Synthetic Studies towards Total Synthesis of Lactacystin Analogue and the related β-Lactone Omuralide Analogue

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Submitted by
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DECLARATION

The research work embodied in this thesis submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. Mukund K. Gurjar,** Deputy Director and Head, Organic Chemistry: Technology, National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

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CERTIFICATE

The research work presented in this thesis entitled ***"Synthetic Studies towards Total Synthesis of Lactacystin Analogue and the related β-Lactone Omuralide Analogue"*** has been carried out under my supervision and is bonafide work of **Mrs. Manjusha Abhijit Joshi**. This work is original and has not been submitted for any other degree or diploma to this or any other University.

Pune - 411 008

Date:

Dr. M. K. Gurjar

(Research Guide)

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Manjusha Abhijit Joshi

General Remarks

- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- 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}.
- ^{1}H Nuclear Magnetic Resonance spectra were recorded on Varian FT-200 MHz (Gemini), AC-200 MHz, MSL-300 MHz, AV-400 MHz and Bruker-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C Nuclear Magnetic Resonance spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz and Bruker-125 MHz spectrometer.
- Mass spectra were recorded on a CEC-21-110B, AP-1 QSTAR PULSAR, Finnigan Mat 1210 or MICRO MASS 7070 spectrometer at 70 eV using a direct inlet system.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 and anisaldehyde reagent in ethanol as development reagents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
BAIB	-	Bis-acetoxyiodobenzene
Bn	-	Benzyl
BnBr	-	Benzyl bromide
CCl_4	-	Carbontetrachloride
CH_2Cl_2	-	Dichloromethane
CH_2I_2	-	Diiodomethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	*N, N'*-Diisopropylethylamine
DMAP	-	4-*N, N'*-Dimethylaminopyridine
DMF	-	*N, N'*-Dimethylformamide
DMSO	-	Dimethyl sulfoxide
DMP	-	2,2-Dimethoxypropane
DMP	-	Dess-Martin periodinane
Et	-	Ethyl
EtOAc	-	Ethyl acetate
Et_2O	-	Diethylether
EtOH	-	Ethanol
HCHO	-	Formalin
$HgCl_2$	-	Mercuric chloride
HgO	-	Mercuric oxide
IBX	-	Iodoxybenzoic acid
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
MeOH	-	Methanol
MOMCl	-	Methoxymethylchloride
MEMCl	-	Methoxyethoxymethylchloride
NaH	-	Sodium hydride

Pd/C	-	Palladium on carbon
PDC	-	Pyridiniumdichromate
PMB	-	*para*-Methoxy benzyl
*p*TSA	-	*para*-Toluenesulfonic acid
Py	-	Pyridine
TBDMS-Cl	-	*tert*-Butyldimethylchlorosilane
TEA	-	Triethyl amine
TEMPO	-	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TMS	-	Trimethyl silyl
TPP	-	Triphenylphosphine

Contents

Abstract

Abstract

The thesis entitled **"Synthetic Studies towards Total Synthesis of Lactacystin Analogue and the related *β*-Lactone Omuralide Analogue"** consists of four parts namely Introduction, Present work, Experimental and References.

Introduction

Lactacystin (**1**), a novel microbial product, was isolated from a *streptomyces* bacterial strain (OM-6519) found in a Japanese soil sample in 1991 and the structure elucidated by Omura *et al*. Lactacystin (**1**) and the related *β*-lactone **2** are remarkably selective and potent irreversible inhibitors of 20 *S* proteasome. These features have led to speculation that lactacystin (**1**) has a therapeutic use in treatment of debilitating conditions such as arthritis, asthma and Alzheimer's disease. The biological uniqueness and utility of lactacystin (**1**) and the *β*-lactone **2** have made these molecules and their analogues attractive targets for chemical synthesis and the design of several analogues with stereochemical and functional group modifications to study their structure activity relationships.

In order to study the changes in activity due to structural variations, an oxa-analogue of lactacystin (**3**) and the related oxa *β*-lactone (**4**) were designed as targets to understand the role of ring hetero atom in the designated biological activity of these compounds. Our studies towards the synthesis of **3** and **4** form the topic of this thesis.

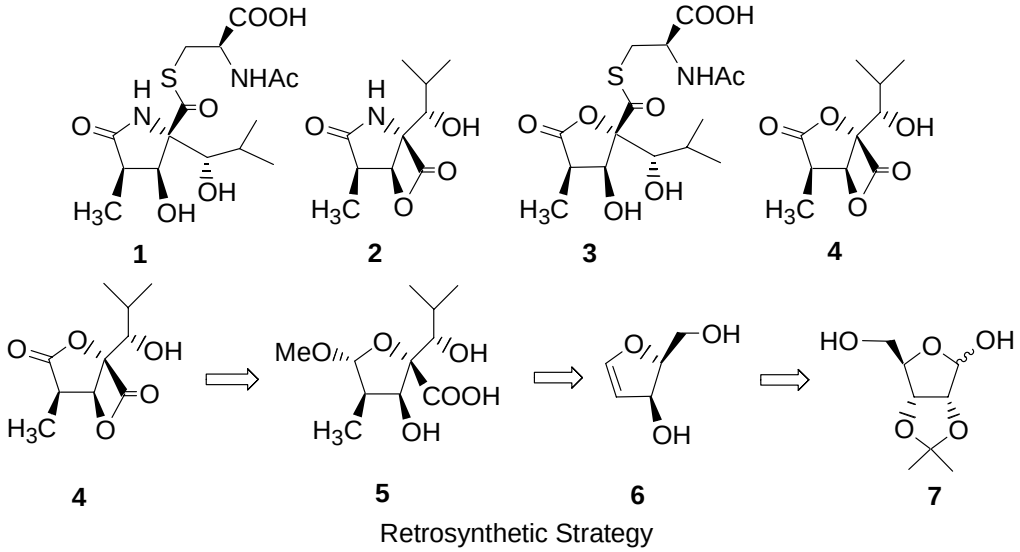
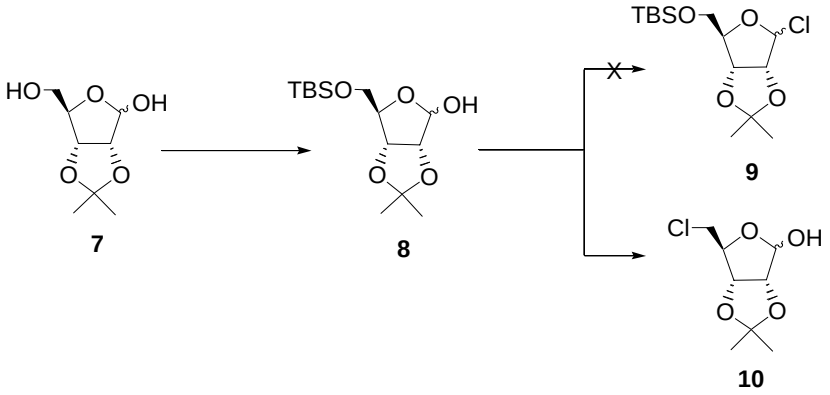


Figure 1. *Lactacystin and related β-lactone containing natural products/analogues*

Present Work

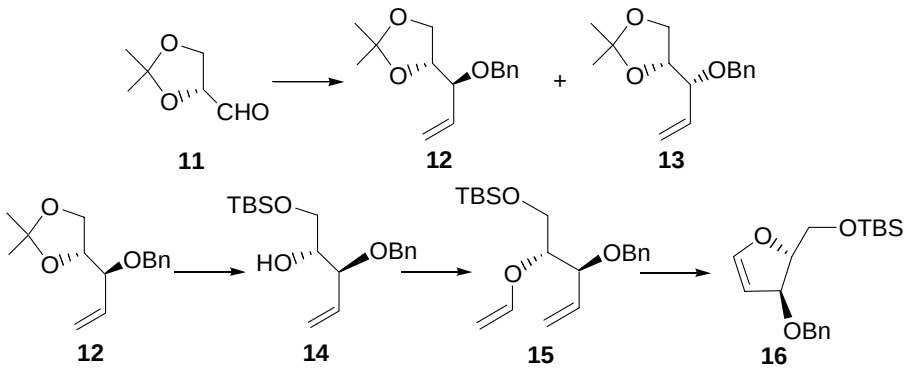
After a careful retrosynthetic analysis, synthesis of the advanced intermediate **6** identified as the primary task and the stereochemical comparison led to the known 2,3-*O*-isopropylidene-D-*ribo*-furanose (**7,** Scheme 1) as a starting point. Protection of C-5 hydroxyl group of **7** as silyl ether using imidazole, TBDMS-Cl in DMF gave compound **8**. However, the desired chlorination of **8** leading to the anomeric chloro derivative **9** turned out to be a difficult proposition and gave the 5-chloro-2,3-*O*-isopropylidene-D-*ribo*-furanose (**10**), resulting from an internal glycosidation.

Scheme 1



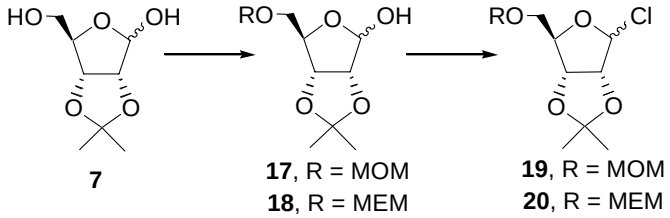
Taking into consideration the required stereocentres in compound **6**, D-mannitol was chosen as the starting material. (*R*)-1,2-*O*-Isopropylideneglyceraldehyde (**11**) was prepared from 1,2:5,6-*O*-diisopropylidene-D-mannitol in the presence of sodium metaperiodate in CH_2Cl_2. Reaction of aldehyde **11** with vinyl magnesium bromide afforded diastereomeric mixture of alcohols which was protected as benzyl ethers **12** and **13**. To fix the required stereochemistry of the key intermediate **6**, benzyl ether **12** was further deprotected to diol with acid catalysed hydrolysis in MeOH. The diol was then treated with imidazole, TBDMS-Cl in CH_2Cl_2 to procure silyl ether **14**. Compound **14** was converted to the corresponding diene **15** which was obtained in good yield. Ring closing metathesis of **15** using 1st generation Grubb's catalyst turned out to be a failure. Use of 2nd generation Grubb's catalyst yielded the required key intermediate **16** (scheme 2). The structure of **16** was confirmed with ^{1}H, ^{13}C NMR spectra, mass spectrum and elemental analysis.

Scheme 2



Considering the cost efficiency of the above reaction as it involves 2nd generation Grubb's catalyst, we still proposed to explore the second chiral pool method towards the intermediate **16**. If this strategy was successful, it could be cost effective and perhaps scalable. We turned back to 2,3-*O*-isopropylidene-D-*ribo*-furanose (**7**) and opted for different protecting groups at C-5 to minimise the possible intramolecular glycosidation. The chlorination reaction was attempted with MOM and MEM ethers (compounds **17** and **18** respectively), but it resulted in very low yields of chloro compounds (**19** and **20** respectively (scheme 3). Hence this synthetic approach was abandoned.

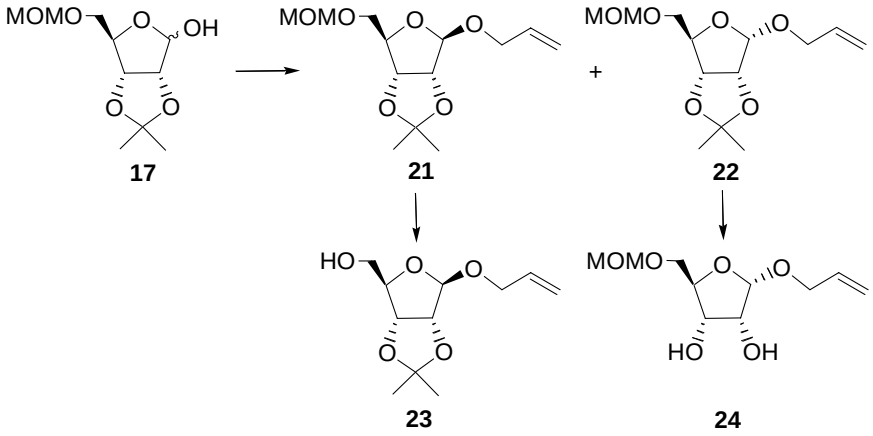
Scheme 3



After being met with low yields of the furanosyl chloride derivatives, we thought of modification at C-5 position prior to the chlorination at anomeric position in order to synthesize the key intermediate **16** from compound **17**. Compound **17** was treated with allyl bromide and NaOH in benzene to afford a mixture of anomers **21** and **22** (8:2). They were separated by silica gel chromatography and deprotection of MOM group present in **21** with trifluoroacetic acid in CH_2Cl_2 at room temperature afforded compound **23**. In the ^1H NMR spectrum of major compound **23**, the characteristic signals due to MOM group were absent and henceforth the compound **23** was resulted from the cleavage of MOM ether as expected. On the other hand, reaction of compound **22** with TFA-CH_2Cl_2 gave a polar derivative **24**

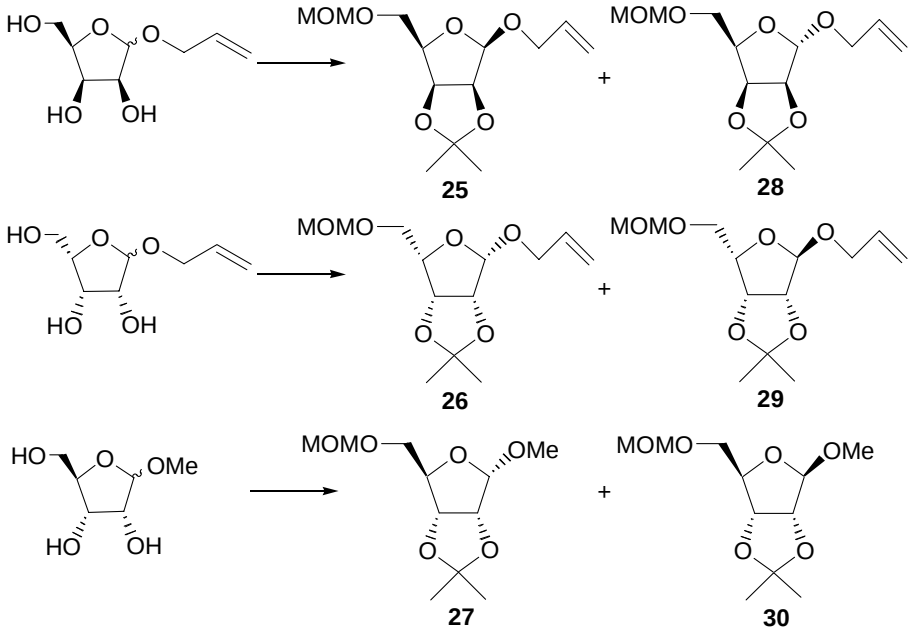
whose ^{1}H NMR spectrum showed the absence of characteristic signals due to the isopropylidene group, thus confirming the assigned structure of the diol **24** which was the unexpected product (scheme 4).

Scheme 4



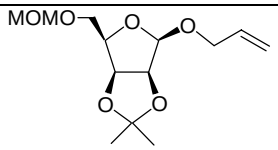
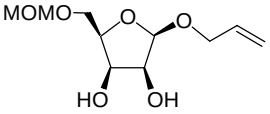
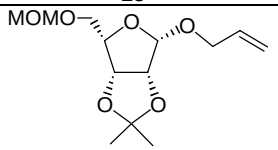
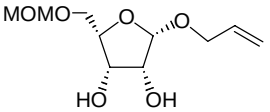
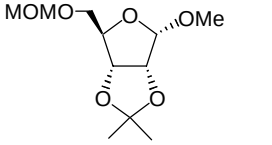
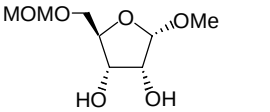
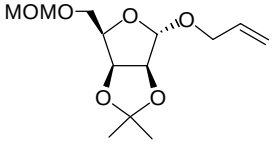
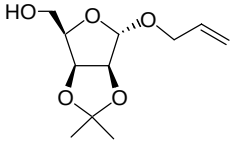
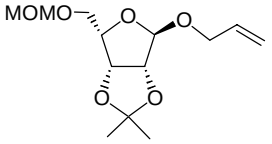
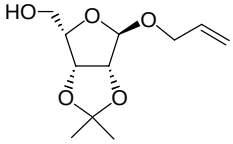
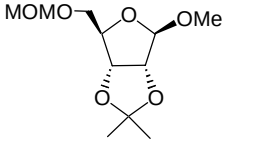
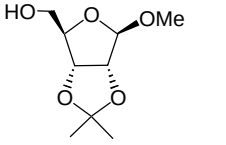
Keeping in mind the *syn*-orientation of isopropylidene and the anomeric allyl ether, we reasoned that the selective cleavage of isopropylidene in the α-anomer **22** might be due to the anchimeric assistance by anomeric oxygen. In order to validate our hypothesis, we prepared alkyl-2,3-*O*-isopropylidene-5-*O*-methoxymethyl furanoside derivatives **25** – **30** by a general method involving the treatment of alkyl furanosides with *p*-TSA and 2,2-dimethoxypropane in excess dry acetone followed by methoxymethyl chloride in the presence of DIPEA in CH_2Cl_2 (scheme 5) and separation by silica gel column chromatography was done.

Scheme 5



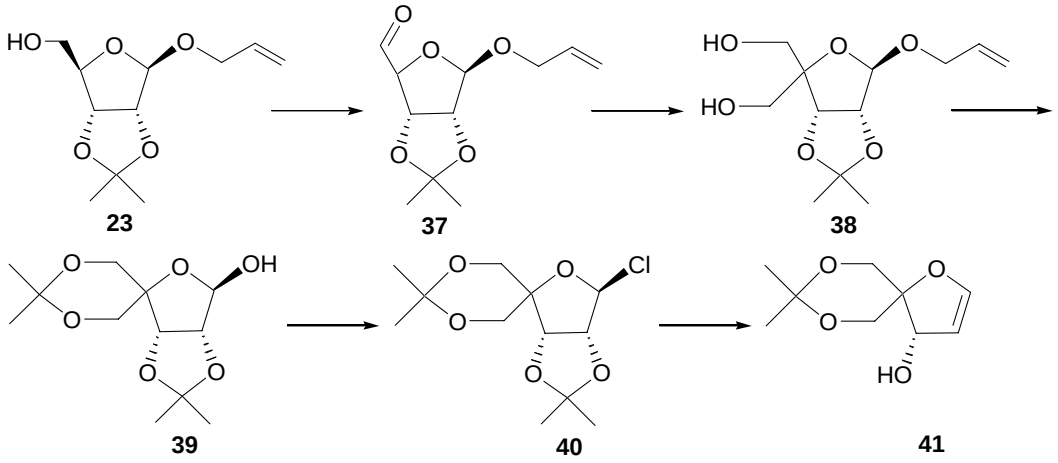
As expected in all the cases, the deprotection by trifluoroacetic acid in CH_2Cl_2 was extremely selective and resulted exclusively in one product (Table 1).

Table 1

Entry	Substrate	Time (h)	Product	Yield (%)
1	 **25**	2	 **31**	86
2	 **26**	2	 **32**	88
3	 **27**	3	 **33**	90
4	 **28**	8	 **34**	77
5	 **29**	7	 **35**	79
6	 **30**	9	 **36**	92

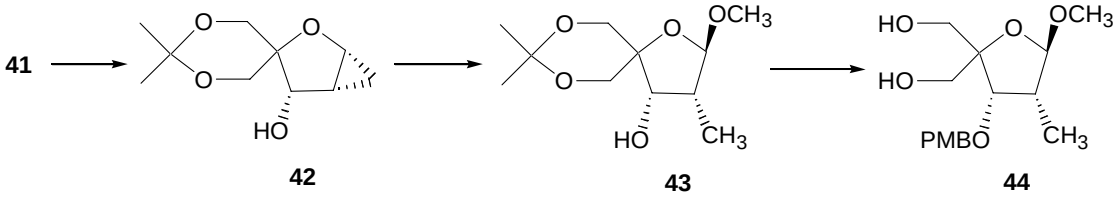
After generalizing the interesting observation, we focused our attention to the original synthetic route. The alcohol **23** was oxidized to aldehyde **37** followed by aldol and cross-Cannizzaro reaction with 1N NaOH and formalin to give 1,3-diol **38**. The diol **38** was protected as isopropylidene derivative which was deallylated in two steps to lactol **39**. The attempted chlorination using triphenylphosphine and CCl_4 in refluxing THF afforded chloro compound **40**. Finally, the chloro derivative **40** was converted to key intermediate **41** using lithium in liq. ammonia (scheme 6).

Scheme 6



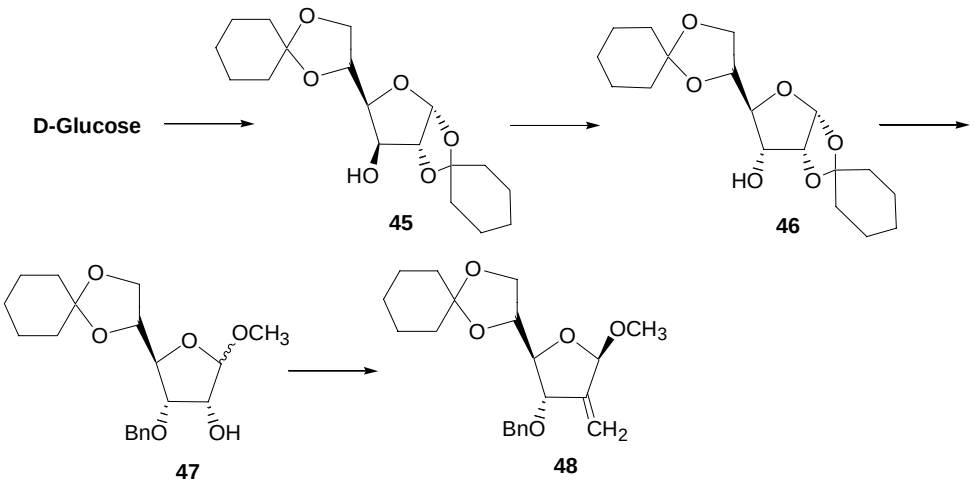
As expected, the Simmons-Smith cyclopropanation of compound **41** with CH_2I_2 and diethyl zinc in CH_2Cl_2 at –40 °C was regio and stereoselective and resulted in the required 1,2-cyclopropane derivative **42**. Compound **42** was allowed to react with mercuric acetate in methanol followed by reductive workup ($LiAlH_4$, THF, 0 °C) and the cyclopropane moiety was cleaved regioselectively to afford the compound **43**. The C-3 hydroxyl group of compound **43** was protected as PMB ether and the deprotection of isopropylidene group was carried out with catalytic H_2SO_4 in MeOH to procure the diol **44** (scheme 7).

Scheme 7



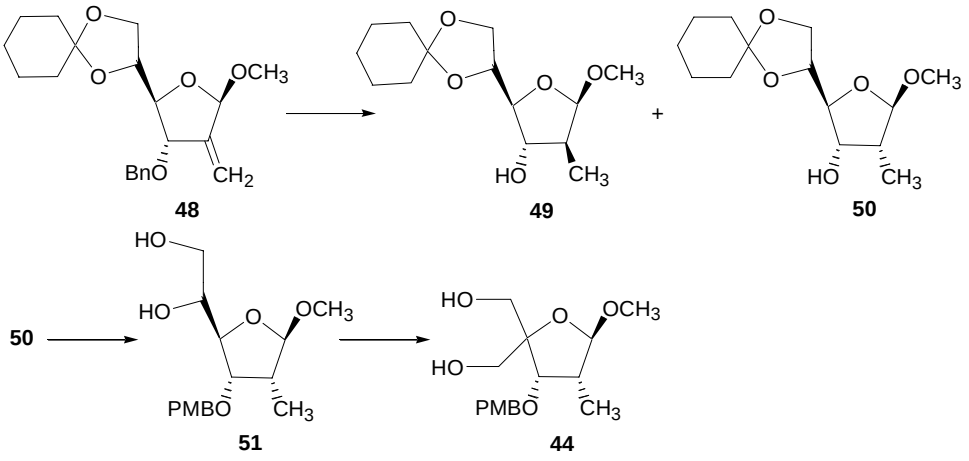
Considering the practical difficulties in scale-up starting from D-ribose and the number of steps involved in the synthetic endeavor ahead, another strategy was planned to synthesize the intermediate **44** from D-glucose (scheme 8). D-Glucose was protected as its dicyclohexylidene derivative **45** and a known sequence of oxidation and reduction over **45** led to the dicyclohexylidene allofuranose **46**. The C3-OH of **46** was protected as its benzyl ether and subjected for selective deprotection of 1,2-cyclohexylidene using catalytic acid in MeOH to afford anomeric mixture **47**. Oxidation of **47** with IBX in DMSO gave the ketone which was subjected to wittig olefination to yield the olefin **48**.

Scheme 8



The attempted olefin hydrogenolysis of **48** with Raney-Ni in EtOH followed by debenzylation furnished the diastereomers **49** and **50** (3:1). After establishing the stereochemistry of **50**, we proceeded further to prepare the key intermediate **44**. The C-3 hydroxyl of the compound **50** was protected as PMB ether and 5,6-cyclohexylidene group was deprotected to procure the diol **51**. Oxidative cleavage of the diol **51** using sodium metaperiodate in CH_2Cl_2 furnished the aldehyde which subjected to aldol followed by cross-Cannizzaro reaction to get the intermediate **44**.

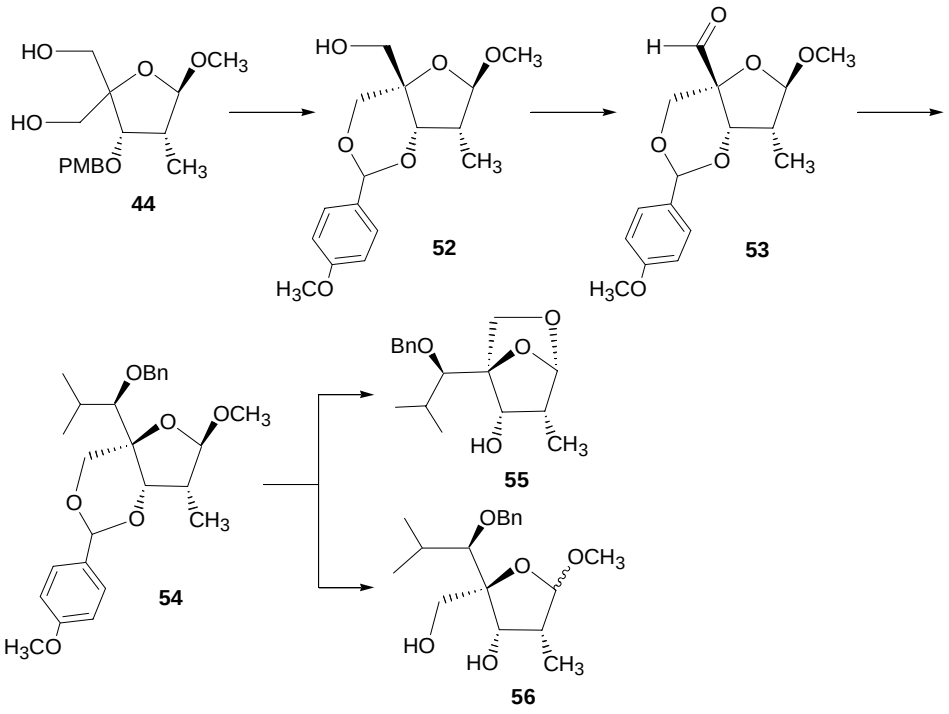
Scheme 9



In order to selectively differentiate the diol, the PMB ether **44** was treated with DDQ in CH_2Cl_2 to form *p*-methoxybenzylidene derivative **52** which was further treated with Dess-Martin periodinane in CH_2Cl_2 to form the aldehyde **53**. Aldehyde **53** was treated with

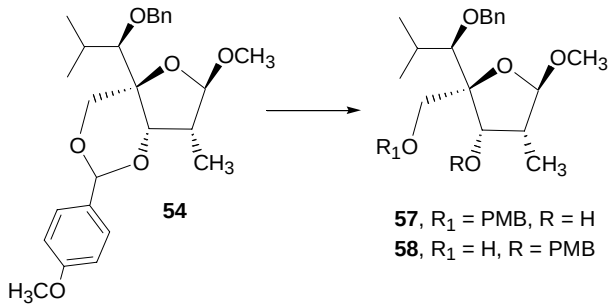
isopropyl magnesium bromide to form single diastereomer exclusively and the X-ray studies showed the structure in which the hydroxyl group at C-5 had D-configuration. Although the D-configuration was unexpected, we decided to pursue the synthesis of C-5 epimer of oxa-lactacystin (**3**). The C(5)-OH was protected as its benzyl ether to afford compound **54**. In order to deprotect the *p*-methoxybenzylidene acetal, the benzyl ether **54** was treated with DDQ in acetonitrile:water (9:1) and it resulted in the cyclized product **55** instead of the required diol. Replacing water with MeOH as a protic solvent, the reaction led to the formation of anomeric mixture of methyl glycoside **56** (scheme 10).

Scheme 10



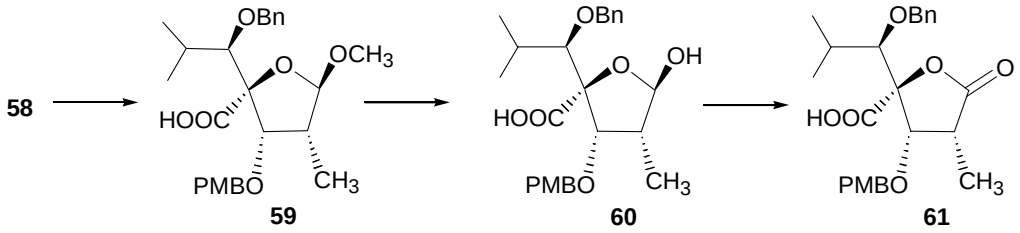
Having met with these problems, the reductive opening of the compound **54** with LAH/$AlCl_3$ was attempted, where in general the secondary-OPMB should result from the hydride attack at the least hindered side of the acetal. The reaction resulted exclusively in the formation of primary-OPMB regiomer **57**. In similar lines, compound **58** was obtained exclusively when the reaction was carried out with DIBAL-H in toluene.

Scheme 11



Oxidation of **58** was carried out with DMP in CH_2Cl_2 and the resulting aldehyde was transformed into the required acid **59**. Finally, the treatment of acid **59** with 2N HCl in THF and water gave the lactol **60** which was oxidized to lactone **61** (scheme 12).

Scheme 12



Synthesis of the target C-5 epimer of oxa-lactacystin (**3**) from **61** by means of deprotection of PMB ether followed by β-lactone formation, debenzylation and thioester formation is currently under progress in the laboratory.

Introduction

Introduction

The search for biologically active natural products for the development of new drugs has a long tradition. When modern synthetic chemistry came into being in the middle of the 19th century, Nature had already been generating a plethora of substances for millions of years. Many of those equipped the producing organism with an evolutionary advantage to survive in a more or less hostile environment, thus the percentage of biologically active substances in Nature is relatively high relative to substances from artificial sources. In fact, man has always taken advantage of Nature as a pharmacy: approximately 40% of the drugs that have been approved in the last years are either natural products or derivatives and analogues thereof.[1] Among anticancer and antiinfective agents, the percentage is even estimated to exceed 60%, including such well-known examples as penicillin G and erythromycin A, as well as colchicine, vinblastine, vincristine and paclitaxel (taxol). Organ transplantation would not have been possible without immunosuppressive natural products such as cyclosporin A, FK506 or rapamycin. Natural products and their analogues have been put to use not only in pharmacology but also in modern crop protection.[2] They play an important role as highly potent insecticides, for example, pyrethrin, spinosyne A and spinosyne D as fungicides, such as the derivatives of strobilurin A.

Thus the vital role of natural products for treating a wide variety of diseases is impermeable, however, the number of natural products and some times the availability is a major bottleneck in the development of new drugs. Nonetheless, the recently introduced new concepts in the area of organic synthesis like combinatorial synthesis and high throughput synthesis could provide access to millions of synthetic compounds in a short time. This taken together with the skeletal diversity of natural products has led to conceptualize the synthesis of analogues and hybrids as combinations of parts of different natural products in many of the drug discovery programs. This new approach seems to be extremely promising in the development of leads for both medicinal and agrochemical applications and interestingly some times the biological activity of several analogues and new hybrids exceeds that of the parent compounds. Natural product hybrids can be divided into four classes:

1) Naturally occurring hybrids of whole natural products or analogues
2) Naturally occurring hybrids of partial structures of natural products or analogues

3) Synthetic hybrids of whole natural products or analogues
4) Synthetic hybrids of partial structures of natural products or analogues.

In the context of present topic of the thesis, the introduction will mainly focus on *"synthetic hybrids of partial structures of natural products or analogues"* however a few examples will also be presented for the other classes.

Naturally occurring hybrids of whole natural products or analogues:

An interesting example of this class of natural hybrids is the antimicrobial antibiotic thiomarinol (**1**), which was isolated from a culture broth of the marine bacterium *Alteromonas rava* sp. nov. SANK 73390 and was shown to be a hybrid of the pseudomonic acid C analogue **2b** and holothin (**3**).[3] Importantly, the antimicrobial spectrum of **3** shows characteristics of both parent compounds: it is active against Gram-positive and Gram-negative bacteria (e.g. multiresistant *Staphylococcus* aurea strains), and its effects are more pronounced than those of either parent compound.

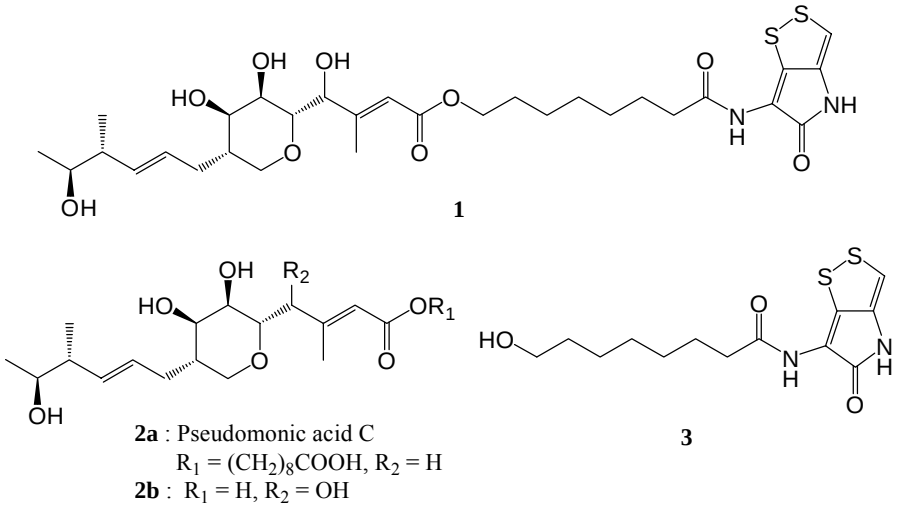
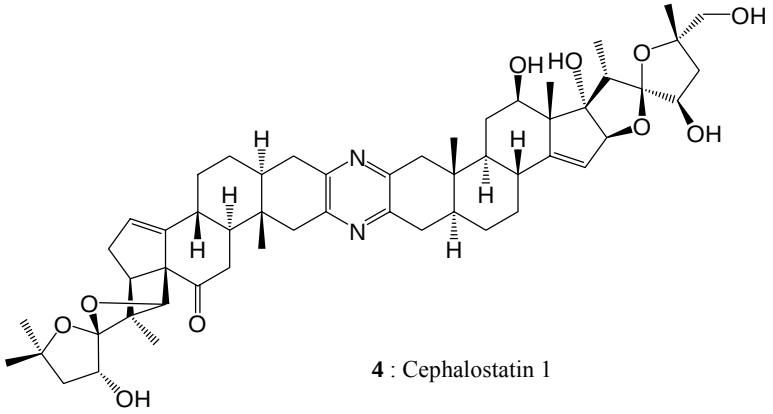


Figure 1. Naturally Occurring Antimicrobial Antibiotic Hybrid **"***Thiomarinol"* (**1**)

The formation of dimers of natural products is a common feature in nature. The new hybrids usually exhibit a different biological activity to that of the monomer. The cephalostatin 1 (**4**), the most potent compound of this type was isolated from the marine worm *Cephalodiscus gilchristi*.[4] This is dimeric natural product hybrid with especially high biological activity, containing a pyrazine unit connected to a highly oxygenated steroid

moiety on each side. In an in vitro screening against a National Cancer Institute (NCI) panel of 60 human cancer cell lines, **4** was shown to have a GI_{50} value of about 2.20 nM.

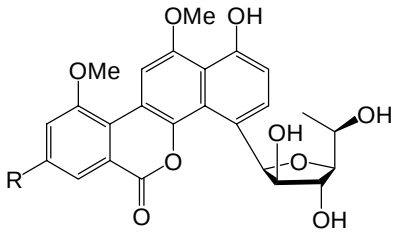


4 : Cephalostatin 1

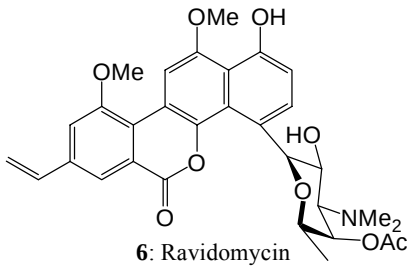
Figure 2. Naturally Occurring Dimeric Hybrid *"Cephalostatin 1"* (**4**)

Naturally occurring hybrids of partial structures of natural products or analogues:

There are thousands of *O*- and *N*-glycosidic natural products, such as the saponines, flavones, ribonucleosides and anthracyclic glycosides, which contain a carbohydrate and another natural compound (the aglycone) and may therefore also be considered as natural product hybrids. Several C-glycosidic antitumor antibiotics are hybrids of carbohydrates and tetracyclines. These compounds generally fall under the anthracycline class of natural products, which is amply covered in the literature.[5] Gilvocarcin (**5**) and ravidomycin (**6**) represent a new class of aryl C-glycoside antitumor antibiotics that have a benzonaphthopyrone tetracycle in common and differ in the carbohydrate at C-4 (a fucose unit in gilvocarcin and an amino sugar in ravidomycin). It has been shown that the amino sugar congener is biologically more potent.



5a : (-)-Gilvocarcin M
R = Me
5b : Gilvocarcin V
R = $CH{=}CH_2$

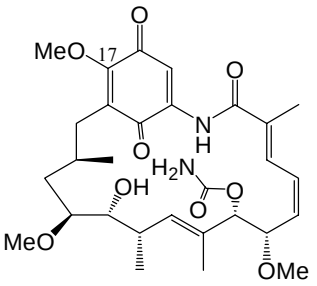


6: Ravidomycin

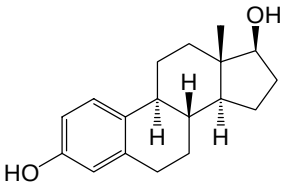
Figure 3. Aryl *C*-Glycosidic Antitumor Antibiotic Hybrids of Carbohydrates

Synthetic hybrids of whole natural products or analogues:

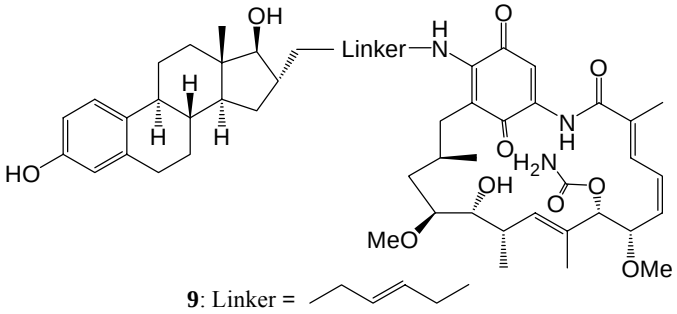
Geldanamycin (**7**), an ansamycin antibiotic first isolated from *Streptomyces hygroscopicus*, binds to the Hsp90 chaperone protein and causes the degradation of several important signalling proteins. Therefore, it was hoped that an appropriately fashioned hybrid drug of geldanamycin and estradiol (**8**) would offer the ability to induce a selective degradation of the estrogen receptor (ER).[6] The coupling to geldanamycin (GDM, **7**) relied on its Michael acceptor character at C-17 and cleavage of the phenolic TBS ether and afforded the final estradiol–GDM hybrid **9**, which was subjected to biological tests. Hybrid **9** is more selective than geldanamycin (**7**) and estradiol (**8**) towards the degradation of HER2 and ER.



7 : Geldanamycin



8 : Estradiol



9: Linker =

Figure 4. Synthetic Estradiol–GDM Hybrid **9**

As HER-kinases, which are inhibited very effectively by geldanamycin, undergo dimerization on activation, it was speculated that both units of the HER-kinase dimer interact with Hsp90.[7] Accordingly, it seemed reasonable that a geldanamycin dimer might be able to interact with both subunits of the HER-kinase dimers, which led to the synthesis of the homohybrids **10a-d**. The two monomers were connected by a diamino alkyl linker of variable length attached to the respective C17 atoms, since this is the only atom not buried in the binding pocket, as revealed by crystal-structure analysis. The selectivity was found to

decrease with increasing chain length of the linker. The best selectivity was exhibited by dimer **10a** with a butyl linker.

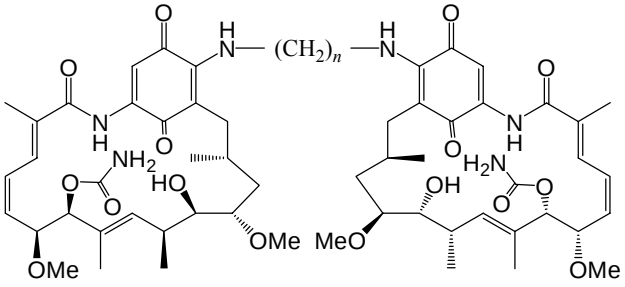


Figure 5. Synthetic Homohybrids of Geldanamycin Dimer (**10a-d**)

Synthetic hybrids of partial structure of natural products or analogues:

Hybrids with a steroid substructure:

The estrogen receptor is present in higher concentrations in breast cancer, ovarian adenocarcinoma, prostatic carcinoma and endometrial carcinoma than in normal tissue. This discovery led to the establishment of estrogens as vectors for cytotoxic agents in the hope that an increased organ and/or tissue specificity could be achieved through a selective accumulation of the cytotoxic compound in the tumor cells. Derivatives of oleanolic acid (**11**), such as **12** – **15** were synthesized and their biological activity evaluated in an inducible nitric oxide synthase (iNOS) assay, which revealed that compound **15** showed a moderate inhibitory activity at the 1 μM level.

