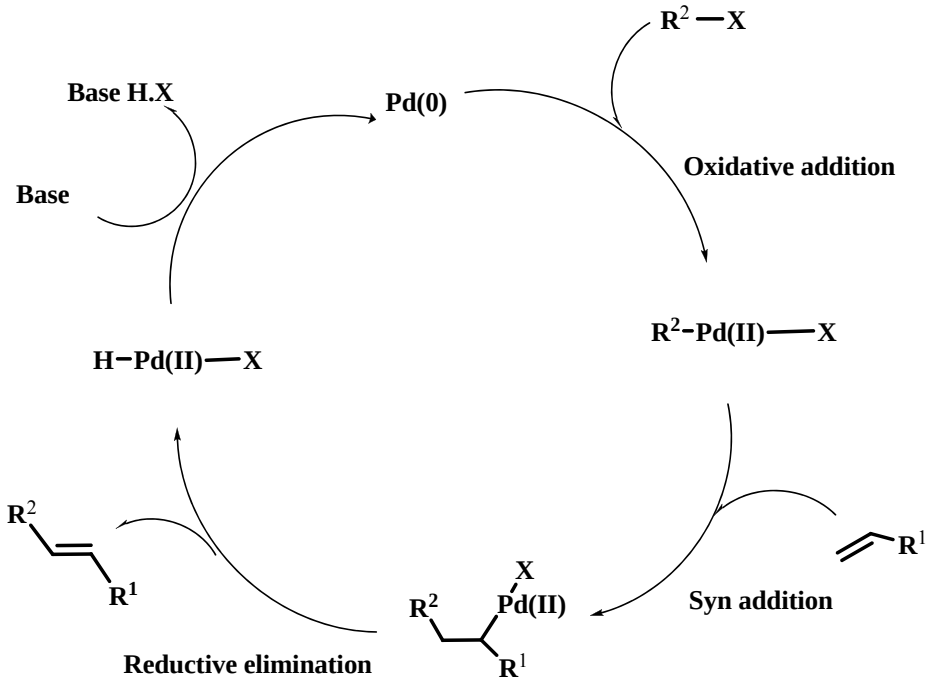
Reaction temperature: Ranges from 50-160 ^oC can be used which generally depends on the organic halide to be activated and the stability limit of the catalyst.

Mechanism

The first step for the catalytic cycle in Heck reaction involves the oxidative addition of Pd(0). The adduct formed due to the insertion of Pd is then coordinates with an unsaturated substrate in the second step. In the next step, reductive elimination releases the product along with palladium-hydride complex that can be converted to the starting Pd(0) with the help of suitable base (Figure 2).

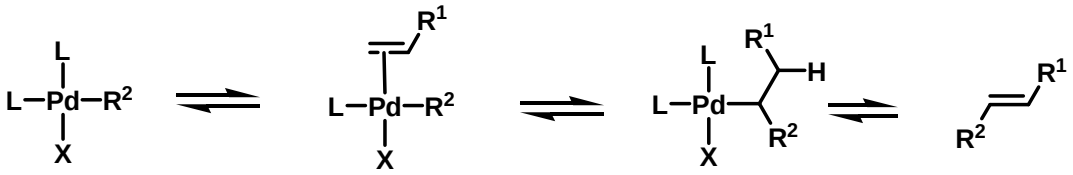
In case of unsymmetrical substrate, the addition of the alkyl group can either take place at α or the β position. The syn addition of the aryl complex to such an unsymmetrical olefin prefers the aryl group addition to the less hindered β position due to the steric reason.

Figure 2: The mechanism for the Heck cross-coupling reaction
(Ligands are not shown)



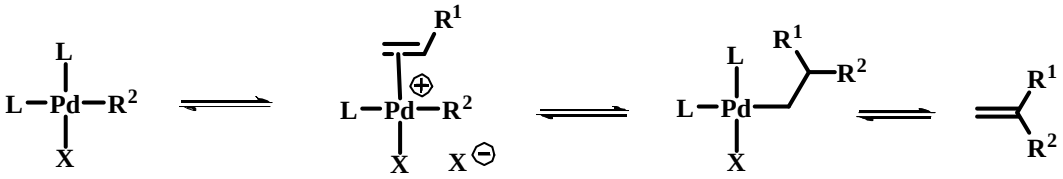
However, this pathway requires the dissociation of one of the ligands coordinated to the Pd as shown in Figure 3.

Figure 3: Neutral pathway



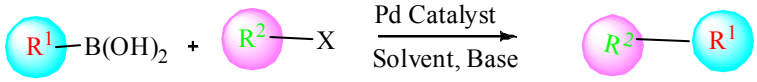
The neutral pathway is favored when X = I, Br or Cl. By contrast when X = OTf the weakly coordinating anion will dissociate readily instead of ligand L. As a result a positive charge generate on the Pd atom placing a negative charge on the R^1 group simultaneously. Accordingly insertion occurs with R^2 group adding to the more substituted carbon.

Figure 4: Cationic pathway



The cationic pathway is shown in Figure 4. The electronic nature of the olefin determines the regioselectivity. The electron rich alkenes favor the neutral pathway while the electron poor alkenes prefer the cationic pathway. Furthermore, the cationic pathway is dominant when halide-sequestering agents such as Ag (I) salts are added. In contrast, the addition of exogenous halide ions will favors the neutral pathway. In case of the asymmetric version of the Heck reaction, the enantioselectivity depends on the pathway of the reaction. The cationic pathway gives the higher % *ee* than the neutral pathway.

Suzuki coupling



R^1 = alkyl, alkynyl, aryl, vinyl

R^2 = alkyl, alkynyl, benzyl, aryl, vinyl

X = Cl, Br, I, OAc, OTs, OTf, $OP(=O)(OR)_2$

The Palladium catalyzed coupling reaction between an aryl halide (electrophile) and aryl boronic acid (nucleophile) is known as Suzuki coupling. This reaction is useful especially for the synthesis of the biaryl systems, which are the important part of many bioactive compounds. The two research groups namely Buchwald[10] and Fu[11] independently explored this reaction for the coupling of aryl chlorides under non-harsh conditions. Like the Heck reaction it also tolerates the many functional groups.

Substrates: The suitable substrates for the Suzuki coupling reaction are the aryl/alkyl/alkyl/benzyl/vinyl halides (chlorides, bromides, and iodides) and

aryl/alkyl/alknyl/vinyl triflates substituted with electron-withdrawing groups. The triflates and sulphonates of these compounds are regarded as the synthetic equivalents of their corresponding halides. But it has been observed that triflates decomposes normally due to their thermal labiality. Moreover triflates are expensive and undergoes hydrolysis easily, which makes them difficult to use in the Suzuki reaction. The sulphonates are an attractive option because they are easily prepared, more stable and cheap staring material. The other coupling partner can be used are boronic acids [$RB(OH)_2$], boronic esters [$RB(OR')_2$] and borinates [R_2BOR'].

Catalytic system: The phosphine ligands like PPh_3, PCy_3, P(*i*-Pr)$_3$, P(*t*-Bu)$_3$, P(*n*-Bu)$_3$, dcpe, BINAP etc. The variety of nucleophilic *N*-heterocyclic carbenes (imidazol-2-ylidenes) i.e. NHC; also called "phosphine mimics" have been developed[25].

Bases and additives: The choice of the suitable base has played an important role in Suzuki coupling reaction. Various bases accelerate the rate of reaction in Suzuki coupling reactions are K_3PO_4, Na_2CO_3, $CsCO_3$, KOMe etc.

Solvents: The nature and the polarity of the solvent play the crucial role in the cross-coupling reactions. It has been observed that the same reaction with different solvents affords different results. The Suzuki cross-coupling reactions generally employ organic solvents such as THF, DME, toluene, benzene, dioxane, diethyl ether, and 1-butanol. They also employed organic solvent with water. Appropriate solvent system is also a solution to favor cross-coupling reaction.

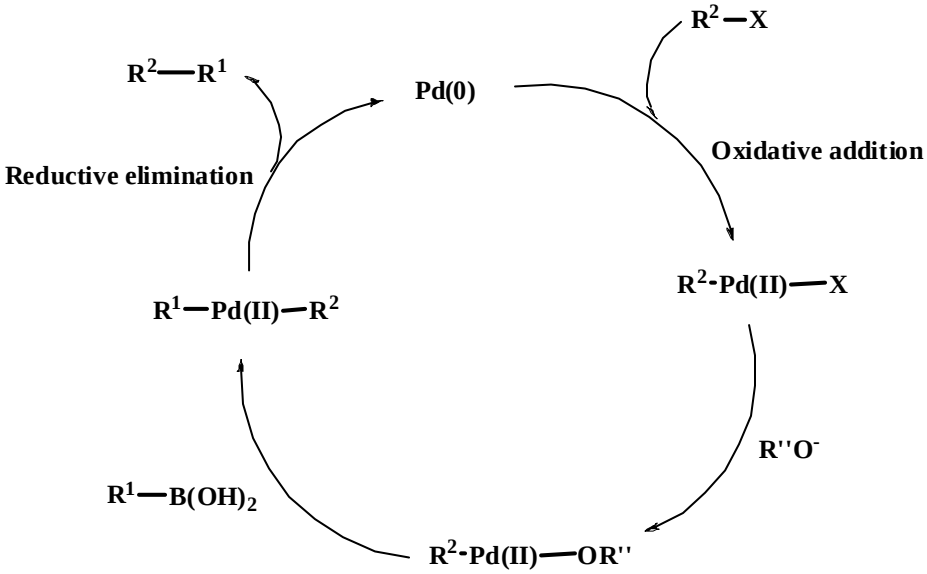
Mechanisms

In the initial step, the halides or triflates oxidatively adds to the Pd catalyst to give R^2-Pd-X complex. This complex then reacts with the base to form more reactive complex R^2-Pd-OR". The next step is the transmetallation of R^2-Pd-OR" with boron derivatives led to R^2-Pd-R^2. In the final step the reductive elimination produced R^1-R^2 and recycling the Pd(0) catalyst (Figure 5).

The low reactivity of the organoborane compounds makes the use of a base necessary because of its low reactivity with R^2-Pd-X complex. However, the

quarternization of the boron atom to form the 'ate'-complex renders the use of a base unnecessary.

Figure 5: Mechanism of Suzuki coupling
(Ligands are omitted for the simplicity)



The enhanced nucleophilicity of the organic substituent attached to the boron enables direct alkylation of the R^2-Pd-X complex. Several reactive 'ate'-complexes are known like Bu_4BLi, $[ArB(Bu)_3]Li$, Ph_4BNa, $[R_3BOMe]Na$, $[ArB(R)(OR)_2]Li$, $[ArBF_3]K$.

In the context of the objective of the present chapter i.e double Suzuki approach for Diarylmethylidenefluorenes, a brief review of available methods for synthesis of Diarylmethylidenefluorenes and also information available about the double Suzuki approach.

Past work

Diarylmethylidenefluorenes

Diarylmethylidenefluorenes and their polymers are subject of extensive synthetic studies due to their role as electrolumenicent compositions and the alkylidine fluorine liquid crystalline semi-conducting polymers as organic field effect transistor devices.

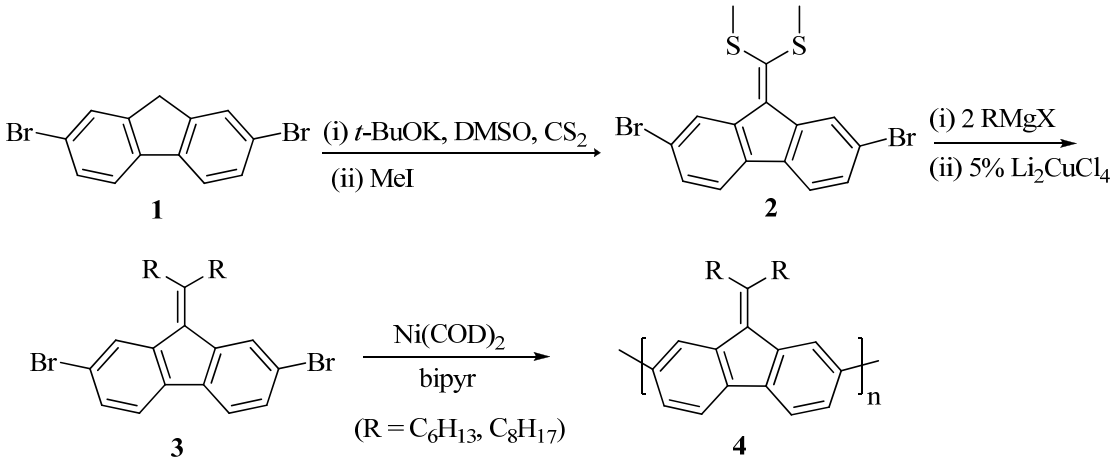
Substantial synthetic work has been documented in the literature for Diarylmethylidenefluorenes.

(i) Mc Culloch approach[12]

Mc Culloch and co-workers synthesized polymers of diarylmethylidenefluorenes of type **4.** The monomers were conveniently synthesized in just two steps from commercially available 2,7-dibromofluorene (**1)**. The initial step involved the formation of a ketene dithioacetal by condensation of a preformed fluorenyl anion with carbon disulfide, followed by an *in situ* alkylation of the resultant ketene dithiolate anion with methyl iodide to give the dimethylated thioacetal **2**. Treatment of the ketene dithioacetal with 2 equiv of an alkyl Grignard reagent in refluxing DME for 12 h initially resulted in moderate yields (20-25%) of the dialkylated product. This reaction presumably occurs *via* an addition-elimination sequence, with the intermediate carbanion at the bridge head position stabilized by resonance. The addition of a catalytic amount of Kuchi's salt (Li_2CuCl_4) both lowered the reaction temperatures and time and improved yields significantly. Derivatives containing hexyl to decyl side chains were synthesized in reasonable yields (50-60%) (Scheme 2).

Polymerizations were performed under Yamamoto conditions. The monomers were heated with a Nickel(0) catalyst in a mixed DMF-toluene solvent for 48 h, followed by *in situ* end-capping that formed polymer **4**.

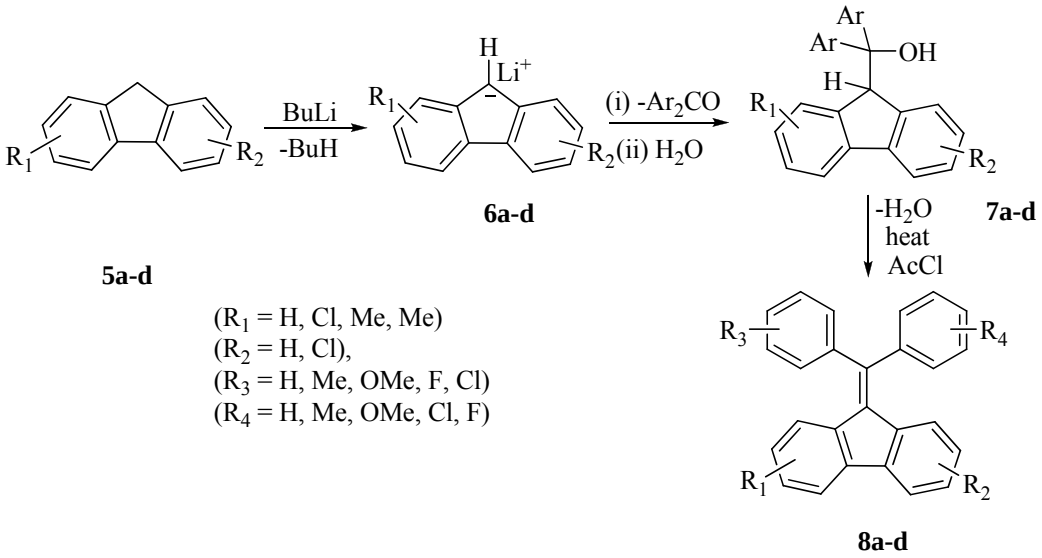
Scheme 2



(ii) B. J. Herold approach[13]

Herold et al. synthesised substituted diarylmethylenefluorenes (**8a-d**) starting from flurorine **5a-b.** The fluorenylidene anion **6a-d** was treated with diarylketone to give the intermediate carbinols **7a-d** which were later converted in to diarylmethylenefluorenes through dehydration process (Scheme 3).

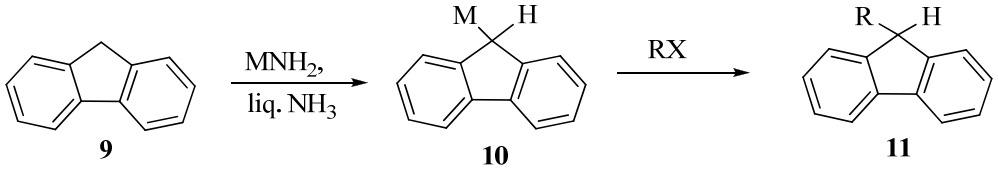
Scheme 3

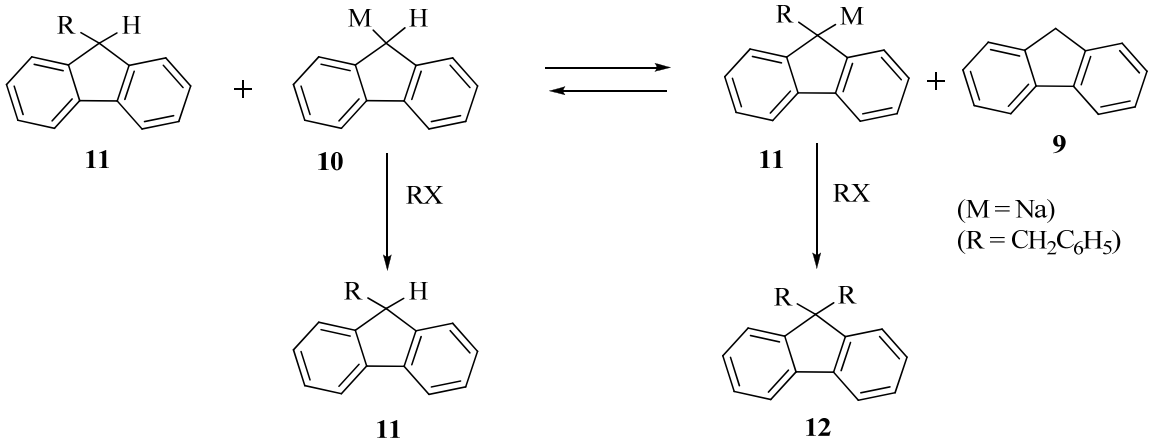


(iii) Alkylations of Fluorenes with Alkali Amides in Liquid Ammonia[14]

The fluorene **9** was treated with 1 equiv. of sodamide in liquid ammonia gave its sodium salt **10** which upon treatment with benzyl halide gave monoalkylated product **11** accompanied by dialkylated product **12** (Scheme 4).

Scheme 4

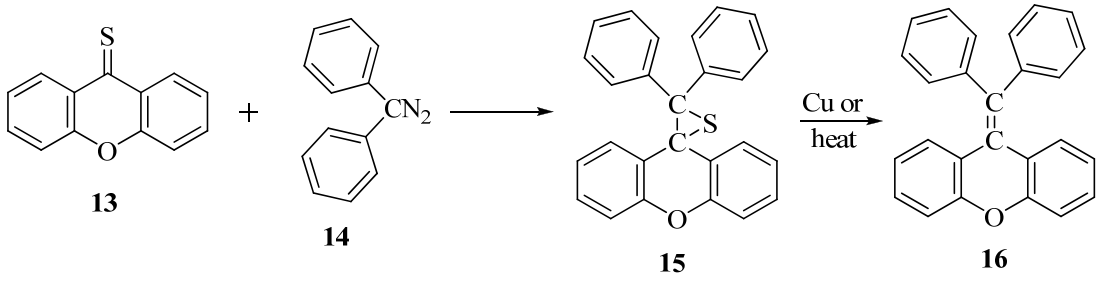




(iv) Schönberg, A. approach[15]

Schonberg and Co-workers found that treatment of xanthone (**13**) with diphenyldiazomethane (**14**) gave the ethylene sulfide derivative **15**, which on treatment with copper bronze produced 9-(diphenylmethylene)-xanthene **16** (Scheme 5).

Scheme 5



Double Suzuki Reactions

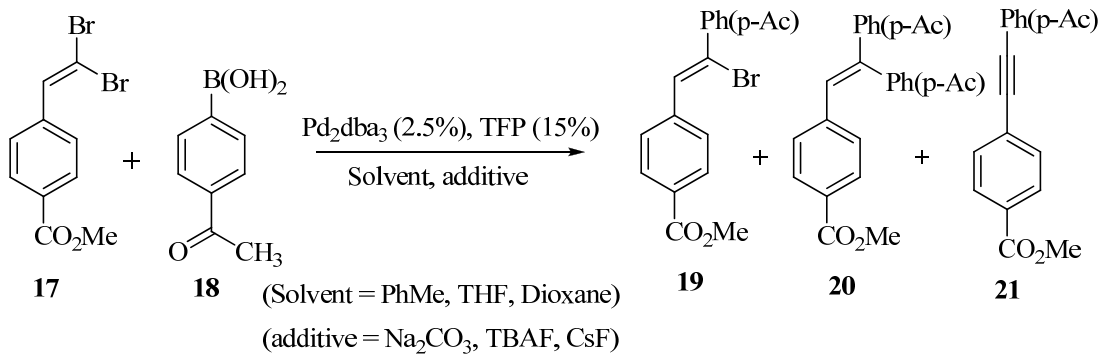
There are very few reports in the literature for the double Suzuki reaction coupling for installing diarylmethylidene subunit.

(i) Wang Shen approach[16]

Suzuki reaction of dibromide **17** and boronic acid (**18**) was catalyzed by TFP and tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) in toluene and aqueous sodium

carbonate, the reaction failed to complete after 24 hour, and three products were isolated in good yields (Scheme 6).

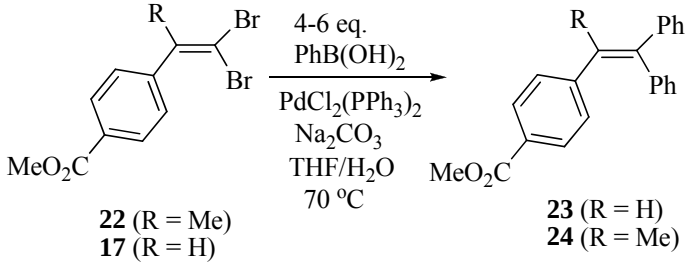
Scheme 6



(ii) Michael W. Miller approach[17]

The 1,1-dibromo-alkene **22**, derived from the corresponding ketone, was reacted with phenyl boronic acid (4-6 eq.) under Suzuki arylation conditions (cat. $PdCl_2(PPh_3)$/3 eq. Na_2CO_3/THF-H_2O) which furnished the tetra-substituted alkene **24** in 95% yield (Scheme 7).

Scheme 7

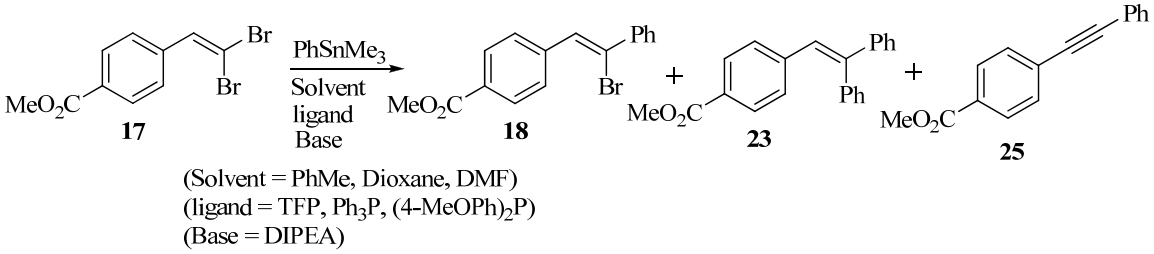


(iii) Wang Shen's approach[18]

The Stille reaction of 1,1-dibromo-1-alkenes **17** with aryl- and vinylstannanes produces different products depending on the reaction conditions. When the reaction is run in toluene or 1,4-dioxane with tris(2-furyl)phosphine (TFP) as the ligand, (*Z*)-bromoalkenes **18** are obtained. This method has been applied to the one-pot syntheses of

stereospecifically trisubstituted alkenes **23**. When the Stille reaction is conducted in a highly dipolar solvent (DMF), monobromides **18** and/or internal alkynes **25** are the products. The less reactive phenylstannane favors the formation of alkynes **25**, regardless of which ligand is used. More reactive organostannanes (vinyl, furyl) require a very electron rich ligand, tris(4-methoxyphenyl)phosphine, for the formation of alkynes **25** (Scheme 8).