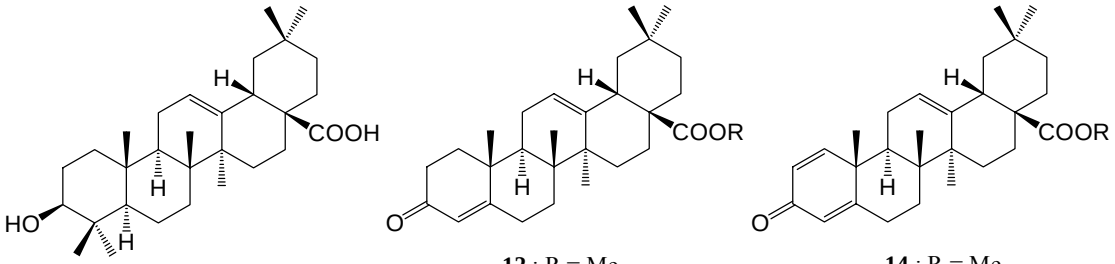
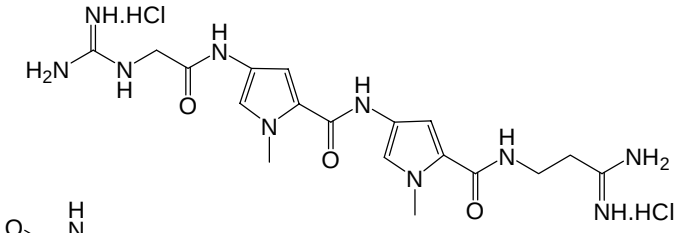


Figure 6. Synthetic Oleanolic Acid (**11**) and Derivatives **12** – **15**

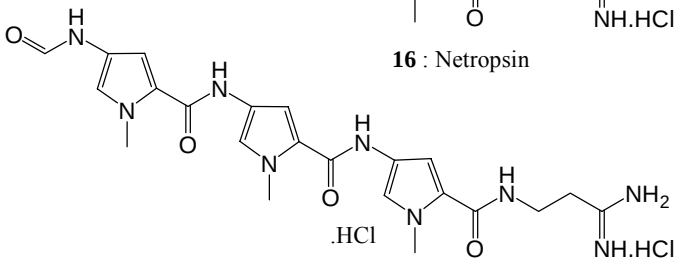
Hybrids with a DNA-binding lexitropsin substructure:

Netropsin (**16**) and distamycin A (**17**) belong to the lexitropsin class of compounds.[8] The two naturally occurring oligopeptides are structurally closely related in that two and three N-methylpyrrole-2-carboxamide units, respectively, are combined. They show a relatively

strong affinity for A–T-rich DNA regions in the minor groove of double-stranded B-DNA. This selectivity was explained by the fact that A–T base pairs are associated with the narrow minor groove and the elongated crescent-shaped distamycin and netropsin molecules allow a tight fit. Furthermore, the presence of the N2 amino group of guanine serves as a major steric block that prevents the pyrrolamide chain from docking fully to the minor groove in G–C-rich segments. However, netropsin and distamycin A themselves show only a weak cytotoxicity, which can be traced back to the absence of a covalent bonding to the DNA. Thus, only reversible binding occurs by electrostatic forces, van der Waals interactions and hydrogen bonds.



16 : Netropsin



17 : Distamycin A

Figure 7. Synthetic Hybrids of Lexitropsin Class of Compounds

Hybrids with a peptide substructure:

To gain some insight into the binding of FK506 (**18**), another potent immunosuppressor, to immunophilin receptors, several cyclic FK506 hybrids **19a - 19c** were synthesized in which parts of the compound were replaced by a peptide moiety.[9] This approach is different from the well-known design of peptidomimetics in which an active peptide is mimicked by, for example, an N-heterocycle to avoid enzymatic cleavage by peptidases. For the synthesis of the hybrids **19a - 19c**, tethers of variable lengths were introduced through a macrocyclization protocol. Interestingly, the X-ray crystallographic studies of the complex of the receptor with hybrid **19b** show a nearly identical overall protein topology to that observed in the FKBP12–FK506 complex. However, as expected, the

affinities of the hybrids **19a - 19c** for the receptor were considerably lower than that of FK506 (**18**).

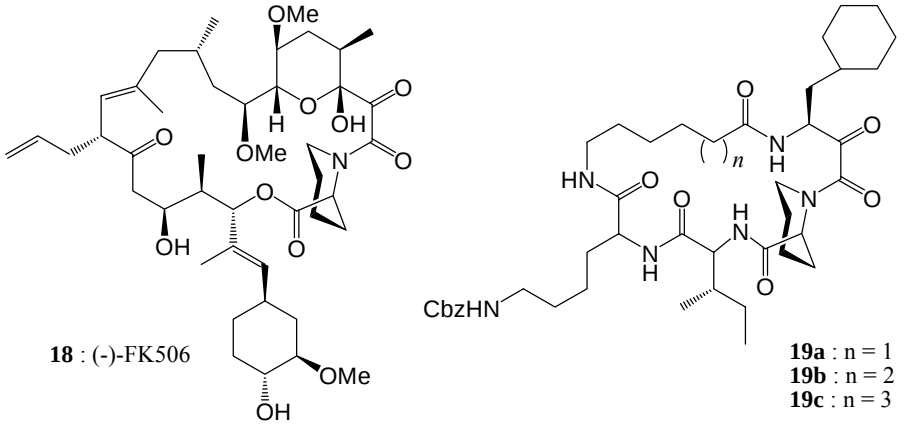


Figure 8. Synthetic Immunosuppressor *"FK506"* (**18**) and Hybrids **19a - 19c**

Miscellaneous hybrid molecules:

Some natural products like lactacystin (**20**), omuralide (**21**), conagenin (**22**), altemicidin (**23**), myriocin (**24**) and sphingofungin E and F (**25** and **26**) have α,α-disubstituted α-amino acid moiety as the characteristic structural feature coupled with various subunits.[10] Due to their interesting and important biological activities (antibiotic, immunomodular, immunosuppressive and enzyme inhibitory), they were expected to be potent lead compounds for novel drugs, and the development of efficient chiral synthetic pathway to these compounds should be a highly important work.

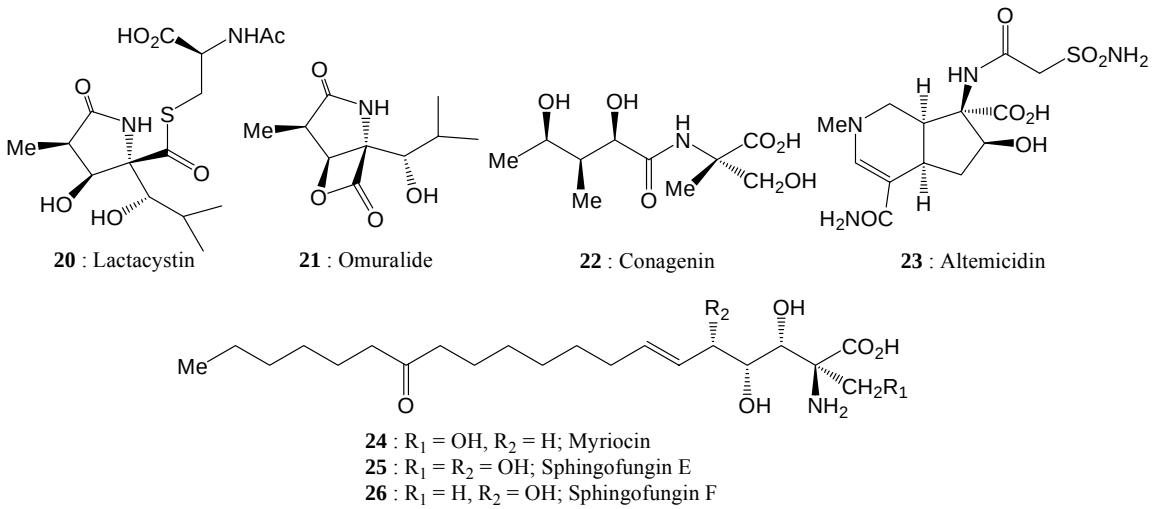


Figure 9. Natural Products with α,α-Disubstituted α-Amino Acid Unit

Lactacystin (**20**), a structurally novel microbial product, was isolated from a *streptomyces* bacterial strain (OM-6519) found in a Japanese soil sample in 1991 and characterized by Ōmura *et al*.[11] Lactacystin (**20**) and the related *β*-lactone omuralide (**21**) are remarkably selective and potent irreversible inhibitors of 20 *S* proteasome, a cylindrical complex of 28 protein subunits which is responsible for the hydrolytic fragmentation of ubiquitinated proteins. The thiol ester function of lactacystin (**20**) is sufficiently reactive to allow spontaneous conversion to the *β*-lactone **21** which similarly deactivates the 20 *S* proteasome, but at much faster rate. The major source of inactivation of the 20 *S* proteasome appears to be the acylation of the *N*-terminal threonine subunit, a key participant in proteolytic catalysis, to form inactivated proteasome. Because the proteasome machinery is involved in the degradation of many proteins, including not only misfolded and denatured molecules but also proteins involved in cell cycle progression and regulation of gene transcription, lactacystin has emerged as very important new tool for the study of protein biochemistry and cell biology.[12]

A short note on ubiquitin-proteasome pathway:

Although the 20*S* proteasome is essential in the ubiquitin pathway, by itself, this particle can not digest ubiquitin conjugates and requires additional components for this process. The ubiquitinated proteins are degraded to small peptides by a very large 26*S* protease complex and some non-ubiquitinated proteins and short peptides also degrade to emphasize that 26*S* proteasome is a proteolytic particle distinct from but related to the 20*S* particle.[13] When the 20*S* protein was chemically inactivated, the breakdown of ubiquitin-conjugated proteins were blocked. The 20*S* proteasome corresponds to component CF3 (600k) and that in the presence of ATP, this particle associates with other components to form larger 26*S* complex that degrades ubiquitinated proteins which requires ATP hydrolysis (see below in figure 10).

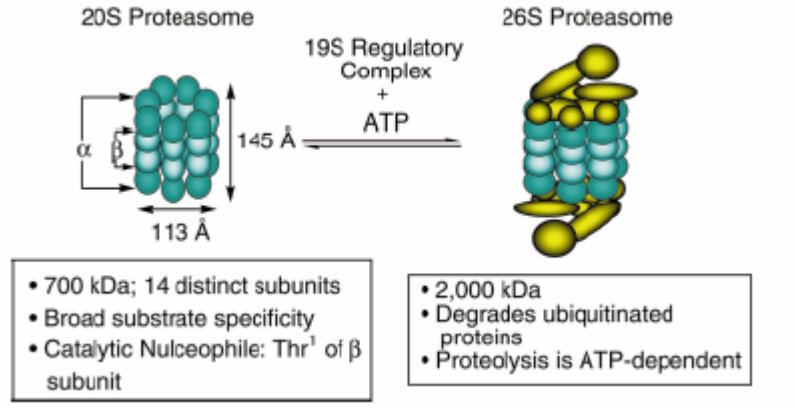


Figure 10. Key Proteins of Ubiquitin-Proteasome Pathway

The role of the proteasome in the ubiquitin pathway[14] is mediated by the regulatory protein, PA700. Polyubiquitination is accomplished by the sequential action of three enzymes: an ATP dependent ubiquitin-activating enzyme (E1), a ubiquitin conjugating enzyme (E2) and ubiqutin protein ligase (E3). This cascade covalently links the C-terminus of ubiquitin to a free amino group on the target protein, usually the E-amino of a lysine residue. Conjugation of a single ubiquitin to a protein is a weak signal for degradation. However, the ubiquitination reaction is processive and additional ubiquitin molecules are conjugated to lysine 48 of the preceding ubiquitin. Thus, entry of substrate into ubiquitin-proteasome proteolytic pathway is regulated independently of selectivity by the proteasome (Figure 11).

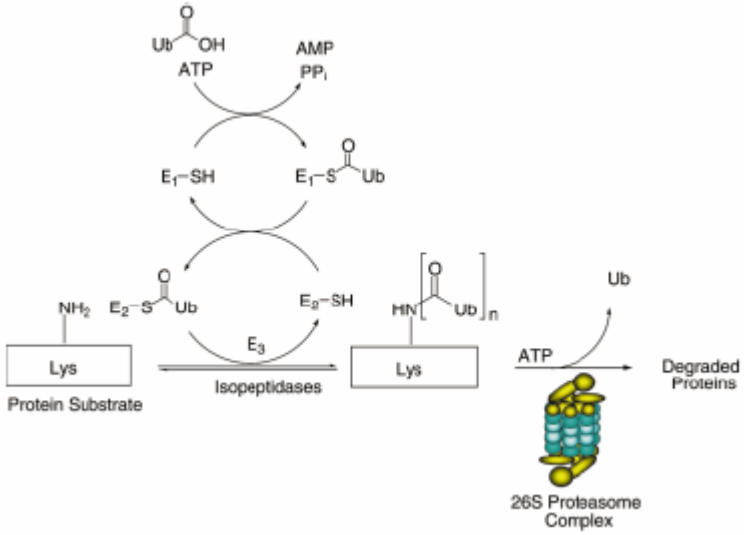


Figure 11. Ubiquitin-Proteasome Proteolytic Pathway

Mechanism of proteasome inhibition by lactacystin:

Lactacystin (**20**) is a streptomyces metabolite that inhibits cell cycle progression and induces differentiation in a murine neuroblastoma cell line. The cellular target of lactacystin (**20**) is the 20*S* proteasome, an essential component of the ubiquitin-proteasome pathway for intracellular protein degradation. In aqueous solution at pH 8, lactacystin (**20**) undergoes spontaneous hydrolysis to yield *N*-acetyl-*L*-cysteine and the inactive lactacystin analogue, clasto-lactacystin dihydroxy acid (**27**). Lactacystin (**20**) hydrolysis under these conditions proceeds exclusively through the intermediacy of the active lactacystin analog, clasto-lactacystin β-lactone (**21**). Lactacystin (**20**) acts as a precursor for clasto-lactacystin β-lactone (**21**) and the latter is the sole species that interacts with the proteasome as shown in figure 12.

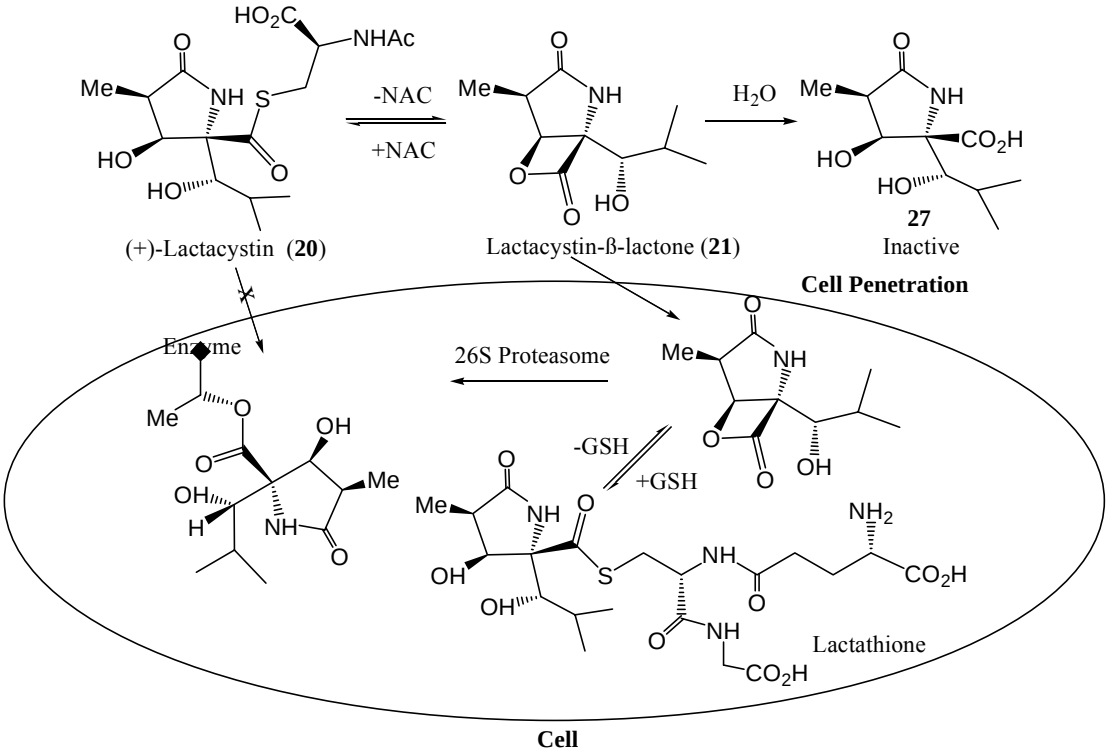


Figure 12. Mechanism of Proteasome Inhibition by Lactacystin (**20**)

Further biochemical experiment by Dick and co-workers[15] elucidated that the natural product, a thiol ester, was infact a pro-drug for the true inhibitor (+)-lactascystin-*β*-lactone (**21**). Lactacystin (**20**) spontaneously eliminates *N*-acetyl-*L*-cysteine in a reversible manner to form **21**, which is the only species that penetrates the cell. Once 'inside the cell', (+)-lactacystin-β-lactone (**21**) suffers one of the three fates: i) inhibition of the proteasome; ii)

formation of a thiol ester with glutathione (lactathione); iii) aqueous hydrolysis with water ($t_{1/2}$ = 15 min). The predominant species upon addition of (+)-lactacystin (**20**) is, in fact, the glutathione adduct which functions as a reservoir for the drug. Paradoxically, although (+)-lactacystin (**20**) forms a covalent ester bond *via* the proteasome threonine OH, this ester is subject to aqueous hydrolysis and inhibition of the proteasome is temporary with full enzymatic activity restores in a matter of hours ($t_{1/2}$ = 30 min). The unique biological activity and structural complexity have made (+)-lactacystin (**20**) and its analogues attractive targets for synthetic efforts.

Biological activity of analogues of lactacystin (20) and omuralide (21):

The remarkable potency and specificity of lactacystin (**20**) and the omuralide (**21**) in proteasome inactivation raised the interesting questions of whether these compounds were optimized during evolution for this purpose and whether they could be improved upon. Apart from the stereochemical manipulation the important positions of the molecule for chemical modification are the C(7) and C(9) alkyl group.

C(7)-Modified analogues:

The relationship between the nature of substitution at C(7) in analogues of omuralide (**21**) and ability to inactivate the mammalian 20*S* proteasome was investigated. The analogues which were prepared and tested (**21a** – **21i**) are shown in figure 13.

Due to the replacement of C(7)-methyl group of omuralide (**21**) by the smaller hydrogen, compound (**21a**) leads to much reduced acitivity. The C(7) diastereomer[16] **21b** and C(7) benzyl (**21c**) substitution are somewhat less active, but still potent. The C(7) gem-dimethyl analogue (**21d**) is as active as omuralide (**21**),[17] while the replacement of the C(7)-methyl group by the larger substituents like ethyl, n-propyl, n-butyl, iso-butyl and iso-propyl (**21e – 21i**) results in an approximate doubling of the proteasome inhibitory activity relative to omuralide (**21**).

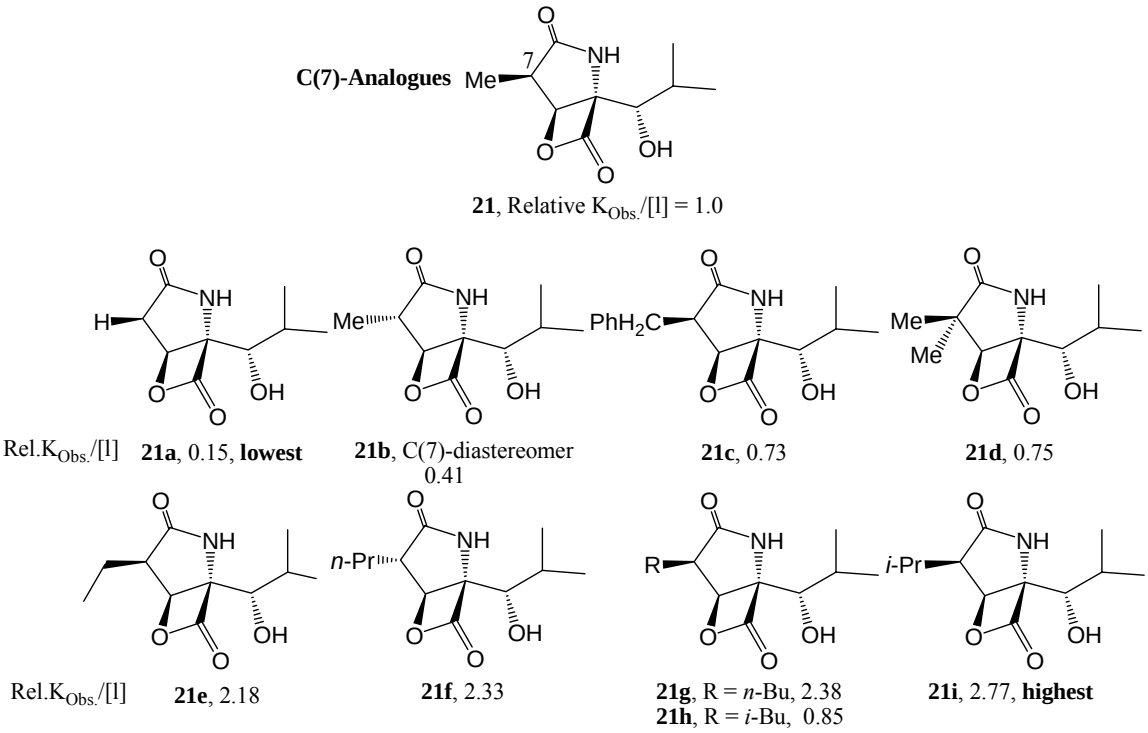


Figure 13. Omuralide (**21**) and its C(7) Modified Analogues **21a** – **21i**

C(9)-Modified analogues:

A wide variety of C(9) substituents can be introduced to generate β-lactone analogues like isopropyl, hydrogen, phenyl, ethyl, vinyl, n-propyl, allyl, iso-butyl, methallyl, etc. The results of the kinetic measurements are summarized in figure 14. Replacemnt of the C(9)-isopropyl group of **21** by phenyl (**21j**) abolishes proteasome inibition and substitution by hydrogen (**21k**) greatly reduces the activity. Similarly, activity relative to **21** greatly diminished with C(9) substituents which are either slightly smaller than isopropyl such as vinyl (**21l**) or ethyl (**21m**)[18] or larger than isopropyl like allyl (**21n**), n-propyl (**21o**), methallyl (**21p**) or isobutyl (**21q**). Analogues (**21r – 21u**) with their respective activities[18b,19] as compared to omuralide (**21**) were included in figure 14. Clearly, the most acive compound is omuralide (**21**). It seems clear that the C(9)-isopropyl substituent of **20** and **21** is optimal for proteasome inhibition, implying a fairly snug fit for isopropyl in the complementary binding pocket of the proteasome.

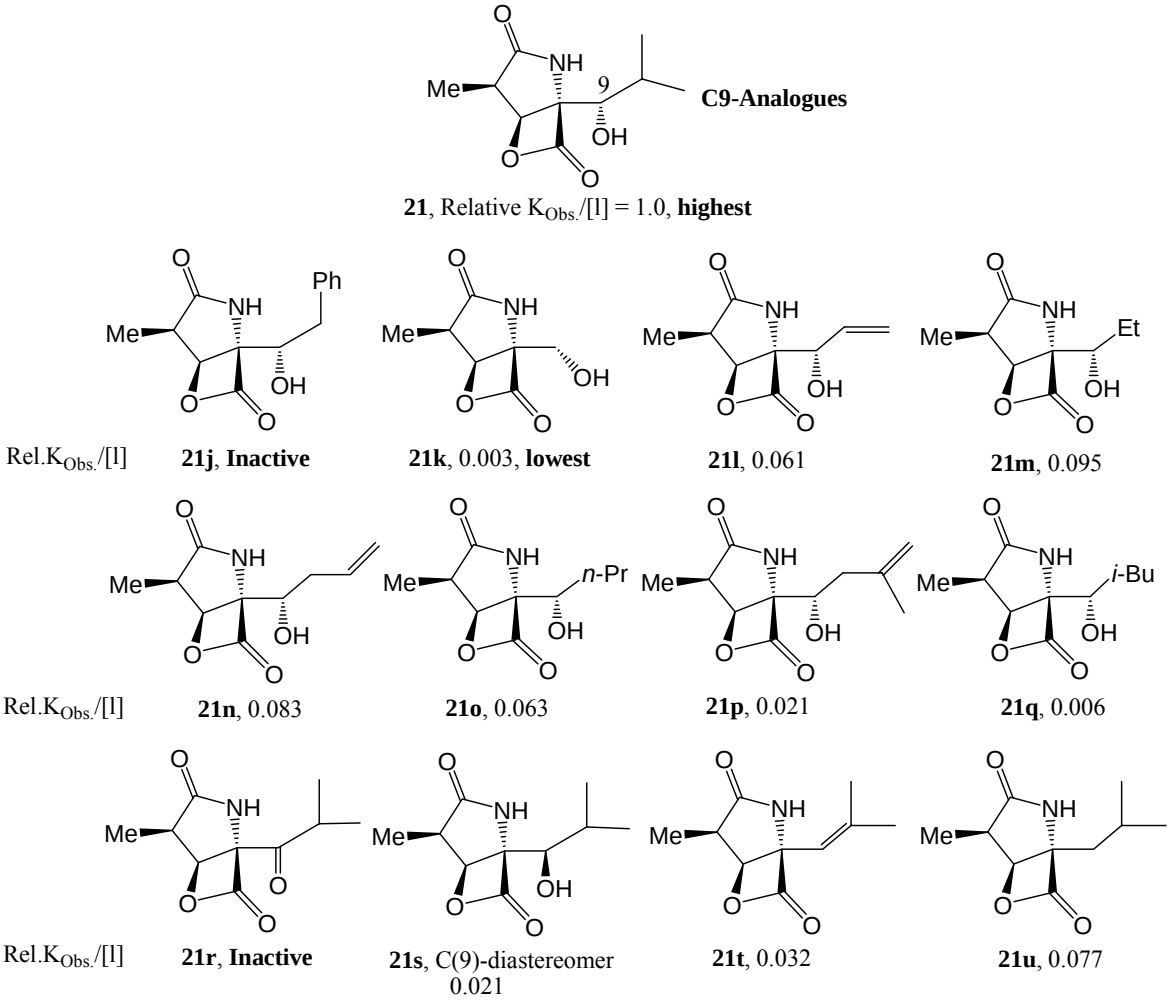


Figure 14. Omuralide (**21**) and its C(9) Modified Analogues **21j** – **21u**

Other analogues:

Other analogues prepared to date accompanied by their biological activity were as shown in figure 15. The (6*R*, 7*S*)- diastereomer (**28**), 6-deoxy analogue (**29**) and (6*R*)-diastereomer (**30**) and methyl ester analogue (**31**) of lactacystin (**20**) were found to be biologically inactive, which suggested the possibility that β-lactone formation may be crucial to (+)-lactacystin's bioactivity.[20,21] The effect of changing the stereochemical orientation of the β-lactone bridge on the γ-lactam nucleus has also been determined by the synthesis of the (5*S*,6*R*,9*R*)-diastereomer (**32**) and (5*S*,6*R*,9*S*)-diastereomer (**33**) of omuralide (**21**).[22] The relative rates of proteasome inactivation by omuralide, (5*S*,6*R*,9*R*)-diastereomer (**32**) and (5*S*,6*R*,9*S*)-diastereomer (**33**) were found to be 1.0, 0.04 and 0, respectively, a clear indication

that the correct *stereo-orientation* of the β-lactone bridge of omuralide is critical for bioactivity.

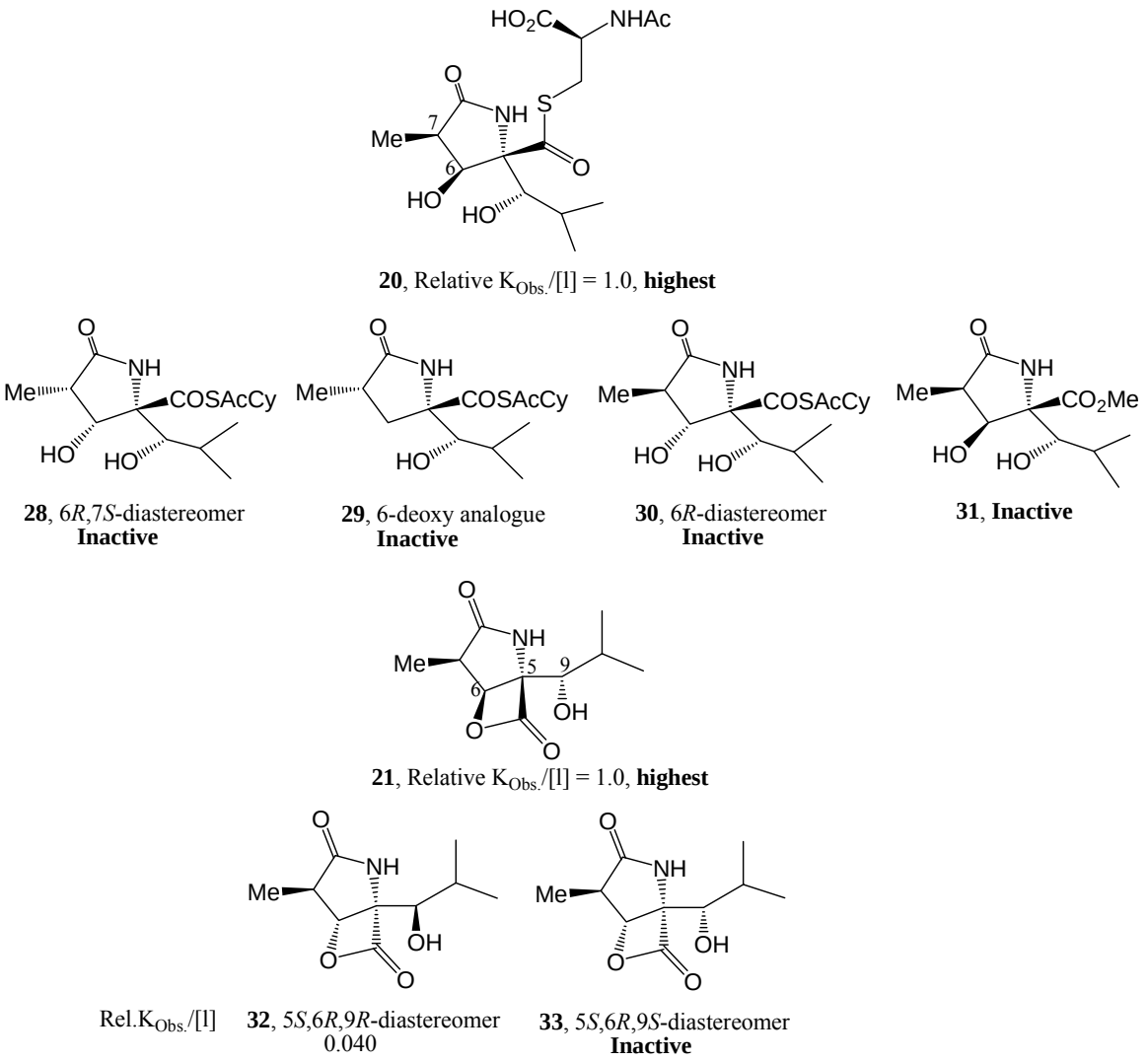


Figure 15. Lactacystin (**20**), Omuralide (**21**) and their related Diastereomers

Summary of SAR studies:

The structure-activity relationship studies demonstrated the importance of the requisite functionality and stereochemical relationships in the natural product. Removal of the methyl substituent at C(7) strongly reduces bioactivity relative to omuralide (**21**). On the other hand, replacement of the methyl substituent at C(7) by isopropyl (**21i**) led to a 2 to 3 fold increase in activity (2.77). The configuration of the hydroxyl at C(9) and the presence of the isopropyl

substituent at C(9) are also very important for bioactivity. The stereochemical orientation of the β-lactone bridge on the γ-lactam nucleus is critical to bioactivity.

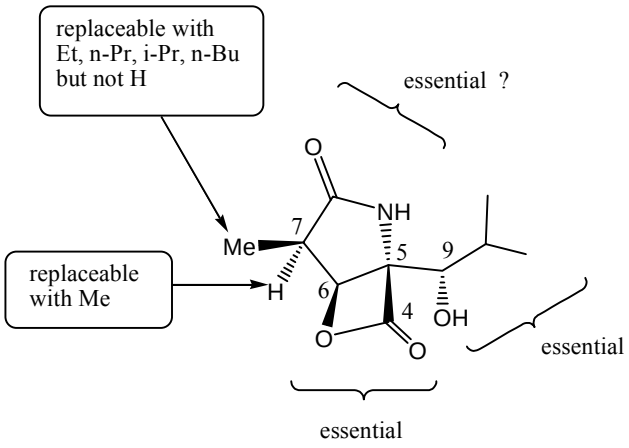


Figure 16.

Initial studies on the total synthesis of lactacystin:

Lactacystin (**20**), a metabolite isolated from *Streptomyces* sp. OM-6519, has attracted considerable interest due to its highly potent and selective inhibition of the 20*S* proteasome. Since the 20*S* proteasome participates in an extraordinarily wide range of cellular processes (e.g. cell cycle progression, antigen presentation to the immune system, and inflammatory responses through protein processing), lactacystin (**20**) and clasto-lactacystin (omuralide, **21**), an active species inhibiting the proteasome in cells, are very important tools for the study of protein biochemistry and cell biology. In addition, these biological features make lactacystin a potential drug candidate for the treatment of arthritis, asthma, and stroke. Their high demand in biological research and the intriguing chemical structure have spurred much research on the synthesis of lactacystin and a number of total and formal syntheses have been achieved. A careful analysis of the available synthetic strategies for lactacystin (**20**) has led to identify the following common intermediates that were prepared in the total synthesis of lactacystin (**20**) (Figure 17).

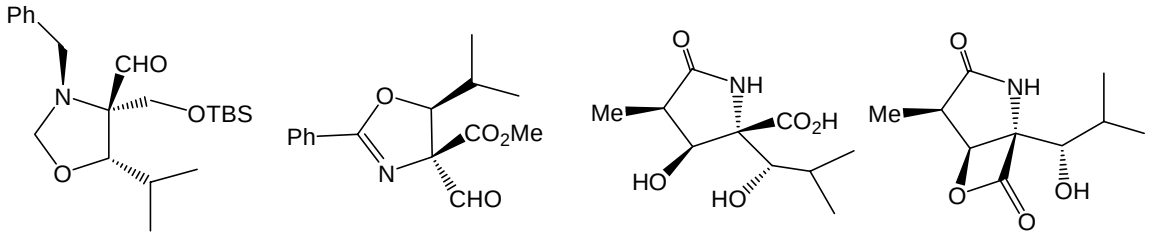
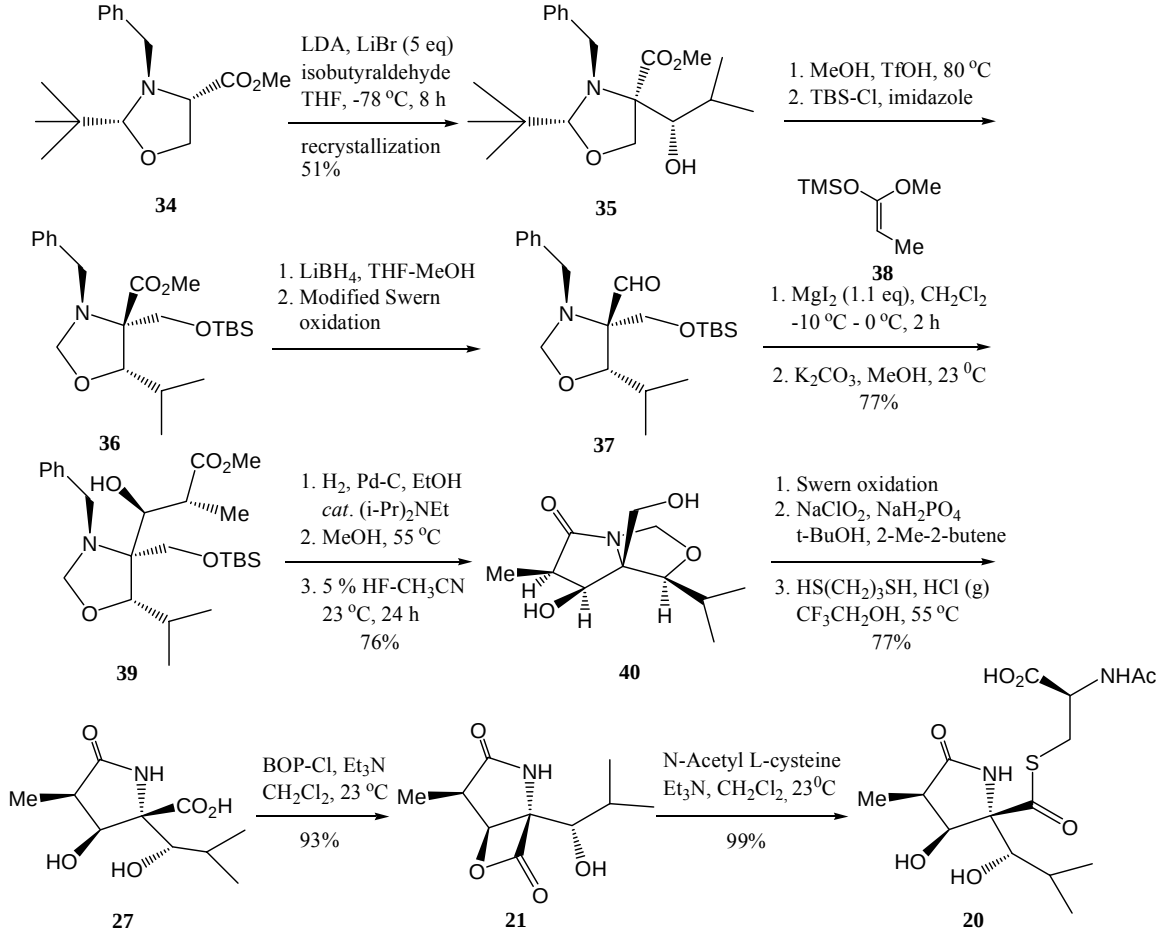


Figure 17.

Corey's synthesis:

The first total synthesis[20a] of lactacystin (**20**) and omuralide (**21**) is summarized in scheme 1. The protected aminal **34** (obtained from (S)-serine in three steps) was converted diastereoselectively to a crystalline product **35** *via* the corresponding lithium enolate by reaction with isobutyraldehyde. Acidic hydrolysis of the aminal subunit in **35**, silylation of primary –OH function and formation of an oxazoline ring by methylene connection gave **36**.

Scheme 1

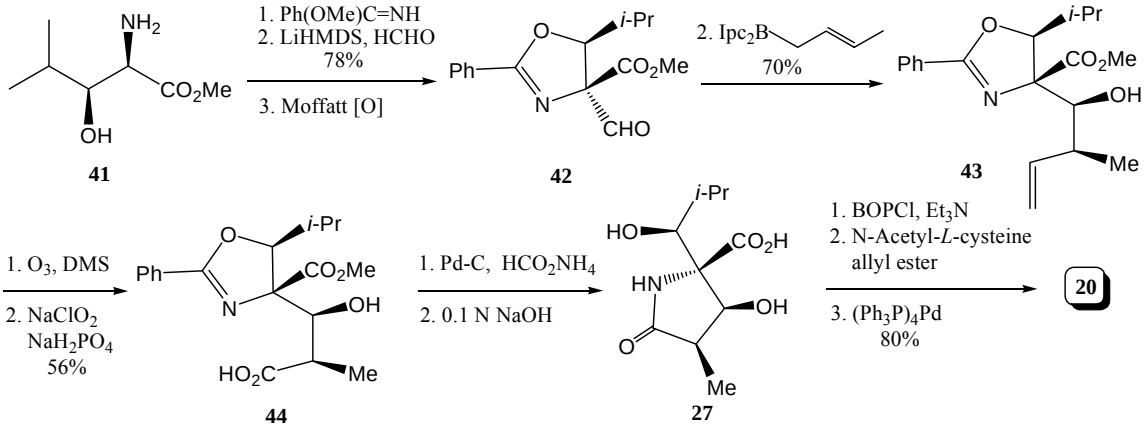


Further reduction of methoxy carbonyl group by $LiBH_4$ and modified Swern oxidation generated aldehyde **37**. The transformation of aldehyde **37** *via* Mukiyama aldol coupling with **38** in presence of MgI_2 as catalyst proceeded stereoselectively in good yield to afford the product **39**. Preferential formation of the anti- aldol product appeared due to steric effects which favor the synclinical transition state. The key aldol intermediate **39** was transformed into the dihydroxy lactam **40** by the sequence: (1) *N*-benzyl cleavage, (2) amino ester to γ-lactam ring closure and (3) desilylation. Oxidation of the primary alcohol function of **40** produced the dihydroxy acid **27** which underwent selective β-lactonisation to omuralide (**21**) when treated with bis(2-oxo-3-oxazolidenyl)phosphinic chloride (BOPCl) and Et_3N. Finally, reaction of omuralide (**21**) with *N*-acetyl-(*S*)-cysteine produced lactacystin (**20**) quantitatively.

Omura's synthesis:

Ōmura, Smith and collaborators[21b,23] used 2(R),3(S)-*β*-hydroxyleucine methyl ester (**41**) which was treated with methyl benzimidate to furnish the trans-disubstituted oxazoline which underwent aldol condensation with formaldehyde *via* the Seebach protocol to give primary alcohol exclusively (78% yield, >98% de); the stereochemical assignment was secured by ^{1}H NOE studies. Moffatt oxidation afforded aldehyde **42** which was subjected without purification to allylboration with (E)-crotyldiisopinocampheylborane to furnish desired 8-methyl homoallylic alcohol **43** thus obtained in 70% yield from primary alcohol after chromatography on silica gel (scheme 2).

Scheme 2

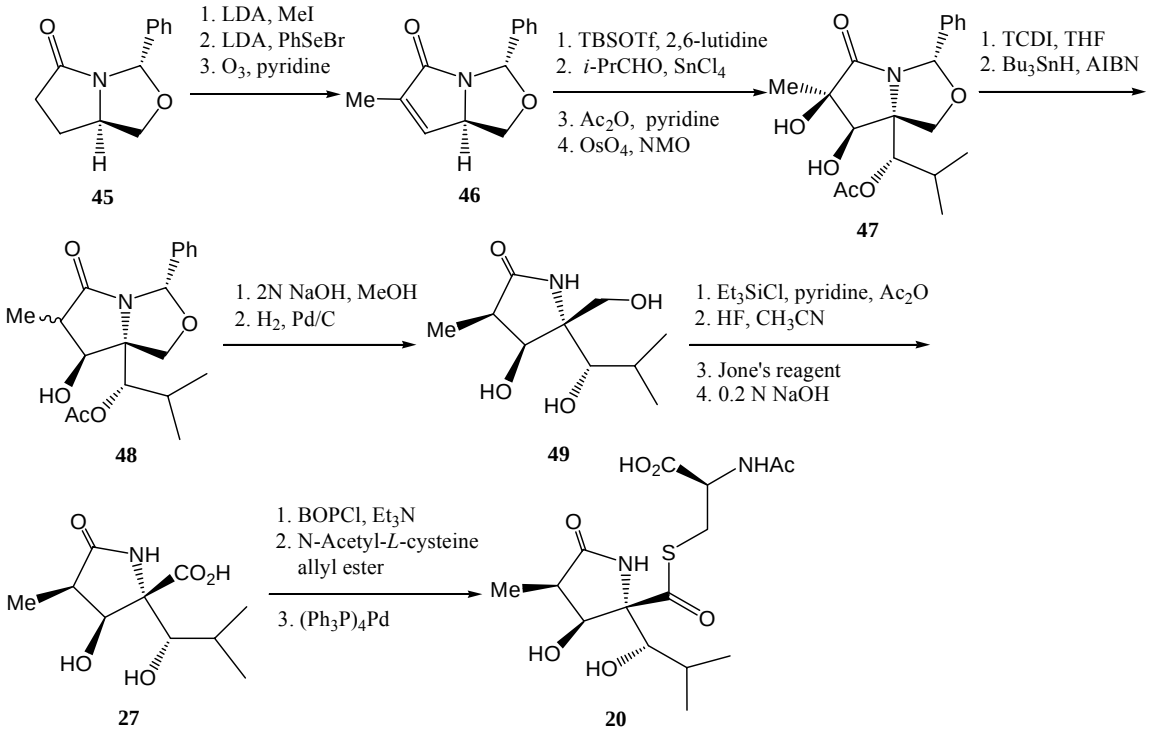


Conversion of **43** to carboxylic acid **44** entailed ozonolysis and reductive workup followed by selective oxidation. The key γ-lactam **27** could be elaborated by catalytic transfer hydrogenation of **44**. For the transformation of **27** to **20**, three-step sequence, first devised by Corey[20a] was employed to give pure (+)-lactacystin (**20**) in 80% yield as colorless needles.

Baldwin's synthesis:

Lactacystin has also been synthesized by Baldwin and coworkers[24] starting with the (R)-glutamic acid-derived intermediate **45** which has the γ-lactam ring of lactacystin already in place as shown in scheme 3. α-Methylation of **45** and introduction of α,β-unsatuation provided **46**. The key siloxypyrrole was obtained by treatement of **46** with TBSOTf which underwent aldol reaction with isobutyraldehyde, then protection of sec-OH with acetyl and osmylation with OsO_4, NMO furnished a single isomer **47**.

Scheme 3



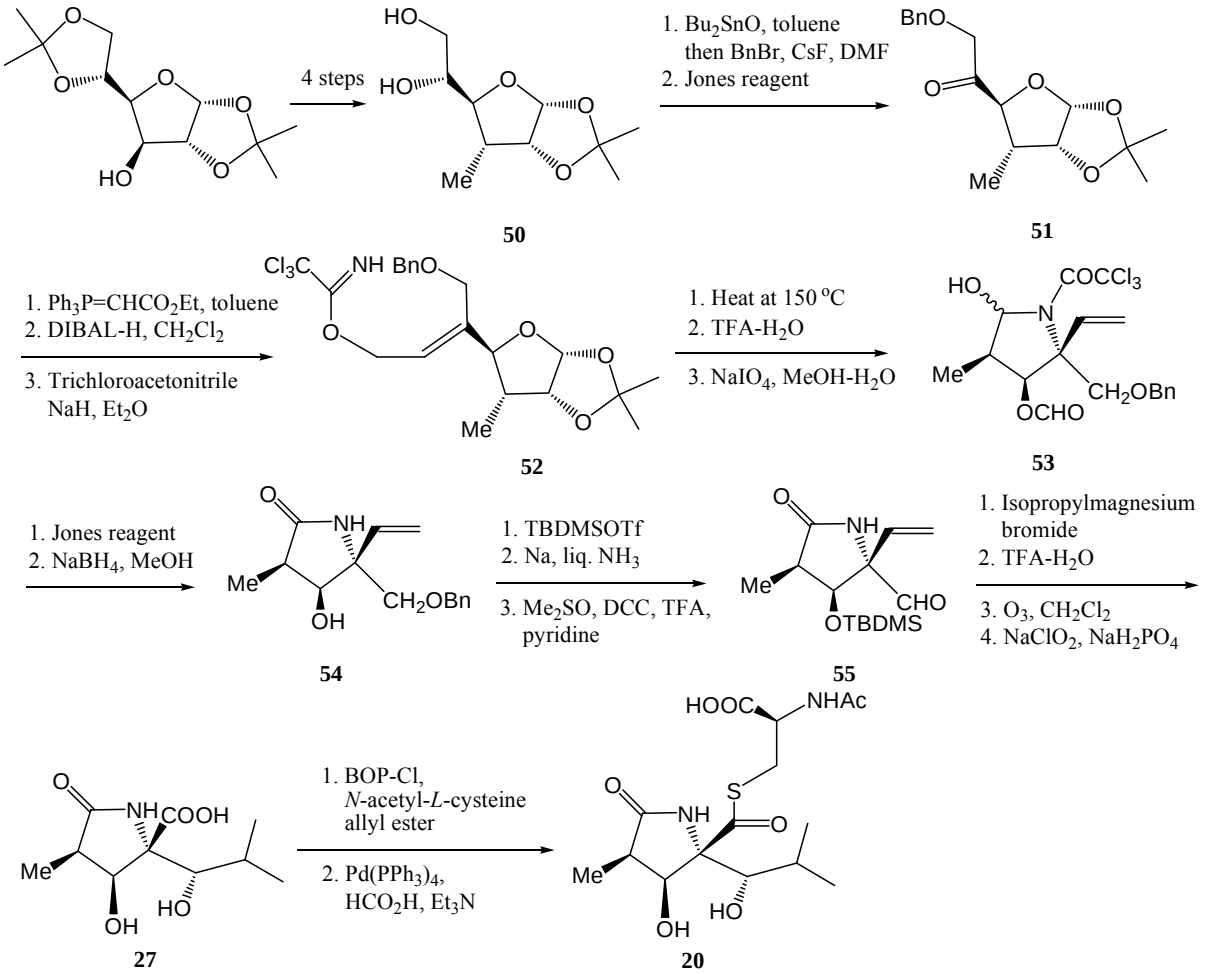
The removal of tertiary hydroxyl group *via* the cyclic thiocarbonate with Bu_3SnH in toluene at reflux resulted in an approximately equal ratio of the C6 epimers **48.** However, treatment of this mixture with 0.5 N NaOH in aqueous MeOH at 0 - 3 °C epimerised C-6 to the more stable and desired syn-isomer. This mixture was hydrogenated to give a mixture of

49 and its C3 epimer (87%). Removal of undesired epimer was achieved by chromatography. Conversion of **49** to **27** was achieved in 4 sequential steps: (1) formation of TES-ether followed by acetate formation (2) removal of TES-ether with HF in CH_3CN (3) oxidation with Jone's reagent (4) saponification of the diacetate acid. Transformation of **27** into (+)-lactacystin (**20**) was carried according to Corey's protocol.[20a]

Chida's synthesis:

Quite a different synthesis of **20** was developed by Chida *et al.* using D-glucose as starting material.[10,25] This synthesis, though lengthy, has several interesting features, as shown in scheme 4. Only four of the six carbons and one of the five stereocenters of D-glucose survive in the final product.

Scheme 4



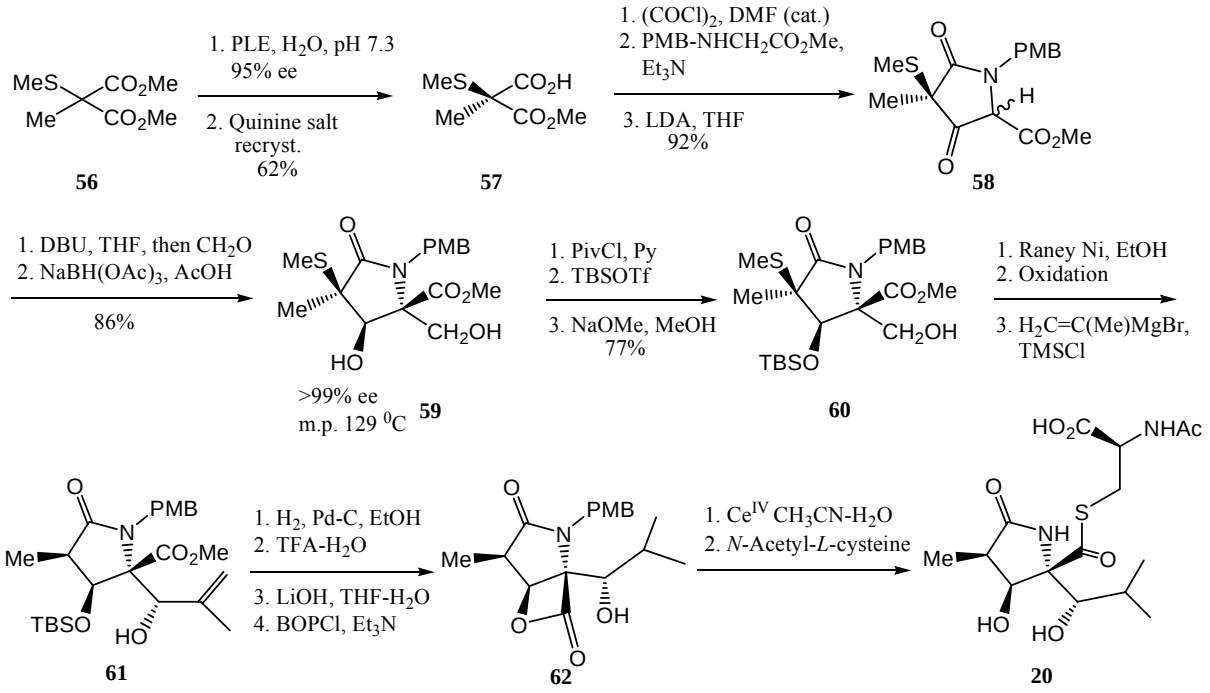
The known 3-deoxy-1,2-ispropylidene-3-C-methyl-α-D-allofuranose **50** was prepared from diacetone-D-glucose in four steps. Reaction of **50** with dibutyltin oxide, then treatment with benzyl bromide and Jones oxidation afforded **51**. The ketone **51** was subjected to Wittig reaction to give alkene, reduction of the ester function with DIBAL-H and treatment with trichloroacetonitrile gave **52**. The trichloroacetimidate **52** was heated in toluene at 150 °C to provide the inseparable mixture of rearranged product which was subjected to acid hydrolysis of the mixture followed by periodate oxidation to provide hemiaminal derivative **53**. Jones oxidation of **53** gave the corresponding lactam, whose protecting groups were cleanly removed by treatment with $NaBH_4$ to furnish the γ-lactam **54**. Silylation of the hydroxy group in **54** followed by removal of the *O*-benzyl group, and Moffatt oxidation afforded **55**. The aldehyde **55** without isolation was subjected to four steps: (1) treatment with isopropylmagnesium bromide (2) acid hydrolysis in TFA-H_2O (3) ozonolysis (4) selective oxidation of the resulting aldehyde to afford carboxylic acid **27** which was finally converted to lactacystin **20**.

Corey's asymmetric synthesis:

The first enantioselective synthesis of lactacystin developed by E. J. Corey *et al.*[18a] from achiral compounds, dimethyl malonate derivative **56** and methyl *N*-*p*-methoxybenzylglycinate, is summarized in scheme 5. Dimethyl methylmalonate derivative **56** was transformed into the chiral monoester **57** by enantioselective hydrolysis with porcine liver esterase (PLE). The crude acid (97% yield) was purified by one recrystallization of the quinine salt from aqueous ethanol to give, after acidification and extractive workup, **57** with 95% enantiomeric excess (ee) as a colorless oil. The acid chloride of **57** was coupled with methyl *N*-*p*-methoxybenzylglycinate and the resulting amide ester was subjected to Dieckmann cyclization to produce the keto lactam **58** as a 1:1 mixture of diastereomers. After highly stereoselective (9:1) α-hydroxymethylation of **58** and stereospecific reduction of the keto group, the crystalline dihydroxy lactam **59** was obtained in 86%. The oily mono tert-butyldimethylsilyl (TBS) ether **60** was prepared from diol **59** by the following sequence: 1) selective esterification at the primary hydroxyl group by pivaloyl chloride, 2) silylation of the secondary hydroxyl group, and 3) cleavage of the pivalate ester. Desulfurization of **60** with Raney nickel proceeded with excellent diastereoselectivity (10:1) to afford aldehyde in 78%

yield after column chromatography and Dess-Martin periodinane oxidation. Addition of 2-propenyl Grignard reagent to the aldehyde and trimethylchlorosilane (TMSCl), afforded the desired addition product **61** stereospecifically and in excellent yield. Isomerically pure **61** was subjected to hydrogenation and desilylation to produce ester which on saponification and subsequent treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 1.5 equiv) and triethylamine (3 equiv) gave the β-lactone **62**, the structure of which was fully confirmed by X-ray crystallographic analysis. Cleavage of the *N*-*p*-methoxybenzyl protecting group of **62** with ceric ammonium nitrate and the treatment with *N*-acetylcysteine (1 equiv) and triethylamine (1.5 equiv) afforded pure **20** in 99% yield; it was identical in all respects to an authentic sample of lactacystin.

Scheme 5

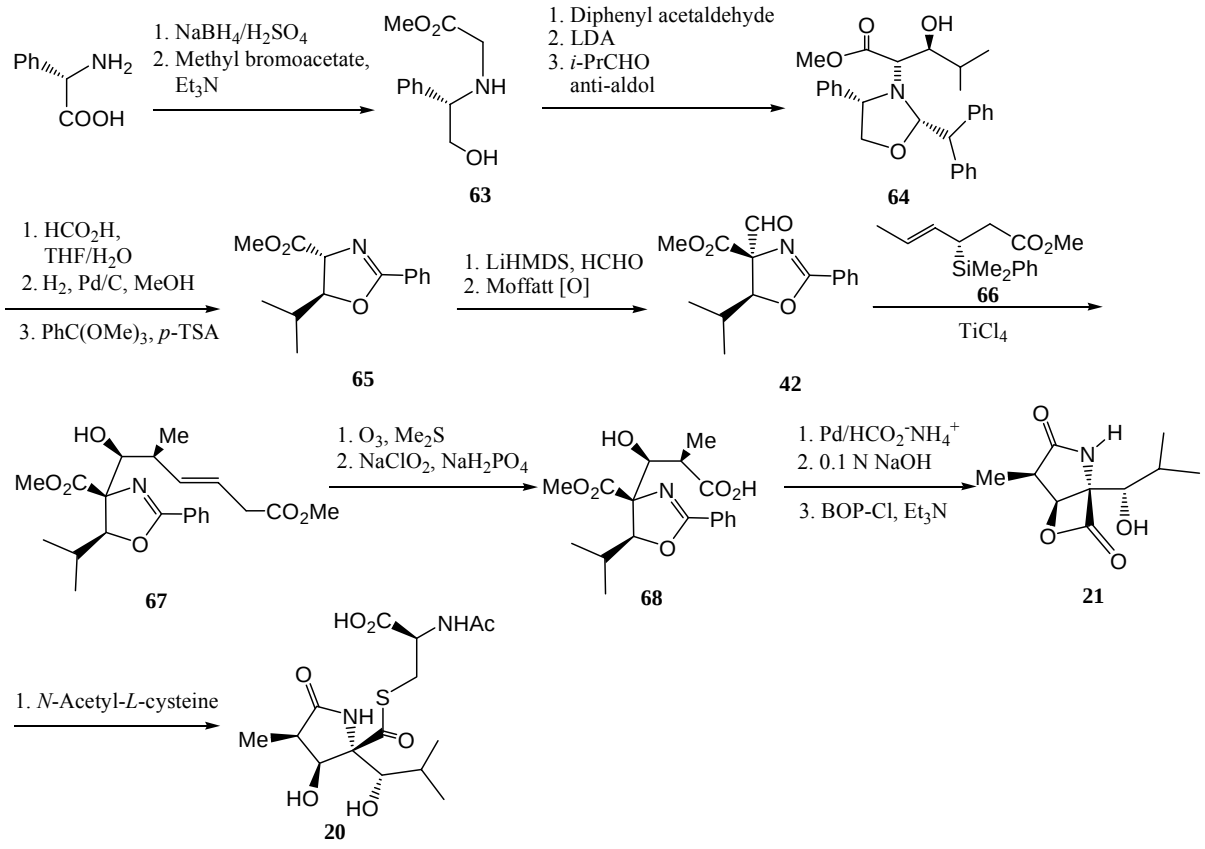


Panek's synthesis:

Panek synthesis[26,27] of lactacystin (**20**) began with chiral oxazolidine auxillary **65** derived from (*S*)-phenylglycinol as outlined in scheme 6. *N*-Alkylation of (*S*)-phenylglycinol with methyl bromoacetate afforded **63**. Condensation of **63** with diphenylacetaldehyde in presence of anhydrous magnesium sulfate at ambient temperature afforded the 2,4-disubstituted oxazolidine as a single diastereomer. The *anti*-selective aldol reaction between

the lithium enolate of the phenylglycinol derived oxazolidine with isobutyraldehyde afforded the aldol product **64** as a single diastereomer. Amino alcohol was then treated with formic acid to hydrolyze the oxazolidine, subsequent heterogeneous hydrogenation to remove the phenylglycinol derived amino protecting group afforded the (2*S*,3*S*)-3-hydroxyleucine methyl ester. Finally, treatment with trimethyl orthobenzoate in the presence of *p*-TSA afforded the *cis*-oxazolidine **65**. The preparation of the heterocyclic aldehyde **42** was accomplished according to a literature precedent established by Smith *et al*.[21b,23] Any attempt to purify this product resulted in deformylation, so this aldehyde was used without purification. The double stereodifferentiating reaction was readily accomplished with **66** in the presence of $TiCl_4$ to afford homoallylic alcohol **67** with high levels of diastereoselectivity (anti:syn >30:1). This anti-bond construction was presumably achieved through simultaneous coordination of the aldehyde oxygen atom and the nitrogen atom in the oxazolidine ring.

Scheme 6



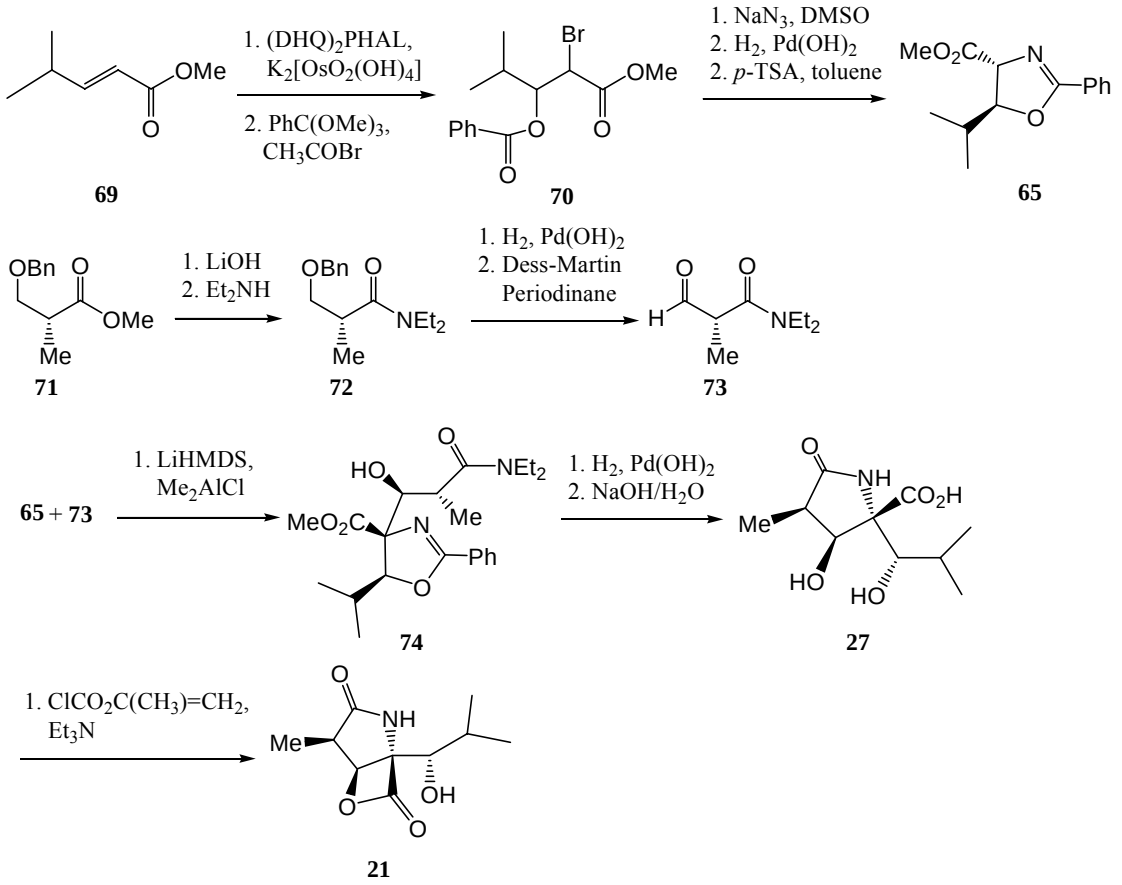
Oxidative cleavage of (E)-olefin **67** under standard ozonolysis conditions and subsequent oxidation with sodium chlorite furnished carboxylic acid **68**. The completion of

synthesis of (+)-lactacystin was initiated by catalytic transfer hydrogenation of the oxazolidine moiety with Pd-black to give the γ-lactam methyl ester after cyclization. Saponification of the methyl ester under mild conditions afforded the dihydroxy acid, which was directly converted into β-lactone **21** by treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). Treatment of **21** with *N*-acetyl-L-cysteine/Et_3N furnished synthetic (+)-lactacystin (**20**) identical in all respects to the natural product (^1H and ^{13}C NMR, IR spectroscopies, HRMS, optical rotation, and TLC).

Millennium's Approach:

An interesting approach to **21** has recently been reported by researchers at Millennium,[28] utilizing a double stereodifferentiating aldol bond construction between the known oxazoline **65** and a β-amido aldehyde (Scheme 7). Oxazoline **65** was prepared from methyl-4-methyl-(*E*)-pentenoate (**69**). Sharpless catalytic asymmetric dihydroxylation of olefin **69** with AD-mix-β afforded the chiral diol (70% *ee*) which was subsequently treated with trimethylorthobenzoate to form an intermediate cyclic orthoester which in turn, was reacted with acetyl bromide to form bromohydrin **70**. The required α-amino moiety was then introduced *via* nucleophilic displacement with sodium azide to afford the azido benzoate followed by hydrogenation with Pearlman's catalyst to yield the (2*R*,3*R*)-hydroxyleucine derivative which underwent acid-catalyzed cyclization in refluxing toluene to afford oxazoline **65**. The required β-amido aldehyde **73**, needed for aldol coupling to oxazoline **65**, was prepared in a straightforward four-step sequence from the known ester **71**. The critical aldol coupling of **65** and **73** was accomplished by treatment of the lithium enolate of **65** with dimethylaluminum chloride (Me_2AlCl) followed by addition of **73** to provide aldolate **74** with high levels of diastereoselection favoring the (6*S*)-isomer. Nucleophilic addition of the enolate from the less hindered *re*-face predicts a (6*S*)-stereochemistry. Unmasking of the oxazoline under hydrogenolysis conditions and cyclization of the resultant aminoamide gave the γ-lactam which was subjected to saponification conditions to afford the dihydroxy acid **27**. β-Lactonization of **27** with isopropenyl chloroformate afforded **21**.

Scheme 7



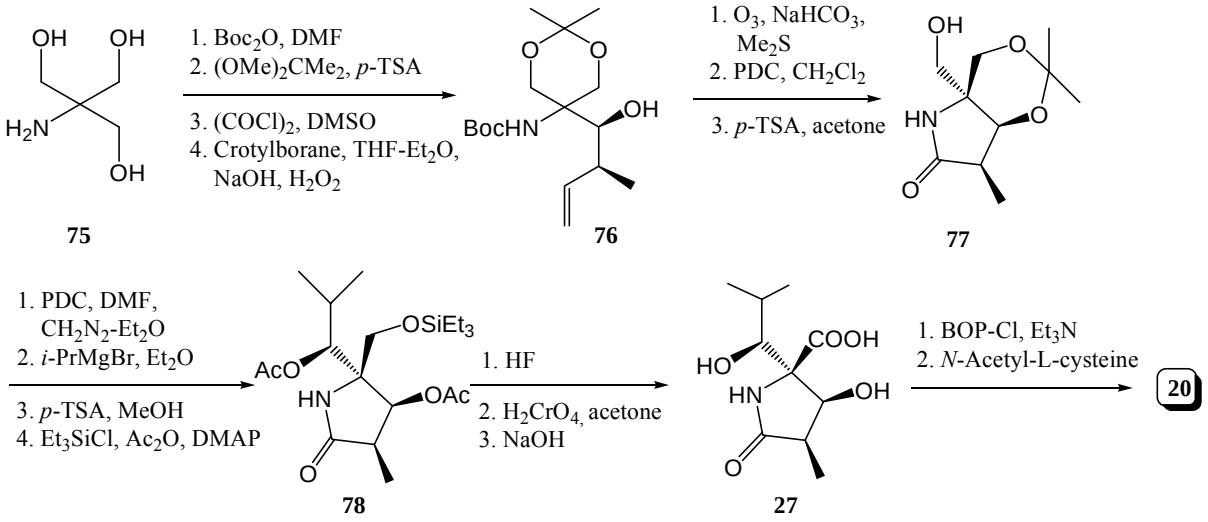
Hatakeyama's synthesis:

A facile chromatography-free route to Kang's intermediate[29] for the synthesis of (+)-lactacystin (**20**) has been developed starting with Brown's asymmetric crotylation of *tert*-butyl 5-formyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate, easily available from 2-amino-2-(hydroxymethyl)propane-1,3-diol (**75**) by Hatakeyama and co-workers.[30]

2-Amino-2-(hydroxymethyl)propane-1,3-diol (Tris) (**75**) was successively subjected to *tert*-butoxycarbonylation and acetalization in one pot to give the intermediate alcohol in 87% yield. Swern oxidation of alcohol afforded aldehyde in 98% yield, asymmetric crotylation of which was then accomplished using crotylborane at -78 °C in THF-Et_2O, and after oxidative workup of the reaction mixture with alkaline hydrogen peroxide, removal of isopinocampheol by vacuum distillation followed by recrystallization of the residue from Et_2O-hexane gave **76** with 99% ee in 68% yield. Ozonolysis and oxidation with PDC gave lactam which on treatment with *p*-TsOH.H_2O in acetone at room temperature led to cleavage of the *tert*-

butoxycarbonyl group and concomitant migration of the acetonide group to produce **77** quantitatively. The spectral data of **77** were identical with those reported by Kang *et al.*[29] It is noteworthy that the above-mentioned synthesis of **77** from Tris did not require any chromatographic purification. According to the procedure developed by Kang *et al.* lactam **77** was successfully converted to Baldwin's intermediate[24] **78** in 69% overall yield although the initial Jones oxidation was replaced by PDC oxidation to attain good reproducibility. Thus, PDC oxidation of **77** followed by esterification of the resulting carboxylic acid with diazomethane gave the corresponding ester in 71% yield. Upon treatment of ester with isopropylmagnesium bromide at room temperature in Et_2O, alcohol was obtained stereoselectively through a concomitant addition-reduction process which on acidic methanolysis gave triol quantitatively, the specific rotation and spectral data of which were identical with those reported by Baldwin *et al.*[24] Following Baldwin's method, triol thus prepared was transformed into intermediate **78**, which finally converted to carboxylic acid **27** in good overall yield. Finally, according to the established procedure, (-)-omuralide (**21**) and (+)-lactacystin (**20**) were successfully synthesized (Scheme 8).

Scheme 8



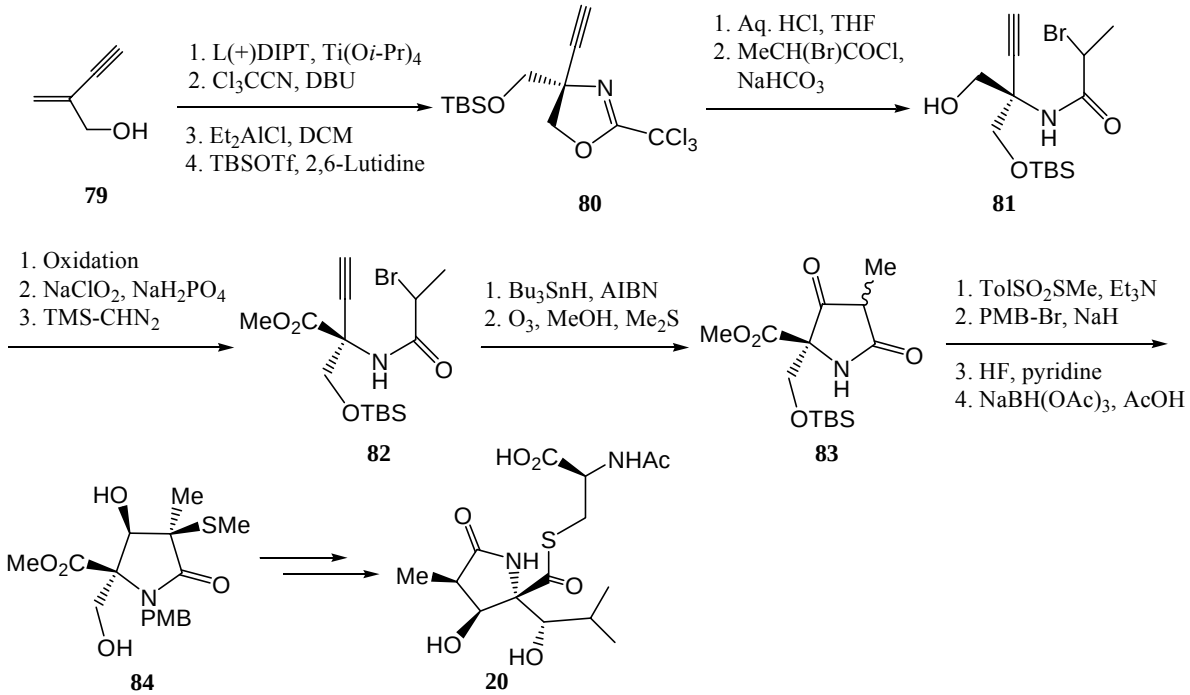
75 **76** **77** **78** **27**

Pattenden's synthesis:

Formal synthesis of (+)-lactacystin based on a novel radical cyclisation of an α-ethynyl substituted serine was developed by Pattenden and co-workers[31] (scheme 9). Thus, a Sharpless epoxidation of the 2-ethynylpropenol **79** using (+)-DIPT, Ti(O*i*Pr)$_4$ in DCM at −10 °C first gave the chiral epoxide (66% and 90% ee), which was next converted into the

oxazoline by cyclisation of the corresponding trichloromethylacetamidate intermediate in the presence of Et_2AlCl to give alcohol. Treatment of the alcohol with TBSOTf (DCM, 0 – 25 °C) gave the crystalline TBS–ether **80** (92%) whose stereochemistry was confirmed by X-ray crystallography. When a solution of the 2-trichloromethyl substituted oxazoline **80** in THF was treated with 1 M aqueous HCl, the intermediate amino alcohol was formed, which was then immediately converted into a mixture of methyl epimers of the amide **81** on acylation with 2-bromopropionoylchloride (76% over two steps). The hydroxymethyl unit in **81** was next converted into the corresponding methyl ester **82** in three steps (i.e. Dess–Martin periodinane, then $NaClO_2$, NaH_2PO_4 and finally Me_3SiCHN_2) and in 60% overall yield. When a solution of the bromoamide **82** in toluene under reflux was treated with a solution of Bu_3SnH (1:1 equiv.) and AIBN (catalytic) in toluene over 30 min and the resulting mixture was heated under reflux for 2 h, work-up gave the corresponding pyrrolidinone in 70% yield. The pyrrolidinone results from a facile 5-*exo*-dig cyclisation of the ethynyl substituted bromoamide **82**. Ozonisation of the alkene in MeOH at −78 °C followed by a reductive work-up using Me_2S (−78 °C to r. t.) next gave the corresponding 4-ketopyrrolidinone **83**.

Scheme 9



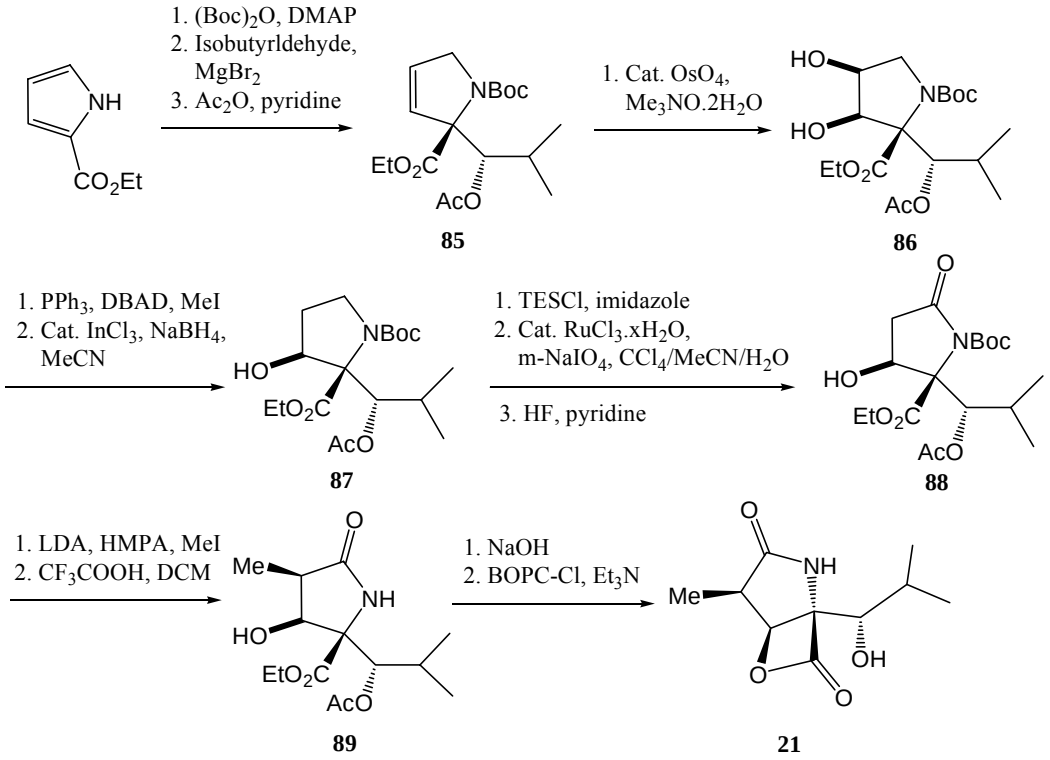
The 4-ketopyrrolidinone **83** reacted with methylsulfanyl tolylsulfonate in the presence of Et_3N at r. t. which was stereoselective and led to the 3-methylsulfanyl derivative with the

α-methyl stereochemistry at C-3. The protection of the nitrogen centre as its PMB derivative followed by deprotection of the silyl ether group led to the known substituted pyrrolidinone and finally, reduction of the 4-keto group using sodium triacetoxyborohydride at r. t., gave the pyrrolidinone derivative **84** which is a key intermediate in Corey's total synthesis of (+)-lactacystin.

Donohoe's synthesis:

A short alternative approach to (+)-lactacystin β-lactone (**21**) through a diastereoselective reductive aldol reaction of Boc-protected pyrrole carboxylate was developed by Donohoe *et al*.[32] The reaction of N-protected pyrrole carboxylate with isobutyraldehyde in the presence of $MgBr_2$ led to an anti selectivity greater than 20:1 (Scheme 10) and the alcohol obtained was acetylated to afford **85**. A key step in this synthesis was the diastereoselective dihydroxylation of **85**. Treatment of **85** with catalytic OsO_4 and $Me_3NO{\cdot}2H_2O$ (3 equiv) in DCM afforded diol **86** as a single diastereoisomer in an excellent yield of 95%.

Scheme 10



The C4-OH of diol **86** was selectively converted into iodide by selective Mitsunobu reaction. The resulting iodide was deiodinated through a recently reported method for producing (catalytic) indium hydride *in situ* to **87**. Next, the C3-OH functionality of **87** was protected with a triethylsilyl group (TES), the product was oxidized with catalytic RuO_4 to form a lactam, and the TES group was then removed to furnish **88**. The second key step then followed which involved the introduction of the methyl group at C4 with LDA (2 equi.) and methyl iodide and cleavage of the tert-butoxycarbonyl group with TFA in CH_2Cl_2 to afford the lactam **89** in quantitative yield. Basic hydrolysis of the ethyl ester gave acid, which was used without purification to give **21** (scheme 10). The spectroscopic data of compound **21** was identical to that reported in the literature.

Recently, Fenical and associates[33] at the Scripps Institute of Oceanography reported on the cultivation and phylogenetic characterization of a new group of actinomycete bacteria, widely distributed in oceanic sediments. The term *Salinospora* was advanced to correlate the strains. Following preliminary screening, a highly active metabolite, termed salinosporamide A (**90**, Figure 18), was identified and isolated from these sediments. Salinosporamide A displays remarkable *in vitro* cytotoxicity (IC_{50} of approximately 10 nM), and its activity appears to be directed to the inhibition of the 20*S* proteasome. Thus, salinosporamide A (**90**) is approximately 35 times more potent than is omuralide (**21**), which is directed to the same molecular target. There was a single report on total synthesis of salinosporamide A (i.e., that of E. J. Corey and associates[34]).

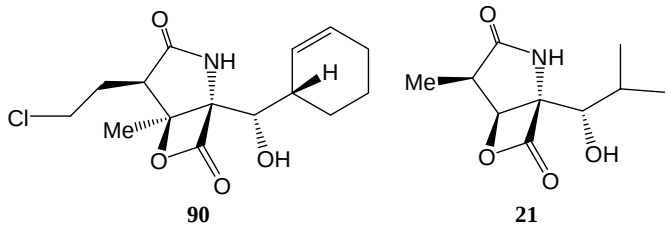


Figure 18.

Lactacystin exemplifies dramatically the ability of a small molecule (molecular weight 376) to shut down the functioning of a very large poly-macromolecular machine and to exert this inhibition with great selectivity on the 20*S* proteasome in the presence of countless other proteins as potential targets. Most of the structural features of **20** are critical to its activity.

First, the C(4) carboxylic function and the hydroxyl at C(6) must be *cis,* as expected for the essentiality of β-1actone (**21**) function for proteasome inactivation. The configuration of the hydroxyl at C(9) and the presence of the isopropyl substituent at C(9) are also very important for activity. For example, when the C(9) substituent is CH_2OH (**21k**) the rate of inactivation of the 20 S proteasome is reduced at least 300 fold. Removal of the methyl substituent at C(7) strongly reduces bioactivity relative to lactacystin (**20**). On the other hand, replacement of the methyl substituent at C(7) by ethyl (**21e**), n-propyl (**21f**), or isopropyl (**21i**) led to a 2 to 3 fold *increase* in activity. 7,7-Dimethyl analogue (**21d**) of β-lactone (**21**) had nearly the same activity (0.75). Taking into account the interesting changes in activity due to structural variations, we thought of making various analogues of lactacystin by replacing ring nitrogen with either oxygen (**91**), sulfur (**92**) or CH_2 (**93**) and the related *β*-lactone (**94** - **96**) given below and to study their biological activities (Figure 19).

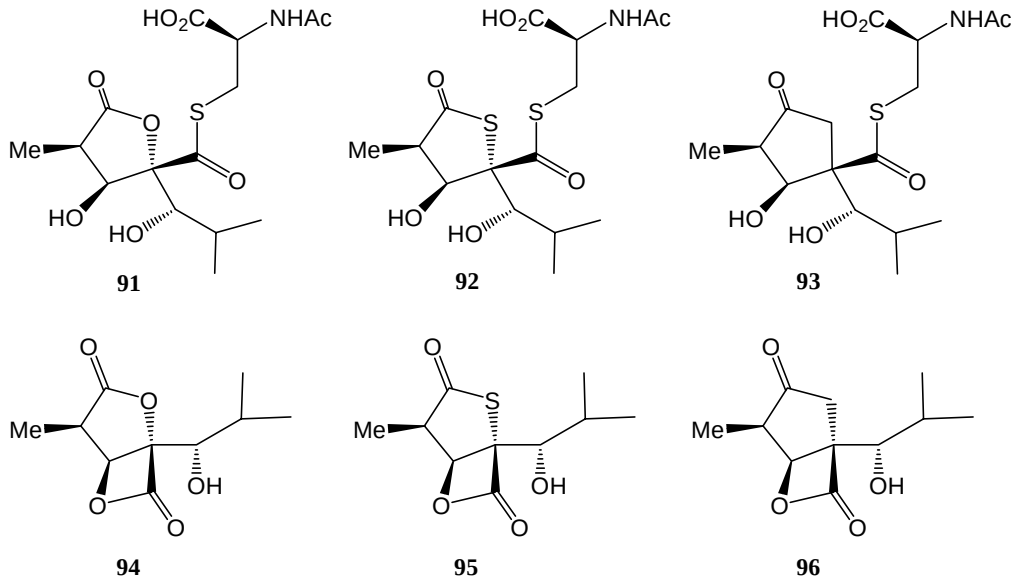


Figure 19. Various Analogues of Lactacystin and the related β-Lactone Designed

Present Work

Present Work

Lactacystin (**1**) is a streptomyces metabolite that inhibits cell cycle progression and induces neurite outgrowth in a murine neuroblastoma cell line. Lactacystin also inhibits proliferation of other cell types, suggesting that its target is not exclusive to Neuro-2a cells. Tritium-labeled lactacystin was used to identify the 20*S* proteasome as its specific cellular target. Three distinct peptidase activities of this enzyme complex (trypsin-like, chymotrypsin-like, and peptidylglutidyl hydrolyzing activities) were inhibited by lactacystin, the first two irreversibly and all at different rates. None of five other proteases were inhibited, and the ability of lactacystin analogues to inhibit cell cycle progression and induce neurite outgrowth co-related with their ability to inhibit the proteasome. Lactacystin appears to modify covalently the highly conserved amino-terminal threonine of the mammalian proteasome subunit X (also called MB1), a close homolog of the LMP7 proteasome subunit encoded by the major histocompatibility complex. This threonine residue may therefore have a catalytic role and subunit X/MB1 may be a core component of an amino-terminal threonine protease activity of the proteasome.[19] These and other data suggested that an electrophilic carbonyl at C-4 was essential for the biological activity of lactacystin and thus its target might be the enzyme containing a catalytic nucleophile such as a protease or a lipase. The C-4 carbonyls of both the thioester and the lactacystin β-lactone (**2**) are reactive electrophiles, whereas the carboxylate of the dihydroxy acid is essentially inert to nucleophilic attack.

Incubation of crude extracts from Neuro-2a cells or bovine brain with [^{3}H] lactacystin (or [^{3}H] β-lactone), followed by SDS-polyacrylamide gel electrophore and fluorography, revealed the presence of an intensely labeled protein band of ~24 kD and a weakly labeled band at ~32 kD. The latter is appeared only with prolonged exposure times, but the 24 kD band was visibly radiolabeled even after 5-min treatment with 1 μM [^{3}H] β-lactone or [^{3}H] lactacystin. Leading by [^{3}H] lactacystin (or [^{3}H] β-lactone) was completely prevented by the simultaneous addition of an excess of unlabeled lactacystin, β-lactone or other biologically active analogues, but not by the addtion of dihydroxy acid (**3**) or other biologically inactive analogues. These results suggest that the interaction is saturable, specific and relevant to the cellular effects of lactacystin.

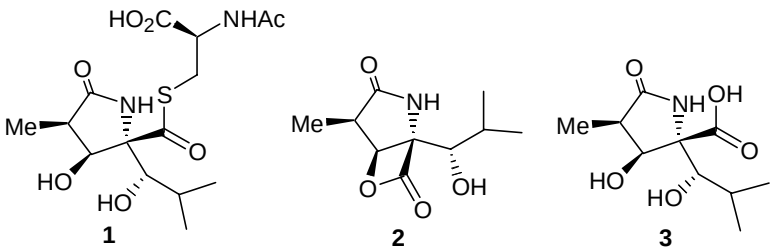


Figure 1. *Lactacystin (**1**), the related β-lactone (**2**) and dihydroxy acid (**3**)*

Structure-activity relationships (SAR):

The structure-activity relationship by Fenteany and co-workers[19,35] demonstrated the importance of the requisite functionality and stereochemical relationships in the natural product lactacystin (**1**) and the related β-lactone, omuralide (**2**). Further detailed ananlysis have been pursued by the Corey's laboratories,[18,22] and independently by the Soucy group at Millennnium[28] showed that SAR requirements were rather stringent. A pictorial summary of these results is shown in Figure 2. The one area of the molecule that supported chemical modification was the C-7 alkyl group. Removal of the methyl group at C-7 strongly reduces bioactivity relative to omuralide (**2**) while replacement of the methyl substituent at C-7 with short aliphatic chains enhanced the potency of the lactone inhibitor. There is an absolute requirement for the β-lactone bridge on the γ-lactam nucleus and the stereochemical fidelity as dictated by the natural product. In addition, *N*-methylation of the γ-lactam abolishes activity. The hydroxyl at C-9, the presence of the isopropyl substituent at C-9 and their configuration were also very important for bioactivity. In general, most structural modifications to the natural product led to a dramatic loss of activity.