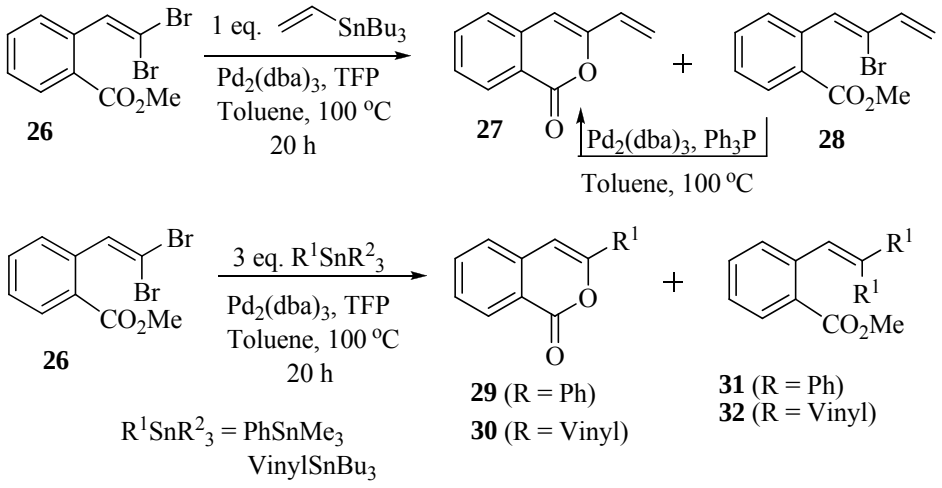
Scheme 8



(iv) Synthesis of Isocoumarins via Methyl 2-(2',2'-Dibromovinyl)benzoates[19]

When dibromide (**26**) was reacted with vinyltributyltin, the intermediate product **28** resulting from the Stille reaction was isolated, and then converted to isocoumarin **27** in good yield. When excess trimethylphenyltin was used, a mixture of both the corresponding isocoumarin (**29**, **30**) and the disubstituted product (**31**, **32**) was obtained (Scheme 9).

Scheme 9



Considering the importance of Diarylmethylidenefluorene derivatives here in we propose a strategy for the synthesis of substituted diarylmethylidenefluorenes by employing double Suzuki reaction of dibromomethylidenefluorene and boronic acids.

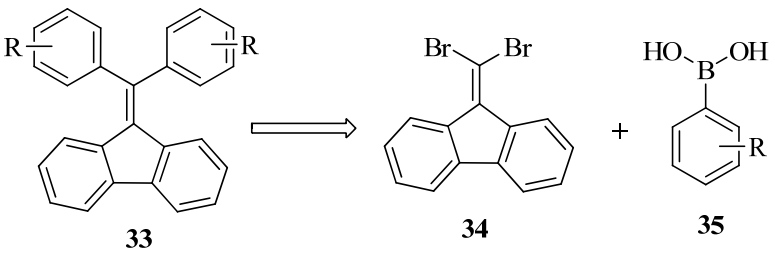
Present Work

There is great current interest in the chemistry of fluorenes and their polymers as electroluminescent compositions,[20] and the alkylidene fluorene liquid crystalline semi-conducting polymers[21] organic field effect transistor devices. Diarylmethylidenefluorenes in general, and the dications[22] or radical anions[23] derived from them in particular, are subjects of extensive physical studies. The studies are related to anti-aromaticity or electron-spin distribution/conformation, and are evaluated by means of either magnetic criteria focusing on the consequences of the existence of a ring current, or ESR and ENDOR spectra. While there appears to be a great deal of discussion about the derived transient intermediates by theoretical and experimental calculations, little has focused on the synthesis of these diarylmethylidenefluorene derivatives.

Substituted diarylmethylidenefluorene derivatives are generally synthesized by addition of fluorenylidene anions to benzophenone and subsequent dehydration[24] and very recently using Peterson olefination.[22a] There are a few reports in which the addition of diazofluorene to a thioketone,[25] Wittig olefination,[26] [2+2] addition of fluorenylidene stannene[27] to a benzophenone and subsequent [2+2] decomposition have been described. In many of these approaches, the use of strong bases to generate the requisite benzylic anion and strong acids to dehydrate the intermediate alcohol limits the variation of the substituents on aromatic rings, especially the lack of a protocol compatible with base-sensitive groups. We introduce a facile synthesis of diarylmethylidenefluorenes by means of Suzuki coupling of dibromomethylidenefluorene (**34**) with arylboronic acids **35** (Scheme 10).

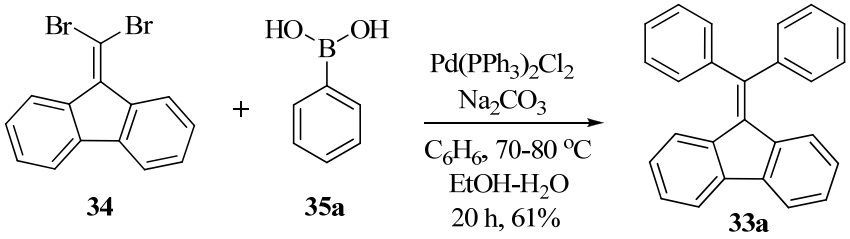
The Suzuki reaction, consisting of a palladium-mediated cross-coupling of organoboronic acids with alkenyl or aryl halides, is a great tool in synthetic organic chemistry.[28] The Suzuki reaction of 1,1-dibromo-1-alkenes with alkenyl or arylboronic acids is well known and well used in the synthesis of tri- and tetrasubstituted olefins and also for the stereoselective formation of (*Z*)-1-aryl- or (*Z*)-alkenyl- 1-bromo-1-alkenes.[29] Because a variety of organoboronic acid derivatives are now readily available, we examined the feasibility of a double Suzuki reaction with the known dibromomethylidenefluorene (**34**)[30] to synthesize symmetric diarylmethylidenefluorene derivatives.

Scheme 10: Retrosynthetic analysis



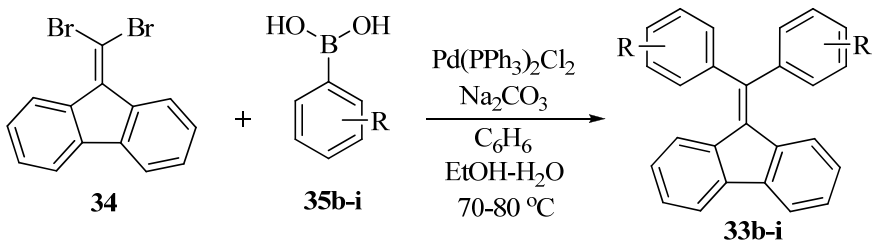
Our initial attempts to optimize the reaction conditions were carried out with simple phenylboronic acid (**35a**). After a careful examination of various reaction conditions, such as reaction temperature, reaction time, base, solvent, and amount of phenylboronic acid, we concluded that the best results for the intended double Suzuki reaction were achieved by using a suspension of benzene–ethanol–water as a solvent, sodium carbonate as a base, conducting the reaction at 70–80 °C and addition of the catalyst $Pd(PPh_3)_2Cl_2$ (7.5 mol%) and phenylboronic acid (1.5 equiv) twice to the reaction mixture with a 10 hour interval (Scheme 11).

Scheme 11



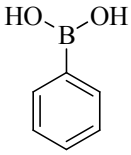
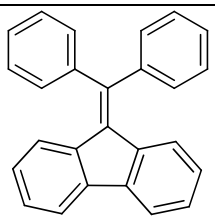
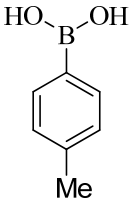
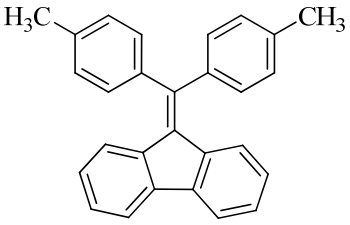
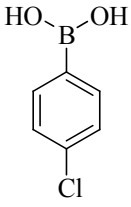
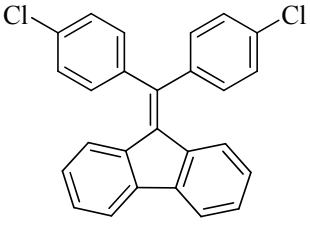
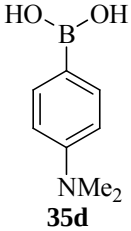
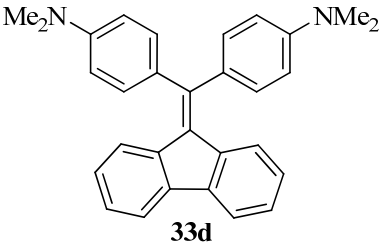
Thus, the reaction of **34** with differently substituted aryl boronic acids **35b–i** following the above conditions led to the previously known and a couple of unknown diarylmethylidenefluorene derivatives **33b–i** (Scheme 12). In general, the reactions with electron-deficient boronic acids were facile and good yields were obtained. For the boronic acids with an electron-donating group, the reactions were sluggish and resulted in low yields.

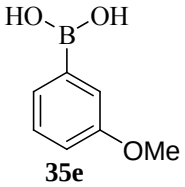
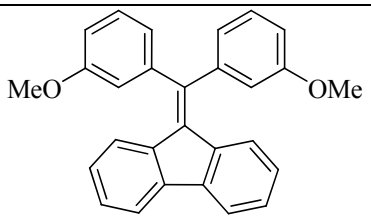
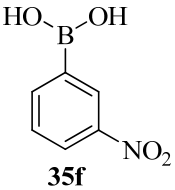
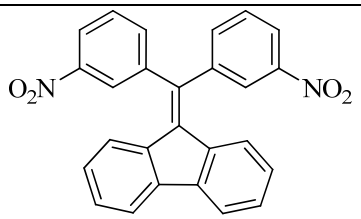
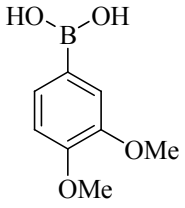
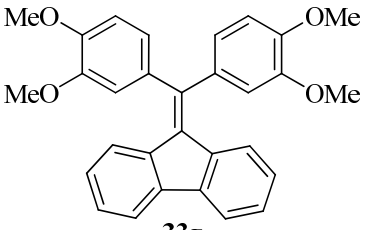
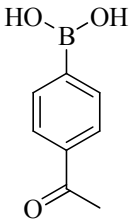
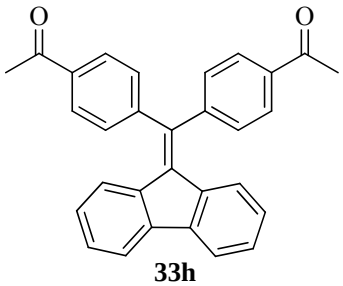
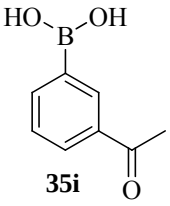
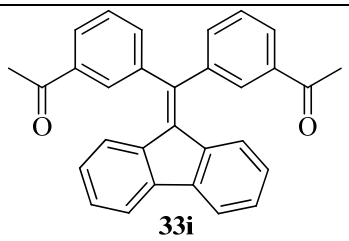
Scheme 12: Double Suzuki coupling reaction with Dibromomethylidenefluorene (**34**)



34 **35b-i** **33b-i**

Table 1

Entry	Substrate Boronic acid	Product	Yield
1	 **35a**	 **33a**	61%
2	 **35b**	 **33b**	67%
3	 **35c**	 **33c**	81%
4	 **35d**	 **33d**	69%

5	 **35e**	 **33e**	73%
6	 **35f**	 **33f**	79%
7	 **35g**	 **33g**	44%
8	 **35h**	 **33h**	88%
9	 **35i**	 **33i**	81%

The physical data of all the known compounds are in agreement with those of the reported data. All the new compounds were characterized by their spectral and analytical data and a single-crystal X-ray structure for compound **33h**, and the structures of **33i**, **33c** are also conformed by single crystal X-ray.

Figure 6: X-Ray structure for the compound **33h**

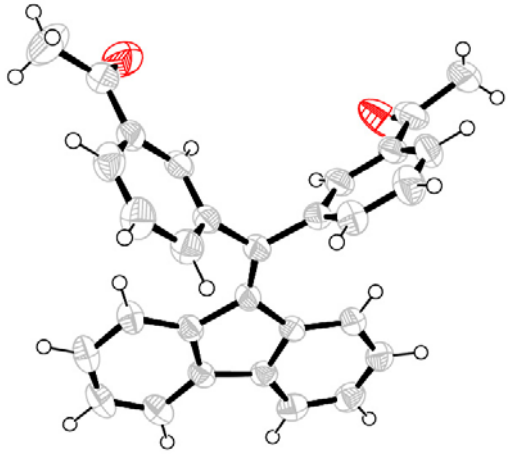


Figure 7: X-Ray structure for the compound **33i**

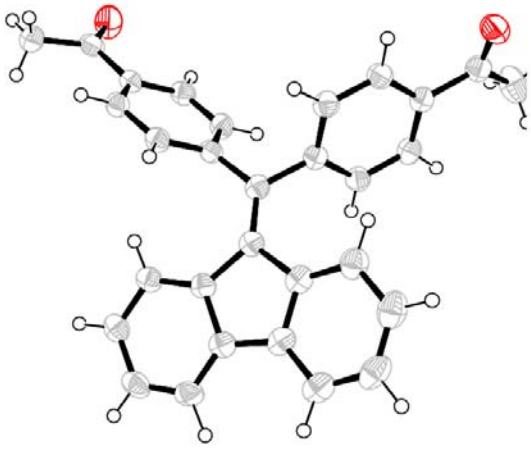
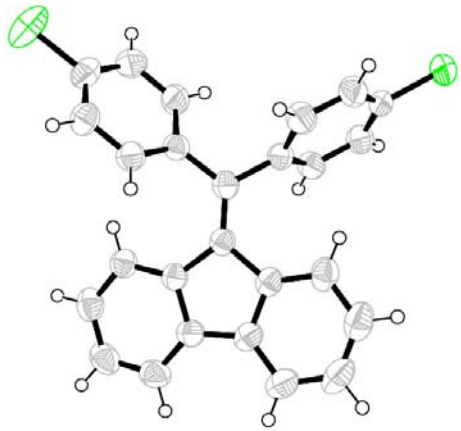


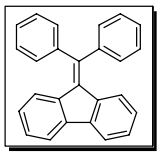
Figure 8: X-Ray structure for the compound **33e**



Conclusion: A simple method for the synthesis of symmetric and substituted diarylmethylidenefluorenes has been reported using a double Suzuki reaction. Work in the direction of stepwise coupling of different boronic acids to address the synthesis of unsymmetric derivatives is in progress.