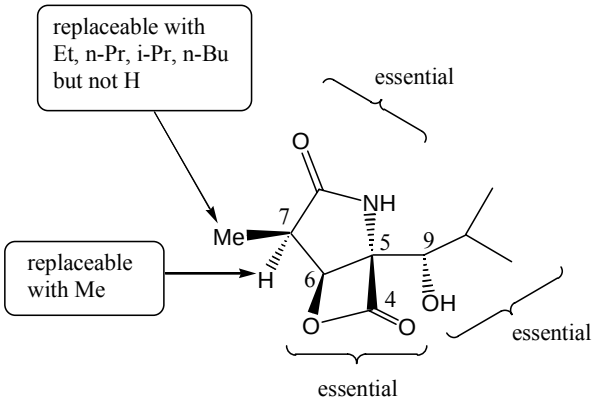


Figure 2. *Summary of SAR studies*

From the Figure 2, which is related to structure-activity relationship, it was apparent that no attempts have been made to explore the biological effect if ring nitrogen is replaced with any other atom either oxygen (**4**), sulfur (**5**) or CH_2 (**6**). Realising the importance of lactacystin (**1**) and number of structural changes that have been made, it was relevant to study the oxa-lactacystin (**4**) and the related β-lactone derivative (**7**) without disturbing the main 'pharmacological core' particularly from structure-activity point of view. Based on the success of synthesis of **4** coupled with biological activity, other synthesis of thia (**5**), carba-lactacystin (**6**) and their related β-lactones (**8** and **9** respectively) could be undertaken at a later stage of the program.

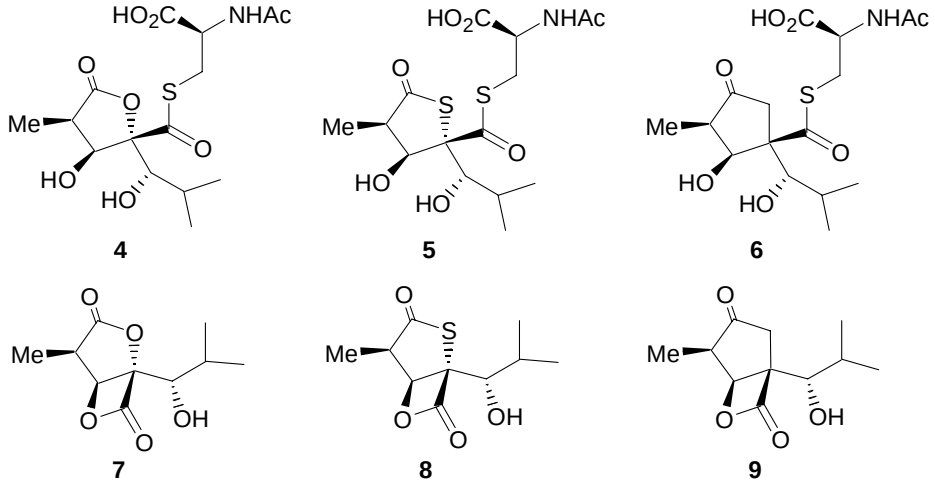
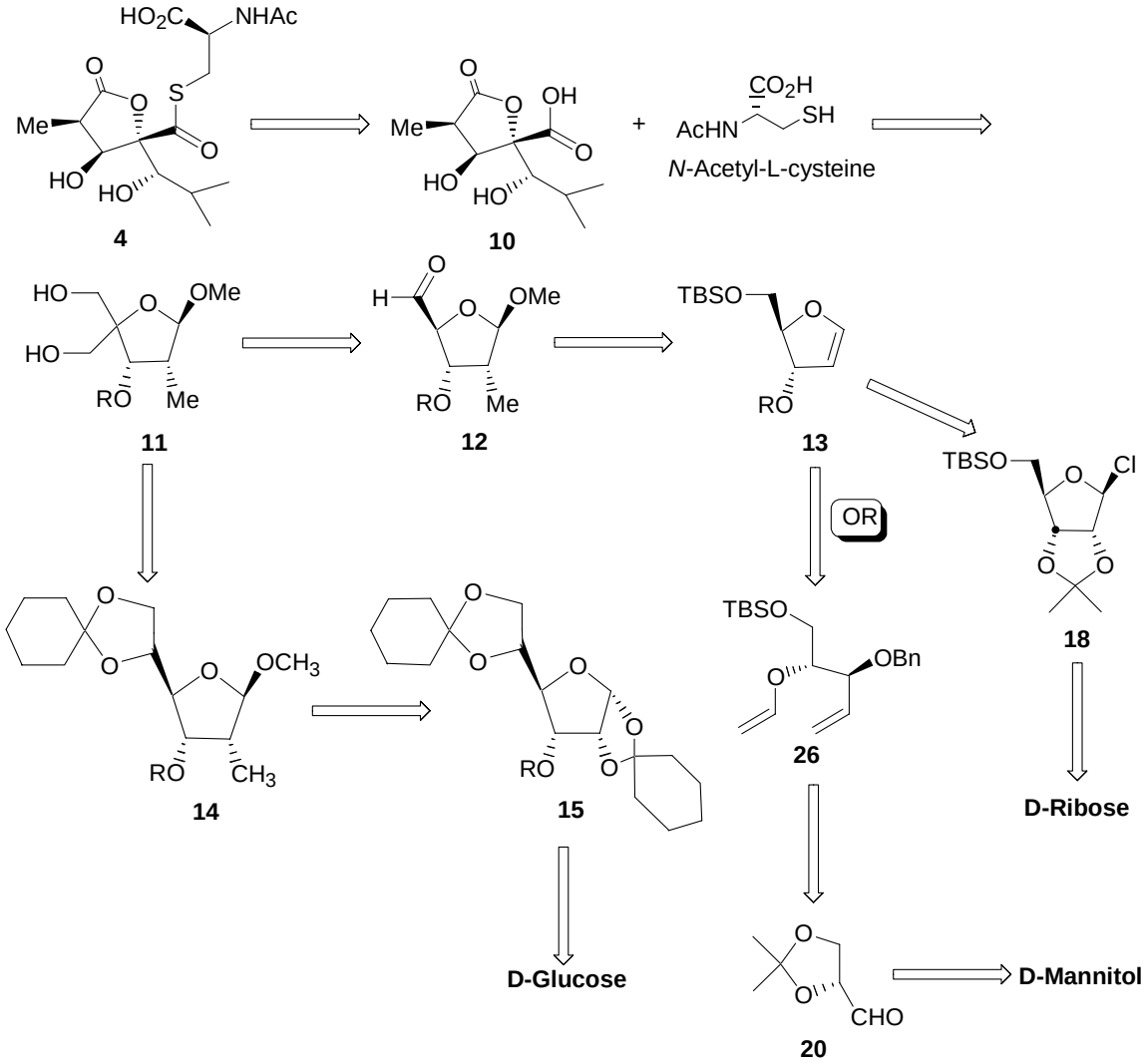


Figure 3. *Various analogues of lactacystin and the related β-lactone designed*

The structural feature of oxa-lactacystin (**4**) is the presence of highly functionalised dihydrofuran-2-one with four contiguous chiral centers including a quaternary carbon atom. Keeping this in mind, the retrosynthetic analysis for our endeavor was planned using various combinations of transformations as outlined in scheme 1. Oxa-lactacystin (**4**) could be obtained from dihydroxy acid **10** by forming its thiol ester with *N*-acetyl-L-cysteine. Construction of tetra-substituted carbon possessing γ-lactone in dihydroxy acid **10** was envisioned to arise from the diol **11** by effecting the required modifications at 1,3-diol moiety. The diol **11** could be either obtained from 5,6-*O*-cyclohexylidene protected compound **14** through the reaction sequence: a) deprotection of cyclohexylidene group, b) oxidative cleavage of diol, c) followed by aldol and cross-Cannizzaro reaction. The intermediate **14** was to be obtained from 1,2:5,6-di-*O*-cyclohexylidene derivative **15** which could be prepared from

D-glucose. Otherwise the diol **11** could be obtained from the aldehyde **12** by performing aldol and cross-Cannizzaro reaction. The aldehyde **12** was to be derived from the glycal derivative **13** through a reaction sequence in which stereospecific cyclopropanation was the key step. Finally, the glycal derivative **13** was to be prepared in either of two ways: a) from furanosyl chloride **18** prepared from D-ribose or b) from the diene **26** obtained from (R)-1,2-*O*-isopropylideneglyceraldehyde (**20**). The aldehyde **20** could be prepared from D-mannitol.

Scheme 1

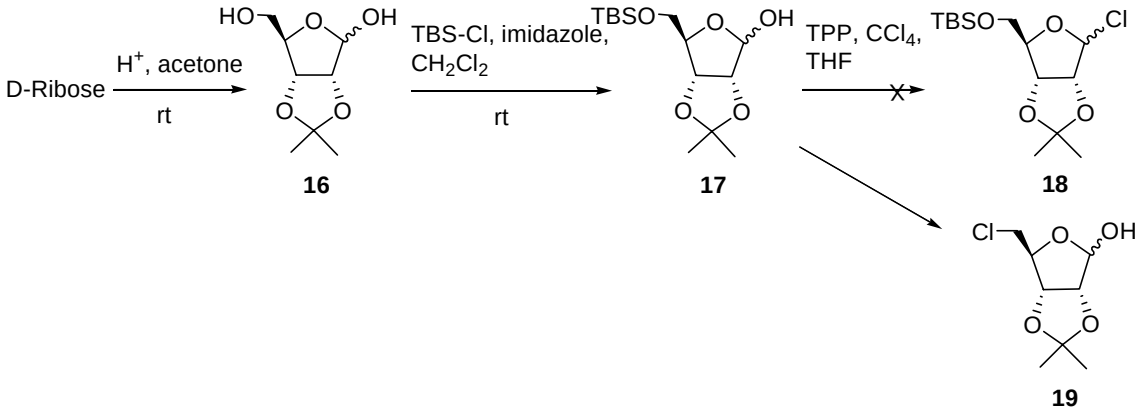


*Retrosynthetic strategy for oxa-lactacystin (**4**)*

The synthesis was initiated with the preparation of the 2,3-*O*-isopropylidene derivative **16** with acid catalysed reaction in excess of dry acetone at room temperature from D-ribose (scheme 2). The ^{1}H NMR spectrum of compound **16** indicated characteristic singlets due to

isopropylidene group at 1.31 and 1.47 ppm. The C-5 hydroxyl group was silylated with imidazole, TBS-Cl in DMF at room temperature to give the TBS-derivative **17**. The ^{1}H and ^{13}C NMR spectra of compound **17** were in agreement with the data reported in the literature.[36] Compound **17** was subjected to chlorination using triphenylphosphine and CCl_4 in refluxing THF, however the desired chloro derivative **18** was not obtained. The NMR studies revealed the structure compatible with 5-chloro-2,3-*O*-isopropylidene-D-*ribo*-furanose (**19**). The ^{1}H NMR spectrum of compound **19** showed absence of characteristic signals due to TBS group at δ 0.13 (s, 6H), 0.92 (s, 9H) and presence of H-1 at 5.47 ppm which position was unexpected for **19**. In the IR spectrum, absorption due to OH group was observed at 3438 cm^{-1}. The mass spectrum (m/z 209, $[M+1]^{+}$) and elemental analysis supported the structure of compound **19**.

Scheme 2

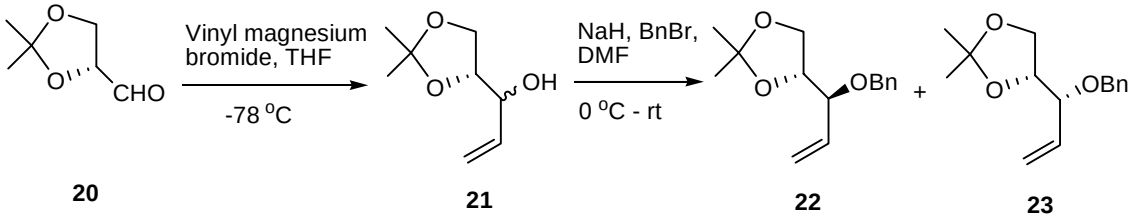


Keeping the failure (to obtain **18**) in mind, it was decided to change the strategy towards the glycal derivative **13**. Two strategies were designed based on asymmetric and chiral pool approaches.

Taking into consideration the required stereocentres in **13**, (R)-1,2-*O*-isopropylideneglyceraldehyde (**20**) was selected as the starting material whose preparation from 1,2:5,6-di-*O*-isopropylidene-D-mannitol was well documented.[37] Reaction of (R)-1,2-*O*-isopropylideneglyceraldehyde (**20**) with vinyl magnesium bromide (prepared from vinyl bromide[38] and magnesium) afforded a diastereomeric mixture of the alcohol **21**[39] which unfortunately was inseparable by silica gel chromatography. The alcohol **21** was then treated with sodium hydride and benzyl bromide to afford the benzyl ethers **22** and **23**, which were separated by silica gel chromatography (scheme 3). In the ^{1}H NMR spectrum of compound **22**, benzylic protons were present at δ 4.39 (d, J = 12.1 Hz, 1H) and 4.64 (d, J = 12.1 Hz, 1H),

while in compound **23**, these protons were present at δ 4.45 (d, *J* = 12.3 Hz, 1H) and 4.68 (d, *J* = 12.3 Hz, 1H). The ^{13}C NMR spectrum, mass spectrum and elemental analysis of compounds **22** and **23** were in agreement with the structures.[40]

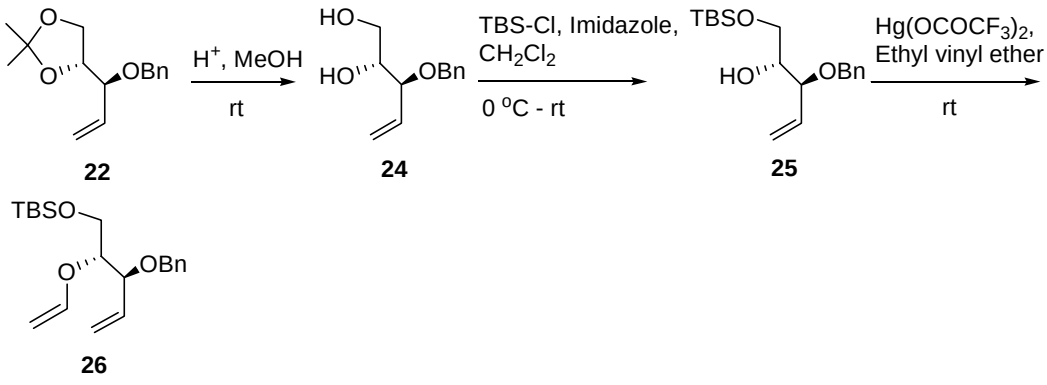
Scheme 3



20 **21** **22** **23**

In order to assign the required stereochemistry of the key intermediate **13** unambiguously, benzyl ether **22** was deprotected in the presence of acid in MeOH to give **24**. The structure of **24** was proposed by its ^{1}H NMR spectrum, in which peaks due to the isopropylidene group were absent. The ^{13}C NMR, mass spectrum (m/z 209, $[M+1]^{+}$) and elemental analysis supported the structure of compound **24**. The diol **24** was treated with imidazole, *t*-butyldimethylsilyl chloride in CH_2Cl_2 to procure the silyl ether **25**.[41] The ^{1}H and ^{13}C NMR spectra of compound **25** were in agreement with the structure. Compound **25** was treated with freshly distilled ethyl vinyl ether and 0.1 equivalent of $Hg(OCOCF_3)_2$ at room temperature to afford the vinyl ether derivative **26**[42] (scheme 4). In its ^{1}H NMR spectrum, the characteristic signals of *O*-vinyl group were distinctly seen as a set of multiplet at δ 3.91 – 4.75 (m, 1H) and doublet at δ 4.32 (*J* = 14.0 Hz, 1H) for two terminal olefinic protons and a multiplet at 6.30 – 6.45 ppm for *O*-vinylic proton. The diene **26** was to be converted into the substituted dihydrofuran **27** by ring closing metathesis.

Scheme 4



22 **24** **25** **26**

A brief overview on olefin metathesis (RCM):

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes. With the advent of efficient catalysts, this reaction has emerged as a powerful tool for the formation of C-C bonds. The number of applications of this reaction has dramatically increased in the past few years. Of particular significance, this type of metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the only other product from the reaction is, in most cases, a volatile olefin such as ethylene. The broad applicability of olefin metathesis has attracted attention from both academic and industrial scientists.

Olefin metathesis can be utilized in three closely related type of reactions: (A) ring opening metathesis polymerization (ROMP), (B) ring closing metathesis (RCM), and (C) acyclic cross metathesis which when carried out on diolefins results in polymers (ADMET). It is now generally accepted that the mechanism of both cyclic and acyclic olefin metatheses proceeds through a series of metallacyclobutanes and carbene complexes (Figure 4).

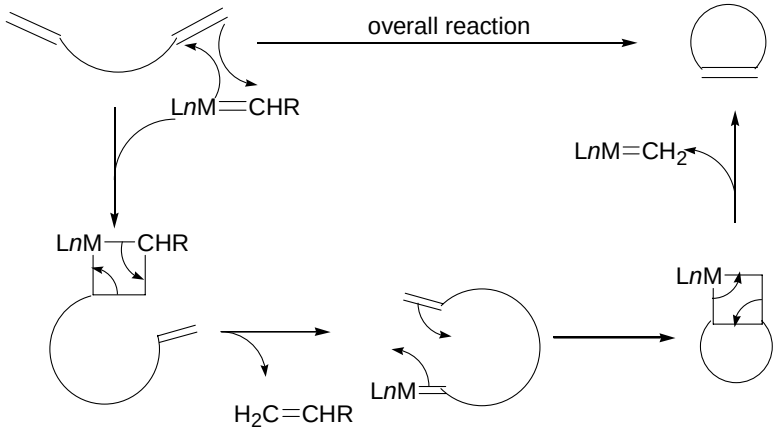


Figure 4.

In recent years ring-closing olefin metathesis has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. This intensive study is primarily due to the development of well-defined metathesis catalysts, which are tolerant to many functional groups as well as reactive towards a diverse range of substrates.

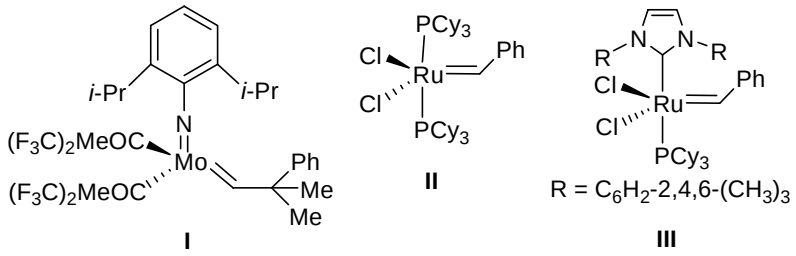
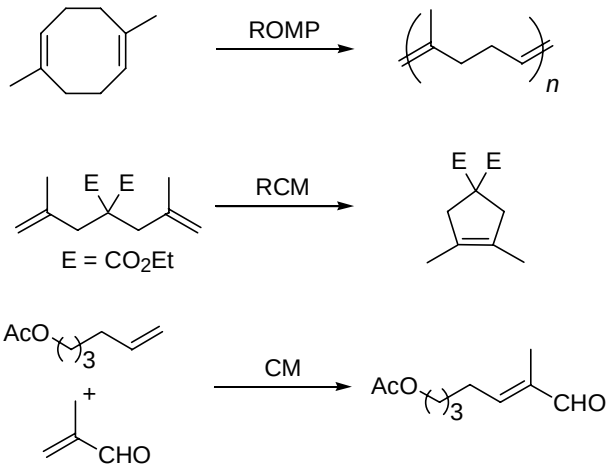


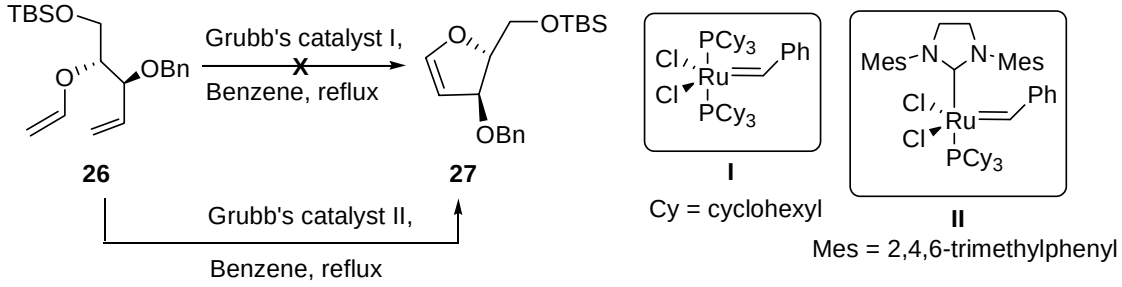
Figure 5.

The alkylidene – metal complexes, which are widely used for the RCM, include the alkoxy-imido molybdenum complex ***I*** *and the benzylidene ruthenium complex* ***II****. The molybdenum complex* ***I*** *exhibits the higher reactivity of the two towards a broad range of substrates with many steric or electronic variations; however, it also suffers from extreme sensitivity to air and moisture as well as decomposition upon storage. To increase the utility of the ruthenium family of the complexes by increasing their activity, Grubbs et al. recently prepared ruthenium based complexes coordinated with 1,3- dimesitylimidazol-2-ylidene ligands* ***III****. These complexes exhibited a high ring-closing metathesis activity similar to that of the molybdenum complex* ***I****, yet have also retained the remarkable air and water stability characteristic of the parent benzylidene ruthenium complex* ***II****. The superior activity of* ***III*** *includes high rates of ROMP for low-strain substrates and even the ROMP of sterically hindered substrates containing trisubstituted olefins such as 1,5-dimethyl-1,5-cyclooctadiene. The catalyst* ***III*** *was able to perform the RCM of sterically demanding dienes to form tri- and tetrasubstituted olefins. In addition, catalyst* ***III*** *produced the first example of cross-metathesis to yield a trisubstituted olefin, as well as CM and RCM reactions where one partner is directly functionalized with a deactivating group, such as acrylate or siloxane. Although the exact mechanism of this complex* ***III*** *activity remains unclear, recent results indicate that this may be due to slower phosphine dissociation. Other studies suggest that the bulky mesityl groups in this catalyst may contribute to high activity, in part because of interactions with the alkylidene moiety.*



After the synthesis of the key intermediate **26**, the next focus was the ring closing metathesis. Ring closing metathesis using Grubb's 1st generation catalyst (**I**), in refluxing benzene for 24 h, was found to be unsuccessful. As indicated earlier, the presence of an allylic alkoxy substituent has a negative influence on the ring-closing reaction.[43] Inspite of this, ring closing metathesis of the diene **26** was achieved using Grubb's 2nd generation catalyst (5 mol%) (**II**) in refluxing benzene for 8 h to afford the required dihydrofuran derivative (**27**).[44] The structure of **27** was confirmed by its ^{1}H NMR spectrum in which the characteristic signals due to double bond were observed at 5.14 ppm as a triplet and 6.56 ppm as a double- doublet. The structure was further confirmed by the ^{13}C NMR spectrum in which olefinic carbons were positioned at 100.5 and 150.3 ppm. The mass spectrum (m/z 320, $[M]^{+}$) and elemental analysis further supported the structure of compound **27** (scheme 5).

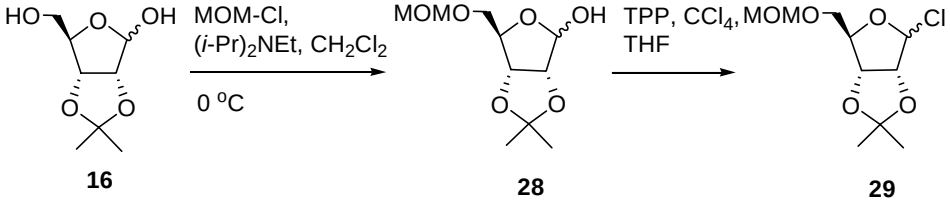
Scheme 5



Although RCM based approach to the key intermediate **27** was successful, we still proposed to explore the second chiral pool method toward the intermediate **27**. If this strategy

was successful, it could be cost effective and perhaps scalable. The C-5 hydroxyl group of 2,3-*O*-isopropylidene derivative **16** was converted into its MOM derivative **28** by treatment with MOM-Cl and *N*,*N*′-di-isopropylethylamine in CH_2Cl_2. The ^1H and ^{13}C NMR spectra of compound **28** were in accordance with the literature values.[45] Compound **28** was subjected to chlorination reaction, but resulted in very low yield of chloro compounds **29**[45] (scheme 6). In the ^1H NMR spectrum of compound **29**, the anomeric proton resonated at 6.15 ppm. IR spectrum showed absence of absorption due to hydroxyl group.

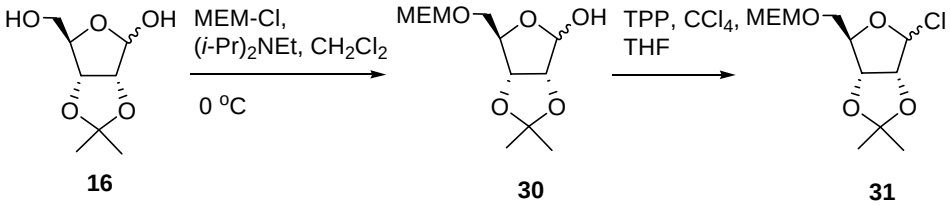
Scheme 6



16 **28** **29**

Instead of MOM, we installed MEM-group at C-5 hydroxyl group (**30**)[46] followed by chlorination with TPP, CCl_4 in THF. However, with MEM substitution, the outcome was not too different. Herein, low yield of the furanosyl chloride derivative (**31**) due to conversion to furanose (**30**) was observed. Therefore, what these experiments suggested that we needed to explore other chemical manipulations first and then perhaps think of introducing double bond at C(1)-C(2) segment (scheme 7).

Scheme 7



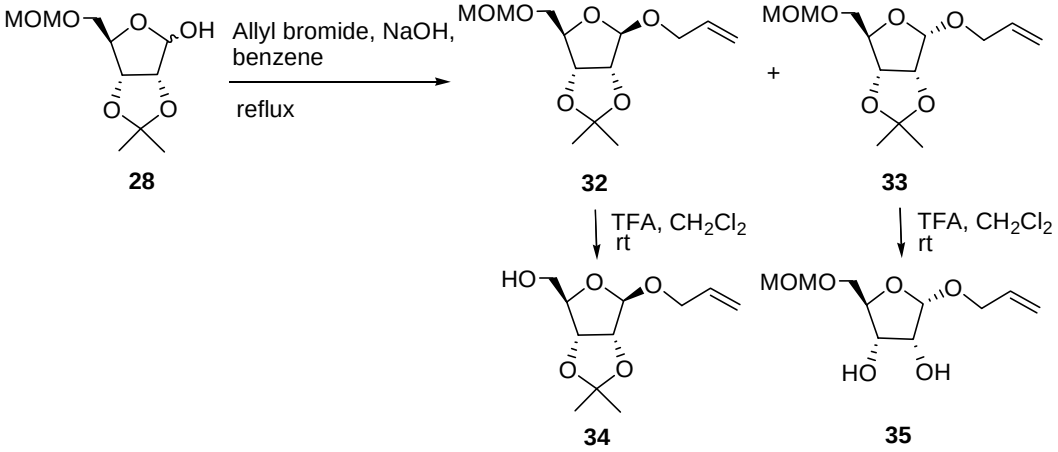
16 **30** **31**

Thus, the aldol followed by cross-Cannizzaro reaction was undertaken for which the anomeric hydroxyl was protected with an allyl group by treating compound **28** with allyl bromide, NaOH in refluxing benzene[47] to furnish the β and α-anomers **32** and **33** (8:2). They were separated by silica gel chromatography and then independently analysed spectroscopically. The structure of the compound **32** was confirmed by its ^1H NMR spectrum, in which signal due to the anomeric proton was observed as a singlet at 5.11 ppm indicating the formation of β-anomer. The rest of the protons resonated at their expected values. In ^{13}C

NMR spectrum of compound **32**, the anomeric carbon of the β-anomer was located at 107.1 ppm. The ^{1}H NMR spectrum of compound **33** exhibited the anomeric proton at δ 5.04 (d, J = 4.0 Hz, 1H) confirming the structure as an α-anomer. In ^{13}C NMR spectrum of compound **33**, the anomeric carbon of was localised at 100.9 ppm.

The deprotection of MOM group present in **32** with trifluoroacetic acid in CH_2Cl_2[48] at room temperature afforded compound **34**. In the ^{1}H NMR spectrum of **34**, the characteristic singlets due to MOM group were absent. Thus, compound **34** was resulted from the cleavage of MOM ether as expected. On the other hand, reaction of compound **33** with TFA-CH_2Cl_2 gave a polar derivative **35** whose ^{1}H NMR spectrum showed the presence of characteristic singlets due to MOM group at 3.32, 4.60 ppm but those due to the isopropylidene group were conspicuously absent, thus confirming the assigned structure of the diol **35** which was the unexpected product (scheme 8). The differential behaviour of **32** and **33** towards trifluoroacetic acid was quite interesting. In case of β-glycoside (**34**), the isopropylidene group was intact and MOM group was cleaved selectively while in the α-glycoside (**35**), the isopropylidene group was cleaved, MOM group remained intact. We believed that this was an interesting observation, which needed more attention.

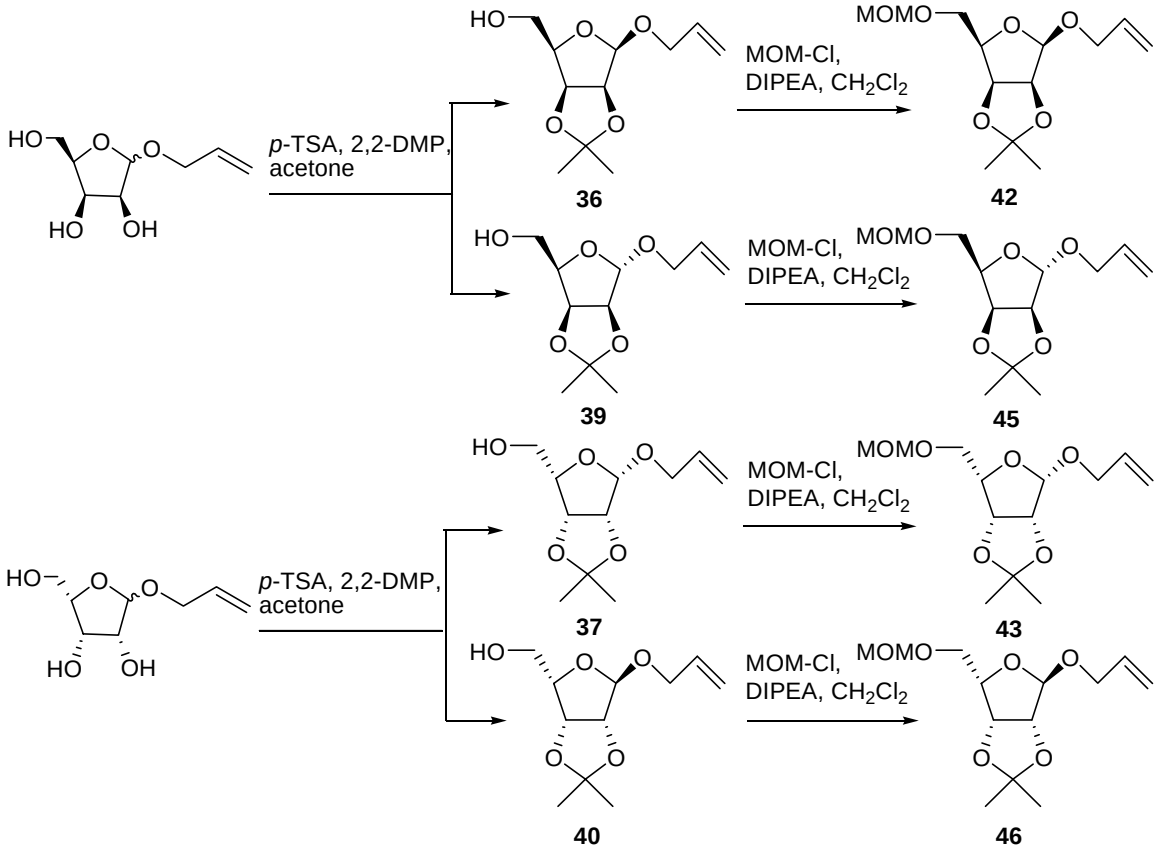
Scheme 8



The *syn*-orientation between the isopropylidene and anomeric oxygen as incorporated in **33** plays a crucial role due to the anchimeric assistance. This was apparent in case of **33** where TFA selectively cleaved the isopropylidene group at the cost of MOM. The *syn*-orientation between MOM and anomeric oxygen as present in **32** resulted in the cleavage of MOM at the expense of the isopropylidene group. In order to generalize these observations,

we produced several substrates containing all the three critical functional groups namely alkyl glycosides, isopropylidene and MOM ether. The alkyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl furanoside derivatives **42** to **47** were prepared by a general method[36,45] involving the treatment of alkyl 2,3-*O*-isopropylidene furanoside (**36** – **41**) with methoxymethyl chloride in the presence of *N,N'*-diisopropylethylamine in CH_2Cl_2 (scheme 9).

Scheme 9

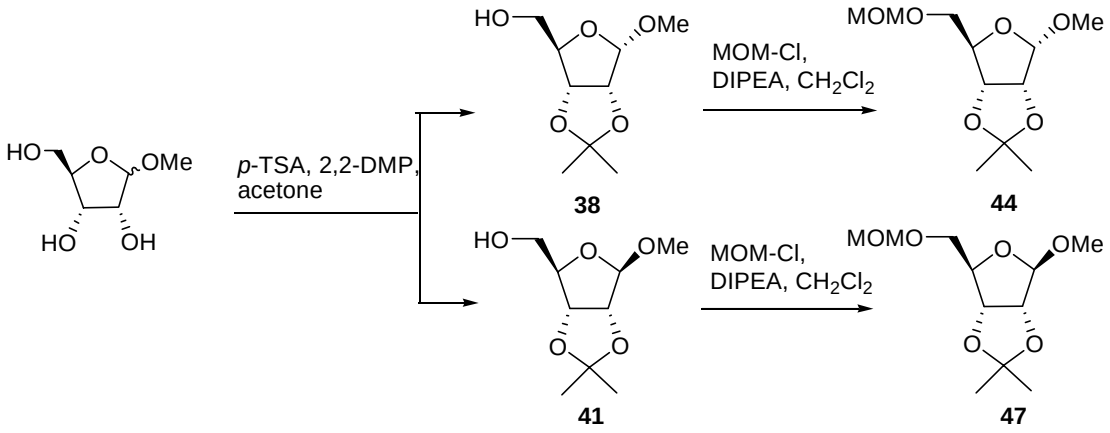


D-Lyxose was first converted into the allyl furanoside derivatives using allyl alcohol and HCl. Subsequent treatment with 2,2-dimethoxypropane and *p*-TSA in acetone gave allyl-2,3-*O*-isopropylidene-D-lyxofuranoside derivatives, separated by silica gel chromatography to produce anomerically pure β-glycoside **36** and α-glycoside **39**. In the ^{1}H NMR spectrum of compound **36**, the anomeric proton was observed as a doublet at δ 4.74 (J = 2.5 Hz) indicating the formation of β-glycoside while the ^{1}H NMR spectrum of compound **39** showed singlet at δ 5.09 for anomeric proton confirming the presence of α-glycoside. The ^{13}C NMR spectrum, mass spectrum and elemental analysis were in agreement with the structures of **36** and **39**.

Individually, treatment of compounds **36** and **39** with methoxymethyl chloride in the presence of DIPEA in CH_2Cl_2 furnished MOM protected derivatives **42** and **45** respectively. In the ^1H NMR spectrum of compounds **42** and **45**, the characteristic signals due to MOM group were present. Similarly, L-lyxose was converted to anomeric mixture of allyl furanoside followed by the 2,3-*O*-isopropylidination to procure allyl-2,3-*O*-isopropylidene-L-lyxofuranoside derivatives **37** and **40** separated by column chromatography. In the ^1H NMR and ^{13}C NMR spectra, the characteristic signals due to allyl and isopropylidene group were observed for compounds **37** and **40**. Independently, compounds **37** and **40** were further converted to their MOM derivatives **43** and **46** respectively.

As earlier, transformation of D-ribose to methyl-2,3-*O*-isopropylidene-D-ribofuranoside derivatives **38** and **41** was furnished followed by silica gel column chromatography and formation of methyl-2,3-*O*-isopropylidene-5-*O*-methoxymethyl-D-ribofuranoside derivatives was effected to obtain compounds **44** and **47** (scheme 10).

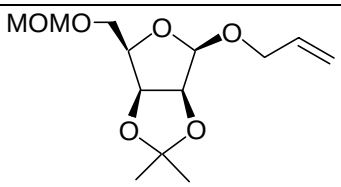
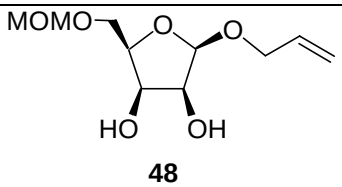
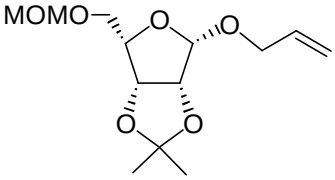
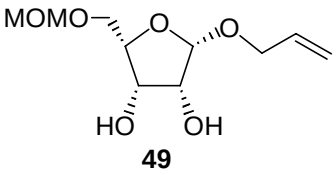
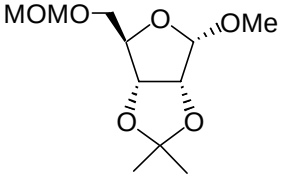
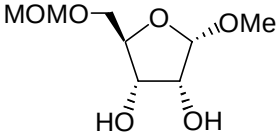
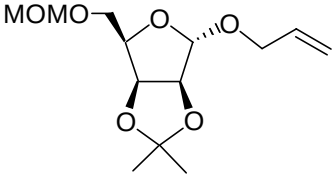
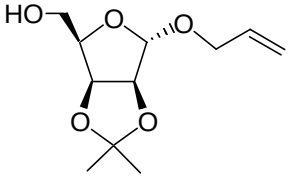
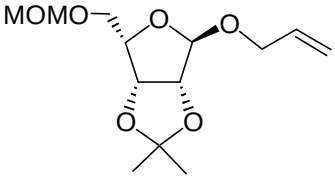
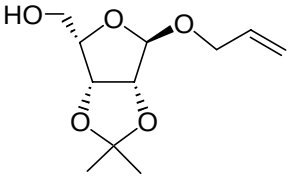
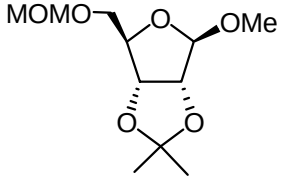
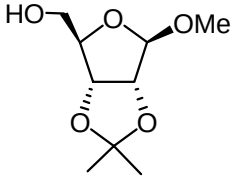
Scheme 10



All these substrates were subjected to the hydrolysis reaction using 4 equivalents of TFA in CH_2Cl_2 and monitored by TLC. The results are given in table 1. As expected in all the cases, the deprotection was extremely selective. Compound **42** was exposed to 4 equivalents of trifluoroacetic acid in CH_2Cl_2 at ambient temperature. After 2 h, compound **48** with 5-*O*-methoxymethyl group was isolated (yield 86%, entry 1). The assigned structure of **48** was based on ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. Similarly, treatment of allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-β-L-lyxofuranoside **(43)** with trifluoroacetic acid in CH_2Cl_2 provided the 2,3-dihydroxy derivative **49** in 2 h with 88 % yield

(entry 2). Compound **50** was obtained in 99% (entry 3) yield after 3 h from methyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-α-D-ribofuranoside (**44**).

Table 1.

Entry	Substrate	Time (h)	Product	Yield (%)
1	 **42**	2	 **48**	86
2	 **43**	2	 **49**	88
3	 **44**	3	 **50**	90
4	 **45**	8	 **39**	77
5	 **46**	7	 **40**	79
6	 **47**(ref. 49)	9	 **41**(ref. 50)	92

However, with substrate **45**, which contained both the 2,3-*O*-isopropylidene and the 5-*O*-methoxymethyl groups in opposite orientation to the α-*O*-glycoside, the sluggish hydrolysis of methoxymethyl group was noticed and the product **39** with acetonide group intact was isolated after 8 h (entry 4). In the absence of *O*-glycosidic assistance (compounds **46** and **47**), the cleavage of methoxymethyl group with weak anchimeric assistance from isopropylidene group was observed in 7 h and 9 h to afford compounds **40** and **41** respectively. In the ^{1}H NMR spectrum of compounds **40** and **41**, the characteristic signals due to MOM group were absent. The ^{13}C NMR, mass spectroscopy and elemental analysis were in support with the structures of **40** and **41**.

From these observations, it is pertinent to mention that the anchimeric assistance from the glycosidic oxygen to the isopropylidene cleavage was far more pronounced than the anchimeric assistance of the isopropylidene group over the methoxymethyl hydrolysis.

After generalizing interesting observation of anchimeric assistance in the selective cleavage of isopropylidene group, we focused our attention to original synthetic route. The alcohol **34** was oxidized with IBX in dimethylsulfoxide at room temperature in 3 h to get the aldehyde **51**.[51] In the ^{1}H NMR spectrum, the characteristic signal due to aldehydic proton was observed downfield at 9.55 ppm and the aldehydic carbon resonated at 200.2 ppm in the ^{13}C NMR spectrum. In the IR spectrum, absorption due to C=O was observed at 1730 cm^{-1}.

A brief overview on aldol followed by cross Cannizzaro reaction :

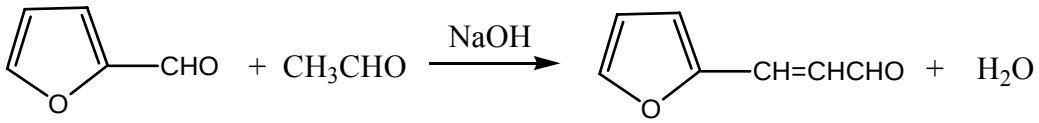
The aldol condensation[52] takes its name from aldol, a name introduced by Wurtz who first prepared this β-hydroxy aldehyde from acetaldehyde in 1872. The aldol condensation includes reactions producing β-hydroxy aldehydes (β-aldols) or β-hydroxy ketones (β –ketols) by self condensation or mixed condensation of aldehydes and ketones, as well as reactions leading to α,β-unsaturated aldehydes or α,β-unsaturated ketones formed by dehydration of intermediate β-aldols or β-ketols.

$$2CH_3CHO \xrightarrow{\text{Aq. HCl}} CH_3CHOHCH_2CHO$$

Formation of mesityl oxide by self-condensation of acetone, a reaction discovered by Kane in 1838.

$$2CH_3COCH_3 \xrightarrow{H_2SO_4} (CH_3)_2C{=}CHCOCH_3 + H_2O$$

The Claisen-Schmidt condensation is an aldol condensation discovered by Schmidt in 1880 (condensation of furfural with acetaldehyde or acetone). It is taken to be the condensation of an aromatic aldehyde with an aliphatic aldehyde or ketone to yield α,β-unsaturated aldehyde or ketone usually in the presence of basic catalyst.



However, the term has been extended to include many types of alddehyde and ketone condensations (e.g. chalcone formation) employing either acidic or basic catalyst. Schmidt was the first to employ a basic catalyst for the aldol condeansation.

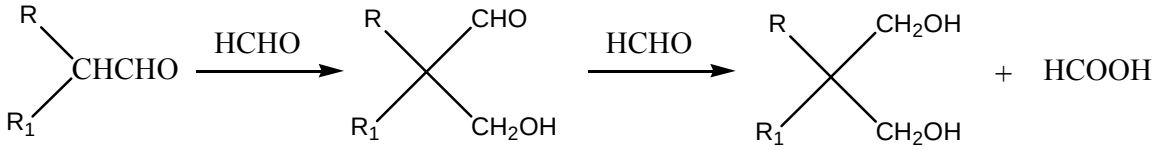
$$C_6H_5CHO + CH_3COC_6H_5 \xrightarrow{H^{\oplus} \text{ or } OH^{\ominus}} C_6H_5CH{=}CHCOC_6H_5 + H_2O$$

The term aldol condensation has sometimes been applied to many "aldol-type" condensations involving reactions like Claisen, Knoevenagel, Doebner, Perkin, Stobbe and Reformatsky etc. and they produce a hydroxyl compound or its dehydration product.

***Stereochemistry**: Available data suggest a general lack of stereoselective control in the C-C bond forming process. Slightly more vigorous condition or longer reaction times result in the complete conversion to the most stable epimer. The transition state for the condensation has relatively long developing C-C bond. The most stable and highly favored product is the trans isomer of α,β-unsaturated compound derived from ketols and aldols. Cis isomers may sometimes be isomerised to trans isomers with acidic or basic catalyst.*

Aldol condensations are further divided into: a) self condensation of aldehydes b) mixed condensations of aldehydes c) self condensartion of ketones and d) mixed condensation of ketones.

***Mixed condensation of aldehydes**: The condensation of formaldehyde with aromatic or aliphatic aldehyde (Tollens condensation) with no α-hydrogen atom in the presence of NaOH or other strong base can readily produce methylol aldehydes. n-Alkanals have been condensed with formaldehyde to yield 1,3-diols.*



Unless the reaction conditions are sufficiently mild, however, reduction of the aldehyde group by HCHO often leads, irreversibly, to diols or triols (cross-Cannizzaro reaction). Although basic condensing agents (hydroxides) are most frequently employed, the reaction is also effected by H_2SO_4. Aromatic or aliphatic aldehydes with no α-hydrogen atom give the Cannizzaro reaction when treated with NaOH or other strong bases. Normally the best yield of acid or alcohol is 50% each, which can be altered in certain cases. High yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde. In this case, formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. Role of solvent, catalyst and temperature as well as substrate are important in determining the product composition.

Mechanism of cross-Cannizzaro reaction:

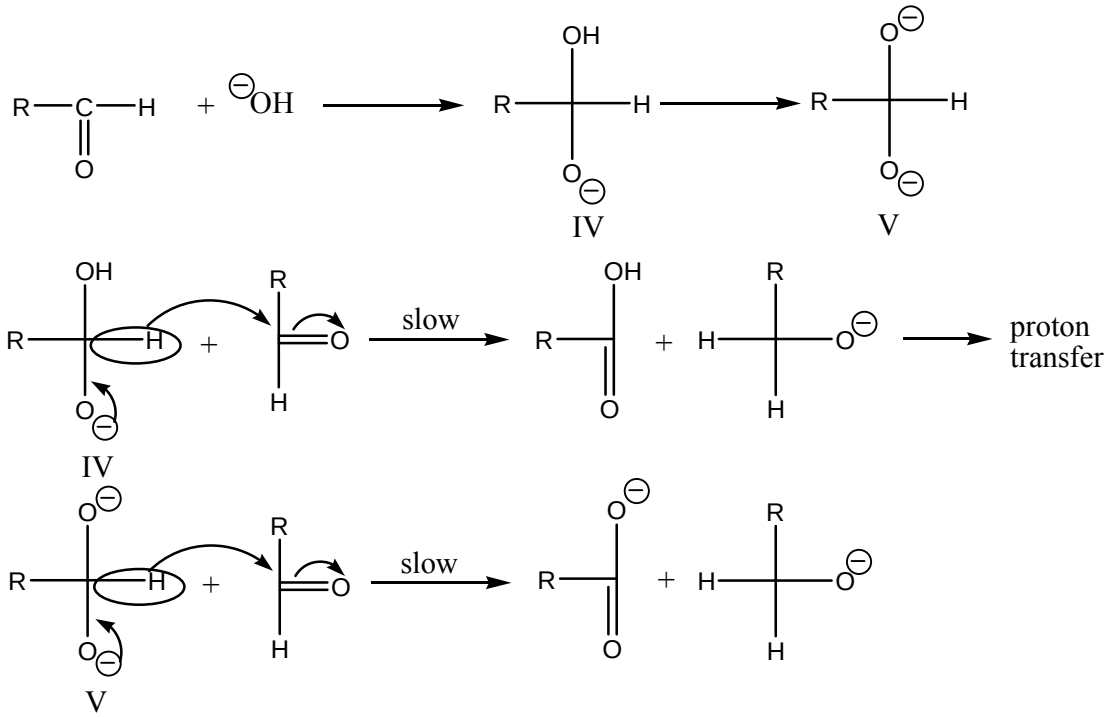


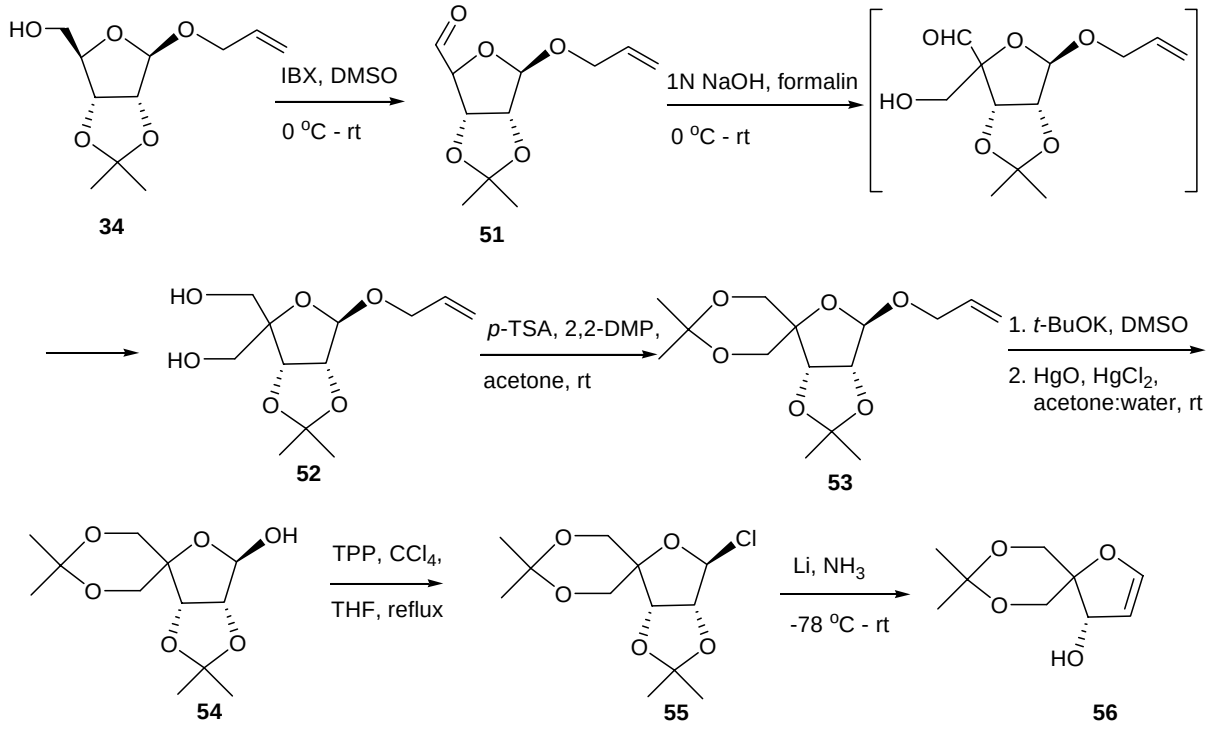
Figure 6.

The cross-Cannizzaro reaction involves a hydride shift. The strong electron donating character of O^- greatly facilitates the ability of aldehydic hydrogen to leave with its electron

pair. Of course, this effect is even stronger in dianion V. When the hydride does leave, it attacks another molecule of aldehyde. The hydride can come from hydroxyanion IV or dianion V. If the hydride ion comes from IV, the final step is rapid proton transfer. In the other case, the acid salt is formed directly and the alkoxide ion acquires a proton from the solvent.

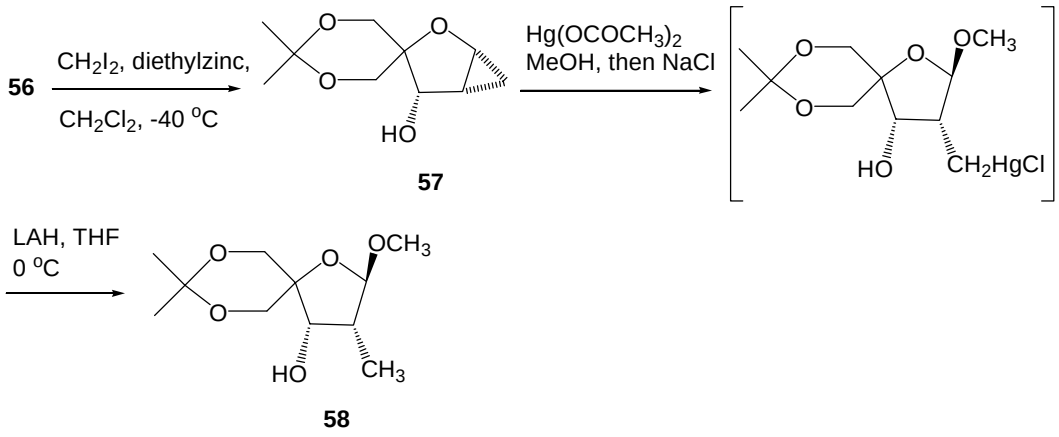
Compound **51** was then subjected to the aldol and cross-Cannizzaro reaction with 1N NaOH and formalin in water for 18 h to give the 1,3-diol **52**[53] (scheme 11). The structure of the compound **52** was confirmed by its ^{13}C NMR, in which signals due to two methylene carbons appeared at 63.0 and 65.5 ppm and the ^{1}H NMR spectrum was in accordance with assigned structure **52**. The IR spectrum showed absorption due to OH at 3447 cm^{-1}. Compound **52** was protected as its isopropylidene derivative **53** with catalytic *p*-TSA and 2,2-dimethoxypropane in acetone. The appearance of signal due to isopropylidene in the upfield region as a singlet at δ 1.48 (6H) confirmed the transformation. Compound **53** was deallylated in two steps: i) treatment with potassium *t*-butoxide in refluxing DMSO to form the isomerised product, ii) deprotection with mercuric oxide, mercuric chloride in acetone:water (10:1) at r. t. to afford the lactol **54**.[54] In the ^{1}H NMR spectrum of **54**, the anomeric proton was shifted to downfield region at δ 5.36 as a singlet. Further, in the IR spectrum, absorption was observed at 3420 cm^{-1}. Finally, the lactol **54** was chlorinated using triphenylphosphine, CCl_4 in THF to yield the chloro derivative **55**. The ^{1}H NMR spectrum of **55** revealed the characteristic singlet for anomeric hydrogen at 6.02 ppm. The structure was further confirmed by ^{13}C NMR spectrum and elemental analysis. The chloro derivative **55** was transformed to the key intermediate **56** using lithium in liquid ammonia at –78 °C.[45] The structure of glycal **56** was confirmed by its ^{1}H NMR spectrum which revealed the characteristic peaks of the olefinic protons at 5.08 ppm as a triplet and 6.49 ppm as double-doublet while the ^{13}C NMR spectrum showed signals at 102.6 and 149.3 ppm for olefinic carbons. The electron ionization mass spectra showed mass peak at m/z 186 (M^{+}) and the IR spectrum revealed absorption at 1612 cm^{-1} thus confirming the structure of glycal **56**.

Scheme 11



As expected, the Simmons-Smith cyclopropanation of compound **56** with CH_2I_2, diethyl-zinc in CH_2Cl_2 at –40 °C was diastereospecific and resulted with the required 1,2-cyclopropane derivative **57**. As indicated earlier, in the Simmons-Smith reaction with cyclic allylic and homoallylic alcohols, the hydroxyl group plays an important role not only towards the reactivity of the olefin, but also the stereospecificity of the reaction. In most cases, the cyclopropane ring attains *cis* geometry to the hydroxyl group.[55] The ^{1}H NMR spectrum of compound **57** clearly showed disappearance of the signals due to double bond functionality and presence of the characteristic methylene protons at 0.5-0.7 ppm and 0.92-1.07 ppm as multiplets. In the ^{13}C NMR spectrum, the methylene carbon appeared at δ 13.6. All the other resonances were in conformity with the structure **57**. Further, mercury-mediated opening of monocyclopropanes are well-documented and are known to occur with high regio and stereoselectivity.[56] Compound **57** was allowed to react with $Hg(OCOCH_3)_2$ in methanol followed by the addition of sodium chloride and reductive workup ($LiAlH_4$, THF, 0 °C). The cyclopropane was cleaved regio and stereoselectively to afford compound **58** (scheme 12).

Scheme 12



The high level of stereoselectivity to obtain **58** can be explained by a concerted mechanism in which bond breaking (C1-CH_2) and bond forming (C-$HgOCOCF_3$ and C-OCH_3) occur at almost the same time (figure 7). The stereochemical assignment has been done further to substantiate our claims.

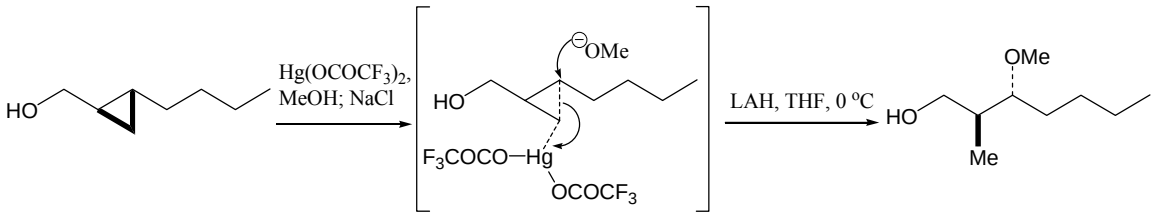


Figure 7.

In the ^{1}H NMR spectrum of **58**, the methyl group appeared in the upfield region at δ 1.10 (d, J = 7.1 Hz) and methoxyl protons at δ 3.35 (singlet). The observed NOE's between H_3-H_2 and H_1-methyl in the NOESY spectrum of **58** clearly indicated the presence of α-methyl substitution as the stereochemistry of H-3 was already fixed. The ^{13}C NMR spectrum of **58** was in accordance with the assigned structure (figure 8).

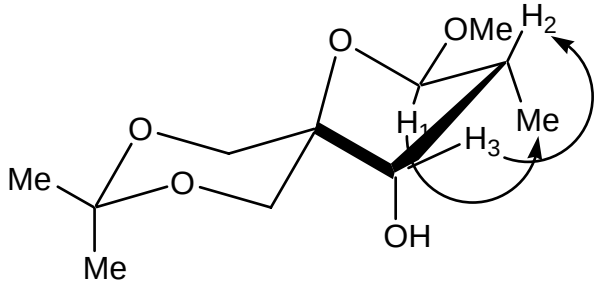
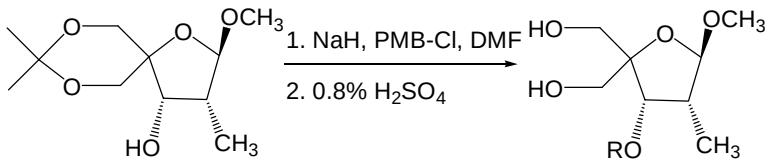


Figure 8. *NOE observed for compound* ***58***

The C-3 hydroxyl group of **58** was treated with NaH, *p*-methoxybenzyl chloride in DMF to obtain the *p*-methoxybenzyl ether[57] whose deprotection with 0.8% H_2SO_4 in methanol cleaved the isopropylidene group to procure the diol **59**. The ^{1}H NMR and ^{13}C NMR spectra clearly showed the absence of characteristic isopropylidene signals, thus confirming the assigned structure of the diol **59**. In the IR spectrum, absorption was observed at 3444 cm^{-1}. The mass spectrum and elemental analysis were in support of the structure **59** (scheme 13).

Scheme 13

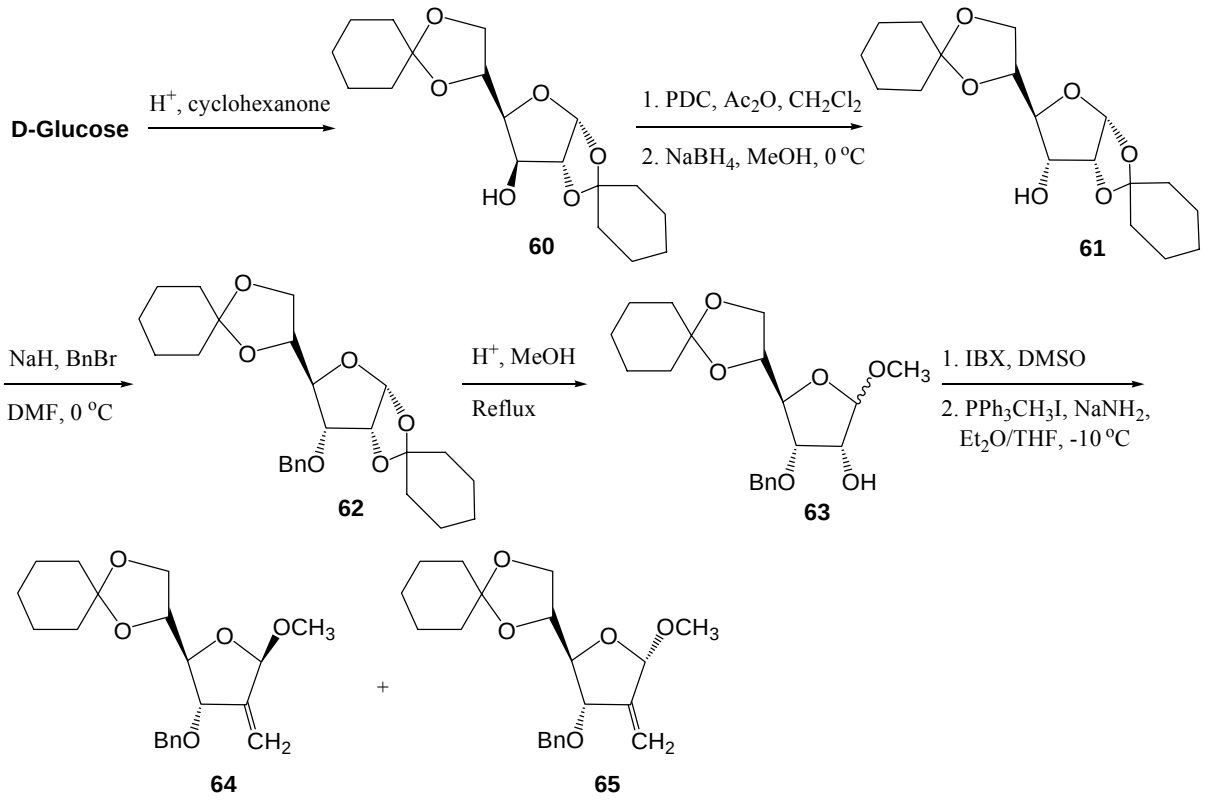


58 **59,** R = PMB

Considering the practical difficulties in scale-up starting from D-ribose, another strategy was planned to synthesize the intermediate **59** from D-glucose as described in scheme 14. D-Glucose was protected as its dicyclohexylidene derivative **60** with catalytic H_2SO_4 in cyclohexanone and the hydroxyl group at C-3 was oxidized (PDC, Ac_2O, CH_2Cl_2, 0 °C to r. t.) and reduced with sodium borohydride in MeOH to give the D-allose derivative **61**.[58] The structure of **61** was analysed by comparing the ^{1}H and ^{13}C NMR spectra and optical rotation values with that of literature values.[58] The alcohol **61** was protected as its benzyl ether **62** with NaH, BnBr in DMF.[59] In the ^{1}H NMR spectrum, benzylic protons were seen at 4.58 and 4.76 ppm as doublets. Compound **62** underwent selective deprotection of 1,2-cyclohexylidene group with catalytic H_2SO_4 in refluxing methanol to give the mixture of anomeric glycosides **63**.[60] The hydroxyl group at C-2 of **63** was oxidized to the 2-ulose derivative with IBX in DMSO and subsequently subjected to the Wittig olefination using PPh_3CH_3I and sodamide at –20 °C to give the C-2 methylene derivatives **64** and **65**, which were separated on silica gel column chromatography.[61] The gross structure of major compound **64** was proposed by the ^{1}H NMR spectrum, in which signals due to the olefinic protons appeared at 5.51 ppm as a triplet and the ^{13}C NMR spectrum further supported the structure of **64**. Similarly, the spectroscopic data for minor compound **65** was in agreement with the assigned gross structure. At this point,

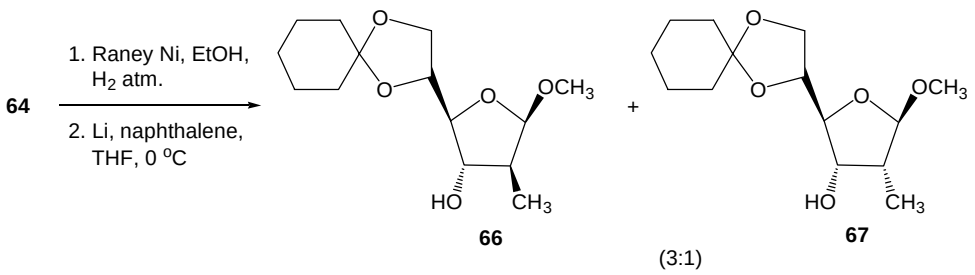
the correct stereochemistry of the anomeric carbons of **64** and **65** could not be confirmed. But we believed that after subsequent reduction of C=C, the new chiral centers would have defined ^{1}H NMR spectrum and based on coupling constant between H-1 and H-2, the stereochemistry could be assigned.

Scheme 14



The methylene group of **64** was reduced with Raney Ni in EtOH under H_2 atmosphere at 50 psi and subsequent debenzylation with Li-naphthalene complex in THF at 0 °C to get the chromatographically separable diastereomers **66** and **67** (3:1, overall yield 67%).[62] In the ^{1}H NMR spectrum of compound **66**, H-3 appeared in the upfield region at δ 3.99 (dd, J = 6.3, 9.5 Hz, 1H) as compared to compound **67**, where H-3 appeared in the downfield region at δ 4.40 (t, J = 4.9 Hz, 1H) (scheme 15). The H-1 of compound **66** resonated at δ 4.69 (d, J = 4.8 Hz, 1H) while in compound **67**, it appeared at δ 4.60 (d, J = 1.9 Hz, 1H). Comparison of coupling constants between H-1 and H-2 revealed the formation C-2 diastereomers.

Scheme 15



But to confirm the stereochemistry of diastereomers **66** and **67**, analysis using 2D-NMR techniques was undertaken. The observed NOE's between H_1-H_2, H_2-H_4 and H_3-methyl group in the NOESY spectrum of **66** indicated the presence of β-methyl group, since the stereochemistry of H-3 and H-4 protons were fixed. While in the spectrum of **67**, the NOE observed between H_1-methyl, methyl-H_4, and H_3-H_2 clearly showed the presence of α-methyl group which was the desired product (figure 9).

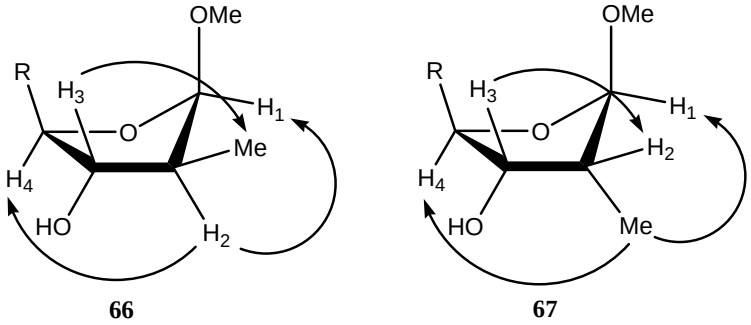
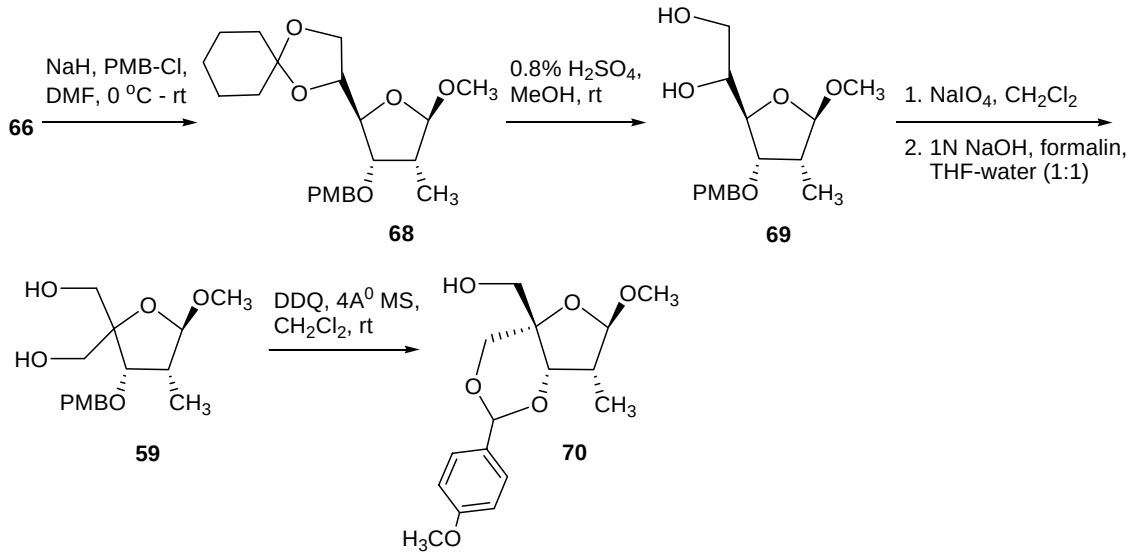


Figure 9. *NOE observed for compounds **66** and **67***

The hydroxyl group at C-3 of the compound **67** was protected as *p*-methoxybenzyl ether **68** (NaH, PMB-Cl, DMF, 0 °C to r. t.) and 5,6-cyclohexylidene group of **68** was deprotected with 0.8% H_2SO_4 in MeOH to the diol **69**. Disappearance of signals due to the cyclohexylidene group in the upfield region of ^{1}H NMR spectrum was noted. In the IR spectrum, absorption due to OH appeared at 3449 cm^{-1}. The diol **69** was cleaved with sodium metaperiodate in CH_2Cl_2 at r. t. to the aldehyde followed by aldol and cross-Cannizzaro reaction in 1N NaOH, formalin and THF-water (1:1) to procure the intermediate **59**.[53] The spectroscopic data of this sample compared well with the product prepared earlier in scheme 12. In order to selectively differentiate the hydroxymethyl groups, **59** was treated with DDQ, 4 A° molecular sieves in CH_2Cl_2 at r. t to give *p*-methoxybenzylidene derivative **70**[63] (scheme

16). Compound **70** was however the expected product formed by the intramolecular participation of hydroxyl group of hydroxymethyl substituent. As expected, the downfield shift of the benzylidene proton at δ 5.33 (s, 1H) was observed in the ^{1}H NMR spectrum of compound **70**. The ^{13}C NMR spectrum, mass spectra and elemental analysis further suggested the structure to be **70**.

Scheme 16



For convenience in establishing the identity of the hydroxyl group involved in the acetal formation, NOE studies were carried out. The observed NOE between benzylidene H-H_3, benzylidene H-$H_{5'}$ (1,3-diaxial) and H_3-H_5 protons were useful in assigning the structure **70**. These observations further indicated that the 5'-hydroxyl group was involved in the formation of *p*-methoxybenzylidene acetal leaving 5-hydroxyl group free (figure 10). This was attributed to the formation of cis-[4,3,0] bicyclic ring.

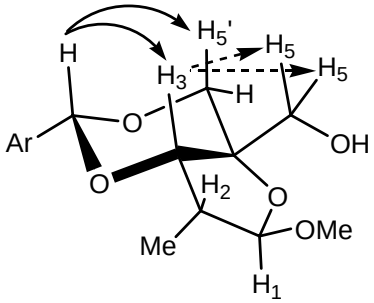
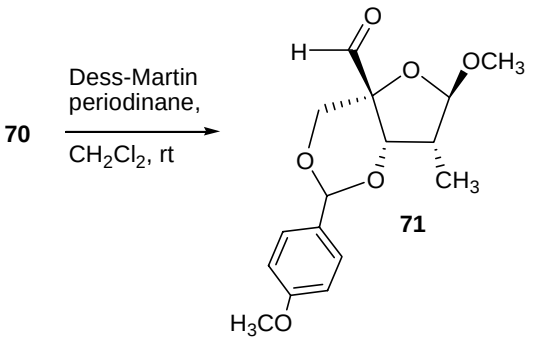


Figure 10. *NOE observed for compound **70***

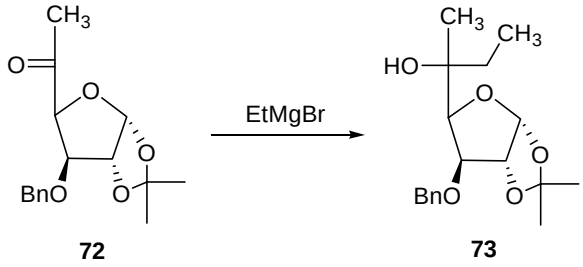
The free hydroxymethyl group of compound **70** was further treated with Dess-Martin periodinane in CH_2Cl_2 to form the aldehyde **71**.[64] The ^1H NMR spectrum of **71** showed a characteristic singlet due to aldehydic proton at 9.84 ppm. Similarly, in the ^{13}C NMR spectrum, the aldehydic carbon resonated at 204.3 ppm (scheme 17).

Scheme 17



According to literature procedure,[65] the Grignard reaction of **72** with ethyl magnesium bromide afforded **73** in which Mg was coordinated with ring oxygen and carbonyl oxygen. This chelation allowed the approach of ethyl group in a specific direction providing L-configuration exclusively (scheme 18).

Scheme 18



The aldehyde **71** underwent Grignard reaction with isopropyl magnesium bromide in diethyl ether at –40 °C to form **74** as a sole product.[10] In the ^1H NMR spectrum of **74**, the characteristic doublets due to two methyls of isopropyl group were present in the upfield region at δ 0.99 (J = 6.4 Hz, 3H), 1.09 (J = 6.9 Hz, 3H). Although the Grignard reaction gave a single product, the correct stereochemical assignment was a difficult proposition. Fortunately, **74** crystallised out from the benzene-pet ether and its single crystal X-ray crystallograph was recorded. The X-ray studies showed the structure of **74** in which the hydroxyl group at C-5 had D–configuration (figure 11).

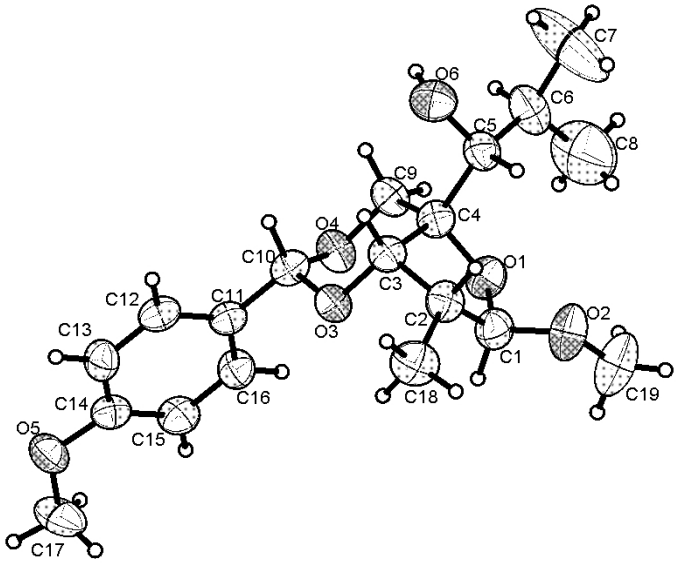


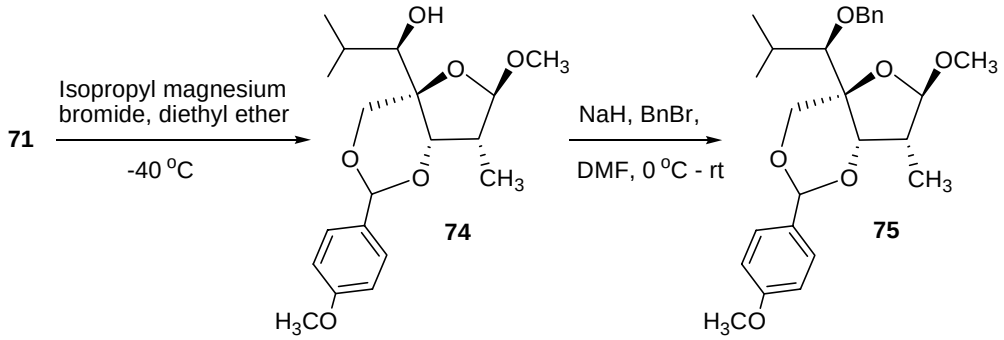
Figure 11. *ORTEP drawing of compound* ***74***

The details of crystal data and structure refinement (Table 2), bond lengths (Table 3), bond angles (Table 4) and torsion angles (Table 5) for compound **74** are given at the end of this section (Page No.71 to 74).

In our case, the results are exactly opposite as assigned by the X-ray studies. This observation was opposite to the literature precedents.[65] This may be attributed to the difficulty in chelate formation due to the bulk of isopropyl group itself as well as the rigid *p*-methoxybenzylidene ring present in **71**. The stereochemical outcome of the reaction could be due to the steric control, which allowed the approach of isopropyl group from exactly opposite phase giving the D–configuration. Although the synthetic strategy was based on literature precedents, this outcome was disheartening. However, we decided to pursue our synthetic goal with opposite stereochemistry at C-5. We felt that once the synthesis of C-5 epimer of oxa-lactacystin (**4**) would be completed with present substrate **74**, alteration could then be drawn to study the C-C bond forming reaction which would give the right stereochemistry at C-5.

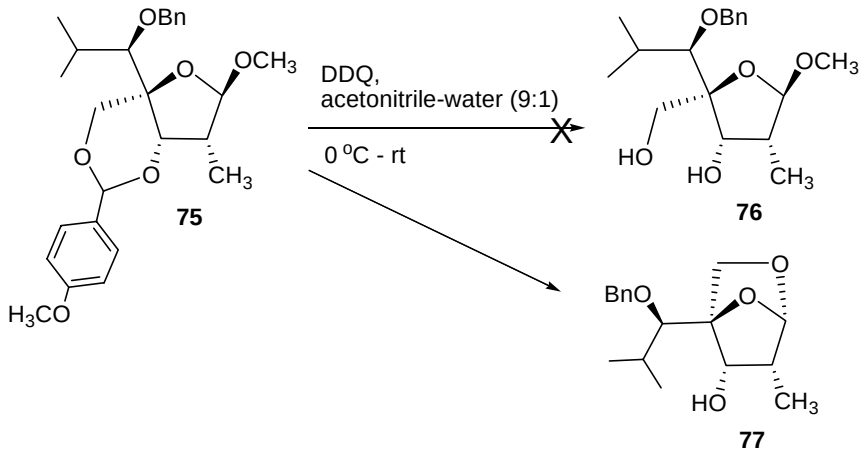
Further, the hydroxyl group of compound **74** was protected as its benzyl ether **75** using sodium hydride, benzyl bromide in DMF at 0 °C (scheme 19). The ^{1}H and ^{13}C NMR spectra and elemental analysis were in accordance with the structure **75**.

Scheme 19



In order to deprotect the *p*-methoxybenzylidene acetal, **75** was treated with DDQ (0.2 equiv) in acetonitrile-water (9:1).[66] This reaction gave the cyclized product **77** instead of the required diol **76** (scheme 20). The ^{1}H NMR spectrum of compound **77** showed absence of singlet due to anomeric methoxyl group that usually appears at δ 3.44 and the presence of characteristic signals due to C-5' methylene protons at δ 3.52 (dd, J = 1.3, 12.0 Hz, 1H), 4.13 (d, J = 12.0 Hz, 1H). In the IR spectrum, absorption at 3500 cm^{-1} was present. The ^{13}C NMR spectrum, mass spectrum, elemental analysis and NOE studies were in agreement with the assigned structure **77**.

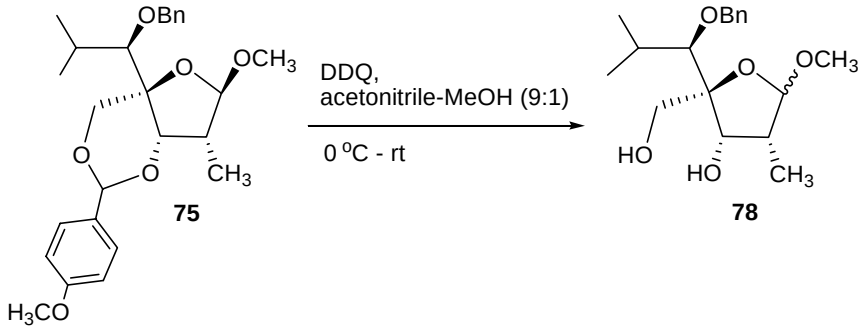
Scheme 20



However, replacing water with MeOH as a protic solvent, the same reaction led to the formation of inseparable mixture of methyl glycosides **78** (scheme 21). Appearance of anomeric methoxyl singlets at δ 3.41, 3.42 (ratio 1:0.6) in the ^{1}H NMR spectrum revealed that the stereochemistry at the anomeric position of **78** was epimerised. All other resonances were

in agreement with the assigned structure**78**. In the IR spectrum, absorption at 3500 cm^{-1} was observed indicating the cleavage of the *p*-methoxybenzylidene acetal.

Scheme 21



A short note on oxidative/reductive opening of p-methoxybenzylidene acetal :

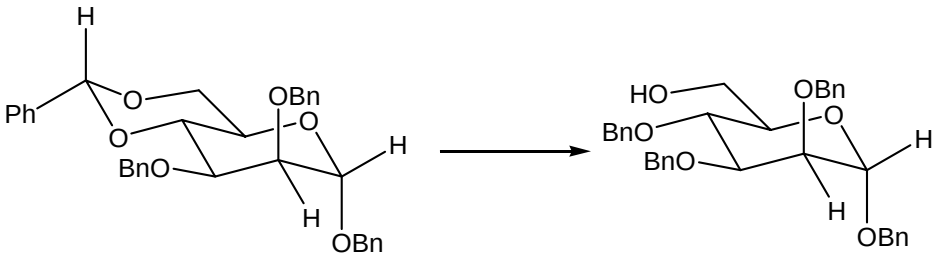
Cyclic benzylidene acetals are versatile protecting groups for 1,2 and 1,3-diols and have found widespread use in carbohydrate synthesis. In case of 1,2,3-triols, the 1,3-acetal is the preferred product, in contrast to the acetonide, which gives 1,2-derivative. As with benzylidene derivative, the 1,3-derivative is thermodynamically favored over the 1,2-derivative. Well-known examples include 3,4-O-isopropylidene and 4,6-O-benzylidene protection in hexopyranosides and 1,2:5,6-di-O-isopropylidene protection in hexofuranosides. In addition to protection/deprotection, regioselective cleavage of benzylidene acetals by both reductive and oxidative procedures gives access to partly protected sugars with only one unprotected hydroxyl group, suitable as e.g. glycosyl acceptors. The direction of cleavage is dependent upon steric and electronic factors as well as on the nature of the cleavage reagent.

Hanessian found in 1966 that 4,6-O-benzylidene acetals could be transformed into the corresponding 4-O-benzoyl-6-deoxy bromo derivatives, by treatment with N-bromosuccinimide (NBS) in tetrachloromethane. This procedure has developed into one of the standard reactions for regioselective functionalisation of carbohydrates. Following these initial examples, further search for effective methods for regioselective ring-opening of sugar acetals has yielded other valuable procedures for the preparation of partially protected sugars.

Oxidative cleavage gives benzoyl esters which are labile under alkaline conditions and can therefore be simply and selectively removed in later stages of synthetic route. With non-saccharidic acetals, a number of oxidants have been evaluated including ozone, pyridinium dichromate/t-BuOOH, $NaBO_3.4H_2O/Ac_2O$ and t-BuOOH/$Pd(OCOCF_3)$(t-BuOOH). However, the regioselectivity obtained with most of these reagents was rather poor. Treatment of some p-methoxybenzylidene acetals of furanoses with DDQ gave the two expected regioisomeric p-methoxybenzoyl esters in the ratio 7:3.

In contrast, the reductive cleavage reactions give benzyl ether. Reagents such as $LiAlH_4/AlCl_3$, $NaBH_3CN/HCl$ and i-Bu_2AlH give benzyl ether sugars with one unprotected hydroxyl group. The regioselectivity varies between these methods. Generally speaking, $LiAlH_4/AlCl_3$ and $NaBH_3CN/HCl$ give products with unprotected 6-OH and 4-OH, respectively. The latter reagent is now generally accepted for reliable regioselective preparation of pyranosidic glycosyl acceptors.

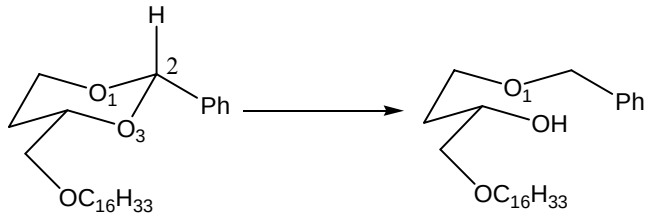
*The $LiAlH_4/AlCl_3$ reagent used for the cleavage of acetals of carbohydrates, in which the polar effects influence the direction of cleavage of 1,3-dioxane and 1,3-dioxolane rings have been extensively examined, but steric effects may also be involved. As expected, the cleavage of benzyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (V***I***) with $LiAlH_4/AlCl_3$ gave only the 4-O-benzyl compound (V***II***). The manno-pyranoside derivatives contain a trans-fused ring system and trans-diequatorial orientation of O-3 and O-4. Accordingly, $AlHCl_2$ can form a complex only with the free electron-pair of O-6, because of the shielding of O-4 by the bulky 3-O-benzyl group. Consequently, the benzylidene ring cleaves at position 6.*



VI VII

Benzylidene acetal is generally reduced at the less sterically hindered oxygen, yielding the more hindered alcohol protected as the benzyl ether. The unsusal regioselectivity observed when VIII was reacted with DIBAL-H in toluene affording IX as the major product.

The result may be due to the initial coordination of the aluminium atom of DIBAL to O-3 atom of the dioxane ring and the ether oxygen of the side chain and subsequent chelation-directed site-selective cleavage of the dioxane ring at O-3/C-2 bond.