Experimental

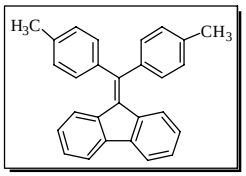
9-(Diphenylmethylene)-9H-fluorene (33a)



Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35a** (108 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h in dark condition. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35a** (108 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether) gave **33a** (120 mg, 61%) as yellow color solid.

Mol. Formula	: $C_{26}H_{18}$
M. P.	: 74-76 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 6.62 (d, *J* = 7.96 Hz, 2H), 6.92 (dt, *J* = 1.1, 7.96 Hz, 2H), 7.20–7.28 (m, 2H), 7.35–7.44 (m, 10H), 7.69 (d, *J* = 7.46 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 119.2 (d), 124.8 (d), 126.3 (d), 127.6 (d), 128.1 (d), 128.7 (d), 129.6 (d), 134.1 (s), 138.6 (s), 140.4 (s), 142.9 (s), 145.4 (s) ppm.
ESI-MS (*m/z*)	: 353.61 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 94.51; H, 5.49. Found: C, 94.21; H, 5.29.

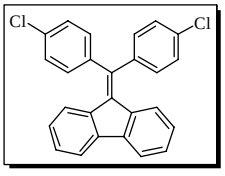
9-(Di *p*-tolylmethylene)-9H-fluorene (33b)



Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35b** (121 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35b** (121 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether) gave **33b** (140 mg, 67%) as a yellow color solid.

Mol. Formula	: $C_{28}H_{22}$
M. P.	: 137 ^oC.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.42 (s, 6H), 6.73 (d, *J* = 7.95 Hz, 2H), 6.94 (dt, *J* = 1.1, 7.9 Hz, 2H), 7.17–7.27 (m, 10H), 7.70 (d, *J* = 7.32 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.3 (q), 119.1 (d), 124.7 (d), 126.2 (d), 127.3 (d), 129.3 (d), 129.8 (d), 133.6 (s), 138.0 (s), 138.9 (s), 140.23 (s), 140.29 (s), 145.9 (s) ppm.
ESI-MS (*m/z*)	: 359.64 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 93.81; H, 6.19. Found: C, 93.11; H, 6.16.

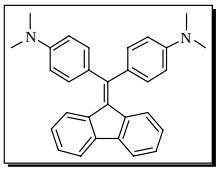
9-(Bis(4-chlorophenyl)methylene)-9H-fluorene (33c)



Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35c** (140 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35c** (140 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether). Recrystallization from toluene gave **33c** (191 mg, 81%) as yellow color crystals suitable for single crystal X-ray diffraction studies.

Mol. Formula	: $C_{26}H_{16}Cl_2$
M. P.	: 215 ^oC.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 6.70 (d, *J* = 8.8 Hz, 2H), 6.97 (dt, *J* = 1.2, 7.9 Hz, 2H), 7.22–7.32 (m, 6H), 7.36–7.45 (m, 4H), 7.69 (d, *J* = 7.3, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 119.4 (d), 124.7 (d), 126.5 (d), 128.0 (d), 129.1 (d), 131.3 (d), 134.5 (s), 135.1 (s), 138.1 (s), 140.6 (s), 140.9 (s), 142.1 (s) ppm.
ESI-MS (*m/z*)	: 422.21 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 78.20; H, 4.04; Cl, 17.76. Found: C, 78.20; H, 4.04; Cl, 17.76.

4-((4-(Dimethylamino)phenyl)(9H-fluoren-9-ylidene)methyl)-N,N-dimethylbenzenamine (33d)

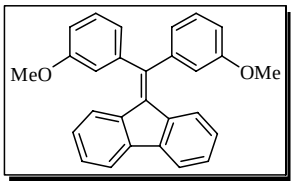


Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg,

0.06 mmol) and boronic acid **35d** (147 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35d** (147 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether) gave **33d** (170 mg, 69%) as a yelooe color solid.

Mol. Formula	: $C_{30}H_{28}N_2$
M. P.	: 235 ^oC.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.03 (s, 12H), 6.69 (d, *J* = 8.85 Hz, 4H), 6.98 (d, *J* = 3.91 Hz, 4H), 7.18–7.24 (m, 6H), 7.74 (d, *J* = 7.58 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 40.2 (q), 111.6 (d), 118.9 (d), 124.1 (d), 125.7 (d), 125.9 (d), 130.6 (s), 131.0 (s), 132.6 (d), 139.4 (s), 139.9 (s), 148.0 (s), 150.5 (s) ppm.
ESI-MS (*m/z*)	: 416.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 86.50; H, 6.78; N, 6.72.
	Found: C, 86.50; H, 6.78; N, 6.72.

9-(Bis(3-methoxyphenyl)methylene)-9H-fluorene (33e)

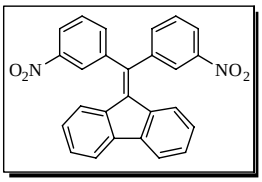


Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35e** (135 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg,

0.06 mmol) and boronic acid **35e** (135 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether) gave **33e** (169 mg, 73%) as a yellow color solid.

Mol. Formula	: $C_{28}H_{22}O_2$
M. P.	: 129-130 ^oC.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.69 (s, 6H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.83–6.93 (m, 8H), 7.12–7.16 (m, 2H), 7.20–7.29 (m, 2H), 7.61 (d, *J* = 7.4 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.2 (q), 113.8 (d), 114.5 (d), 119.1 (d), 121.7 (d), 125.0 (d), 126.4 (d), 127.6 (d), 129.8 (d), 134.0 (s), 138.4 (s), 140.4 (s), 144.0 (s), 144.8 (s), 159.8 (s) ppm.
ESI-MS (*m/z*)	: 391.20 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 86.13; H, 5.68. Found: C, 86.03; H, 5.45.

9-(Bis(4-nitrophenyl)methylene)-9H-fluorene (33f)

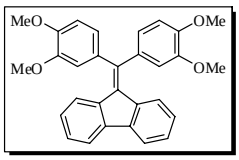


Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35f** (148 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35f** (148 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with

water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether) gave **33f** (196 mg, 79%) as yellow color solid.

Mol. Formula	: $C_{26}H_{16}N_2O_4$
M. P.	: 165-167 ^oC.
IR ($CHCl_3$) $\tilde{\nu}$	: 3072 1609, 1528, 1477, 1446, 1347, 1096, 908, 830, 784, 732 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 6.50 (d, *J* = 8.05 Hz, 2H), 6.94 (t, *J* = 7.57 Hz, 2H), 7.30 (t, *J* = 7.58 Hz, 2H), 7.68–7.72 (d, *J* = 7.45 Hz, 6H), 8.18–8.36 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 119.81 (d), 123.57 (d), 124.53(s), 124.64 (d), 126.9 (d), 129.0 (d), 130.3 (d), 137.3 (s), 137.9 (s), 141.1 (s), 143.3 (s), 148.8 (s) ppm.
ESI-MS (*m/z*)	: 443.20 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.28; H, 3.84; N, 6.66. Found: C, 74.14; H, 3.64; N, 6.53.

9-(Bis(3,4-dimethoxyphenyl)methylene)-9H-fluorene (33g)

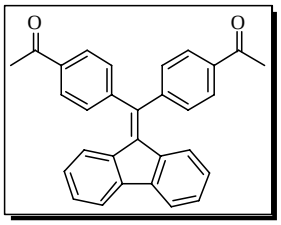


Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35g** (162 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35g** (162 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by

silica gel column chromatography (10% ethyl acetate in pet ether) gave **33g** (117 mg, 44%) as a yellow colour solid.

Mol. Formula	: $C_{30}H_{26}O_4$
M. P.	: 176 ^oC.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.88–3.89 (m, 10H), 6.69 (q, *J* = 7.96 Hz, 2H), 6.84–7.05 (m, 12H), 7.17 (dt, *J* = 1.01, 7.33 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.8 (q), 110.3 (d), 111.0 (d), 111.4 (d), 113.5 (d), 119.0 (d), 124.6 (d), 126.1 (d), 127.1 (d), 133.3 (s), 134.1 (s), 138.8 (s), 140.0 (s), 145.4 (s), 148.7 (s), 149.2 (s) ppm.
ESI-MS (*m/z*)	: 473.67 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 79.98; H, 5.82.
	Found: C, 79.98; H, 5.82.

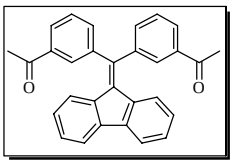
1,1'-(4,4'-((9H-Fluoren-9-ylidene)methylene)bis(4,1-phenylene))diethanone (33h)



Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35h** (146 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35h** (146 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether). Recrystallization from toluene gave **33h** (216 mg, 88%) as yellow color crystals suitable for single crystal X-ray diffraction studies.

Mol. Formula	: $C_{30}H_{22}O_2$
M. P.	: 231-233 ^oC.
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 1682, 1601, 1446, 1403, 1360, 1266, 1215, 1075, 958, 849 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	: δ 2.66 (s, 6H), 6.62 (d, *J* = 7.8 Hz, 2H), 6.93 (dt, *J* = 1.14, 7.96 Hz, 2H), 7.27 (dt, *J* = 1.0, 7.4 Hz, 2H, 2H), 7.49 (br dt, *J* = 1.6, 8.1 Hz, 4H), 7.67–7.75 (m, 2H), 8.64 (br dt, *J* =1 .18, 8.1 Hz, 4H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.5 (q), 119.4 (d), 124.8 (d), 126.6 (d), 128.4 (d), 128.9 (d), 129.9 (d), 135.6 (s), 136.6 (s), 137.8 (s), 140.7 (s), 141.8 (s), 146.9 (s), 197.4 (s) ppm.
ESI-MS (*m/z*)	: 437.76. $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 86.93; H, 5.35. Found: C, 86.73; H, 5.25.

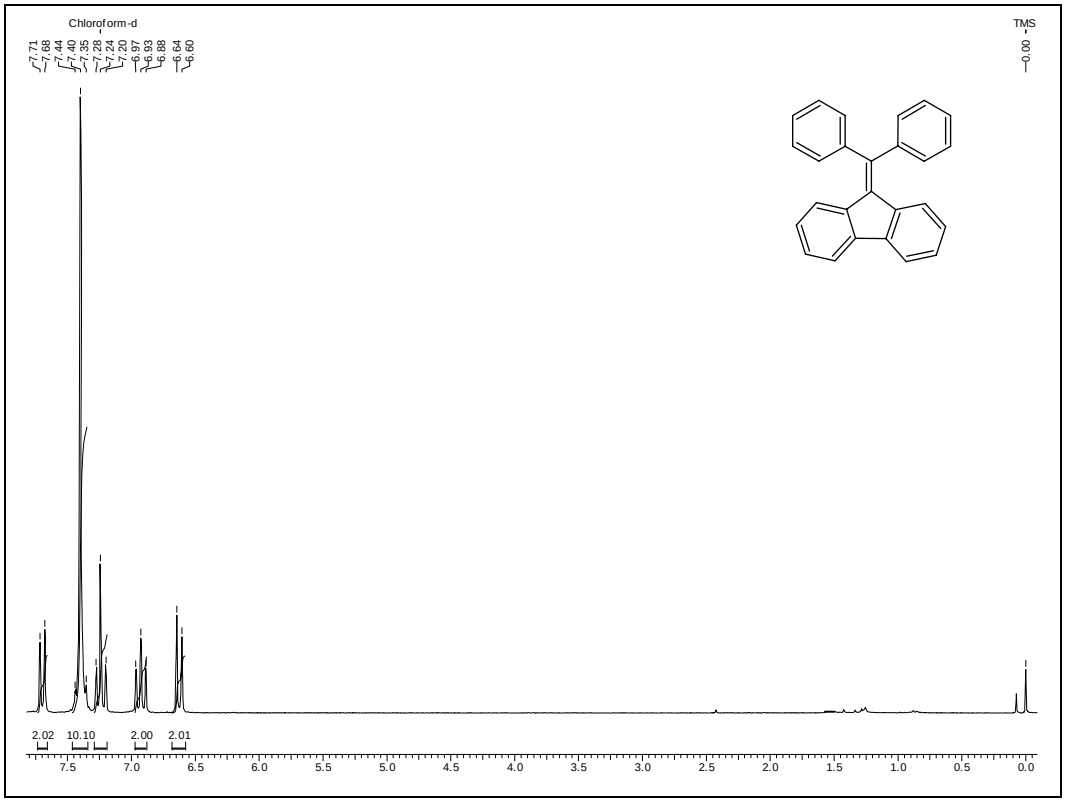
1,1'-(3,3'-((9H-Fluoren-9-ylidene)methylene)bis(3,1-phenylene))diethanone (33i)