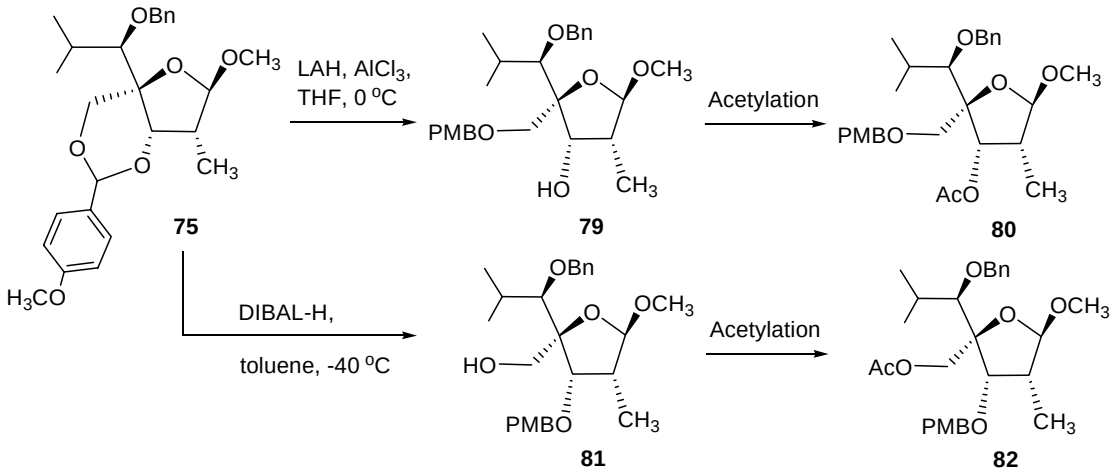


VIII IX

In conclusion, treatment of 4,6-O-benzylidene group with $LiAlH_4/AlCl_3$ resulted in cleavage at the least hindered side of the acetal, giving the more hindered ether, whereas treatment with DIBAL-H resulted in the formation of the benzyl ether at the least hindered alcohol.

In an alternate protocol, we also studied the reductive opening of **75** (scheme 22). For instance, the reaction of compound **75** with LAH/$AlCl_3$ in THF at 0 °C resulted in the exclusive formation of the regiomer **79**.[67] In order to prove the structure of **79**, it was converted into the acetate derivative **80** with acetic anhydride, pyridine and catalytic DMAP. In the ^{1}H NMR spectrum of compound **80**, the H-3 proton was located in the downfield region at 5.61 ppm. Although under the reductive ring opening reaction conditions, we expected based on the literature precedents,[67] the formation of the secondary-PMB derivative **81**, in this particular case the primary-PMB derivative **79** was isolated.

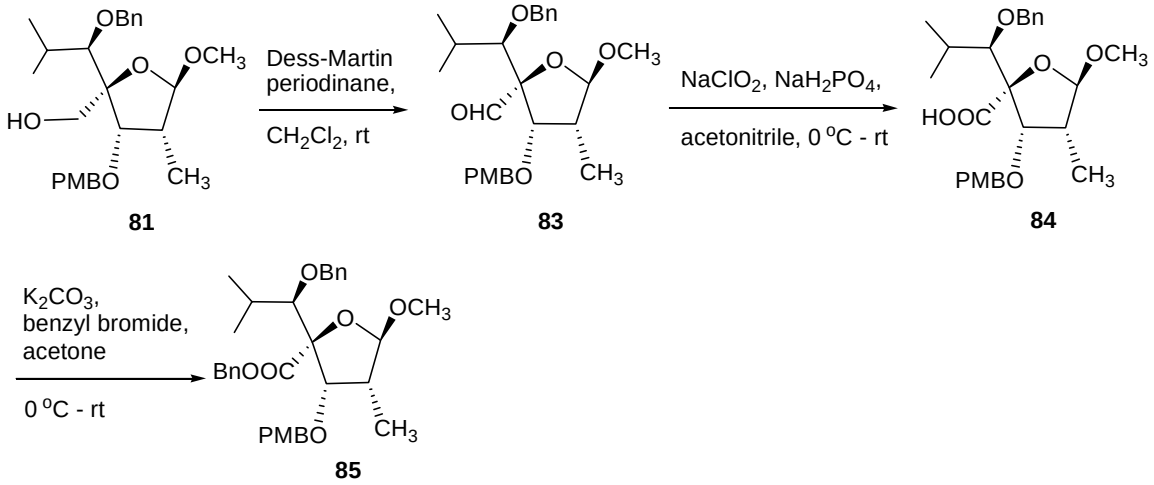
Scheme 22



We also studied the reaction of **75** with DIBAL-H in toluene at –40 °C.[68] This reaction gave the required product **81** whose structure was confirmed by studying the ^{1}H NMR spectrum of its acetate derivative **82**. The ^{1}H NMR spectrum of **82** showed two doublets of methylene protons in the downfield region at 4.08 and 4.49 ppm.

Oxidation of **81** was carried out with Dess-martin periodinane in CH_2Cl_2 at r. t. and the resulting aldehyde **83** was confirmed by analyzing spectroscopic data. In the ^{1}H NMR spectrum of **83**, aldehydic proton was situated at 9.84 ppm. Moreover, in the ^{13}C NMR spectrum, the aldehydic carbon resonated at 201.7 ppm. In the IR spectrum, absorption due to C=O was observed at 1729 cm^{-1}. Compound **83** was oxidised into the acid **84** by using sodium chlorite, sodium dihydrogen phosphate in acetonitrile at 0 °C - r. t.[69] Disappearance of signal due to the aldehydic proton in the ^{1}H NMR spectrum indicated the transformation had occured. In the ^{13}C NMR spectrum of **84,** the carbonyl carbon resonated at δ 170.8. The elemental analysis was in agreement with the assigned structure **84**. However, we converted **84** into the corresponding benzyl ester **85** by treating with K_2CO_3, benzyl bromide in acetone (scheme 23). In the ^{1}H NMR spectrum of **85**, the characteristic AB quartet of benzylic methylene group was located at 5.00 and 5.16 ppm.

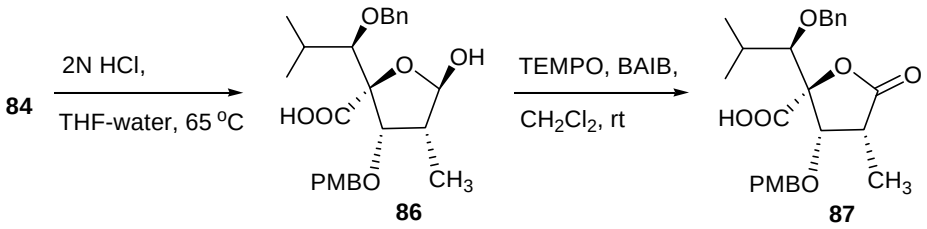
Scheme 23



Finally, treatment of acid **84** with 2N HCl in THF-water at 65 °C gave the lactol **86**.[70] In the ^{1}H NMR spectrum of lactol **86**, anomeric proton was shifted in the downfield region at δ 5.23 (d, J = 5.1 Hz). Compound **86** was oxidized with bis-acetoxyiodobenzene, TEMPO in CH_2Cl_2 at r. t. to the lactone **87**.[71] The ^{1}H NMR spectrum of **87** showed absence of H-1 proton at 5.23 ppm while H-2 was found to be shifted downfield and located at 2.64 ppm compared

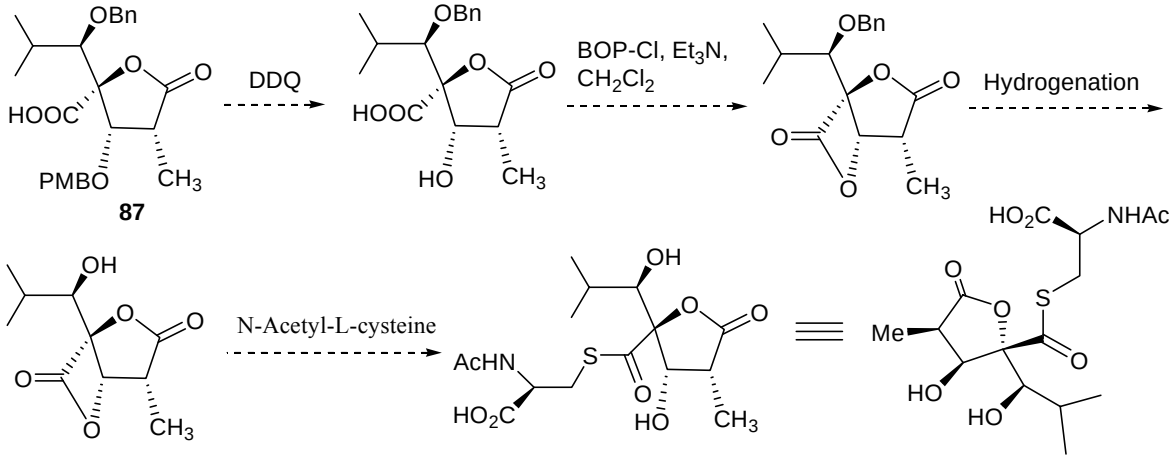
to its chemical shift at 2.17 ppm in case of **86**. The IR spectrum revealed absorption due to lactone carbonyl at 1781 cm^{-1} alongwith acid carbonyl at 1728 cm^{-1}. The mass spectrum (m/z 442, $[M]^+$) and elemental analysis further supported the structure of compound **87** (scheme 24).

Scheme 24



The transformation of **87** into the C-5 epimer of oxa-lactacystin (**4**) by adopting a strategy as shown in scheme 25 is currently under progress in the laboratory by my colleague.

Scheme 25



Crystal data and structure refinement for compound 74

Table 2

Empirical formula	$C_{19}\ H_{28}\ O_6$
Formula weight	352.41
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 9.5015(7) Å b = 5.6870(4) Å beta = 96.999(1) deg. c = 17.649(1) Å
Volume	946.57(12) $Å^3$
Z, Calculated density	2, 1.236 mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	380
Crystal size	0.47 x 0.13 x 0.10 mm
Theta range for data collection	1.16 to 25.00 deg.
Reflections collected / unique	6608 / 3272
Completeness to theta = 25.00	99.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3272 / 1 / 232
Goodness-of-fit on F^2	1.141
Final R indices [I>2sigma(I)]	R1 = 0.0723, wR2 = 0.1908
R indices (all data)	R1 = 0.0796, wR2 = 0.2000

Table 3. Bond lengths [Å] for compound 74

O(1)-C(1)	1.419(5)	C(7)-H(7C)	0.9600
O(1)-C(4)	1.431(4)	C(8)-H(8A)	0.9600
O(2)-C(1)	1.394(5)	C(8)-H(8B)	0.9600
O(2)-C(19)	1.414(8)	C(8)-H(8C)	0.9600
O(3)-C(10)	1.410(4)	C(9)-H(9A)	0.9700
O(3)-C(3)	1.438(4)	C(9)-H(9B)	0.9700
O(4)-C(10)	1.410(4)	C(10)-C(11)	1.497(5)
O(4)-C(9)	1.422(4)	C(10)-H(10)	0.9800
O(5)-C(14)	1.372(4)	C(11)-C(12)	1.383(5)
O(5)-C(17)	1.440(5)	C(11)-C(16)	1.393(5)
O(6)-C(5)	1.423(5)	C(12)-C(13)	1.382(5)
O(6)-H(6)	0.8200	C(12)-H(12)	0.9300
C(1)-C(2)	1.528(6)	C(13)-C(14)	1.387(6)
C(1)-H(1)	0.9800	C(13)-H(13)	0.9300
C(2)-C(3)	1.528(5)	C(14)-C(15)	1.371(5)
C(2)-C(18)	1.539(6)	C(15)-C(16)	1.377(5)
C(2)-H(2)	0.9800	C(15)-H(15)	0.9300
C(3)-C(4)	1.544(5)	C(16)-H(16)	0.9300
C(3)-H(3)	0.9800	C(17)-H(17A)	0.9600
C(4)-C(9)	1.521(5)	C(17)-H(17B)	0.9600
C(4)-C(5)	1.571(5)	C(17)-H(17C)	0.9600
C(5)-C(6)	1.537(6)	C(18)-H(18A)	0.9600
C(5)-H(5)	0.9800	C(18)-H(18B)	0.9600
C(6)-C(8)	1.435(10)	C(18)-H(18C)	0.9600
C(6)-C(7)	1.549(10)	C(19)-H(19A)	0.9600
C(6)-H(6A)	0.9800	C(19)-H(19B)	0.9600
C(7)-H(7A)	0.9600	C(19)-H(19C)	0.9600
C(7)-H(7B)	0.9600		

Table 4. Bond angles [deg] for compound 74

C(1)-O(1)-C(4)	110.4(3)	C(5)-C(6)-H(6A)	107.6
C(1)-O(2)-C(19)	112.5(5)	C(7)-C(6)-H(6A)	107.6
C(10)-O(3)-C(3)	112.0(2)	C(6)-C(7)-H(7A)	109.5
C(10)-O(4)-C(9)	110.6(3)	C(6)-C(7)-H(7B)	109.5
C(14)-O(5)-C(17)	116.6(3)	H(7A)-C(7)-H(7B)	109.5
C(5)-O(6)-H(6)	109.5	C(6)-C(7)-H(7C)	109.5
O(2)-C(1)-O(1)	111.2(3)	H(7A)-C(7)-H(7C)	109.5
O(2)-C(1)-C(2)	109.4(4)	H(7B)-C(7)-H(7C)	109.5
O(1)-C(1)-C(2)	107.0(3)	C(6)-C(8)-H(8A)	109.5
O(2)-C(1)-H(1)	109.7	C(6)-C(8)-H(8B)	109.5
O(1)-C(1)-H(1)	109.7	H(8A)-C(8)-H(8B)	109.5
C(2)-C(1)-H(1)	109.7	C(6)-C(8)-H(8C)	109.5
C(1)-C(2)-C(3)	102.3(3)	H(8A)-C(8)-H(8C)	109.5
C(1)-C(2)-C(18)	114.6(4)	H(8B)-C(8)-H(8C)	109.5
C(3)-C(2)-C(18)	116.8(3)	O(4)-C(9)-C(4)	112.6(3)
C(1)-C(2)-H(2)	107.5	O(4)-C(9)-H(9A)	109.1
C(3)-C(2)-H(2)	107.5	C(4)-C(9)-H(9A)	109.1
C(18)-C(2)-H(2)	107.5	O(4)-C(9)-H(9B)	109.1
O(3)-C(3)-C(2)	107.7(3)	C(4)-C(9)-H(9B)	109.1
O(3)-C(3)-C(4)	109.9(3)	H(9A)-C(9)-H(9B)	107.8
C(2)-C(3)-C(4)	100.9(3)	O(3)-C(10)-O(4)	109.3(3)
O(3)-C(3)-H(3)	112.6	O(3)-C(10)-C(11)	109.9(3)
C(2)-C(3)-H(3)	112.6	O(4)-C(10)-C(11)	109.3(3)
C(4)-C(3)-H(3)	112.6	O(3)-C(10)-H(10)	109.5
O(1)-C(4)-C(9)	108.6(3)	O(4)-C(10)-H(10)	109.5
O(1)-C(4)-C(3)	104.0(3)	C(11)-C(10)-H(10)	109.5
C(9)-C(4)-C(3)	112.4(3)	C(12)-C(11)-C(16)	118.2(3)
O(1)-C(4)-C(5)	109.6(3)	C(12)-C(11)-C(10)	119.3(3)
C(9)-C(4)-C(5)	110.6(3)	C(16)-C(11)-C(10)	122.5(3)
C(3)-C(4)-C(5)	111.4(3)	C(11)-C(12)-C(13)	120.5(3)
O(6)-C(5)-C(6)	111.0(3)	C(11)-C(12)-H(12)	119.8
O(6)-C(5)-C(4)	109.8(3)	C(13)-C(12)-H(12)	119.8
C(6)-C(5)-C(4)	115.6(4)	C(12)-C(13)-C(14)	120.7(3)
O(6)-C(5)-H(5)	106.6	C(12)-C(13)-H(13)	119.6
C(6)-C(5)-H(5)	106.6	C(14)-C(13)-H(13)	119.6
C(4)-C(5)-H(5)	106.6	O(5)-C(14)-C(15)	125.8(3)
C(8)-C(6)-C(5)	117.2(5)	O(5)-C(14)-C(13)	115.3(3)
C(8)-C(6)-C(7)	109.4(6)	C(15)-C(14)-C(13)	118.9(3)
C(5)-C(6)-C(7)	107.1(5)	C(14)-C(15)-C(16)	120.7(4)
C(8)-C(6)-H(6A)	107.6	C(14)-C(15)-H(15)	119.7

C(16)-C(15)-H(15)	119.7	C(2)-C(18)-H(18B)	109.5
C(15)-C(16)-C(11)	120.9(3)	H(18A)-C(18)-H(18B)	109.5
C(15)-C(16)-H(16)	119.5	C(2)-C(18)-H(18C)	109.5
C(11)-C(16)-H(16)	119.5	H(18A)-C(18)-H(18C)	109.5
O(5)-C(17)-H(17A)	109.5	H(18B)-C(18)-H(18C)	109.5
O(5)-C(17)-H(17B)	109.5	O(2)-C(19)-H(19A)	109.5
H(17A)-C(17)-H(17B)	109.5	O(2)-C(19)-H(19B)	109.5
O(5)-C(17)-H(17C)	109.5	H(19A)-C(19)-H(19B)	109.5
H(17A)-C(17)-H(17C)	109.5	O(2)-C(19)-H(19C)	109.5
H(17B)-C(17)-H(17C)	109.5	H(19A)-C(19)-H(19C)	109.5
C(2)-C(18)-H(18A)	109.5	H(19B)-C(19)-H(19C)	109.5

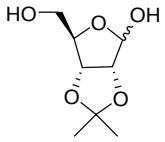
Table 5. Torsion angles [deg] for compound 74

C(19)-O(2)-C(1)-O(1)	-68.0(5)	O(6)-C(5)-C(6)-C(8)	177.0(6)
C(19)-O(2)-C(1)-C(2)	174.0(4)	C(4)-C(5)-C(6)-C(8)	-57.1(7)
C(4)-O(1)-C(1)-O(2)	-118.7(4)	O(6)-C(5)-C(6)-C(7)	53.7(6)
C(4)-O(1)-C(1)-C(2)	0.8(4)	C(4)-C(5)-C(6)-C(7)	179.6(5)
O(2)-C(1)-C(2)-C(3)	143.8(3)	C(10)-O(4)-C(9)-C(4)	54.1(4)
O(1)-C(1)-C(2)-C(3)	23.2(4)	O(1)-C(4)-C(9)-O(4)	72.3(4)
O(2)-C(1)-C(2)-C(18)	-88.8(4)	C(3)-C(4)-C(9)-O(4)	-42.2(4)
O(1)-C(1)-C(2)-C(18)	150.6(3)	C(5)-C(4)-C(9)-O(4)	-167.3(3)
C(10)-O(3)-C(3)-C(2)	-163.2(3)	C(3)-O(3)-C(10)-O(4)	67.7(3)
C(10)-O(3)-C(3)-C(4)	-54.2(4)	C(3)-O(3)-C(10)-C(11)	-172.4(3)
C(1)-C(2)-C(3)-O(3)	79.0(3)	C(9)-O(4)-C(10)-O(3)	-66.3(3)
C(18)-C(2)-C(3)-O(3)	-47.0(5)	C(9)-O(4)-C(10)-C(11)	173.4(3)
C(1)-C(2)-C(3)-C(4)	-36.1(3)	O(3)-C(10)-C(11)-C(12)	91.7(4)
C(18)-C(2)-C(3)-C(4)	-162.1(4)	O(4)-C(10)-C(11)-C(12)	-148.4(3)
C(1)-O(1)-C(4)-C(9)	-144.2(3)	O(3)-C(10)-C(11)-C(16)	-89.3(4)
C(1)-O(1)-C(4)-C(3)	-24.3(4)	O(4)-C(10)-C(11)-C(16)	30.6(4)
C(1)-O(1)-C(4)-C(5)	94.9(3)	C(16)-C(11)-C(12)-C(13)	1.8(5)
O(3)-C(3)-C(4)-O(1)	-76.0(3)	C(10)-C(11)-C(12)-C(13)	-179.1(3)
C(2)-C(3)-C(4)-O(1)	37.5(3)	C(11)-C(12)-C(13)-C(14)	-0.3(6)
O(3)-C(3)-C(4)-C(9)	41.3(4)	C(17)-O(5)-C(14)-C(15)	14.0(6)
C(2)-C(3)-C(4)-C(9)	154.8(3)	C(17)-O(5)-C(14)-C(13)	168.8(4)
O(3)-C(3)-C(4)-C(5)	166.0(3)	C(12)-C(13)-C(14)-O(5)	-178.3(3)
C(2)-C(3)-C(4)-C(5)	-80.5(3)	C(12)-C(13)-C(14)-C(15)	-0.9(6)
O(1)-C(4)-C(5)-O(6)	-165.2(3)	O(5)-C(14)-C(15)-C(16)	177.7(4)
C(9)-C(4)-C(5)-O(6)	75.0(4)	C(13)-C(14)-C(15)-C(16)	0.5(6)
C(3)-C(4)-C(5)-O(6)	-50.7(4)	C(14)-C(15)-C(16)-C(11)	1.1(6)
O(1)-C(4)-C(5)-C(6)	68.3(4)	C(12)-C(11)-C(16)-C(15)	-2.2(5)
C(9)-C(4)-C(5)-C(6)	-51.5(4)	C(10)-C(11)-C(16)-C(15)	178.7(3)
C(3)-C(4)-C(5)-C(6)	-177.2(3)		

Experimental

Experimental

2,3-*O*-Isopropylidene-D-*ribo*-furanose (16)



Conc. H_2SO_4 (0.12 ml) was added to a slurry of D-ribose (5 g, 33.3 mmol) in dry acetone (50 ml) at r. t. A clear solution was obtained after 30 minutes. Stirring was continued for 1 h. The *p*H of solution was adjusted to 7 with $Ca(OH)_2$. The resulting slurry was filtered through a *Celite* pad and evaporated in *vacuo* to afford a light yellow viscous oil, which was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford compound **16** (4.0 g, 63%) as a colourless oil.

IR ($CHCl_3$) : 3390, 3019, 1620, 1457, 1384, 1215, 1159, 1068, 990, 871, 756 cm^{-1}

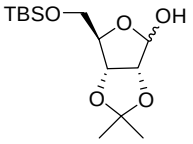
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.31 (s, 3H), 1.47 (s, 3H), 3.69 (s, 2H), 4.12 (br s, 1H), 4.37 (t, *J* = 2.3 Hz, 1H), 4.55 (d, *J* = 5.9 Hz, 1H), 4.79 (d, *J* = 5.9 Hz, 1H), 5.39 (s, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 24.6, 26.2, 63.3, 81.5, 86.5, 87.4, 102.5, 112.0

Mass (*m/z*, relative intensity, ESI-MS) : 190 (50, $[M]^+$), 173 (80), 139 (100)

Anal : Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42; Found: C, 50.27; H, 7.50%.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-D-*ribo*-furanose (17)



To a solution of **16** (1.0 g, 5.26 mmol) and imidazole (0.89 g, 13.15 mmol) in anhydrous DMF (15 ml) was added TBS-Cl (0.87 g, 5.79 mmol) in one portion. The resulting mixture was stirred for 2 h, diluted with H_2O and extracted with ethyl acetate. The combined organic extract was washed with H_2O, dried (Na_2SO_4) and evaporated to yield a crude product whose purification on silica gel (5% ethyl acetate in petroleum ether) gave **17** (1.3 g, 81%) as a colourless liquid.

IR ($CHCl_3$) : 3391, 3020, 1619, 1384, 1216, 1086, 938, 839, 758 cm^{-1}

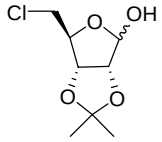
^1H NMR ($CDCl_3$, 200 MHz) : δ 0.13 (s, 6H), 0.92 (s, 9H), 1.30 (s, 3H), 1.47 (s, 3H), 3.74 (s, 2H), 4.32 (s, 1H), 4.47 (d, *J* = 5.9 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 5.28 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 5.7 (2C), 18.2, 24.9, 25.7 (3C), 26.4, 64.8, 81.7, 86.9, 87.5, 103.2, 111.9

Mass (*m/z*, relative intensity, ESI-MS) : 305 (6, $[M+1]^+$), 287 (100)

Anal : Calcd. for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27; Found: C, 54.98; H, 9.16%.

5-Chloro-2,3-*O*-isopropylidene-D-*ribo*-furanose (19)



To a stirred solution of **17** (0.5 g, 1.64 mmol) and CCl_4 (0.8 ml, 8.22 mmol) in 10 ml of dry THF under argon was added Ph_3P (0.85 g, 3.29 mmol). The reaction mixture was heated under reflux for 2 h and concentrated. The residue was purified on silica gel using 7% ethyl acetate in petroleum ether to afford **19** (0.2 g, 60%) as a colourless liquid.

IR ($CHCl_3$) : 3438, 2933, 1449, 1384, 1216, 1158, 982, 759 cm^{-1}

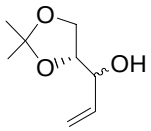
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (s, 3H), 1.48 (s, 3H), 3.59 (s, 2H), 4.35 (t, *J* = 6.4 Hz, 1H), 4.64 (s, 1H), 4.78 (s, 1H), 5.47 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.9, 26.4, 44.8, 82.5, 85.7, 86.8, 103.2, 112.7

Mass (*m/z*, relative intensity, ESI-MS) : 209 (23, $[M+1]^+$), 191 (100), 171 (35), 123 (65)

Anal : Calcd. for $C_8H_{13}O_4Cl$: C, 46.05; H, 6.28; Found: C, 46.28; H, 6.37%.

1,2-Dideoxy-4,5-isopropylidene-D-pent-1-enitol (21)



To the mixture of 1,2:5,6-*O*-diisopropylidene-D-mannitol (20.0 g, 76.3 mmol) in CH_2Cl_2 (200 ml) was added of sodium metaperiodate (33 g, 152.7 mmol) and saturated $NaHCO_3$ solution (10 ml) over 5 minutes. The resulting mixture was stirred for 2 h. Sodium sulphate (10 g) was added to the reaction mixture and filtered through *Celite*. The filtrate was concentrated and the residual oil was distilled under vacuum to give (R)-1,2-*O*-isopropylideneglyceraldehyde (6.3 g, 64%).

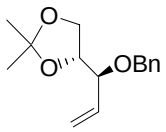
To the above product (5.0 g, 38.5 mmol) in dry THF (50 ml) was added, a solution of vinyl magnesium bromide (1 M in THF, 135 ml, 135 mmol) at –78 °C under nitrogen. After 1 h, the temperature was raised to –10 °C and stirred for 2 h. The reaction was quenched with NH_4Cl solution and two layers were separated. The organic layer was dried (Na_2SO_4), concentrated and the crude product was purified on silica gel using 5% ethyl acetate in petroleum ether to afford **21** (4.2 g, 69%) as a colourless liquid.

IR ($CHCl_3$) : 3350, 3040, 1845, 1640, 920 cm^{-1}

^1H NMR ($CDCl_3$, 300MHz) : δ 1.35 (s, 3H), 1.43 (s, 3H), 2.15 (br s, 1H), 3.82 – 4.02 (m, 2H), 4.05 – 4.22 (m, 1H), 4.29 (br s, 1H), 5.15 – 5.55 (m, 2H), 5.70 – 6.00 (m, 1H)

Anal : Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92; Found: C, 60.54; H, 8.70%.

3-*O*-Benzyl-1,2-dideoxy-4,5-isopropylidene-D-*threo*-pent-1-enitol (22) and 3-*O*-Benzyl-1,2-dideoxy-4,5-isopropylidene-D-*erythro*-pent-1-enitol (23)



To a solution of **21** (4.2 g, 26.6 mmol) in dry DMF (40 ml) was added sodium hydride (60% dispersion in oil, 1.6 g, 39.9 mmol). After 1 h, benzyl bromide (3.8 ml, 31.9 mmol) was introduced. The solution was stirred for 10 h, excess sodium hydride was decomposed with ice water and the reaction mixture extracted with ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with 2% ethyl acetate in petroleum ether to afford **22** (3.0 g) as colourless liquid.

$[\alpha]_D$: +45° (c 1.1, $CHCl_3$); lit.[40] $[\alpha]_D$: +30.4° (c 0.68, $CHCl_3$)

IR ($CHCl_3$) : 2986, 1643, 1455, 1370, 1213, 930, 850, 737 cm^{-1}

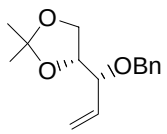
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.34 (s, 3H), 1.40 (s, 3H), 3.70 – 3.79 (m, 1H), 3.81 – 3.92 (m, 1H), 4.00 – 4.16 (m, 2H), 4.39 (d, J = 12.1 Hz, 1H), 4.64 (d, J = 12.1 Hz, 1H), 5.27 – 5.43 (m, 2H), 5.73 – 5.92 (m, 1H), 7.31 (s, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.1, 26.3, 66.5, 70.3, 77.4, 80.7, 109.1, 119.1, 127.5 (2C), 128.1 (3C), 135.1, 137.9

Mass (*m/z*, relative intensity, GC-MS) : 233 (22, $[M-15]^+$), 101 (67), 91 (78), 43 (100)

Anal : Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; Found: C, 72.54; H, 8.36%.

Further elution gave the diastereomeric product **23** (2.0 g) as colourless liquid (overall yield 76%).



$[\alpha]_D$: -22° (c 1.7, $CHCl_3$); lit.[40] $[\alpha]_D$: -18.7° (c 0.72, $CHCl_3$)

IR ($CHCl_3$) : 2986, 1725, 1455, 1370, 1214, 932, 853, 737 cm^{-1}

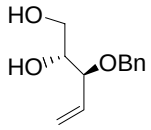
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (s, 3H), 1.39 (s, 3H), 3.69 – 3.87 (m, 2H), 3.94 (dd, *J* = 6.6, 8.2 Hz, 1H), 4.19 (dd, *J* = 6.6, 12.9 Hz, 1H), 4.45 (d, *J* = 12.3 Hz, 1H), 4.68 (d, *J* = 12.3 Hz, 1H), 5.27 – 5.39 (m, 2H), 5.63 – 5.82 (m, 1H), 7.24 – 7.37 (m, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.0, 26.1, 65.2, 69.8, 77.0, 80.5, 109.1, 119.3, 127.0, 127.2, 127.8 (3C), 134.0, 137.9

Mass (*m/z*, relative intensity, GC-MS) : 233 (22, $[M-15]^+$), 101 (98), 91 (100), 43 (76)

Anal : Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; Found: C, 72.80; H, 8.37%.

3-*O*-Benzyl-1,2-dideoxy-D-*threo*-pent-1-enitol (24)



A solution of compound **22** (4.0 g, 16.1 mmol) and 0.8% aqueous H_2SO_4 (4 ml) in MeOH (40 ml) was stirred at r. t. for 4 h. The reaction mixture was neutralized with aqueous $NaHCO_3$, concentrated and extracted. The combined ethyl acetate extract was dried (Na_2SO_4), concentrated and the crude product was purified by SiO_2 column with 40% ethyl acetate in petroleum ether to give the diol **24** (2.3 g, 69%) as colourless oil.

$[\alpha]_D$: +41° (c 5, $CHCl_3$); lit.[40] $[\alpha]_D$: +46.6° (c 0.81, $CHCl_3$)

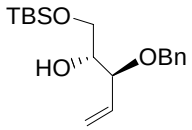
^1H NMR ($CDCl_3$, 200 MHz) : δ 2.50 (br s, 1H), 2.80 (br s, 1H), 3.68 (s, 3H), 3.89 (br d, *J* = 7.4 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 5.29 – 5.45 (m, 2H), 5.72 – 5.92 (m, 1H), 7.31 (s, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 62.8, 69.8, 73.2, 80.9, 119.0, 127.1, 127.2 (3C), 127.8, 134.8, 137.7

Mass (*m/z*, relative intensity, ESI-MS) : 209 (100, $[M+1]^+$), 196 (9), 173 (34), 131 (36)

Anal : Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; Found: C, 69.10; H, 7.54%.

3-*O*-Benzyl-5-*O-tert*-butyldimethylsilyl-1,2-dideoxy-D-*threo*-pent-1-enitol (25)



Compound **24** (4.5 g, 21.6 mmol), imidazole (3.7 g, 54.1 mmol) and TBS-Cl (3.9 g, 25.9 mmol) in dry CH_2Cl_2 (40 ml) were stirred for 3 h and washed with water. The organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel (4% ethyl acetate in petroleum ether) to afford **25** (4.6 g, 66%) as a colourless oil.

$[\alpha]_D$: +21° (c 0.8, $CHCl_3$)

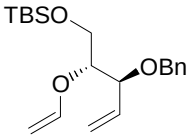
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H), 0.88 (s, 9H), 2.43 (br s, 1H), 3.69 (s, 3H), 3.81 (br d, *J* = 6.0 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 5.24 – 5.44 (m, 2H), 5.77 – 5.98 (m, 1H), 7.30 (s, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 5.6 (2C), 18.0, 25.6 (3C), 63.3, 70.1, 73.2, 80.1, 119.2, 127.2, 127.5 (3C), 128.0, 135.0, 138.0

Mass (*m/z*, relative intensity, ESI-MS) : 322 (50, $[M]^+$), 231 (100)

Anal : Calcd. for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38; Found: C, 66.83; H, 9.41%.

3-*O*-Benzyl-5-*O-tert*-butyldimethylsilyl-1,2-dideoxy-4-*O*-ethynyl-D-*threo*-pent-1-enitol (26)



A solution of **25** (2.0 g, 6.2 mmol), ethyl vinyl ether (100 ml) and $Hg(OCOCF_3)_2$ (0.26 g, 0.62 mmol) was stirred for 16 h at r. t. The reacion mixture was neutralised with the addition of saturated $NaHCO_3$ and then concentrated. The residue was extracted with diethyl ether, dried (Na_2SO_4) and concentrated. The residue was chromatgraphed on silica gel (2% ethyl acetate in petroleum ether) to obtain **26** (1.4 g, 65%) as a colourless oil.

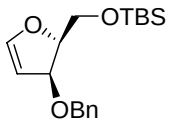
$[\alpha]_D$: +23° (c 0.8, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.06 (s, 6H), 0.89 (s, 9H), 3.60 – 3.90 (m, 3H), 3.91 – 4.75 (m, 2H), 4.32 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 5.20 – 5.45 (m, 2H), 5.70 – 6.00 (m, 1H), 6.30 – 6.45 (m, 1H), 7.33 (s, 5H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 5.3 (2C), 18.0, 25.9 (3C), 62.8, 63.7, 70.6, 73.5, 80.9, 119.3, 127.5, 127.7 (2C), 128.2 (2C), 135.5, 135.7, 139.0

Anal : Calcd. for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25; Found: C, 68.70; H, 9.42%.

1,4-Anhydro-3-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-*erythro*-pent-1-enitol (27)



A solution of **26** (0.5 g, 1.44 mmol) and Grubb's 2nd generation catalyst (24 mg, 0.028 mmol) in benzene (50 ml) was refluxed under argon for 8 h. The reaction mixture was cooled, concentrated and the crude product was purified on silica gel with 3% ethyl acetate in petroleum ether to afford **27** (0.3 g, 65%) as a colourless liquid.

$[\alpha]_D$: +68° (c 1, $CHCl_3$)

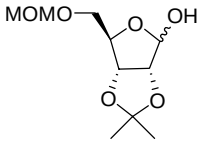
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.07 (s, 6H), 0.91 (s, 9H), 3.48 (dd, *J* = 7.1, 10.5 Hz, 1H), 3.67 – 3.78 (m, 2H), 4.54 (d, *J* = 4.5 Hz, 2H), 4.65 – 4.70 (m, 1H), 5.14 (t, *J* = 2.7 Hz, 1H), 6.56 (dd, *J* = 1.0, 2.7 Hz, 1H), 7.33 (s, 5H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 5.3 (2C), 18.5, 25.9 (3C), 62.8, 69.5, 82.8, 86.3, 100.5, 127.4, 127.5, 127.7, 128.2, 128.4, 139.0, 150.3

Mass (*m/z*, relative intensity, ESI-MS) : 320 (20, $[M]^+$), 280 (60), 102 (100)

Anal : Calcd. for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81; Found: C, 67.27; H, 8.73%.

2,3-*O*-Isopropylidene-5-*O*-methoxymethyl-D-*ribo*-furanose (28)



A solution of compound **16** (1.0 g, 5.26 mmol), *N*,*N*′-diisopropylethylamine (4.6 ml, 26.31 mmol) and methoxymethyl chloride (1.6 ml, 21.04 mmol) in dry CH_2Cl_2 (15 ml) was stirred at 0 °C for 12 h and quenched with saturated $NaHCO_3$. The organic layer was washed

with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography (15% ethyl acetate in petroleum ether) to afford **28** (0.8 g, 65%) as a colourless liquid.

IR ($CHCl_3$) : 3437, 3019, 2943, 1458, 1384, 1216, 1157, 923, 757 cm^{-1}

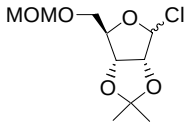
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.31 (s, 3H), 1.48 (s, 3H), 3.39 (s, 3H), 3.67 (d, *J* = 4.0 Hz, 2H), 4.39 (t, *J* = 4.0 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.68 (s, 2H), 4.72 (d, *J* = 6.0 Hz, 1H), 5.31 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.8, 26.4, 55.6, 68.7, 81.9, 85.3, 86.9, 96.5, 103.3, 112.1

Mass (*m/z*, relative intensity, EI-MS) : 219 (16, $[M-15]^+$), 217 (100), 189 (36), 127 (75), 115 (70), 85 (61)

Anal : Calcd. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75; Found: C, 51.07; H, 7.70%.

2,3-*O*-Isopropylidene-5-*O*-methoxymethyl-D-*ribo*-furanosyl chloride (29)



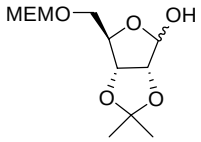
The solution of lactol **28** (0.2 g, 0.86 mmol), CCl_4 (0.8 ml, 8.6 mmol) and triphenylphosphine (1.13 g, 4.3 mmol) in dry THF (10 ml) under argon was refluxed at 65 °C for 3 h and concentrated. The residue was triturated with diethyl ether and concentrated. Again trituration of residue with petroleum ether and removal of solvent afforded **29** (0.06 g, 28%) as a colourless liquid.

IR ($CHCl_3$) : 3020, 1438, 1385, 1216, 1120, 1039, 927, 869, 758 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) : δ 1.34 (s, 3H), 1.48 (s, 3H), 3.39 (s, 3H), 3.70 – 3.81 (m, 2H), 4.50 (dt, *J* = 1.4, 6.4 Hz, 1H), 4.67 (s, 2H), 4.82 (dd, *J* = 1.4, 5.9 Hz, 1H), 5.01 (d, *J* = 5.9 Hz, 1H), 6.15 (s, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 24.9, 26.2, 55.0, 67.1, 81.3, 88.2, 89.1, 96.4, 98.1, 113.0.

2,3-*O*-Isopropylidene 5-*O*-methoxyethoxymethyl-D-*ribo*-furanose (30)



A solution of **16** (1.0 g, 5.26 mmol), *N*,*N*′-diisopropylethylamine (4.6 ml, 26.31 mmol) and methoxyethoxymethyl chloride (2.4 ml, 21.04 mmol) in dry CH_2Cl_2 (20 ml) was stirred at 0 °C for 10 h and quenched with saturated $NaHCO_3$. The organic layer was washed with water followed by brine and dried (Na_2SO_4). The organic layer was concentrated and the crude product purified on silica gel with 25% ethyl acetate in petroleum ether to afford **30** (1.2 g, 82%) as a colourless oil.

IR ($CHCl_3$) : 3437, 3019, 2940, 1456, 1384, 1216, 1160, 870, 758 cm^{-1}

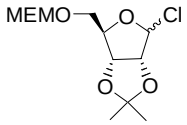
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (s, 3H), 1.49 (s, 3H), 3.40 (s, 3H), 3.50 – 3.90 (m, 6H), 4.38 (s, 1H), 4.53 (d, *J* = 5.3 Hz, 1H), 4.71 (d, *J* = 5.3 Hz, 1H), 4.76 (s, 2H), 5.33 (d, *J* = 6.4 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.0, 26.5, 58.9, 67.3, 69.2, 71.7, 81.9, 85.6, 86.8, 95.5, 103.4, 112.1

Mass (*m/z*, relative intensity, ESI-MS) : 279 (10, $[M+1]^+$), 261 (89), 231 (100), 130 (95)

Anal : Calcd. for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97; Found: C, 51.55; H, 7.97%.

2,3-*O*-Isopropylidene 5-*O*-methoxyethoxymethyl-D-*ribo*-furanosyl chloride (31)



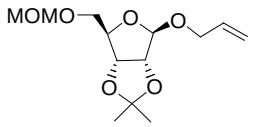
Experimental procedure for the preparation of **31** was same as that of compound **29**. The chloro compound **31** was obtained as a colourless liquid (0.065 g, 26%).

IR ($CHCl_3$) : 2980, 1591, 1438, 1383, 1189, 1120, 753 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) : δ 1.34 (s, 3H), 1.48 (s, 3H), 3.40 (s, 3H), 3.67 – 3.76 (m, 5H), 3.78 – 3.82 (m, 1H), 4.76 (s, 2H), 4.79 – 4.86 (m, 2H), 5.00 (d, *J* = 5.7 Hz, 1H), 6.14 (d, *J* = 1.4 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 25.2, 26.5, 58.9, 66.9, 67.5, 71.6, 81.5, 88.4, 89.4, 95.6, 98.2, 113.3.

Allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-*β*-D-*ribo*-furanoside (32) and allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-*α*-D-*ribo*-furanoside (33)



To a solution of compound **28** (0.8 g, 3.42 mmol) in benzene (10 ml) were added NaOH (0.3 g, 6.84 mmol) and allyl bromide (0.35 ml, 4.10 mmol). The reaction mixture was heated at 75 °C for 5 h. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (5% ethyl acetate in petroleum ether) to afford **32** (0.5 g) as colourless liquid.

$[\alpha]_D$: -82° (c 2.5, $CHCl_3$)

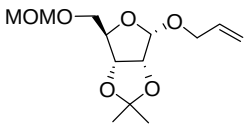
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.32 (s, 3H), 1.48 (s, 3H), 3.37 (s, 3H), 3.49 – 3.62 (m, 2H), 3.91 – 3.97 (m, 1H), 4.12 – 4.20 (m, 1H), 4.33 (t, J = 7.7 Hz, 1H), 4.63 (s, 2H), 4.64 – 4.71 (m, 2H), 5.11 (s, 1H), 5.15 – 5.30 (m, 2H), 5.80 – 5.92 (m, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 24.8, 26.2, 55.0, 67.7, 68.7, 82.0, 85.2 (2C), 96.4, 107.1, 112.1, 116.9, 133.7

Mass (*m/z*, relative intensity, EI-MS) : 259 (13, $[M-15]^+$), 199 (8), 157 (13), 126 (19), 113 (30), 85 (39), 68 (100), 59 (78)

Anal : Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; Found: C, 56.71; H, 8.32%.

Further elution gave **33** (0.25 g) as colourless liquid (*α*:*β* = 1:2, overall yield 80%).