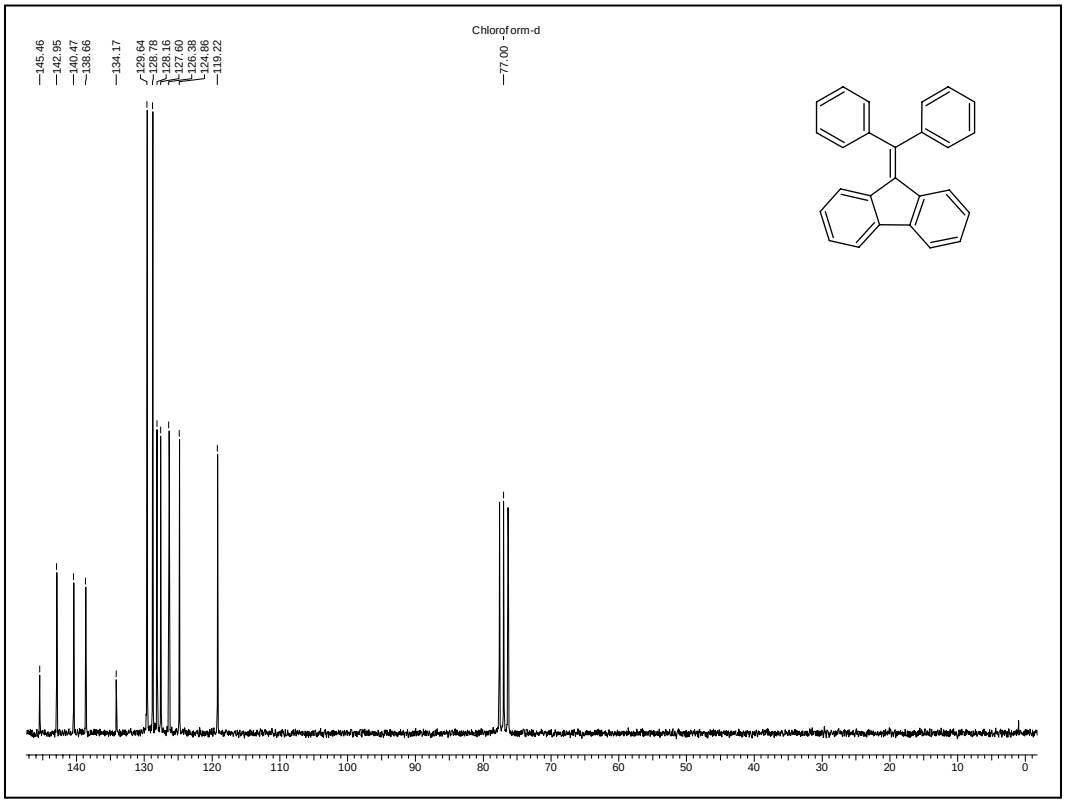
Under argon atmosphere, a solution of dibromide **34** (200 mg, 0.6 mmol) in benzene (15 ml) was treated with solid Na_2CO_3 (157 mg, 1.5 mmol), $PdCl_2PPh_3$ (40 mg, 0.06 mmol) and boronic acid **35i** (146 mg, 0.9 mmol) and the contents were degassed for 5 minutes. To this, ethanol (0.5 ml) and water (0.5 ml) were added and the reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled, catalyst (40 mg, 0.06 mmol) and boronic acid **35i** (146 mg, 0.9 mmol) were introduced and the heating at 80 °C was continued for additional 10 h in dark condition. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (30 ml) and washed with water. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (10% ethyl acetate in pet ether). Recrystallization from toluene gave **33i** (200 mg, 81%) as yellow color crystals suitable for single crystal X-ray diffraction studies.

Mol. Formula	: $C_{30}H_{22}O_2$
M. P.	: 230- 231 ^{o}C.
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 1682, 1601, 1446, 1403, 1360, 1266, 1215, 1075, 958, 849 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.58 (s, 6 H), 6.55 (d, *J* = 7.9 Hz, 2H), 6.91 (dt, *J* = 1.14, 7.96 Hz, 2H), 7.22–7.30 (m, 2H), 7.51–7.62 (m, 3H), 7.70 (d, *J* = 7.3 Hz, 3H), 7.95–8.06 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.6 (q), 119.4 (d), 124.5 (d), 126.5 (d), 128.1 (d), 129.3 (d), 134.3 (d), 135.59 (s), 137.6 (s), 137.9 (s), 140.6 (s), 142.2 (s), 142.7 (s), 197.4 (s) ppm.
ESI-MS (*m/z*)	: 437.84 $[M+Na]^{+}$.
Elemental Analysis	Calcd.: C, 86.93; H, 5.35. Found: C, 86.23; H, 5.15.

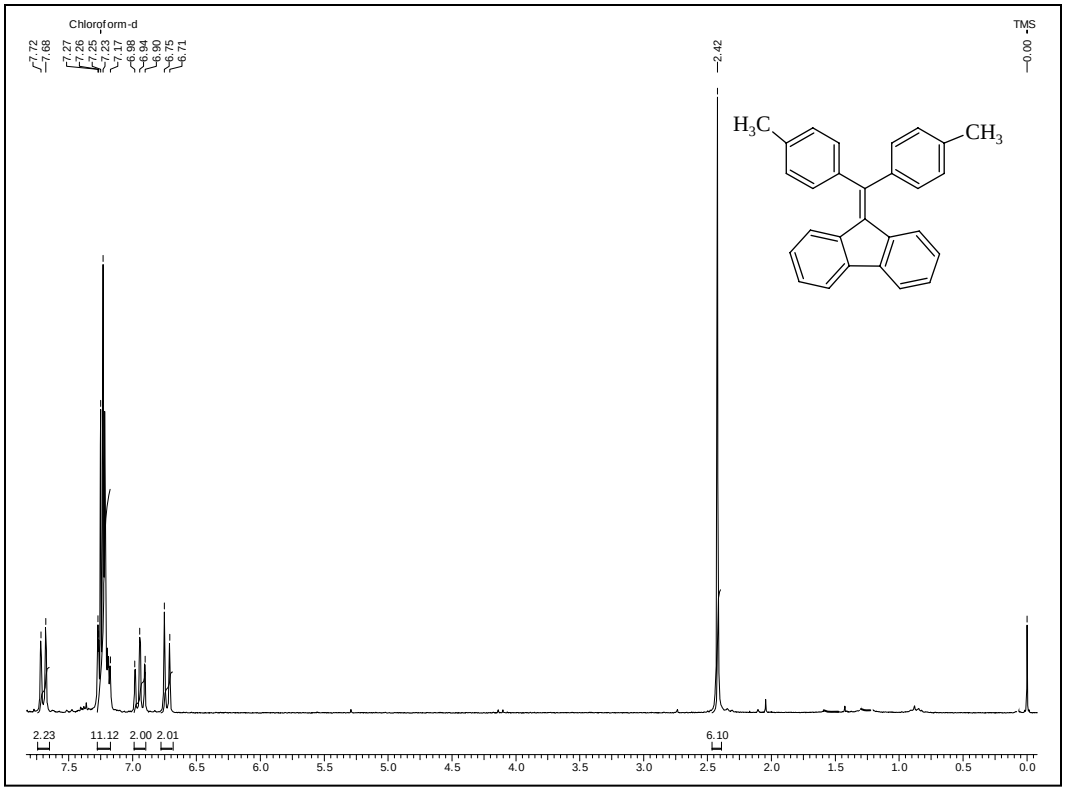
Spectra



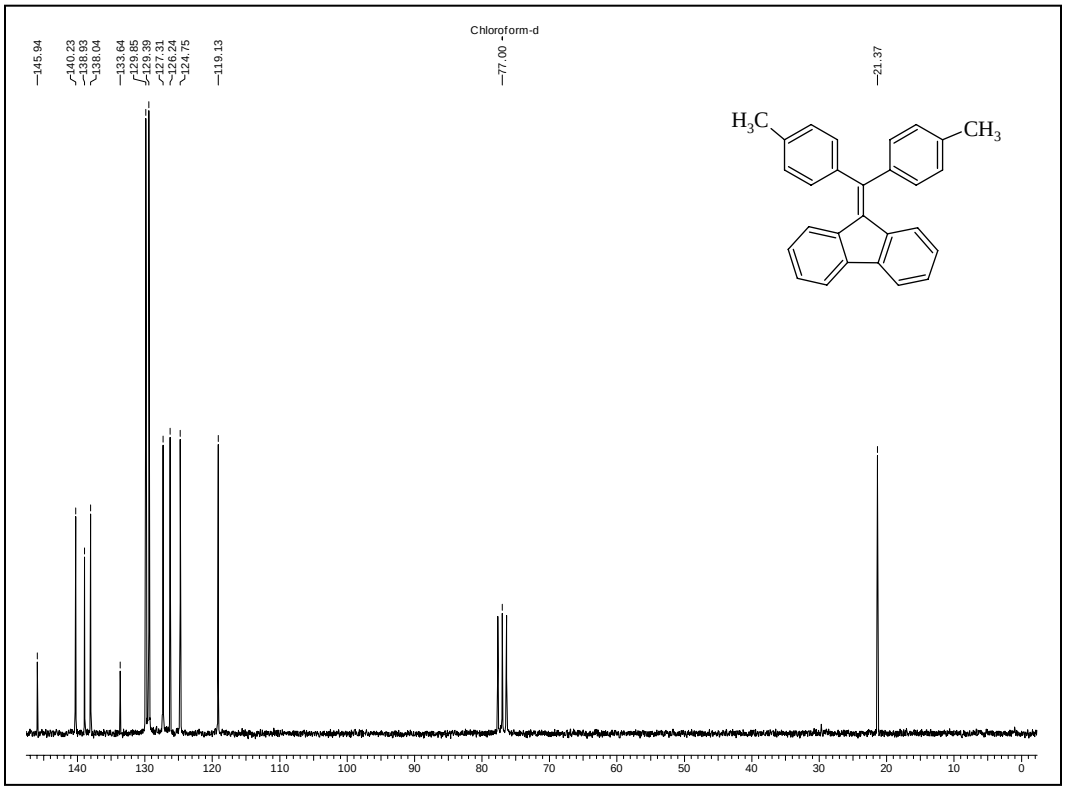
^{1}H NMR Spectrum of 33a in $CDCl_3$



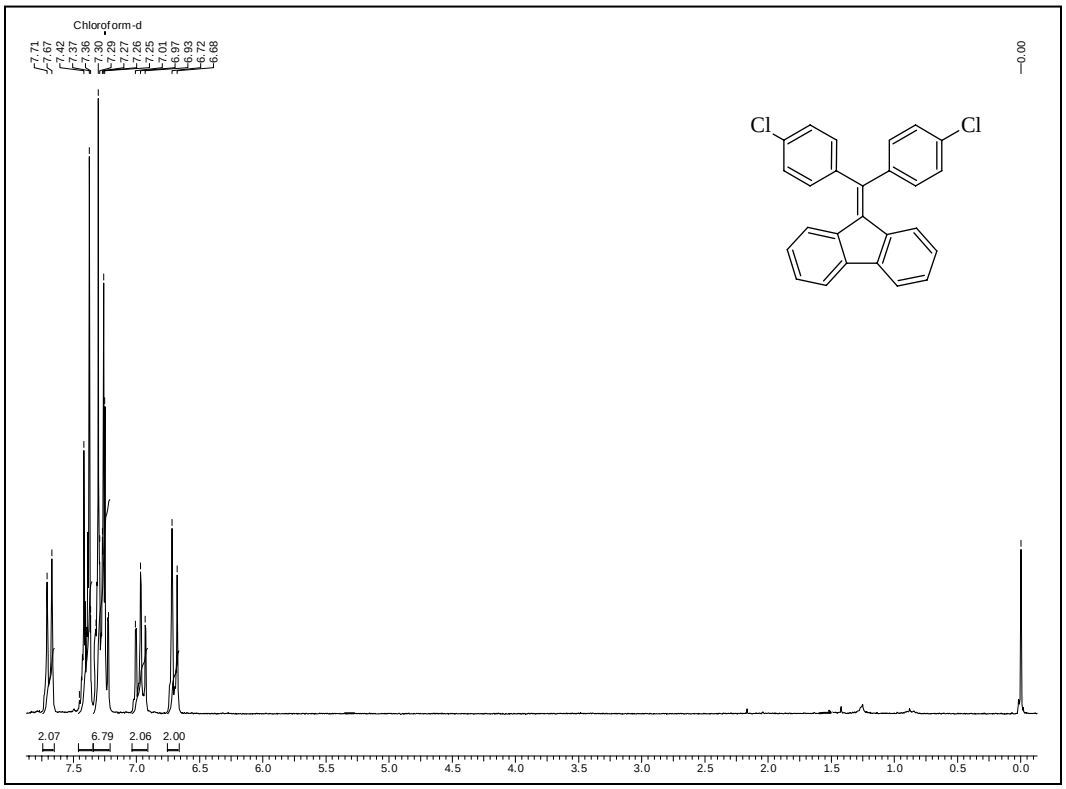
^{13}C NMR Spectrum of 33a in $CDCl_3$



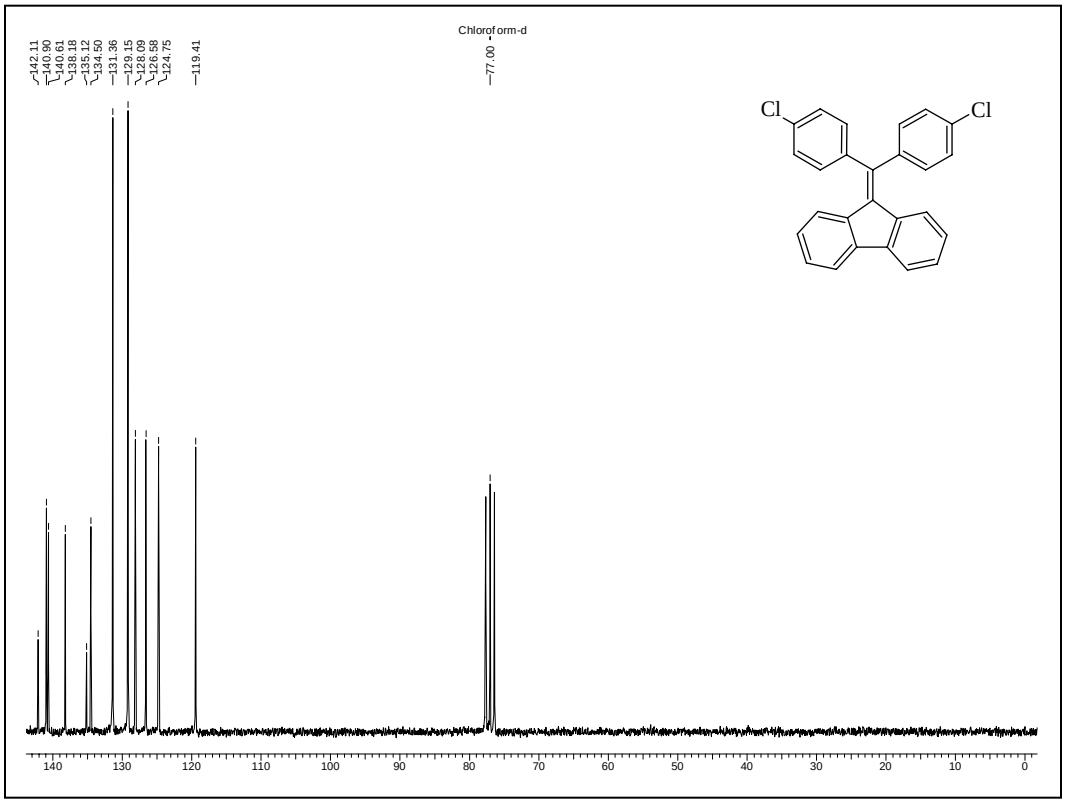
^{1}H NMR Spectrum of 33b in $CDCl_3$



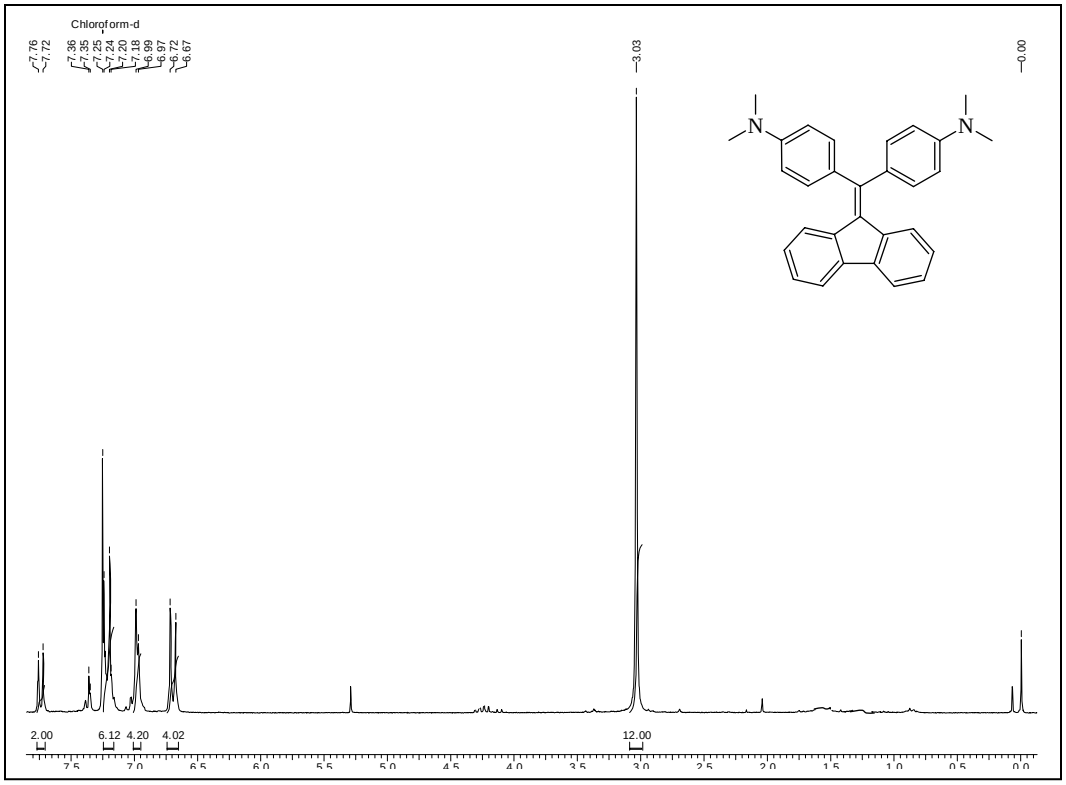
^{13}C NMR Spectrum of 33b in $CDCl_3$



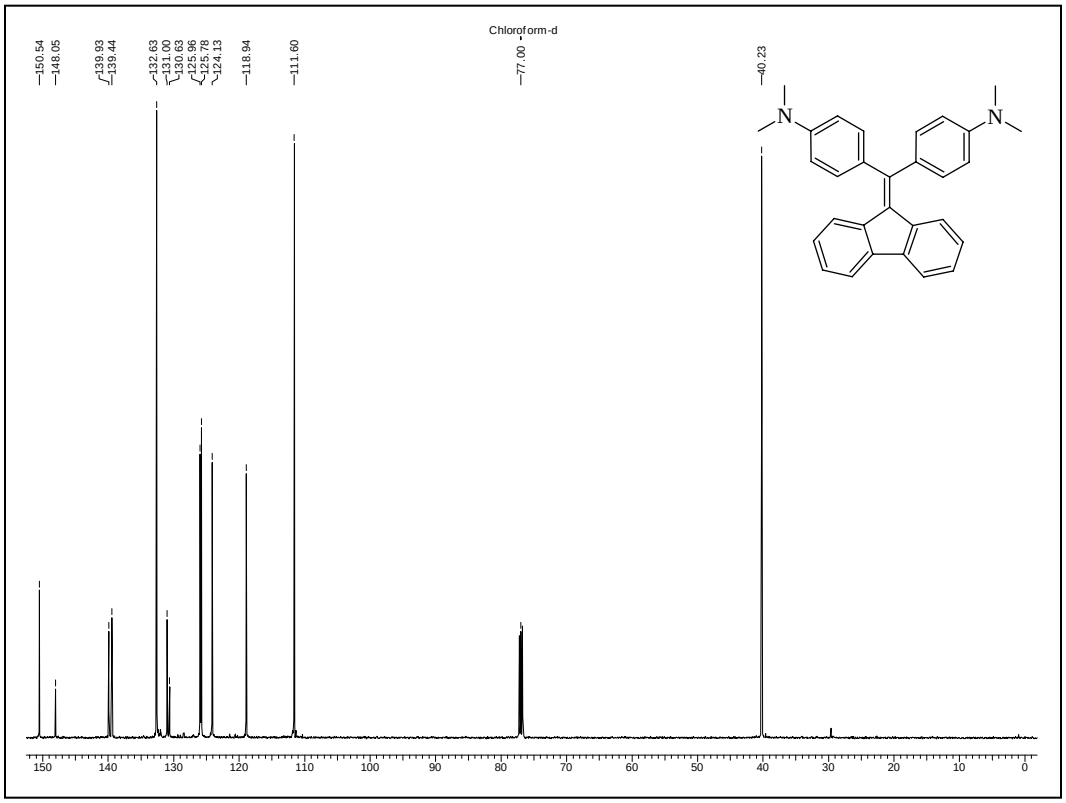
^{1}H NMR Spectrum of 33c in $CDCl_3$



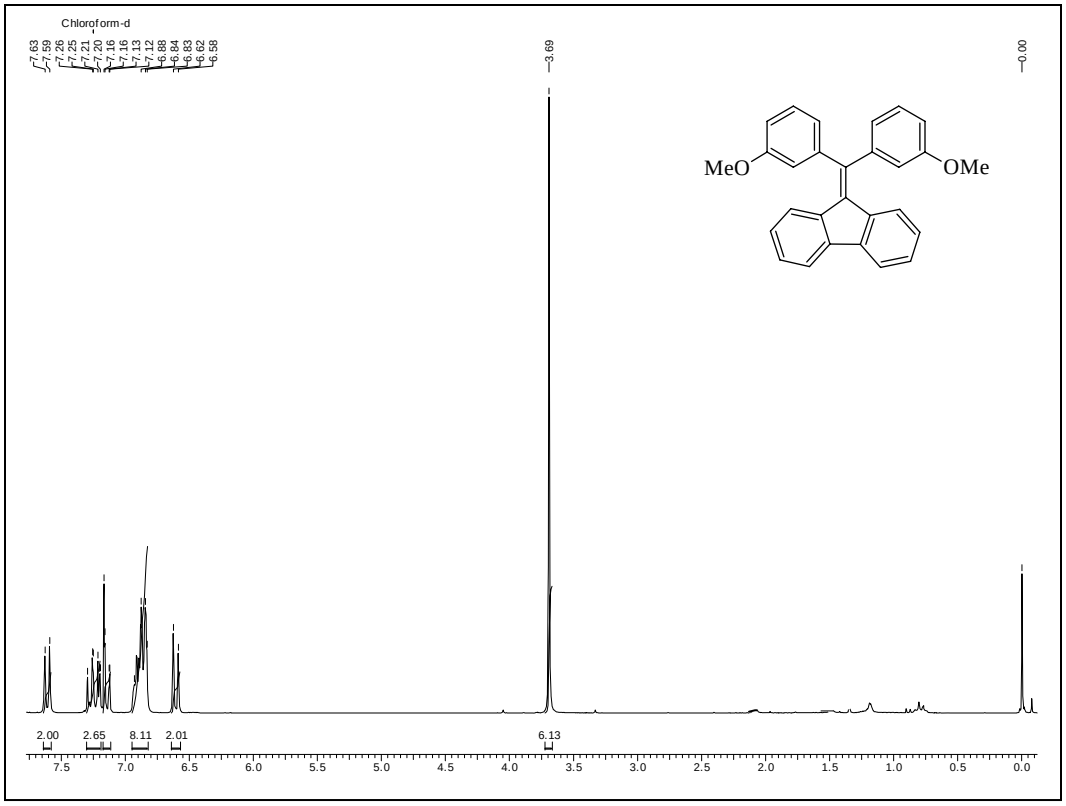
^{13}C NMR Spectrum of 33c in $CDCl_3$



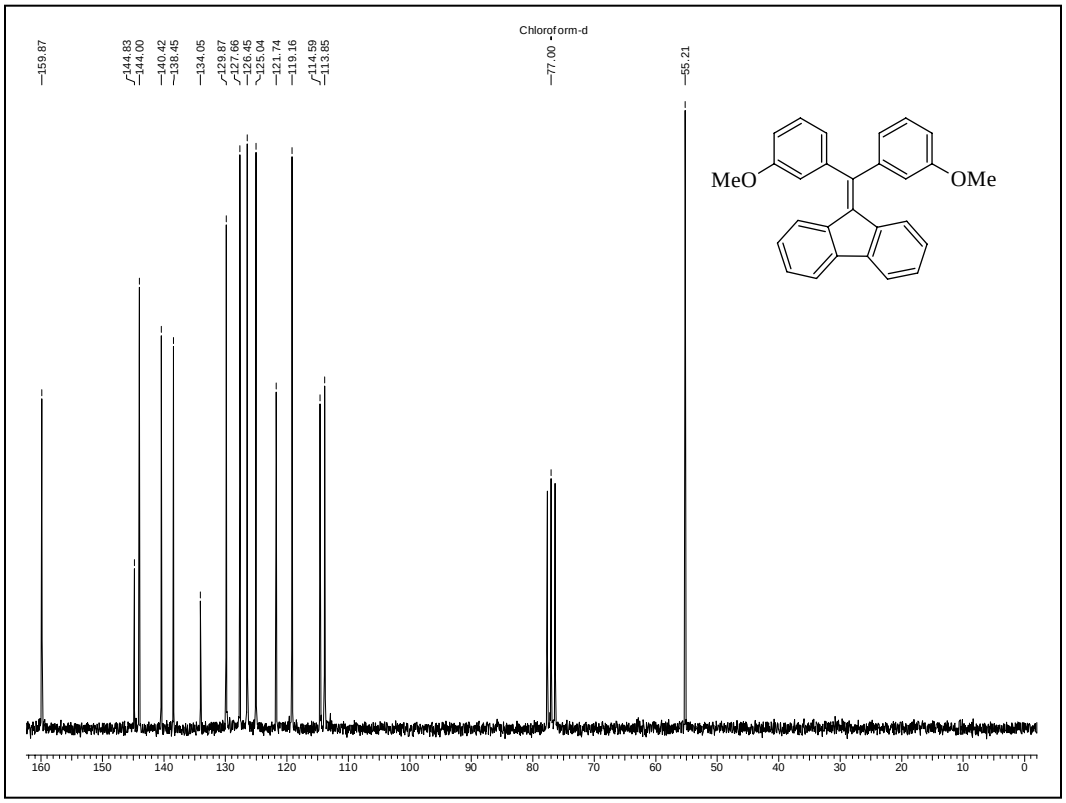
^{1}H NMR Spectrum of 33d in $CDCl_3$



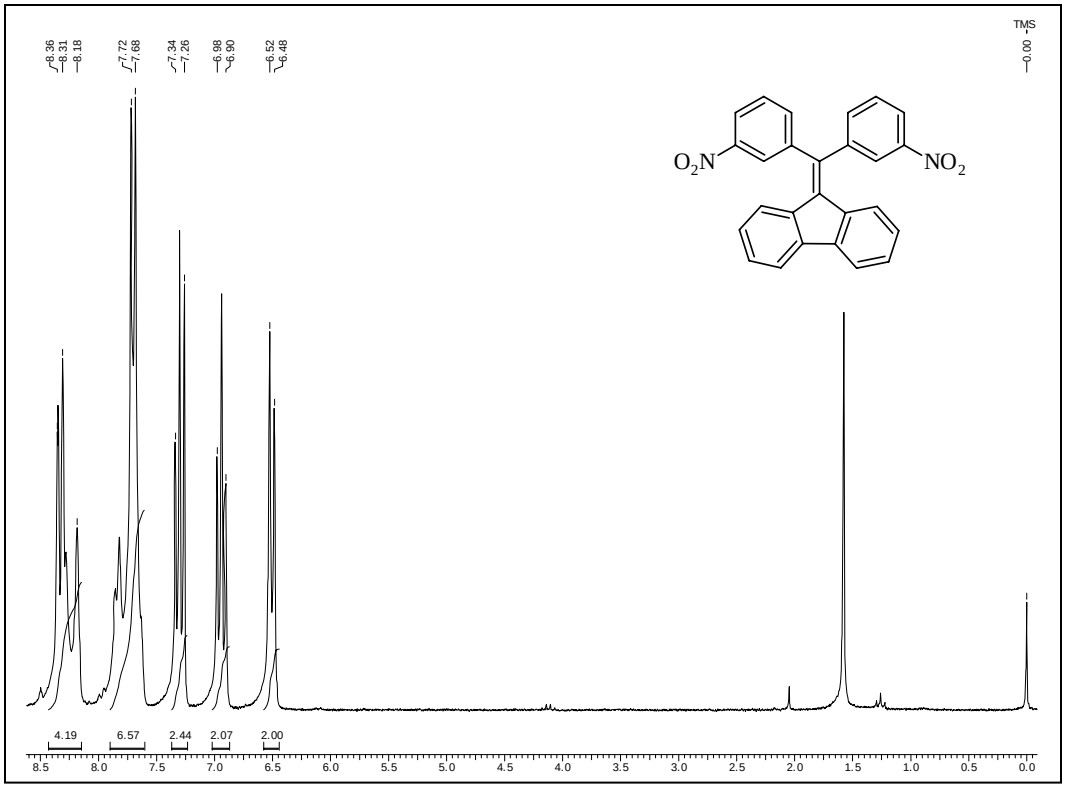
^{13}C NMR Spectrum of 33d in $CDCl_3$



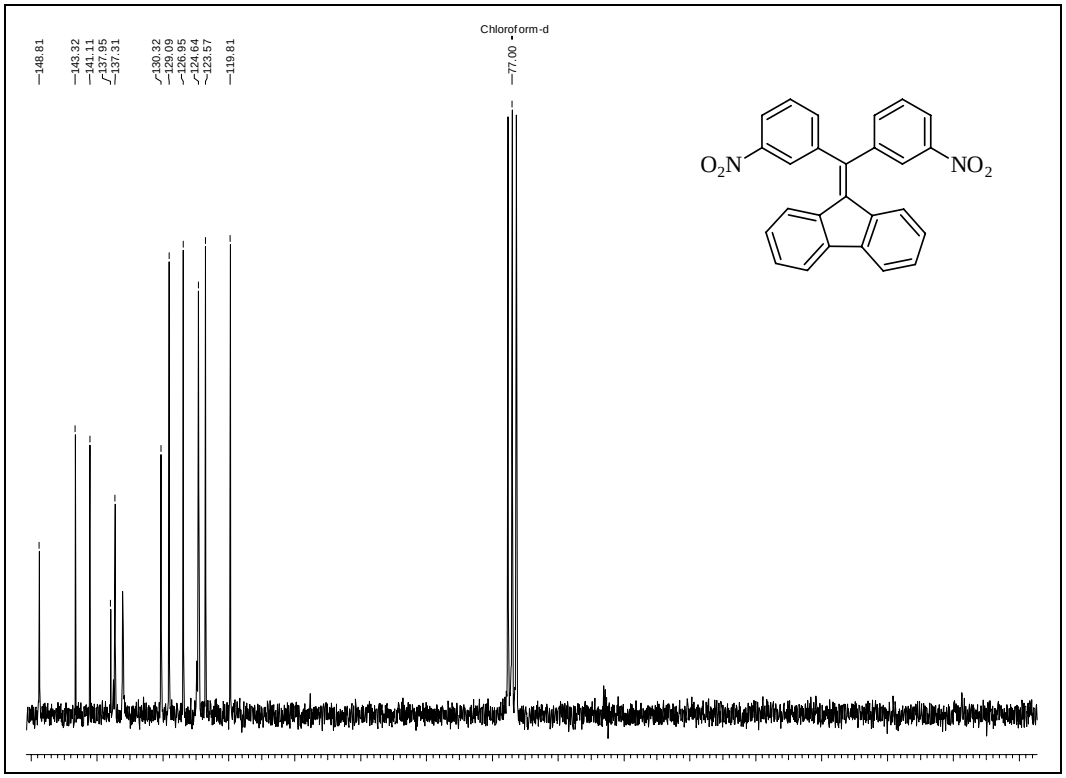
^{1}H NMR Spectrum of 33e in $CDCl_3$



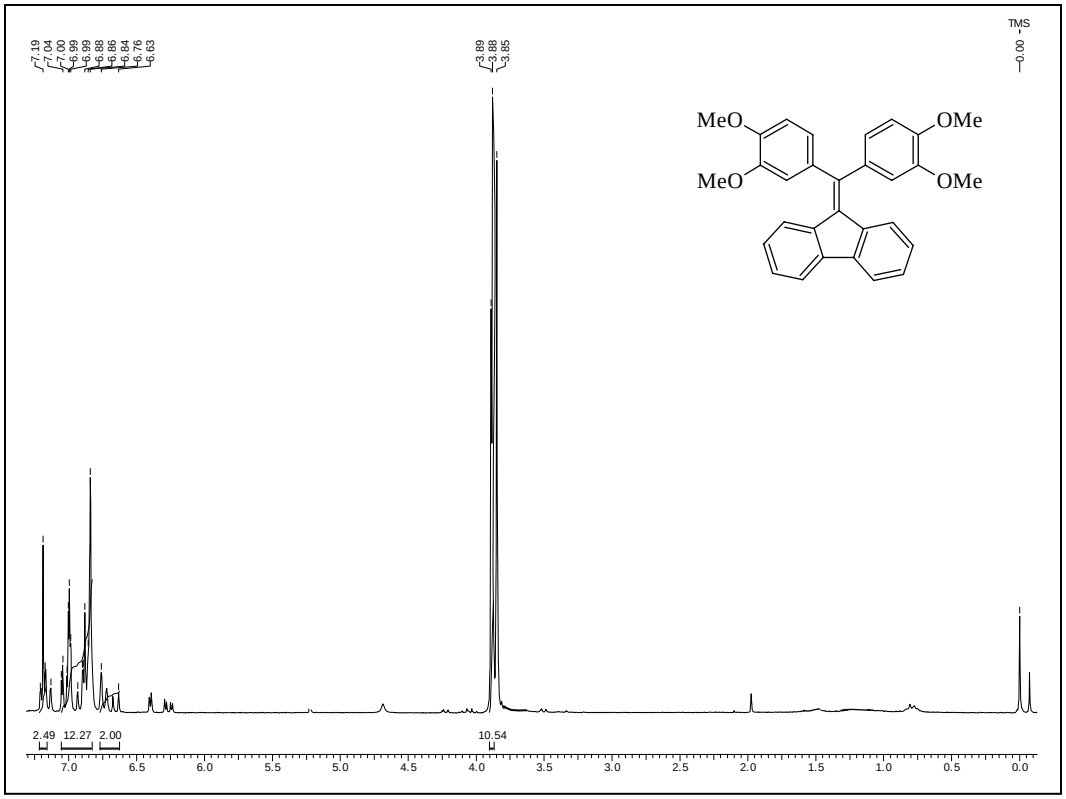
^{13}C NMR Spectrum of 33e in $CDCl_3$



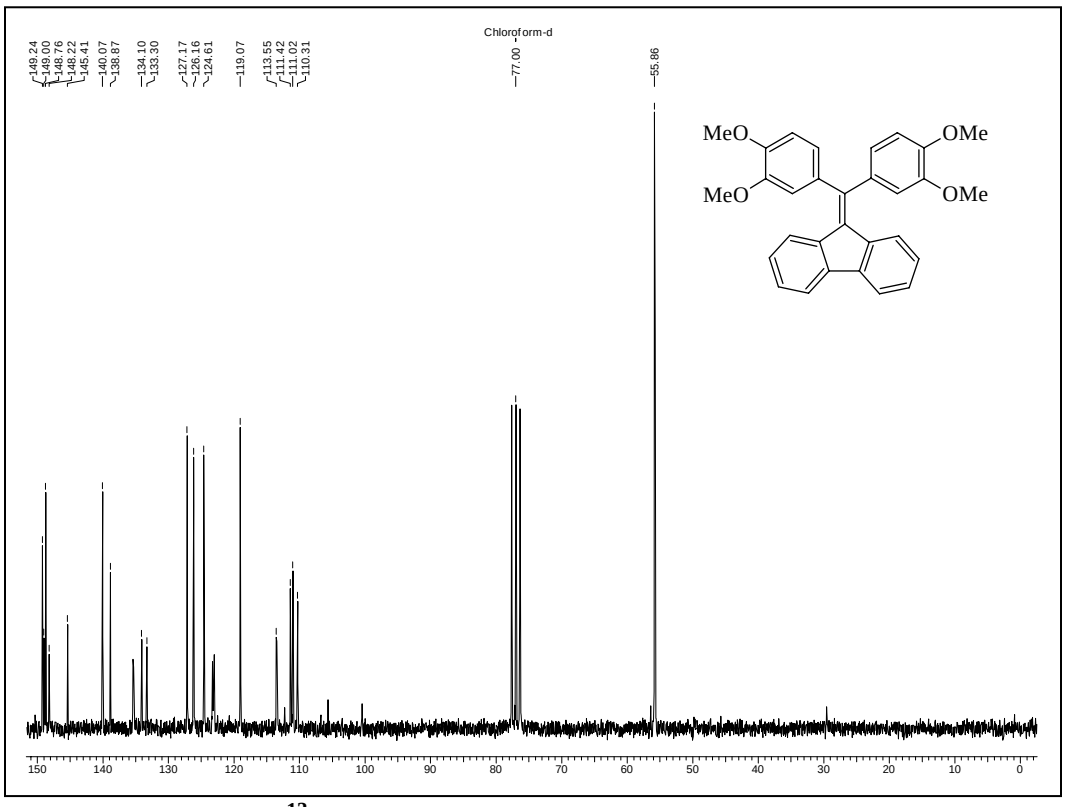
^{1}H NMR Spectrum of 33f in $CDCl_3$



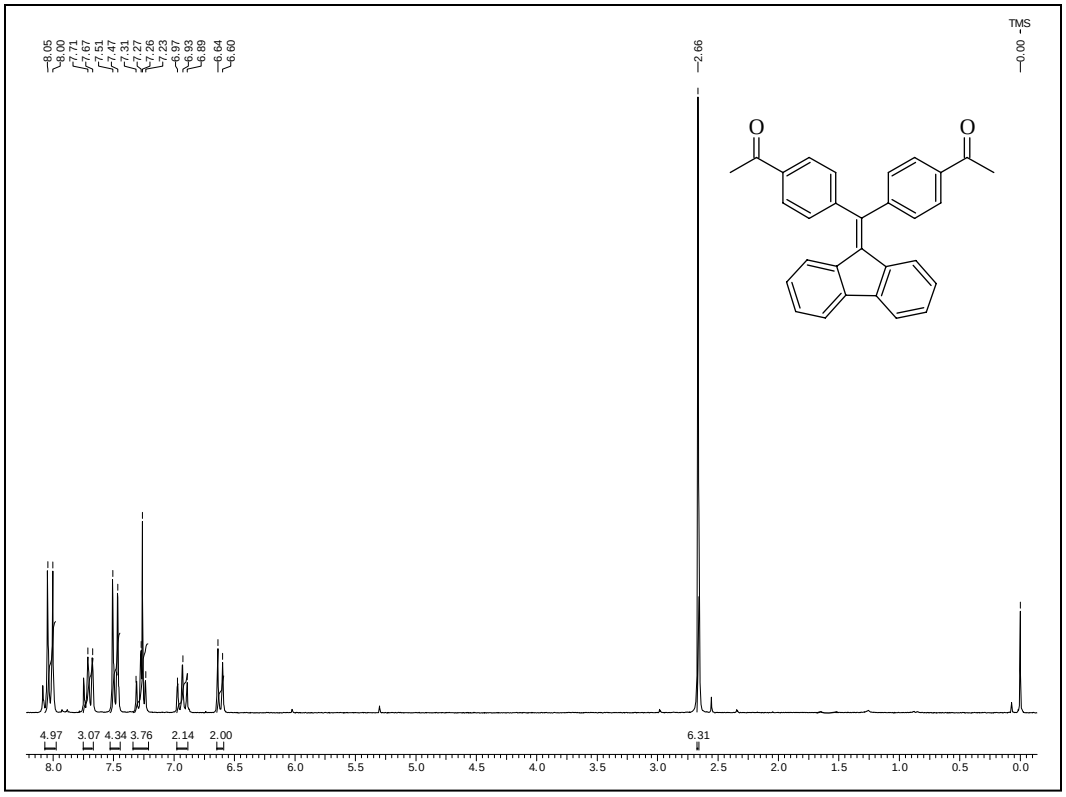
^{13}C NMR Spectrum of 33f in $CDCl_3$



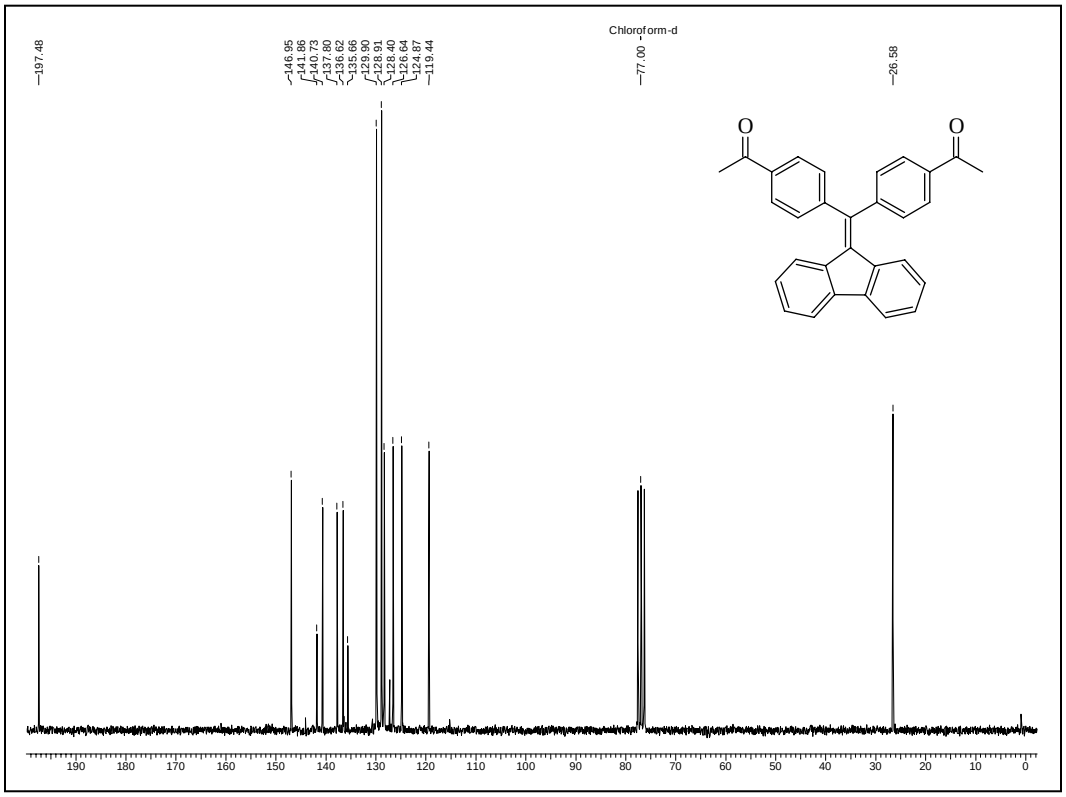
^{1}H NMR Spectrum of 33g in $CDCl_3$



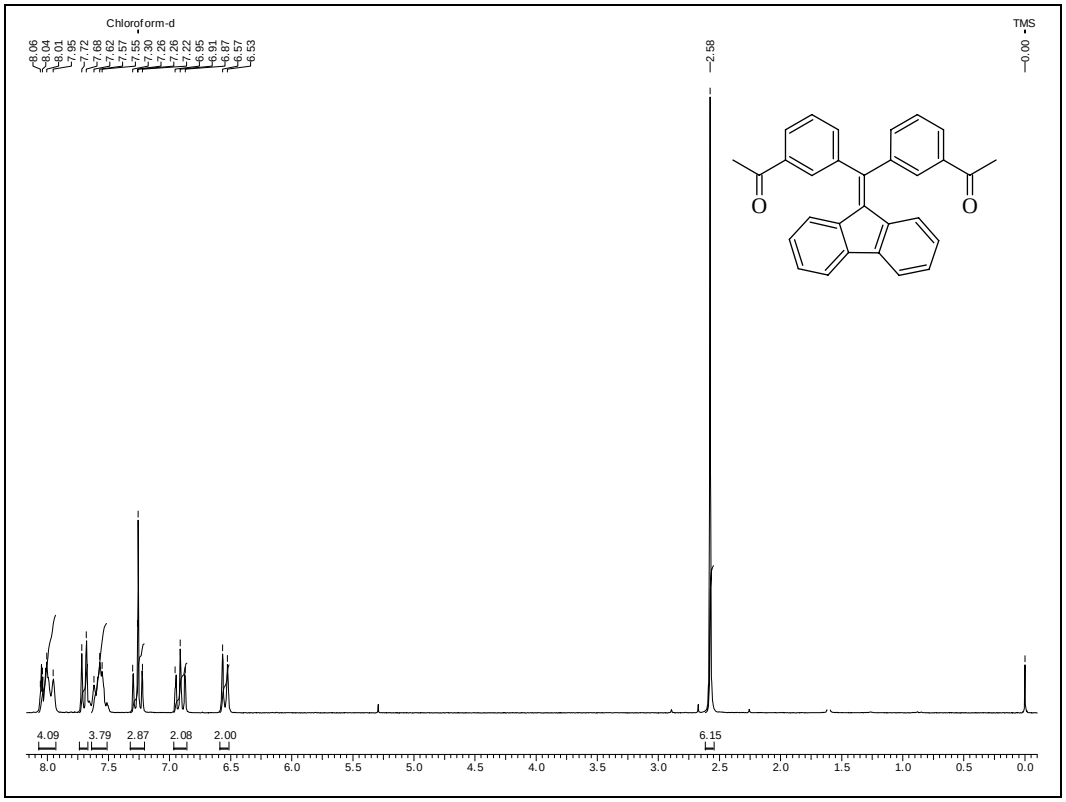
^{13}C NMR Spectrum of 33g in $CDCl_3$



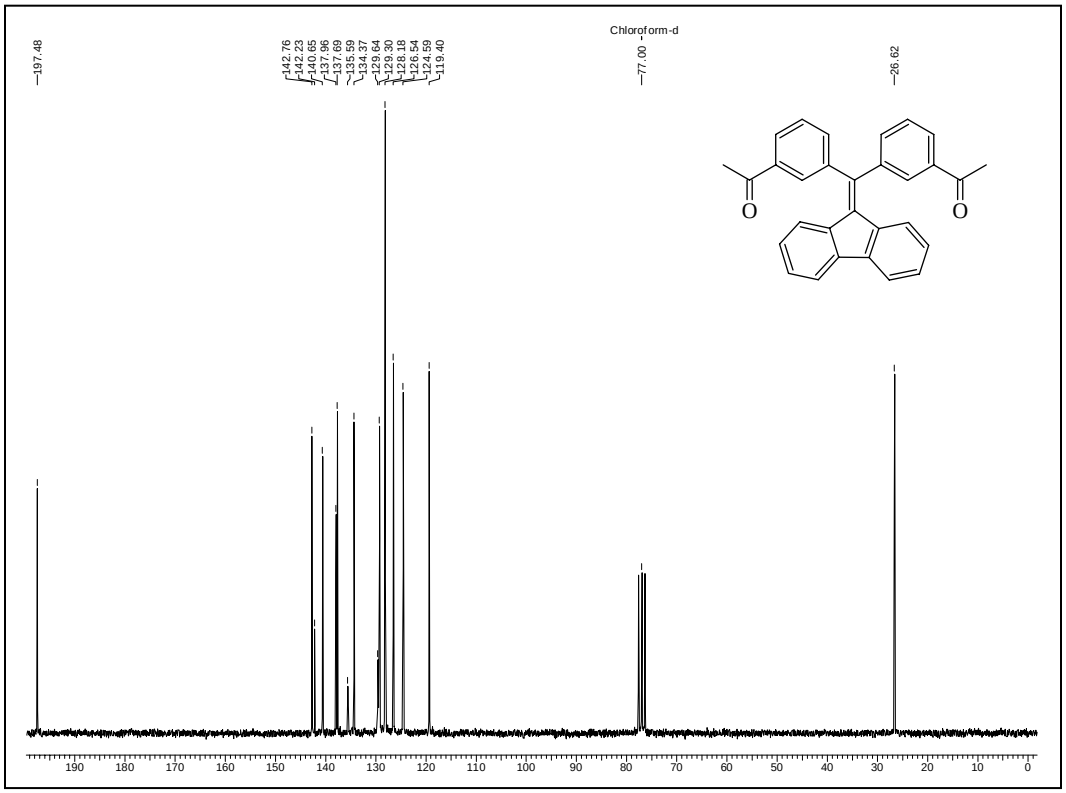
^{1}H NMR Spectrum of 33h in $CDCl_3$



^{13}C NMR Spectrum of 33h in $CDCl_3$



^{1}H NMR Spectrum of 33i in $CDCl_3$



^{13}C NMR Spectrum of 33i in $CDCl_3$

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List of Publications

List of publications

1. A Double-Suzuki Approach for Synthesis of Substituted Diarylmethylidene-fluorenes- *Synlett* **2007**.
2. An expeditious one-step entry to the central core of integrastatins - *Chem. Commun.* **2008**.
3. Studies toward the total synthesis of Carba analogue of motif C of M.tb cell wall AG complex- *Tetrahedron: Asymmetry* **2008** (communicated).