$[\alpha]_D$: +82° (c 1.5, $CHCl_3$)

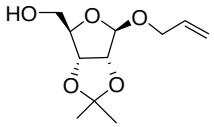
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.36 (s, 3H), 1.57 (s, 3H), 3.36 (s, 3H), 3.66 (d, J = 4.1 Hz, 2H), 4.02 – 4.13 (m, 1H), 4.23 – 4.36 (m, 2H), 4.58 – 4.62 (m, 1H), 4.63 (s, 2H), 4.65 – 4.70 (m, 1H), 5.04 (d, J = 4.0 Hz, 1H), 5.13 – 5.37 (m, 2H), 5.85 – 6.04 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.8, 25.9, 55.2, 67.8, 68.9, 80.1, 80.7, 80.9, 96.6, 101.0, 115.1, 116.9, 134.2

Mass (*m/z*, relative intensity, EI-MS) : 259 (6, $[M-15]^+$), 126 (17), 113 (22), 85 (44), 68 (100), 59 (64)

Anal : Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; Found: C, 57.12; H, 8.10%.

Allyl 2,3-*O*-isopropylidene-*β*-D-*ribo*-furanoside (34)



A solution of **32** (0.27 g, 1 mmol) and trifluoroacetic acid (0.3 ml, 4 mmol) in CH_2Cl_2 (6 ml) was stirred at room temperature for 11 h (monitored by TLC). The organic layer was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel (15% ethyl acetate in petroleum ether) to obtain **34** (0.195 g, 85%) as a colourless syrup.

$[\alpha]_D$: -101° (c 1, $CHCl_3$)

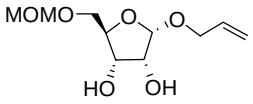
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.31 (s, 3H), 1.47 (s, 3H), 3.22 (br s, 1H), 3.60 (dd, *J* = 2.9, 12.4 Hz, 1H), 3.68 (dd, *J* = 2.2, 12.4 Hz, 1H), 4.05 (dd, *J* = 5.9, 13.2 Hz, 1H), 4.23 (dd, *J* = 5.1, 13.2 Hz, 1H), 4.40 (br t, *J* = 2.9 Hz, 1H), 4.62 (d, *J* = 5.9 Hz, 1H), 4.83 (d, *J* = 5.9 Hz, 1H), 5.10 (s, 1H), 5.20 – 5.35 (m, 2H), 5.81 – 5.97 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.6, 26.2, 63.8, 68.8, 81.4, 85.8, 88.2, 107.8, 112.0, 118.1, 133.0

Mass (*m/z*, relative intensity, EI-MS): 215 (13, $[M-15]^+$), 173 (12), 157 (16), 113 (33), 86 (44), 68 (73), 59 (100)

Anal : Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H 7.88; Found: C, 57.60; H, 7.63%.

Allyl 5-*O*-methoxymethyl-*α*-D-*ribo*-furanoside (35)



A solution of **33** (0.27 g, 1 mmol) and trifluoroacetic acid (0.3 ml, 4 mmol) in CH_2Cl_2 (6 ml) was stirred at room temperature for 4 h (monitored by TLC). The reaction mixture was worked up as described above to give the residue which was purified on silica gel (30% ethyl acetate in petroleum ether) to obtain **35** (0.21 g, 90%) as a colourless syrup.

$[\alpha]_D$: +116° (c 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.00 (br s, 2H), 3.32 (s, 3H), 3.58 – 3.72 (m, 2H), 3.85 – 4.18 (m, 4H), 4.21 – 4.39 (m, 1H), 4.60 (s, 2H), 5.05 (d, *J* = 4.0 Hz, 1H), 5.13 – 5.40 (m, 2H), 5.78 – 5.98 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.1, 67.4, 68.6, 70.8, 71.4, 83.4, 96.5, 100.8, 117.5, 133.7

Mass (*m/z*, relative intensity, EI-MS): 217 (17, $[M-17]^+$), 173 (31), 159 (59), 145 (42), 116 (78), 103 (49), 85 (57), 73 (100), 57 (38)

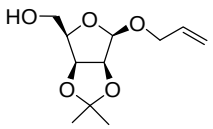
Anal : Calcd. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75; Found: C, 51.48; H, 7.74%.

General method for the preparation of alkyl 2,3-*O*-isopropylidene furanosides

Conc. sulphuric acid (0.15 ml) was added dropwise to a vigorously stirred ice-cold solution of furanose derivative (10 mmol) and sodium sulphate (750 mg) in allyl alcohol (20 ml, 300 mmol) or methyl alcohol (30 ml, 740 mmol). The mixture was stirred vigorously at 25 °C or 0 °C for 12 - 15 h, filtered and the filtrate passed through a column of amberlite IRA 400 (HO^-) resin packed in allyl alcohol or methyl alcohol (15 ml). The resin was washed with allyl alcohol or methyl alcohol (30 ml) and concentrated. The residue was dried and used without any further purification for the next transformation.

To the alkyl furanoside (obtained from the above experiment) and *p*-toluenesulphonic acid (20 mg) in acetone (20 ml) was added 2,2-dimethoxypropane (1.2 ml, 10 mmol). The reaction mixture was stirred at room temperature for 30 minutes and neutralized with saturated sodium bicarbonate and concentrated. Then the residue was extracted with ethyl acetate and washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel with ethyl acetate in petroleum ether as an eluent to give the corresponding alkyl 2,3-*O*-isopropylidene furanoside (**36** – **41**). Yield: for D-lyxose derivative: 83% (*α*:*β* = 1.2:1), for L-lyxose derivative: 82% (*α*:*β* = 1.2:1) and for D-ribose derivative: 70% (*α*:*β* = 0.7:1.3).

Allyl 2,3-*O*-isopropylidene-*β*-D-*lyxo*-furanoside (36)



Colourless solid; MP : 47 °C

$[\alpha]_D$: +58° (c 1, $CHCl_3$)

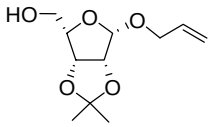
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.29 (s, 3H), 1.44 (s, 3H), 2.56 (br s, 1H), 3.63 (dd, *J* = 5.9, 11.0 Hz, 1H), 3.68 – 3.80 (m, 2H), 3.98 (br ddt, *J* = 1.3, 6.0, 12.8 Hz, 1H), 4.08 (dd, *J* = 2.9, 5.9 Hz, 1H), 4.11 – 4.27 (m, 2H), 4.74 (d, *J* = 2.5 Hz, 1H), 5.05 – 5.35 (m, 2H), 5.70 – 5.95 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.6, 27.5, 62.6, 67.2, 68.5, 74.5, 76.7, 97.6, 109.3, 117.7, 133.3

Mass (m/z, relative intensity, GC-MS) : 215 (13, $[M-15]^+$), 173 (12), 131 (17), 100 (99), 85 (85), 59 (100)

Anal : Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88; Found: C, 57.16; H, 8.08%.

Allyl 2,3-*O*-isopropylidene-*β*-L-*lyxo*-furanoside (37)



Colourless solid; MP : 50 °C

$[\alpha]_D$: -61° (c 0.5, $CHCl_3$)

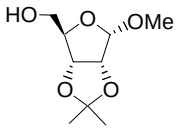
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.33 (s, 3H), 1.48 (s, 3H), 3.63 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.70 – 3.78 (m, 2H), 4.01 (br ddt, *J* = 1.1, 5.9, 12.7 Hz, 1H), 4.11 (dd, *J* = 2.6, 5.9 Hz, 1H), 4.16 – 4.25 (m, 2H), 4.75 (d, *J* = 2.5 Hz, 1H), 5.15 – 5.35 (m, 2H), 5.80 – 5.95 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.6, 27.5, 62.8, 67.3, 68.7, 74.5, 76.5, 97.7, 109.4, 117.9, 133.4

Mass (m/z, relative intensity, EI-MS) : 215 (5, $[M-15]^+$), 131 (9), 100 (100), 85 (72), 69 (36), 59 (78)

Anal : Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88; Found: C, 57.44; H, 7.70%.

Methyl 2,3-*O*-isopropylidene-*α*-D-*ribo*-furanoside (38)



Colourless syrup

$[\alpha]_D$: +142° (c 2, $CHCl_3$)

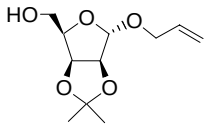
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (s, 3H), 1.45 (s, 3H), 2.87 (br s, 1H), 3.35 (s, 3H), 3.57 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.68 (dd, *J* = 3.7, 11.7 Hz, 1H), 4.03 (d, *J* = 3.4 Hz, 1H), 4.06 (d, *J* = 3.4 Hz, 1H), 4.53 – 4.57 (m, 2H), 4.78 – 4.83 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.4, 25.6, 55.5, 62.3, 80.2, 80.5, 81.4, 102.6, 115.1

Mass (m/z, relative intensity, EI-MS) : 189 (41, $[M-15]^+$), 173 (16), 129 (13), 113 (25), 86 (38), 68 (76), 59 (100)

Anal : Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; Found: C, 52.71; H, 7.83%.

Allyl 2,3-*O*-isopropylidene-*α*-D-*lyxo*-furanoside (39)



Colourless syrup

$[\alpha]_D$: +75° (c 1.5, $CHCl_3$)

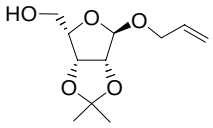
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (s, 3H), 1.46 (s, 3H), 3.00 (br s, 1H), 3.92 – 3.95 (m, 2H), 3.99 (dt, *J* = 1.2, 5.8 Hz, 1H), 4.06 – 4.21 (m, 2H), 4.63 (d, *J* = 6.0 Hz, 1H), 4.80 (dd, *J* = 3.7, 6.0 Hz, 1H), 5.09 (br s, 1H), 5.16 – 5.31 (m, 2H), 5.78 – 5.97 (m, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 24.4, 25.8, 60.6, 67.7, 79.6, 80.0, 85.1, 105.2, 112.5, 117.2, 133.7

Mass (m/z, relative intensity, EI-MS) : 215 (30, $[M-15]^+$), 173 (24), 113 (49), 86 (60), 68 (69), 59 (100)

Anal : Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88; Found: C, 57.36; H, 7.67%.

Allyl 2,3-*O*-isopropylidene-*α*-L-*lyxo*-furanoside (40)



Colourless syrup

$[\alpha]_D$: -77° (c 1, $CHCl_3$)

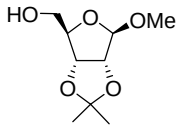
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (s, 3H), 1.43 (s, 3H), 2.73 (br s, 1H), 3.87 – 3.90 (m, 2H), 3.94 – 3.99 (m, 1H), 4.02 – 4.18 (m, 2H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.76 (dd, *J* = 3.7, 5.9 Hz, 1H), 5.05 (s, 1H), 5.12 – 5.29 (m, 2H), 5.75 – 5.94 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.5, 25.8, 60.8, 67.8, 79.5, 80.2, 85.2, 105.2, 112.6, 117.3, 133.8

Mass (m/z, relative intensity, EI-MS) : 215 (15, $[M-15]^+$), 113 (7), 86 (7), 68 (19), 59 (100)

Anal : Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H 7.88; Found: C, 57.14; H, 8.11%.

Methyl 2,3-*O*-isopropylidene-*β*-D-*ribo*-furanoside (41)



Colourless syrup

$[\alpha]_D$: -74° (c 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (s, 3H), 1.47 (s, 3H), 2.82 (br s, 1H), 3.43 (s, 3H), 3.58 (dd, *J* = 3.4, 12.2 Hz, 1H), 3.68 (dd, *J* = 3.4, 12.2 Hz, 1H), 4.41 (br t, *J* = 2.4 Hz, 1H), 4.56 (d, *J* = 5.9 Hz, 1H), 4.81 (d, *J* = 5.9 Hz, 1H), 4.94 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.4, 26.0, 54.7, 63.4, 81.2, 85.2, 87.7, 109.4, 111.7

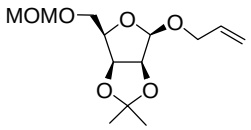
Mass (m/z, relative intensity, EI-MS) : 189 (47, $[M-15]^+$), 173 (35), 157 (41), 129 (18), 113 (76), 86 (100), 68 (88), 59 (83)

Anal : Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; Found: C, 52.68; H, 7.72%.

General method for the preparation of alkyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl furanosides

To an ice-cold solution of alkyl 2,3-*O*-isopropylidene furanoside derivative (1 mmol) in CH_2Cl_2 (15 ml) were added diisopropylethylamine (0.9 ml, 5 mmol) and methoxymethyl chloride (0.4 ml, 5 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. It was then diluted with CH_2Cl_2 (50 ml) and then washed with saturated sodium bicarbonate followed by brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography with ethyl acetate in petroleum ether as the eluent to give the corresponding alkyl 2,3-*O*-isopropylidene-5-*O*-methoxymethylfuranoside derivatives (**42** – **47**).

Allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-*β*-D-*lyxo*-furanoside (42)



Colourless syrup; Yield : 91%

$[\alpha]_D$: +64° (c 1, $CHCl_3$)

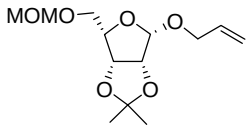
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.29 (s, 3H), 1.46 (s, 3H), 3.31 (s, 3H), 3.41 – 3.64 (m, 2H), 3.68 – 3.78 (m, 1H), 3.89 – 4.23 (m, 4H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.83 (d, *J* = 2.1 Hz, 1H), 5.11 – 5.30 (m, 2H), 5.75 – 5.95 (m, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 26.2, 27.8, 55.2, 59.6, 68.1, 73.0, 75.4, 76.5, 95.8, 97.2, 109.0, 117.3, 133.7

Mass (m/z, relative intensity, GC-MS) : 259 (14, $[M-15]^+$), 217 (14), 157 (23), 100 (100), 85 (77), 69 (50), 59 (54)

Anal : Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; Found: C, 57.16; H, 8.33%.

Allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-*β*-L-*lyxo*-furanoside (43)



Colourless syrup; Yield : 79%

$[\alpha]_D$: -66° (c 1.6, $CHCl_3$)

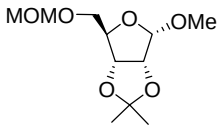
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (s, 3H), 1.52 (s, 3H), 3.37 (s, 3H), 3.47 – 3.69 (m, 2H), 3.71 – 3.83 (m, 1H), 3.94 – 4.28 (m, 4H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 5.16 – 5.36 (m, 2H), 5.80 – 6.00 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.2, 27.8, 55.2, 59.7, 68.2, 73.1, 75.4, 76.6, 95.9, 97.2, 109.1, 117.4, 133.7

Mass (m/z, relative intensity, GC-MS) : 259 (14, $[M-15]^+$), 217 (14), 100 (100), 85 (77), 69 (45), 59 (50)

Anal : Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; Found: C, 57.11; H, 8.31%.

Methyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-α-D-*ribo*-furanoside (44)



Colourless syrup; Yield : 93%

$[\alpha]_D$: +76° (c 1, $CHCl_3$)

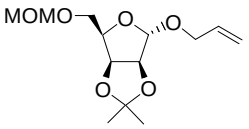
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.29 (s, 3H), 1.50 (s, 3H), 3.30 (s, 3H), 3.41 (s, 3H), 3.60 (d, *J* = 4.1 Hz, 2H), 4.13 – 4.21 (m, 1H), 4.52 – 4.65 (m, 4H), 4.86 (d, *J* = 4.2 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.5, 25.8, 55.1, 55.7, 67.7, 79.9, 80.5, 80.8, 96.5, 102.9, 115.0

Mass (m/z, relative intensity, EI) : 233 (100, $[M-15]^+$), 217 (10), 173 (20), 157 (13), 126 (21), 85 (45), 68 (69)

Anal : Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12; Found: C, 53.04; H, 8.36%.

Allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-α-D-*lyxo*-furanoside (45)



Colourless syrup; Yield : 87%

$[\alpha]_D$: +54° (c 2.2, $CHCl_3$)

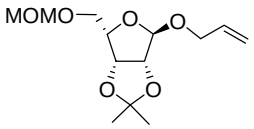
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.28 (s, 3H), 1.42 (s, 3H), 3.36 (s, 3H), 3.70 (dd, *J* = 6.9, 10.8 Hz, 1H), 3.84 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.89 – 4.00 (m, 1H), 4.08 – 4.20 (m, 2H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.65 (s, 2H), 4.72 (dd, *J* = 3.7, 5.9 Hz, 1H), 5.02 (s, 1H), 5.12 – 5.31 (m, 2H), 5.76 – 5.96 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.7, 25.8, 54.8, 65.5, 67.6, 78.8, 79.7, 84.9, 96.5, 105.3, 112.2, 116.8, 133.9

Mass (*m/z*, relative intensity, EI-MS) : 259 (8, $[M-15]^+$), 173 (8), 130 (24), 113 (36), 97 (35), 85 (54), 68 (100)

Anal : Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; Found: C, 56.68; H, 8.15%.

Allyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-*α*-L-*lyxo*-furanoside (46)



Colourless syrup; Yield : 96%

$[\alpha]_D$: -56° (c 1, $CHCl_3$)

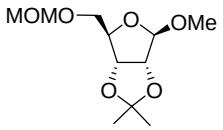
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.21 (s, 3H), 1.35 (s, 3H), 3.29 (s, 3H), 3.65 (dd, *J* = 6.9, 10.7 Hz, 1H), 3.79 (dd, *J* = 4.8, 10.7 Hz, 1H), 3.82 – 3.94 (m, 1H), 4.02 – 4.14 (m, 2 H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.58 (s, 2H), 4.68 (dd, *J* = 3.8, 6.0 Hz,1H), 4.97 (s, 1H), 5.05 –5.24 (m, 2H), 5.69 – 5.89 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.6, 25.8, 54.9, 65.5, 67.6, 78.7, 79.6, 84.8, 96.4, 105.3, 112.2, 117.0, 133.8

Mass (*m/z*, relative intensity, GC-MS) : 259 (25, $[M-15]^+$), 173 (14), 126 (43), 113 (43), 100 (32), 85 (36), 68 (100), 59 (96)

Anal : Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; Found: C, 57.14; H, 8.05 %.

Methyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-*β*-D-*ribo*-furanoside (47)



Colourless syrup; Yield : 82%

$[\alpha]_D$: -73° (c 2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (s, 3H), 1.48 (s, 3H), 3.32 (s, 3H), 3.37 (s, 3H), 3.48 (dd, *J* = 8.3, 9.8 Hz, 1H), 3.58 (dd, *J* = 6.3, 9.8 Hz, 1H), 4.30 (ddd, *J* = 1.0, 6.3, 8.3 Hz, 1H), 4.56 (d, *J* = 5.9 Hz, 1H), 4.64 (s, 2H), 4.66 (d, *J* = 5.9 Hz, 1H), 4.95 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : 24.9, 26.3, 54.5, 55.0, 68.7, 82.0, 85.1, 85.2, 96.6, 109.2, 112.2

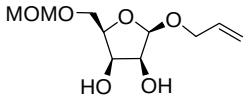
Mass (*m/z*, relative intensity, GC-MS) : 233 (10, $[M-15]^+$), 173 (14), 157 (15), 113 (30), 85 (67), 68 (100), 59 (82)

Anal : Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12; Found: C, 52.96; H, 8.36%.

General method for selective hydrolysis

A solution of alkyl 2,3-*O*-isopropylidene-5-*O*-methoxymethyl furanosides (**42** – **47**) (1 mmol) and trifluoroacetic acid (0.3 ml, 4 mmol) in CH_2Cl_2 (6 ml) was stirred at room temperature (monitored by TLC). The organic layer was washed with saturated $NaHCO_3$ followed by brine and dried (Na_2SO_4). Solvent removal gave the residue which was purified on silica gel using ethyl acetate in petroleum ether as an eluent to give corresponding products (**48** – **50** and **39** – **41**).

Allyl 5-*O*-methoxymethyl-*β*-D-*lyxo*-furanoside (48)



Colourless syrup; Yield : 86%

$[\alpha]_D$: +55° (c 1, $CHCl_3$)

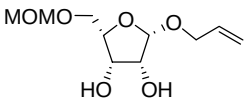
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.41 (s, 3H), 3.43 – 3.48 (m, 2H), 3.52 – 3.63 (m, 1H), 3.67 – 3.88 (m, 3H), 3.93 – 4.02 (m, 2H), 4.15 – 4.24 (m, 1H), 4.66 – 4.74 (m, 2H), 4.80 (d, *J* = 2.1 Hz, 1H), 5.16 – 5.33 (m, 2H), 5.79 – 5.99 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.4, 60.9, 68.0, 70.0, 70.1, 76.0, 97.0, 98.8, 117.1, 133.7

Mass (*m/z*, relative intensity, GC-MS) : 235 (6, $[M+1]^+$), 117 (100), 86 (33), 73 (60), 57 (93)

Anal : Calcd. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75; Found: C, 51.03; H, 7.79%.

Allyl 5-*O*-methoxymethyl-*β*-L-*lyxo*-furanoside (49)



Colourless syrup; Yield : 88%

$[\alpha]_D$: -57° (c 1, $CHCl_3$)

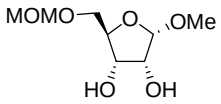
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.42 (s, 3H), 3.51 – 3.64 (m, 3H), 3.65 – 3.88 (m, 3H), 3.92 – 4.06 (m, 2H), 4.15 – 4.26 (m, 1H), 4.67 – 4.74 (m, 2H), 4.80 (d, *J* = 2.4 Hz, 1H), 5.15 – 5.35 (m, 2H), 5.80 – 5.99 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.3, 60.9, 68.0, 70.1 (2C), 75.9, 96.9, 98.7, 117.0, 133.7

Mass (*m/z*, relative intensity, GC-MS) : 235 (3, $[M+1]^+$), 117 (100), 86 (30), 73 (48), 57 (76)

Anal : Calcd. for $C_{10}H_{18}O_6$: C, 51.27; H 7.75; Found: C, 51.20; H, 7.59%.

Methyl 5-*O*-methoxymethyl-α-D-*ribo*-furanoside (50)



Colourless syrup; Yield : 90%

$[\alpha]_D$: +142° (c 2, $CHCl_3$)

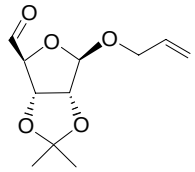
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.53 (br s, 2H), 3.37 (s, 3H), 3.50 (s, 3H), 3.67 (d, *J* = 4.4 Hz, 2H), 3.94 (dd, *J* = 3.4, 6.4 Hz, 1H), 4.10 – 4.15 (m, 2H), 4.64 (s, 2H), 4.94 (d, *J* = 4.4 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.1, 55.2, 67.5, 70.7, 71.5, 83.4, 96.4, 102.7

Mass (m/z, relative intensity, GC-MS) : 207 (2, $[M-1]^+$), 129 (17), 116 (20), 87 (38), 73 (100), 57 (98)

Anal : Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75; Found: C, 46.40; H, 7.79%.

Allyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (51)



To a solution of alcohol **34** (10.7 g, 46.5 mmol) in dry DMSO (40 ml) at 0 °C was added IBX (19.5 g, 69.8 mmol) in portionwise. The reaction mixture was stirred at room temperature for 3 h, diluted with water, ethyl acetate was added and filtered through the bed of *Celite*. The filtrate was washed with water and brine, then dried (Na_2SO_4) and evaporated. The crude product was purified on SiO_2 column (15% ethyl acetate in petroleum ether) to afford **51** (7.9 g, 75%) as a colourless liquid.

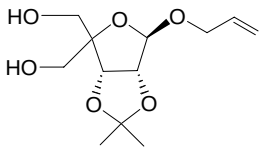
IR ($CHCl_3$) : 2988, 1730, 1210, 1050, 866 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (s, 3H), 1.47 (s, 3H), 4.08 (ddt, *J* = 1.4, 5.9, 12.9 Hz, 1H), 4.28 (ddt, *J* = 1.6, 5.1, 12.9 Hz, 1H), 4.46 (br s, 1H), 4.53 (d, *J* = 5.9 Hz, 1H), 5.06 (d, *J* = 5.9 Hz, 1H), 5.16 – 5.32 (m, 3H), 5.73 – 5.94 (m, 1H), 9.55 (s, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 24.8, 26.1, 68.5, 80.8, 84.0, 89.4, 106.8, 112.6, 117.7, 132.9, 200.2

Mass (*m/z*, relative intensity, EI-MS) : 229 (26, $[M+1]^+$), 213 (12, $[M-15]^+$), 199 (29), 159 (12), 145 (18), 129 (62), 113 (100), 100 (47), 85 (18), 71 (20), 58 (12).

Allyl 4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-*β*-D-*erythro*-pentofuranoside (52)



A 1N solution of sodium hydroxide (9 ml) was added at 0 °C to a stirred solution of **51** (7.5 g, 32.9 mmol) in a mixture of water (9 ml) and 37% aqueous formaldehyde (9 ml) and stirred at room temperature for 18 h. The reaction mixture was neutralized with formic acid, evaporated and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), evaporated and the crude product was purified on silica gel (40% ethyl acetate in petroleum ether) to give **52** (5.6 g, 66%) as a white solid.

MP : 57 °C

$[\alpha]_D$: -54° (c 1, $CHCl_3$)

IR ($CHCl_3$) : 3447, 2989, 1216, 759 cm^{-1}

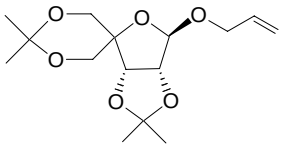
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.31 (s, 3H), 1.49 (s, 3H), 3.00 (br s, 2H), 3.64 (dd, *J* = 8.0, 12.0 Hz, 2H), 3.77 (dd, *J* = 4.0, 12.0 Hz, 2H), 4.03 (dd, *J* = 4.0, 14.0 Hz, 1H), 4.23 (dd, *J* = 4.0, 14.0 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 1H), 4.85 (d, *J* = 6.0 Hz, 1H), 5.11 (s, 1H), 5.15 – 5.40 (m, 2H), 5.75 – 6.00 (m, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 24.3, 25.9, 63.0, 65.5, 68.7, 81.8, 86.4, 90.5, 107.1, 112.3, 118.0, 133.1

Mass (*m/z*, relative intensity, EI-MS) : 245 (6, $[M-15]^+$), 229 (26), 187 (12), 171 (44), 113 (35), 98 (100), 85 (32), 71 (23), 59 (20)

Anal : Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74; Found: C, 55.60; H, 7.87%.

Allyl 4-*C*-hydroxymethyl-2,3:5,5'-di-*O*-isopropylidene-*β*-D-*erythro*-pentofuranoside (53)



A solution of **52** (11.2 g, 43 mmol), *p*-TSA (100 mg) and 2,2-dimethoxypropane (5.5 ml, 45.3 mmol) in acetone (100 ml) was stirred at r. t. for 1 h. The reaction was neutralized with saturated $NaHCO_3$ and evaporated. The residue was extracted with ethyl acetate, washed with H_2O, brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica

gel with 8% ehtyl acetate in petroleum ether as eluent to afford **53** (10.3 g, 80%) as a colourless liquid.

$[\alpha]_D$: -53° (c 1.1, $CHCl_3$)

IR ($CHCl_3$) : 3019, 1216, 1036, 758 cm^{-1}

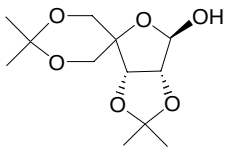
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (s, 3H), 1.41 (s, 3H), 1.48 (s, 6H), 3.65 – 3.85 (m, 3H), 3.87 – 4.00 (m, 1H), 4.05 (d, *J* = 11.8 Hz, 1H), 4.11 – 4.24 (m, 1H), 4.69 (d, *J* = 6.1 Hz, 1H), 4.82 (d, *J* = 6.1 Hz, 1H), 5.00 (s, 1H), 5.14 – 5.38 (m, 2H), 5.75 – 5.99 (m, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 20.6, 24.7, 26.1, 26.4, 61.9, 66.1, 68.0, 81.4, 81.9, 85.5, 98.1, 106.3, 112.5, 117.1, 133.7

Mass (*m/z*, relative intensity, EI-MS) : 301 (6, $[M+1]^+$), 258 (9), 204 (100)

Anal : Calcd. for $C_{15}H_{24}O_6$: C, 59,98; H, 8.05; found : C, 60.20; H, 8.20%.

4-*C*-Hydroxymethyl-2,3:5,5'-di-*O*-isopropylidene-*β*-D-*erythro*-pentofuranose (54)



Compound **53** (11 g, 36.7 mmol) and potassium *t*-butoxide (4.11 g, 36.7 mmol) in dry DMSO (100 ml) were heated to 100 °C. After 1 h, the reaction mixture was poured over crushed ice and extracted with diethyl ether. The ether layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was used for further reaction without any purification.

To a suspension of above crude product (11 g) in acetone-water (10:1, 180 ml), yellow mercuric oxide (9.98 g, 46.0 mmol) and mercuric chloride (9.98 g, 36.7 mmol) were added. The reaction mixture was stirred at r. t. for 1 h, filtered through *Celite* and concentrated. Diethyl ether was added to the residue and washed with a saturated KI solution, dried (Na_2SO_4) and evaporated. The crude product was purified on silica gel column (20% ethyl acetate in petroleum ether) to furnish **54** (6.2 g, 65%) as a white solid.

MP : 80 °C

$[\alpha]_D$: -19° (c 1, $CHCl_3$)

IR ($CHCl_3$) : 3420, 3019, 1592, 1376, 1216, 1158, 758 cm^{-1}

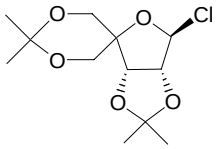
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (s, 3H), 1.36 (s, 3H), 1.40 (s, 6H), 2.11 (br s, 1H), 3.67 (d, *J* = 12.2 Hz, 1H), 3.74 (d, *J* = 12.1 Hz, 1H), 3.85 (d, *J* = 12.2 Hz, 1H), 3.98 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 1H), 4.69 (d, *J* = 5.9 Hz, 1H), 5.36 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 22.0, 24.7, 24.9, 26.0, 62.4, 66.8, 81.4, 82.2, 86.0, 98.4, 101.8, 112.5

Mass (*m/z*, relative intensity, EI-MS) : 245 (15, $[M-15]^+$), 172 (30), 157 (45), 113 (100), 97 (39), 81 (36), 71 (30), 59 (70)

Anal : Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74; found : C, 55.14; H, 7.85%.

4-*C*-Hydroxymethyl-2,3:5,5'-di-*O*-isopropylidene-*β*-D-*erythro*-pentofuranosyl chloride (55)

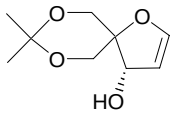


Compound **54** (8 g, 30.8 mmol), CCl_4 (15 ml, 153.8 mmol) and triphenylphosphine (16 g, 61.5 mmol) in dry THF (100 ml) under argon were heated under reflux for 2 h and concentrated. The residue was triturated with diethyl ether and evaporated. Again trituration with petroleum ether and evaporation afforded **55** (5.1 g, 60%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.36 (s, 3H), 1.41 (s, 3H), 1.47 (s, 6H), 3.75 (d, *J* = 11.7 Hz, 1H), 3.95 (s, 2H), 4.06 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 5.9 Hz, 1H), 5.08 (d, *J* = 5.9 Hz, 1H), 6.02 (s, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.3, 24.5, 25.8, 26.1, 61.2, 64.7, 81.6, 85.0, 89.8, 96.9, 98.4, 113.1.

1,4-Anhydro-2-deoxy-4-*C*-hydroxymethyl-5,5'-*O*-isopropylidene-D-*erythro*-pent-1-enitol (56)



To a freshly prepared solution of $LiNH_2$ (from 0.9 g, 129 mmol of lithium) in anhydrous liquid ammonia (300 ml) at –78 °C, a solution of the furanosyl chloride **55** (6 g, 21

mmol) in dry THF (60 ml) was added. After 2 h, anhydrous NH_4Cl (9 g, 167 mmol) was cautiously added, diluted with diethyl ether and anhydrous Na_2SO_4 was added. Ammonia was allowed to evaporate at r. t. overnight. The ethereal suspension was filtered, washed with diethyl ether, dried (Na_2SO_4) and concentrated. The crude product was then purified on silica gel column with 20% ethyl acetate in petroleum ether as eluent to afford **56** (2.5 g, 62%) as a colourless syrup.

$[\alpha]_D$: +124° (c 1.1, $CHCl_3$)

IR ($CHCl_3$) : 3441, 2400, 1612, 1214, 827 cm^{-1}

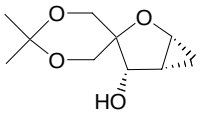
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.41 (s, 3H), 1.46 (s, 3H), 2.52 (br s, 1H), 3.57 (dd, *J* = 1.2, 11.7 Hz, 1H), 3.69 (dd, *J* = 0.8, 11.7 Hz, 1H), 3.83 (br d, *J* = 12.1 Hz, 1H), 4.18 (dd, *J* = 1.2, 12.1 Hz, 1H), 4.66 (d, *J* = 2.7 Hz, 1H), 5.08 (t, *J* = 2.7 Hz, 1H), 6.49 (dd, *J* = 0.8, 2.7 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 22.9, 24.0, 61.0, 64.6, 75.6, 81.1, 98.2, 102.6, 149.3

Mass (*m/z*, relative intensity, EI-MS) : 186 (15, $[M]^+$), 171 (61), 97 (94), 81 (100), 71 (36), 59 (27)

Anal : Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58; found : C, 58.29; H, 7.80%.

1,4-Anhydro-2-deoxy-4-*C*-hydroxymethyl-5,5'-*O*-isopropylidene-1,2-*C*-methylene-D-*erythro*-pentetol (57)



To a solution of CH_2I_2 (7 ml, 87.12 mmol) and diethyl zinc (1M in heptane, 43.55 ml, 43.55 mmol) in dry CH_2Cl_2 (100 ml) at –20 °C was added glycal **56** (2.7 g, 14.52 mmol) in dry CH_2Cl_2 (30 ml). After 9 h, the reaction was quenched with saturated NH_4Cl and extrated with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (20% ethyl acetate in petroleum ether) to obtain **57** (2.2 g, 76%) as a colourless liquid.

$[\alpha]_D$: +83° (c 1, $CHCl_3$)

IR ($CHCl_3$) : 3480, 2930, 1612, 1385, 1084, 759 cm^{-1}

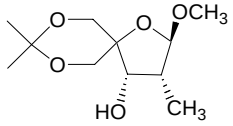
^1H NMR ($CDCl_3$, 200 MHz) : δ 0.5 – 0.7 (m, 1H), 0.92 – 1.07 (m, 1H), 1.34 (s, 3H), 1.42 (s, 3H), 1.82 – 2.05 (m, 1H), 2.56 (br s, 1H), 3.40 – 4.00 (m, 5H), 4.64 (d, *J* = 6.0 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.6, 19.5, 22.5, 27.4, 59.2, 63.0, 66.1, 75.0, 84.0, 98.1

Mass (*m/z*, relative intensity, EI-MS) : 201 (6, $[M+1]^+$), 185 (47), 169 (18), 125 (26), 112 (68), 96 (76), 83 (100), 68 (68), 59 (88)

Anal : Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; found : C, 60.12; H, 8.19%.

Methyl 2-deoxy-4-*C*-hydroxymethyl-5,5'-*O*-isopropylidene-2-*C*-methyl-D-*erythro*-pentofuranoside (58)



A solution of **57** (2.0 g, 10 mmol) and mercuric acetate (6.36 g, 20 mmol) in anhydrous MeOH (30 ml) was stirred at r. t. for 30 minutes and monitored with TLC. Solid NaCl (20 g) was added and vigorously stirred for 3 h. Excess NaCl was removed by filtration and the filtrate was concentrated.

The crude product was dissolved in THF (50 ml) and LAH (1.90 g, 50 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, quenched with saturated Na_2SO_4 solution and diluted with ethyl acetate. The solid was filtered and the filtrate was dried (Na_2SO_4) and concentrated. Purification of crude product on silica gel (25% ethyl acetate in petroleum ether) afforded **58** (1.7 g, 73%) as a white solid.

$[\alpha]_D$: -74° (c 1.3, $CHCl_3$)

IR ($CHCl_3$) : 3455, 2991, 1620, 1455, 1375, 1086, 936, 831, 757 cm^{-1}

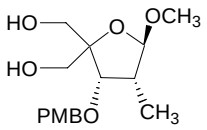
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.10 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 1.49 (s, 3H), 2.29 – 2.37 (m, 1H), 2.45 (br s, 1H), 3.35 (s, 3H), 3.59 (dd, *J* = 2.4, 11.5 Hz, 1H), 3.75 (d, *J* = 11.8 Hz, 1H), 3.80 (d, *J* = 11.8 Hz, 1H), 4.03 (dd, *J* = 2.4, 11.5 Hz, 1H), 4.37 (br d, *J* = 5.7 Hz, 1H), 4.65 (d, *J* = 4.3 Hz, 1H)

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 10.2, 19.5, 27.8, 43.5, 56.0, 62.8, 67.3, 75.2, 79.5, 98.3, 110.8

Mass (*m/z*, relative intensity, EI-MS) : 217 (6, $[M-15]^+$), 144 (20), 111 (32), 98 (100), 85 (56), 73 (70), 59 (70)

Anal : Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68; found : C, 57.10; H, 8.87%.

Methyl 2-deoxy-4-*C*-hydroxymethyl-3-*O*-(*p*-methoxybenzyl)-2-*C*-methyl-D-*erythro*-pentofuranoside (59)



To an ice-cooled solution of **58** (3.4 g, 14.65 mmol) in dry DMF (30 ml), NaH (60% dispersion in oil, 1.17 g, 29.31 mmol) was added. After 30 minutes, PMB-Cl (2.18 ml, 16.11 mmol) was introduced and stirred for additional 3 h at r. t. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was reacted further without any purification.

To a solution of the above product in MeOH (40 ml) was added 0.8% aqueous H_2SO_4 (5 ml) at r. t., stirred for 2 h, neutralised with aqueous $NaHCO_3$ and concentrated. The residue was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. Purification over silica gel column with 50% ethyl acetate in petroleum ether gave **59** (3.2 g, 69%) as a white solid.

$[\alpha]_D$: +4° (c 1.8, $CHCl_3$)

IR ($CHCl_3$) : 3444, 2937, 1515, 1369, 1249, 1034, 823 cm^{-1}

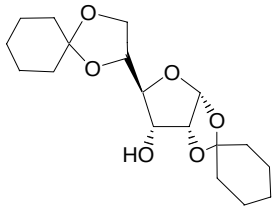
^1H NMR ($CDCl_3$, 300 MHz) : δ 1.09 (d, *J* = 7.3 Hz, 3H), 2.40 – 2.52 (m, 1H), 2.69 (br s, 1H), 2.81 (br s, 1H), 3.35 (s, 3H), 3.58 – 3.69 (m, 4H), 3.79 (s, 3H), 4.30 (d, *J* = 7.4 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.65 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H)

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 11.4, 43.0, 55.1, 55.3, 64.5, 66.5, 73.3, 81.7, 86.5, 110.5, 114.0 (2C), 129.3 (2C), 129.5, 159.6

Mass (*m/z*, relative intensity, ESI-MS) : 313 (83, $[M+1]^+$), 281 (100)

Anal : Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74; found : C, 61.52; H, 7.68%.

1,2,5,6-Di-*O*-cyclohexylidene-*α*-D-*allo*-furanoside (61)



To a solution of **60** (125 g, 368 mmol), activated 4 A° molecular sieves powder (125 g) and PDC (207 g, 552 mmol) in dry CH_2Cl_2 (250 ml) at 0 °C was added acetic anhydride (10.4 ml, 110.4 mmol) dropwise. The reaction mixture was refluxed at 40 °C for 2 h, filtered through *Celite* in sintered funnel and washed with ethyl acetate. The combined organic layer was dried (Na_2SO_4) and concentrated to afford crude ketone (100 g) as green coloured syrup.

A solution of above product (100 g, 295.8 mmol) in dry MeOH (800 ml) at –10 °C was treated with sodium borohydride (22.5 g, 591.7 mmol) over a priod of 1 h. The reaction mixture was stirred at r. t. for 2 h, quenched with ice water, concentrated and extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel with 5% ethyl acetate in petroleum ether to afford **61** (62 g, 62%) as a white solid.

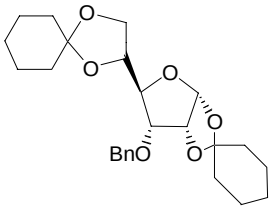
$[\alpha]_D$: +33° (c 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.35 – 1.80 (m, 20H), 2.56 (d, *J* = 8.8 Hz, 1H), 3.76 (dd, *J* = 4.8, 8.5 Hz, 1H), 3.94 – 4.09 (m, 3H), 4.24 – 4.31 (m, 1H), 4.58 (t, *J* = 4.8 Hz, 1H), 5.78 (d, *J* = 4.8 Hz, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 23.4, 23.6, 23.8, 23.9, 24.8, 25.1, 34.8, 35.8, 36.1 (2C), 65.4, 72.4, 75.3, 78.5, 80.0, 103.5, 110.1, 113.2

Anal : Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29; Found: C, 63.76; H, 8.07%.

3-*O*-Benzyl-1,2,5,6-di-*O*-cyclohexylidene-*α*-D-*allo*-furanoside (62)



A solution of alcohol **61** (80 g, 235.3 mmol) in dry DMF (1 lit.) was added NaH (60% dispersion in oil, 15.2 g, 380.0 mmol) at 0 °C. After 1 h, benzyl bromide (33.4 ml, 282.4

mmol) was added and stirred for 2 h. Excess NaH was decomposed with ice water and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was chromatograped on silica gel column with 3% ethyl acetate in petroleum ether as eluent to give **62** (86 g, 85%) as a colourless oil.

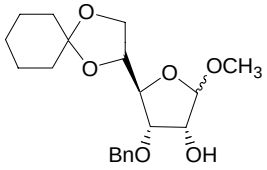
$[\alpha]_D$: +92° (c 1.8, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 – 1.85 (m, 20H), 3.86 (dd, *J* = 4.0, 8.0 Hz, 1H), 3.96 (d, *J* = 6.0 Hz, 2H), 4.08 (dd, *J* = 4.0, 8.0 Hz, 1H), 4.25 – 4.40 (m, 1H), 4.50 – 4.65 (m, 2H), 4.76 (d, *J* = 12.0 Hz, 1H), 5.74 (d, *J* = 4.0 Hz, 1H), 7.20 – 7.50 (m, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.6 (2C), 23.8 (2C), 24.9, 25.1, 34.7, 35.7, 36.2(2C), 64.9, 71.8, 74.8, 77.3, 77.6, 78.4, 103.6, 110.0, 113.2, 127.6, 127.9 (2C), 128.2 (2C), 137.6

Anal : Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; Found: C, 69.50; H, 7.81%.

Methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-D-*allo*-furanoside (63)



A suspension of **62** (40 g, 93.0 mmol) in absolute MeOH (400 ml) was gently refluxed in the presence of H_2SO_4 (1.5 ml) for 5 h. After completion, the reaction mixture was neutralized with saturated $NaHCO_3$, concentrated and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified with 15% ethyl acetate in petroleum ether on silica gel column to afford anomeric mixture **63** (20 g, 59%) as a colourless liquid.

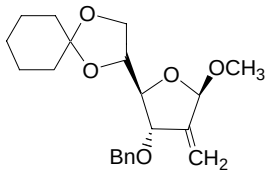
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.50 – 1.70 (m, 10H), 2.87 (br s, 1H), 3.30 (s, 3H), 3.85 – 4.10 (m, 5H), 4.18 (t, *J* = 4.2 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.80 (s, 1H), 7.34 (s, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.4, 23.6, 24.8, 34.5, 36.0, 54.3, 66.5, 71.2, 73.5, 76.4, 80.0, 82.3, 108.2, 109.6, 127.2, 127.4 (2C), 127.9 (2C), 137.1

Mass (*m/z*, relative intensity, ESI-MS) : 365 (5, $[M+1]^+$), 325 (90), 307 (100)

Anal : Calcd. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74; Found: C, 65.67; H, 7.70%.

Methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-2-deoxy-2,2-*C*-methylene-*β*-D-*allo*-furanoside (64) and methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-2-deoxy-2,2-*C*-methylene-*α*-D-*allo*-furanoside (65)



Compound **63** (20.0 g, 54.9 mmol) and IBX (30.8 g, 109.9 mmol) in DMSO (60 ml) were stirred at r. t. for 12 h, quenched with water and diluted with ethyl acetate. After 30 minutes, it was filtered through a bed of *Celite*, the filtrate was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude keto derivative was used further without any purification.

The ketone (20.0 g, 55.2 mmol) and methylene(triphenyl)phosphorane [prepared from PPh_3CH_3I (67 g, 165.7 mmol) and $NaNH_2$ (6 g, 154.6 mmol) in dry Et_2O:THF (300 ml, 2:1)] in THF (100 ml) at –10 °C were stirred at r. t. for 4 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The organic layer was dried (Na_2SO_4), concentrated and the residue chromatographed on silica gel using 5% ethyl acetate in petroleum ether to give **64** (8.0 g) as a colourless liquid.

$[\alpha]_D$: -95° (c 1.8, $CHCl_3$)

IR ($CHCl_3$) : 2933, 1734, 1598, 1449, 1364, 1279, 1191, 1068, 979, 925 cm^{-1}

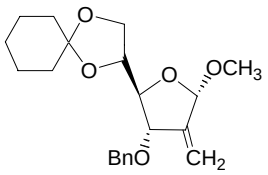
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.30 – 1.70 (m, 10H), 3.37 (s, 3H), 3.85 – 4.10 (m, 4H), 4.43 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.61 (s, 2H), 5.28 (dd, *J* = 1.5, 2.4 Hz, 1H), 5.51 (t, J = 1.5 Hz, 2H), 7.25 – 7.37 (m, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.5, 23.8, 25.0, 34.6, 36.5, 54.9, 66.8, 70.1, 75.0, 80.2, 85.1, 104.1, 109.9, 115.7, 127.4, 127.5 (2C), 128.1 (2C), 137.8, 146.8

Mass (*m/z*, relative intensity, EI-MS) : 361 (3, $[M+1]^+$), 318 (8), 255 (13), 141 (22), 99 (64), 91 (100)

Anal : Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83; Found: C, 69.85; H, 7.84%.

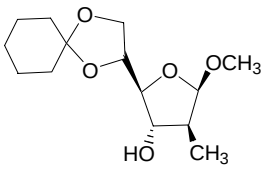
Further elution gave **65** (2.0 g) as a colourless liquid (overall yield 50%).



^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.50 – 1.72 (m, 10H), 3.41 (s, 3H), 3.80 – 4.25 (m, 4H), 4.42 – 4.75 (m, 4H), 4.16 (d, *J* = 12.0 Hz, 1H), 5.96 (d, *J* = 6.0 Hz, 1H), 7.20 – 7.45 (m, 5H)

Anal : Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83; Found: C, 70.10; H, 7.95%.

Methyl 2-deoxy-5,6-*O*-cyclohexylidene-2-*C*-methyl-*β*-D-*altro*-furanoside (66) and methyl 2-deoxy-5,6-*O*-cyclohexylidene-2-*C*-methyl-*β*-D-*allo*-furanoside (67)



A suspension of **64** (8 g, 22.2 mmol) and Raney Ni (3 ml, slurry in EtOH) in absolute ethanol (80 ml) was stirred under H_2 (50 psi) at r. t. for 6 h. The reacion mixture was filtered through a pad of *Celite* and concentrated. The residue was used for further transformation without any purification.

To the above residue (8 g, 22.1 mmol) in dry THF (80 ml) was added Li-naphthalene salt [prepared from Li (0.93 g, 132.6 mmol) and naphthalene (11.31 g, 88.4 mmol) in dry THF (100 ml)] at 0 °C. The reaction mixture was stirred at r. t. for 6 h, quenched with anhydrous NH_4Cl and diluted with ethyl acetate. After 1 h, it was filtered through a bed of *Celite* and concentrated. The crude product was purified on silica gel with 12% ethyl acetate in petroleum ether as eluent to afford **66** (3.0 g) as a colourless liquid.

MP : 60-61 °C

$[\alpha]_D$: -90° (c 1.2, $CHCl_3$)

IR ($CHCl_3$) : 3436, 2935, 1559, 1539, 1366, 1219, 1164, 1015, 925, 847 cm^{-1}

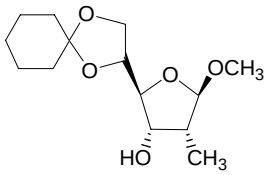
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.08 (d, *J* = 7.2 Hz, 3H), 1.55 – 1.66 (m, 10H), 2.11 – 2.18 (m, 1H), 3.28 (s, 3H), 3.60 (dd, *J* = 6.3, 8.7 Hz, 1H), 3.89 (dd, *J* = 5.2, 8.3 Hz, 1H), 3.95 – 3.97 (m, 1H), 3.99 (dd, *J* = 6.3, 9.5 Hz, 1H), 4.08 (dd, *J* = 5.9, 8.3 Hz, 1H), 4.69 (d, *J* = 4.8 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.4, 23.6, 23.8, 24.9, 34.7, 36.3, 45.5, 54.5, 66.9, 78.0, 79.1, 84.6, 105.7, 109.7

Mass (*m/z*, relative intensity, EI-MS) : 272 (22, $[M]^+$), 243 (22), 229 (58), 139 (42), 101 (25), 73 (42), 55 (100)

Anal : Calcd. for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88; Found: C, 61.68; H, 8.61%.

Further elution gave **67** (1.0 g) as a colourless liquid (overall yield 67%).



$[\alpha]_D$: -50° (c 1.2, $CHCl_3$)

IR ($CHCl_3$) : 3468, 2935, 1719, 1559, 1539, 1367, 1252, 1164, 986, 829 cm^{-1}

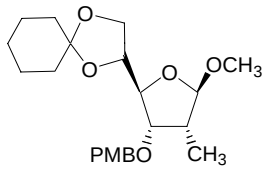
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.07 (d, *J* = 7.3 Hz, 3H), 1.52 – 1.65 (m, 10H), 2.17 (br s, 1H), 2.21 – 2.37 (m, 1H), 3.30 (s, 3H), 3.71 (dd, *J* = 4.9, 7.8 Hz, 1H), 3.87 – 4.14 (m, 3H), 4.40 (t, *J* = 4.9 Hz, 1H), 4.60 (d, *J* = 1.9 Hz, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.9, 23.7, 24.0, 25.1, 34.8, 36.4, 43.2, 55.2, 67.1, 74.8, 77.0, 84.9, 110.0, 110.7

Mass (*m/z*, relative intensity, EI-MS) : 272 (18, $[M]^+$), 243 (17), 229 (37), 139 (33), 101 (25), 73 (37), 55 (100)

Anal : Calcd. for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88; Found: C, 61.75; H, 8.89%.

Methyl 2-deoxy-5,6-*O*-cyclohexylidene-3-*O*-(*p*-methoxybenzyl)-2-*C*-methyl-*β*-D-*allo*-furanoside (68)



To a solution of **67** (4 g, 14.7 mmol) in dry DMF (40 ml) at 0 °C, was added NaH (60% dispersion in oil, 0.88 g, 22.0 mmol). After 30 minutes, PMB-Cl (2.38 ml, 17.6 mmol) was introduced and stirred for additional 3 h at r. t. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4),

concentrated and the residue was purified on silica gel column (3% ethyl acetate in petroleum ether) to furnish **68** (4.8 g, 83%) as colourless oil.

$[\alpha]_D$: -44° (c 1, $CHCl_3$)

IR ($CHCl_3$) : 3019, 1613, 1514, 1216, 1096, 1036, 756 cm^{-1}

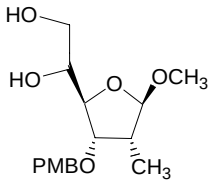
^1H NMR ($CDCl_3$, 200 MHz) : δ 1.05 (d, *J* = 7.0 Hz, 3H), 1.35 – 1.65 (m, 10H), 2.18 –2.35 (m, 1H), 3.32 (s, 3H), 3.80 (s, 3H), 3.90 – 4.10 (m, 5H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 3.1 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.5, 23.9, 24.1, 25.2, 34.9, 36.6, 42.3, 55.2, 55.5, 66.9, 71.3, 76.4, 81.0, 83.5, 110.0, 111.1, 113.7 (2C), 129.3 (2C), 130.3, 159.2

Mass (*m/z*, relative intensity, ESI-MS) : 392 (17, $[M]^+$), 361 (100), 295(43), 263 (40), 223 (57)

Anal : Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22; Found: C, 67.57; H, 8.41%.

Methyl 2-deoxy-3-*O*-(*p*-methoxybenzyl)-2-*C*-methyl-*β*-D-*allo*-furanoside (69)



A solution of **68** (4.8 g, 12.2 mmol) in MeOH (50 ml) and 0.8% H_2SO_4 (5 ml) was stirred at r. t. for 8 h. It was then neutralized with saturated $NaHCO_3$, concentrated, extracted with ethyl acetate. Solvent evaporation gave the crude product which was purified on silica gel column with 50% ethyl acetate in petroleum ether as eluent to obtain **69** (2.9 g, 76%) as a white solid.

$[\alpha]_D$: -59° (c 1, $CHCl_3$)

IR ($CHCl_3$) : 3449, 2936, 1612, 1513, 1458, 1216, 1035, 930, 756 cm^{-1}

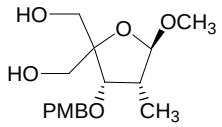
^1H NMR ($CDCl_3$, 500 MHz) : δ 1.04 (d, *J* = 7.2 Hz, 3H), 2.35 (quintet, *J* = 7.0 Hz, 1H), 3.36 (s, 3H), 3.63 (dd, *J* = 6.0, 11.5 Hz, 1H), 3.67 (dd, *J* = 4.4, 11.5 Hz, 1H), 3.75 (dd, *J* = 4.4, 9.9 Hz, 1H), 3.79 (s, 3H), 4.00 (t, *J* = 5.2 Hz, 1H), 4.25 (t, *J* = 5.9 Hz, 1H), 4.40 (br s, 2H), 4.64 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H)

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 10.5, 41.9, 55.1, 55.5, 63.6, 71.7, 72.5, 79.5, 82.6, 111.2, 113.9 (2C), 129.4 (2C), 129.8, 159.4

Mass (*m/z*, relative intensity, ESI-MS) : 297 (3, $[M-15]^+$), 281 (6), 241 (4), 204 (100)

Anal : Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74; Found: C, 61.62; H, 8.00%.

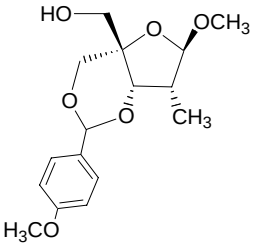
Methyl 2-deoxy-4-hydroxymethyl-3-*O*-(*p*-methoxybenzyl)-2-*C*-methyl-D-*erythro*-pentofuranoside (59)



Compound **69** (2.9 g, 9.3 mmol) and sodium metaperiodate adsorbed silica gel (18.6 g, 2 g/1 mmol) in CH_2Cl_2 (40 ml) were stirred at r. t. for 2 h, filtered through *Celite*, dried (Na_2SO_4) and concentrated. The crude product was used further without any purification.

To the above aldehyde (2.6 g, 9.3 mmol), aqueous 37% formalin (3.5 ml) in water (15 ml) and THF (15 ml), was added 1 N NaOH (14 ml) at 0 °C, stirred at r. t. for 12 h, quenched with formic acid and evaporated to dryness. The residue was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica gel (60% ethyl acetate in petroleum ether) to give **59** (2 g, 69%) as a white solid. The sample was comparable to the specimen prepared earlier.

Methyl 2-deoxy-4-hydroxymethyl-3,5'-*O*-(*p*-methoxybenzylidene)-2-*C*-methyl-*β*-D- *ribo*-furanoside (70)



A suspension of **59** (4 g, 12.8 mmol), powdered dry 4A° molecular sieves (4 g) and DDQ (5.8 g, 25.6 mmol) in CH_2Cl_2 (50 ml) at r. t. were stirred for 10 minutes. The reaction mixture was poured onto *Celite* and washed with 50% ethyl acetate and petroleum ether. The filtrate was concentrated and the residue was purified on silica gel (30% ethyl acetate in petroleum ether as an eluent) to provide **70** (2.8 g, 70%) as a white solid.

$[\alpha]_D$: -13° (c 1.2, $CHCl_3$)

IR ($CHCl_3$) : 3444, 3019, 1615, 1393, 1216, 1036, 832, 756 cm^{-1}

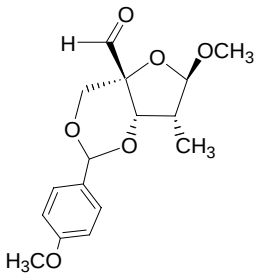
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.16 (d, *J* = 7.1 Hz, 3H), 2.37 (br s, 1H), 2.51 – 2.59 (m, 1H), 3.44 (d, *J* = 11.7 Hz, 1H), 3.49 (s, 3H), 3.50 (d, *J* = 11.7 Hz, 1H), 3.79 (s, 3H), 3.82 (d, *J* = 12.8 Hz, 1H), 4.12 (d, *J* = 12.8 Hz, 1H), 4.17 (d, *J* = 4.6 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 1H), 5.33 (s, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.5, 44.8, 55.1, 56.9, 64.8, 68.7, 79.8, 81.0, 98.4, 112.6, 113.4 (2C), 127.4 (2C), 130.7, 160.0

Mass (*m/z*, relative intensity, ESI-MS) : 311 (28, $[M+1]^+$), 279 (44), 215 (100)

Anal : Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15; Found: C, 62.17; H, 7.16%.

Methyl 4-carbaldehyde-2-deoxy-3,5'-*O*-(*p*-methoxybenzylidene)-2-*C*-methyl-*β*-D-*ribo*-furanoside (71)



A solution of **70** (2.8 g, 9.0 mmol) and Dess-martin periodinane (5.7 g, 13.5 mmol) in CH_2Cl_2 (30 ml) was stirred at r. t. for 2 h. It was then diluted with diethyl ether, saturated $NaHCO_3$ and 1.5 *M* aqueous $Na_2S_2O_3$. The aqueous phase was extracted with diethyl ether and organic layer was washed with water, brine and dried (Na_2SO_4). On removal of solvent, residue was purified on silica gel column with 20% ethyl acetate in petroleum ether as an eluent to give **71** (2.5 g, 89%) as a white solid.

$[\alpha]_D$: -144° (c 0.6, $CHCl_3$)

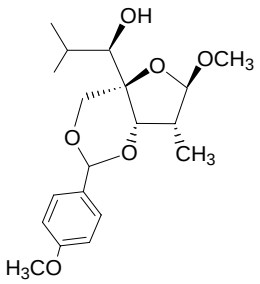
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.17 (d, *J* = 6.0 Hz, 3H), 2.00 – 2.20 (m, 1H), 3.56 (s, 3H), 3.81 (s, 3H), 1.04 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 4.0 Hz, 1H), 5.11 (d, *J* = 6.0 Hz, 1H), 5.42 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 9.84 (s, 1H)

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 9.1, 45.6, 55.1, 57.1, 67.5, 80.4, 87.1, 98.8, 112.9, 113.5 (2C), 127.4 (2C), 129.9, 160.1, 204.3

Mass (*m/z*, relative intensity, ESI-MS) : 309 (100, $[M+1]^+$), 277 (62)

Anal : Calcd. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; Found: C, 62.09; H, 6.52%.

Methyl 2,6-dideoxy-4-hydroxymethyl-2,6,6-tri-*C*-methyl-3,5'-*O*-(*p*-methoxybenzylidene)-*β*-D-*allo*-furanoside (74)



To a freshly prepared solution of isopropyl magnesium bromide [prepared from Mg (1.2 g, 48.7 mmol) and isopropyl bromide (3 ml, 32.4 mmol) in diethyl ether (25 ml)] was added aldehyde **71** (2.5 g, 8.1 mmol) in diethyl ether (30 ml) at –40 °C. After 2 h, it was quenched with saturated aqueous NH_4Cl solution and concentrated. The residue was extracted with ether and washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified on SiO_2 column (20% ethyl acetate in petroleum ether) to afford **74** (1.7 g, 61%) as a white solid and further elution with 30% ethyl acetate in petroleum ether gave **70** (0.5 g, 20%) as a white solid.

$[\alpha]_D$: -36° (c 1, $CHCl_3$)

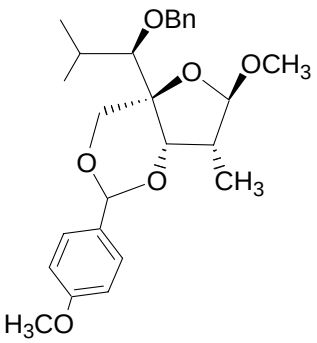
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 0.99 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 7.3 Hz, 3H), 1.85 – 1.95 (m, 1H), 2.01 (br s, 1H), 2.44 – 2.52 (m, 1H), 3.36 (d, *J* = 4.6 Hz, 1H), 3.46 (s, 3H), 3.80 (s, 3H), 4.11 (d, *J* = 12.4 Hz, 1H), 4.14 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J* = 4.1 Hz, 1H), 4.95 (d, *J* = 6.4 Hz, 1H), 5.40 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.5, 19.1, 21.6, 29.4, 43.8, 55.1, 56.9, 67.0, 77.0, 80.0, 83.1, 98.1, 112.5, 113.4 (2C), 127.4 (2C), 130.8, 159.8

Mass (*m/z*, relative intensity, ESI-MS) : 353 (68, $[M+1]^+$), 321 (100), 257 (19)

Anal : Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01; Found: C, 64.70; H, 7.91%.

Methyl 5-*O*-benzyl-2,6-dideoxy-4-hydroxymethyl-2,6,6-tri-*C*-methyl-3,5'-*O*-(*p*-methoxybenzylidene)-*β*-D-*allo*-furanoside (75)



To a solution of **74** (1.7 g, 4.8 mmol) in anhydrous DMF (30 ml) at 0 °C was added NaH (60% dispersion in oil, 0.3 g, 7.2 mmol) and stirred at r. t. for 1 h. The reaction was cooled, benzyl bromide (0.7 ml, 5.8 mmol) was added and further stirred at r. t. for 2 h. Excess NaH was decomposed by adding ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (5% ethyl acetate in petroleum ether) to afford **75** (1.7 g, 81%) as colourless oil.

$[\alpha]_D$: -60° (c 2.7, $CHCl_3$)

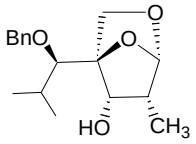
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.03 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 2.09 – 2.19 (m, 1H), 2.31 – 2.39 (m, 1H), 3.35 (d, *J* = 4.6 Hz, 1H), 3.44 (s, 3H), 3.78 (s, 3H), 4.16 (d, *J* = 12.4 Hz, 1H), 4.26 (d, *J* = 12.4 Hz, 1H), 4.34 (d, *J* = 4.1 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.91 (d, *J* = 6.0 Hz, 1H), 5.34 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.35 (s, 5H), 7.36 (d, *J* = 8.7 Hz, 2H)

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 9.7, 19.0, 23.3, 28.6, 44.1, 55.1, 56.7, 67.2, 75.1, 80.0, 83.4, 84.3, 98.1, 112.5, 113.4 (2C), 127.4 (2C), 127.6 (2C), 127.8, 128.5 (2C), 130.9, 138.2, 159.8

Mass (*m/z*, relative intensity, ESI-MS) : 444 (100, $[M+2]^+$), 411 (26), 277 (17)

Anal : Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74; Found: C, 70.42; H, 7.97%.

1,5'-Anhydro-5-*O*-benzyl-2,6-dideoxy-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanose (77)



Compound **75** (0.1 g, 0.23 mmol) and DDQ (10 mg, 0.05 mmol) in acetonitrile-water (3 ml, 9:1) were stirred at r. t. for 8 h. The resulting solution was diluted with ethyl acetate, filtered and washed with aqueous 10% $NaHCO_3$/NaCl solution. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (25% ethyl acetate in petroleum ether) to afford **77** (0.05 g, 71%) as a white solid.

$[\alpha]_D$: +24° (c 0.2, $CHCl_3$)

IR ($CHCl_3$) : 3500, 2253, 1560, 1384, 1216, 1097, 909, 789, 735 cm^{-1}

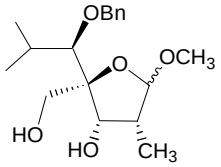
^1H NMR ($CDCl_3$, 400 MHz) : δ 1.06 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.3 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 2.24 (dq, *J* = 1.7, 7.0 Hz, 1H), 2.28 – 2.34 (m, 1H), 3.48 (d, *J* = 1.7 Hz, 1H), 3.52 (dd, *J* = 1.3, 12.0 Hz, 1H), 3.59 (d, *J* = 7.3 Hz, 1H), 3.66 (d, *J* = 7.3 Hz, 1H), 4.13 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 5.06 (t, *J* = 4.0 Hz, 1H), 7.35 (s, 5H)

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 12.8, 16.9, 23.1, 28.2, 33.1, 61.5, 73.4, 74.1, 76.3, 85.4, 95.8, 127.8 (2C), 128.1, 128.6 (2C), 137.7

Mass (*m/z*, relative intensity, ESI-MS) : 293 (100, $[M+1]^+$), 128 (38)

Anal : Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27; Found: C, 69.90; H, 8.32%.

Methyl 5-*O*-benzyl-2,6-dideoxy-4-hydroxymethyl-2,6,6-tri-*C*-methyl-D-*allo*-furanoside (78)



A mixture of **75** (0.1 g, 0.23 mmol) and DDQ (10 mg, 0.05 mmol) in acetonitrile:MeOH (3 ml, 8:2) was stirred at r. t. for 5 h, diluted with ethyl acetate, filtered and washed with aqueous 10% $NaHCO_3$/NaCl. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (40% ethyl acetate in petroleum ether) to afford **78** (0.055 g, *α*:*β* = 0.6:1, 75%) as a colourless liquid.

IR ($CHCl_3$) : 3500, 2928, 1459, 1269, 1093, 909, 790, 735 cm^{-1}

^1H NMR of major isomer ($CDCl_3$, 500 MHz) : δ 0.99 (d, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.92 – 2.00 (m, 1H), 2.27 – 2.35 (m, 1H), 3.32 (d, *J* = 2.8 Hz, 1H), 3.42 (s, 3H), 3.64 (d, *J* = 11.1 Hz, 1H), 3.79 (d, *J* = 11.1 Hz, 1H), 4.28 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.77 (d, *J* = 4.8 Hz, 1H), 7.30 – 7.34 (m, 5H)

^1H NMR of minor isomer ($CDCl_3$, 500 MHz) : δ 1.08 (t, *J* = 7.1 Hz, 6H), 1.11 (d, *J* = 6.7 Hz, 3H), 2.11 – 2.17 (m, 1H), 2.18 – 2.35 (m, 1H), 3.36 (d, *J* = 3.2 Hz, 1H), 3.41 (s, 3H), 3.88 (d, *J* = 11.1 Hz, 1H), 4.00 (d, *J* = 11.1 Hz, 1H), 4.30 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 10.7 Hz, 1H), 4.67 (d, *J* = 10.7 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 7.26 – 7.29 (m, 5H)

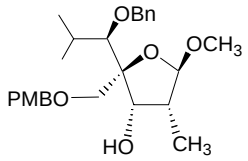
^{13}C NMR of major isomer ($CDCl_3$, 100 MHz) : δ 7.7, 16.4, 22.2, 29.9, 43.9, 55.8, 64.7, 75.0, 76.5, 87.0, 93.4, 106.8, 127.4 (2C), 128.3 (2C), 128.6, 138.7

^{13}C NMR of minor isomer ($CDCl_3$, 100 MHz) : δ 9.8, 17.8, 23.3, 30.9, 43.8, 56.6, 63.7, 75.9, 77.2, 88.4, 97.3, 111.7, 127.5 (2C), 127.8 (2C), 128.0, 138.7

Mass (*m/z*, relative intensity, ESI-MS) : 325 (14, $[M+1]^+$), 301 (82), 275 (36), 128 (100)

Anal : Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70; Found: C, 66.42; H, 8.52%.

Methyl 5-*O*-benzyl-2,6-dideoxy-4-(*p*-methoxybenzyloxymethyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside (79)



To a solution of **75** (0.2 g, 0.45 mmol) and $LiAlH_4$ (0.069 g, 1.81 mmol) in diethyl ether (2 ml) at 0 °C was added a solution of $AlCl_3$ [(0.24 g, 1.81 mmol) in diethyl ether (2 ml)] and stirring was continued for 3 h. Excess of LAH was decomposed with ethyl acetate and $Al(OH)_3$ was precipitated by the addition of water. The organic layer was separated and the residue washed with ethyl acetate. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (18% ethyl acetate in petroleum ether) to afford **79** (0.15 g, 75%) as a colourless oil.

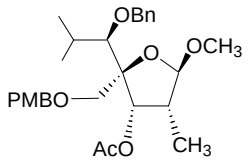
$[\alpha]_D$: -27° (c 2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 0.95 – 1.02 (m, 6H), 1.05 (d, *J* = 7.3 Hz, 3H), 1.85 – 1.99 (m, 1H), 2.14 – 2.26 (m, 1H), 3.32 (d, *J* = 2.9 Hz, 1H), 3.45 (s, 3H), 3.59 (d, *J* = 9.5 Hz, 1H), 3.77 (s, 3H), 3.84 (d, *J* = 9.5 Hz, 1H), 4.38 (d, *J* = 7.3 Hz, 1H), 4.48 (s, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 5.9 Hz, 1H), 4.81 (d, *J* = 11.0 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.38 (m, 5H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 9.6, 17.0, 22.7, 29.5, 44.3, 55.1, 56.5, 71.8, 73.6, 75.9, 76.5, 87.4, 90.2, 110.8, 113.9 (2C), 127.3, 127.7 (2C), 128.1 (3C), 129.3, 129.5, 138.9, 159.4

Anal : Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16; Found: C, 70.10; H, 8.32%.

Methyl 3-*O*-acetyl-5-*O*-benzyl-2,6-dideoxy-4-(*p*-methoxybenzyloxymethyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside (80)



A suspension of **79** (20 mg, 0.04 mmol), DMAP (5 mg) and acetic anhydride (0.019 ml, 0.2 mmol) in pyridine (1 ml) was stirred at r. t. for 3 h. The reaction mixture was concentrated and the residue purified on silica gel column (15% ethyl acetate in petroleum ether) to furnish **80** (15 mg, 68%) as a colourless oil.

$[\alpha]_D$: -7° (c 0.3, $CHCl_3$)

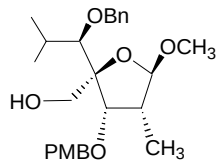
IR ($CHCl_3$) : 3018, 2927, 1736, 1513, 1216, 1029, 757 cm^{-1}

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 0.86 (d, *J* = 5.0 Hz, 3H), 0.92 (d, *J* = 5.0 Hz, 3H), 1.03 (d, *J* = 5.0 Hz, 3H), 1.90 – 1.97 (m, 1H), 1.99 (s, 3H), 2.42 (q, *J* = 10.0 Hz, 1H), 3.39 (d, *J* = 10.0 Hz, 1H), 3.50 (s, 3H), 3.51 (d, *J* = 10.0 Hz, 1H), 3.58 (br s, 1H), 3.81 (s, 3H), 4.44 (d, *J* = 10.0 Hz, 1H), 4.47 – 4.55 (m, 2H), 4.66 (d, *J* = 5.0 Hz, 1H), 4.93 (d, *J* = 10.0 Hz, 1H), 5.61 (d, *J* = 10.0 Hz, 1H), 6.84 (d, *J* = 10.0 Hz, 2H), 7.23 (d, *J* = 10.0 Hz, 2H), 7.27 – 7.40 (m, 5H)

Mass (*m/z*, relative intensity, ESI-MS) : 486 (5, $[M]^+$), 389 (32), 301 (100), 227 (17), 128 (93)

Anal : Calcd. for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87; Found: C, 69.35; H, 7.65%.

Methyl 5-*O*-benzyl-2,6-dideoxy-4-*C*-hydroxymethyl-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside (81)



To the solution of **75** (1 g, 2.3 mmol) in dry toluene (20 ml) at –40 °C was added dropwise 2.21 *M* DIBAL-H in toluene (5 ml, 11.3 mmol). The solution was stirred at –40 °C for 2 h and excess DIBAL-H was quenched with 10% NaOH solution. After 2 h, the aqueous phase was extracted with ethyl acetate and the organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel with 18% ethyl acetate in petroleum ether to afford **81** (0.78 g, 78%) as a colourless oil.

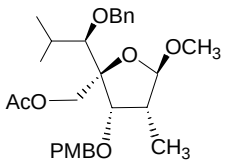
$[\alpha]_D$: -31° (c 0.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.03 (d, *J* = 7.3 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 3H), 1.11 (d, *J* = 7.3 Hz, 3H), 2.08 – 2.22 (m, 1H), 2.26 – 2.40 (m, 1H), 2.82 (br d, *J* = 6.6 Hz, 1H), 3.34 (d, *J* = 3.7 Hz, 1H), 3.41 (s, 3H), 3.78 (s, 3H), 3.79 (d, *J* = 11.7 Hz, 1H), 3.90 (d, *J* = 11.7 Hz, 1H), 4.19 (d, *J* = 6.6 Hz, 1H), 4.38 (s, 2H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.68 (s, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.36 (m, 5H)

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 10.8, 17.8, 23.7, 29.1, 43.6, 55.2, 56.2, 63.3, 73.6, 75.9, 84.2, 88.3, 90.1, 110.8, 113.8 (2C), 127.6 (3C), 128.4 (2C), 129.4 (2C), 129.9, 138.6, 159.4

Anal : Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16; Found: C, 69.99; H, 8.02%.

Methyl 4-acetyloxymethyl-5-*O*-benzyl-2,6-dideoxy-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside (82)



A solution of **81** (20 mg, 0.04 mmol), DMAP (5 mg) and acetic anhydride (0.019 ml, 0.2 mmol) in pyridine (1 ml) was stirred at r. t. for 2 h. The reaction mixture was concentrated and the residue purified on silica gel column (15% ethyl acetate in petroleum ether) to furnish **82** (17 mg, 77%) as a colourless oil.

$[\alpha]_D$: -14° (c 1.3, $CHCl_3$)

IR ($CHCl_3$) : 3019, 1738, 1515, 1373, 1216, 1069, 759 cm^{-1}

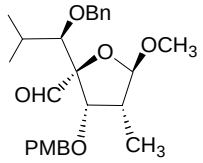
^1H NMR ($CDCl_3$, 500 MHz) : δ 0.97 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 6H), 2.05 (s, 3H), 2.07 (br s, 1H), 2.29 – 2.36 (m, 1H), 3.42 (s, 3H), 3.43 (d, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 4.07 (d, *J* = 12.4 Hz, 1H), 4.21 (d, *J* = 6.9 Hz, 1H), 4.31 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 12.4 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 5.0 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.37 (m, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.6, 17.2, 21.1, 23.3, 29.7, 43.7, 55.2, 56.5, 64.6, 73.1, 76.0, 82.3, 87.3, 88.6, 110.5, 113.7 (2C), 127.6 (2C), 128.2 (2C), 128.9 (2C), 129.1, 130.3, 139.0, 159.1, 170.8

Mass (*m/z*, relative intensity, ESI-MS) : 487 (8, $[M+1]^+$), 431 (100), 341 (26), 301 (13)

Anal : Calcd. for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87; Found: C, 69.30; H, 7.70%.

Methyl 5-*O*-benzyl-4-carbaldehyde-2,6-dideoxy-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside (83)



A solution of **81** (0.65 g, 9.0 mmol) and Dess-martin periodinane (1 g, 2.2 mmol) in CH_2Cl_2 (10 ml) was stirred at r. t. for 2 h. Diethyl ether, saturated $NaHCO_3$ and 1.5 *M* aqueous $Na_2S_2O_3$ were added and stirring was continued until two clear layers formed. The aqueous phase was extracted with diethyl ether and the combined extract was washed with water followed by brine and dried (Na_2SO_4). The solvent was removed and the residue was purified on silica gel with 15% ethyl acetate in petroleum ether as an eluent to give **83** (0.55 g, 85%) as a white solid.

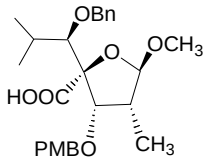
IR ($CHCl_3$) : 2961, 2929, 2253, 1729, 1606, 1513, 1456, 1385, 1257, 1095, 789 cm^{-1}

^1H NMR ($CDCl_3$, 500 MHz) : δ 0.94 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.3 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 3H), 2.12-2.20 (m, 1H), 2.29 – 2.36 (m, 1H), 3.40 (s, 3H), 3.49 (d, *J* = 2.7 Hz, 1H), 3.76 (s, 3H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 6.4 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.36 (m, 5H), 9.84 (s, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 10.6, 17.5, 22.4, 29.4, 42.9, 55.2, 55.9, 72.8, 75.7, 85.8, 89.5, 91.3, 111.0, 113.7 (2C), 127.3 (2C), 127.7, 128.4 (2C), 129.2 (2C), 129.5, 138.4, 159.3, 201.7

Mass (*m/z*, relative intensity, ESI-MS) : 442 (19, $[M]^+$), 375 (100), 345 (62), 301 (81), 217 (37).

Methyl 5-*O*-benzyl-2,6-dideoxy-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside-4-carboxylic acid (84)



To a solution **83** (0.55 g, 1.2 mmol) in acetonitrile (10 ml), NaH_2PO_4 (0.039 g, 0.3 mmol) in water (0.05 ml) and 35% H_2O_2 (0.12 ml, 1.25 mmol) was added sodium chlorite (0.15 g, 1.68 mmol) in water (2 ml) dropwise in 30 minutes keeping the temperature at 10 °C. After 2 h, small amount of Na_2SO_3 was added and the reaction mixture was concentrated. The residue was extracted with ethyl acetate and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was subjected to silica gel chromatography (30% ethyl acetate in petroleum ether) to afford **84** (0.48 g, 84%) as a white solid.

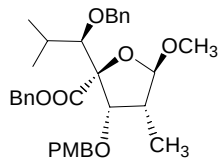
$[\alpha]_D$: -23° (c 0.5, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 0.99 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 2.18 – 2.30 (m, 2H), 3.42 (s, 3H), 3.50 (d, *J* = 3.7 Hz, 1H), 3.76 (s, 3H), 4.22 (d, *J* = 6.0 Hz, 1H), 4.34 (d, *J* = 10.5 Hz, 1H), 4.37 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.33 (m, 5H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 10.1, 17.4, 22.2, 30.1, 42.7, 55.1, 56.4, 73.4, 76.3, 84.3, 88.7, 89.2, 111.5, 113.8 (2C), 127.7 (2C), 128.2, 128.7 (2C), 129.6 (2C), 132.0, 137.2, 159.4, 170.8

Anal : Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47; Found: C, 67.94; H, 7.35%.

Methyl 5-*O*-benzyl-4-benzyloxycarbonyl-2,6-dideoxy-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanoside (85)



A suspension of **84** (30 mg, 0.07 mmol), K_2CO_3 (18 mg, 0.14 mmol) and benzyl bromide (0.008 ml, 0.07 mmol) in acetone (2 ml) was stirred at r. t. for 3 h, quenched with ice water and concentrated. It was then extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (8% ethyl acetate in petroleum ether) to obtain **85** (30 mg, 83%) as a colourless oil.

$[\alpha]_D$: +1° (c 1.4, acetone)

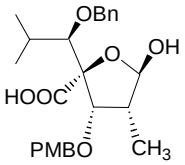
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.99 (d, *J* = 8.0 Hz, 6H), 1.07 (d, *J* = 8.0 Hz, 3H), 1.95 – 2.30 (m, 2H), 3.46 (s, 3H), 3.47 (d, *J* = 2.0 Hz, 1H), 3.76 (s, 3H), 4.19 (d, *J* = 6.0 Hz, 1H), 4.28 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.88 (d, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.40 (m, 10H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 10.2, 18.0, 22.7, 30.1, 43.6, 55.2, 56.7, 66.6, 73.8, 75.7, 83.6, 87.0, 93.4, 111.9, 113.6 (2C), 127.3 (2C), 127.4, 127.8, 128.3 (5C), 129.1 (3C), 130.3, 138.8 (2C), 159.2, 170.3

Mass (*m/z*, relative intensity, ESI-MS) : 549 (8, $[M+1]^+$), 451 (69), 361 (85), 301 (31), 152 (100), 102 (77)

Anal : Calcd. for $C_{33}H_{40}O_7$: C, 72.24; H, 7.35; Found: C, 72.49; H, 7.21%.

5-*O*-Benzyl-2,6-dideoxy-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-*β*-D-*allo*-furanose-4-carboxylic acid (86)



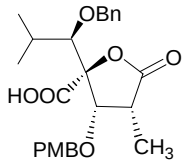
A solution of **84** (0.48 g, 1.05 mmol), HCl (3.0 ml, 2N) in THF (7.8 ml) and water (3 ml) was refluxed to 65 °C over a period of 8 h. It was neutralised with solid $NaHCO_3$ and

extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was subjected to column chromatography with 40% ethyl acetate in petroleum ether to afford **86** (0.23 g, 50%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 0.97 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 7.3 Hz, 3H), 2.00 – 2.20 (m, 2H), 3.56 (d, *J* = 2.9 Hz, 1H), 3.79 (s, 3H), 3.97 (d, *J* = 4.4 Hz, 1H), 4.28 (d, *J* = 10.2 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 10.2 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 5.23 (d, *J* = 5.1 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.33 (s, 5H)

Anal : Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26; Found: C, 67.74; H, 7.35%.

5-*O*-Benzyl-2,6-dideoxy-3-*O*-(*p*-methoxybenzyl)-2,6,6-tri-*C*-methyl-D-*allono*-1,4-lactone-4-carboxylic acid (87)



To a stirred solution of **86** (0.2 g, 0.45 mmol) in CH_2Cl_2 (5 ml) was added sequentially bis-acetoxyiodobenzene (0.72 g, 2.25 mmol) and TEMPO (0.014 g, 0.09 mmol). After stirring at r. t. for 3.5 h, saturated aqueous $Na_2S_2O_3$ and diethyl ether were added. The organic phase was washed with saturated aqueous $NaHCO_3$ followed by H_2O. The organic extract was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography with 30% ethyl acetate in petroleum ether to provide **87** (0.12 g, 60%) as colorless oil.

$[\alpha]_D$: +27° (c 0.1, $CHCl_3$)

IR ($CHCl_3$) : 3479, 3020, 1728, 1781, 1612, 1515, 1216, 1057, 757 cm^{-1}

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.03 (d, *J* = 2.5 Hz, 3H), 1.05 (d, *J* = 2.3 Hz, 3H), 1.08 (d, *J* = 2.1 Hz, 3H), 2.21 – 2.38 (m, 1H), 2.56 – 2.73 (m, 1H), 3.51 (d, *J* = 3.0 Hz, 1H), 3.77 (s, 3H), 4.30 (d, *J* = 6.4 Hz, 1H), 4.38 (d, *J* = 10.7 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.38 (m, 5H)

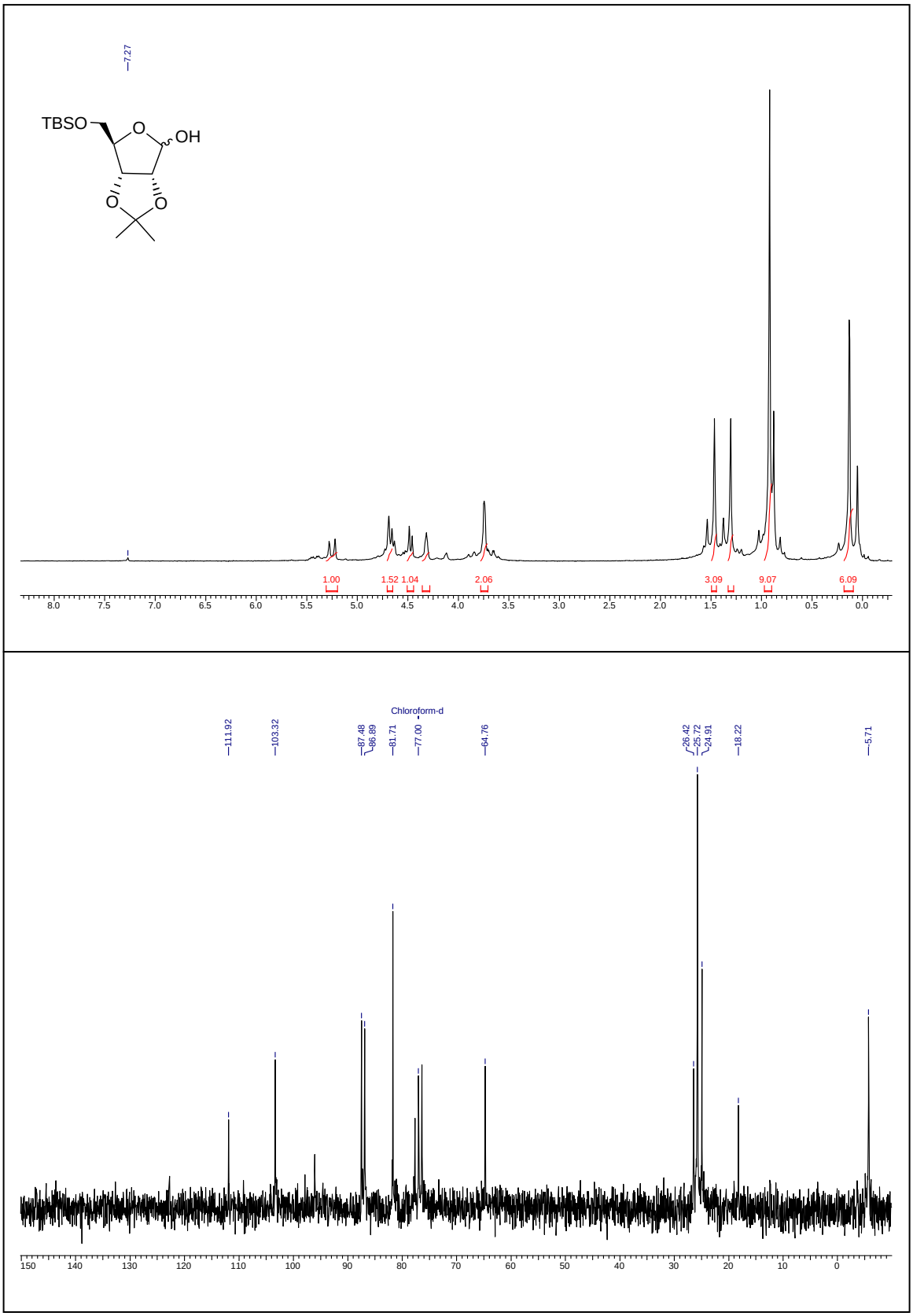
^{13}C NMR ($CDCl_3$, 125 MHz) : δ 9.3, 17.3, 22.4, 30.0, 39.7, 55.2, 74.5, 76.6, 77.6, 79.1, 85.3, 113.9 (2C), 128.4 (3C), 128.7 (4C), 130.0, 137.0, 159.8, 175.9

Mass (*m/z*, relative intensity, ESI-MS) : 442 (3, $[M]^+$), 380 (34), 316 (32), 279 (13), 216 (10), 158 (100)

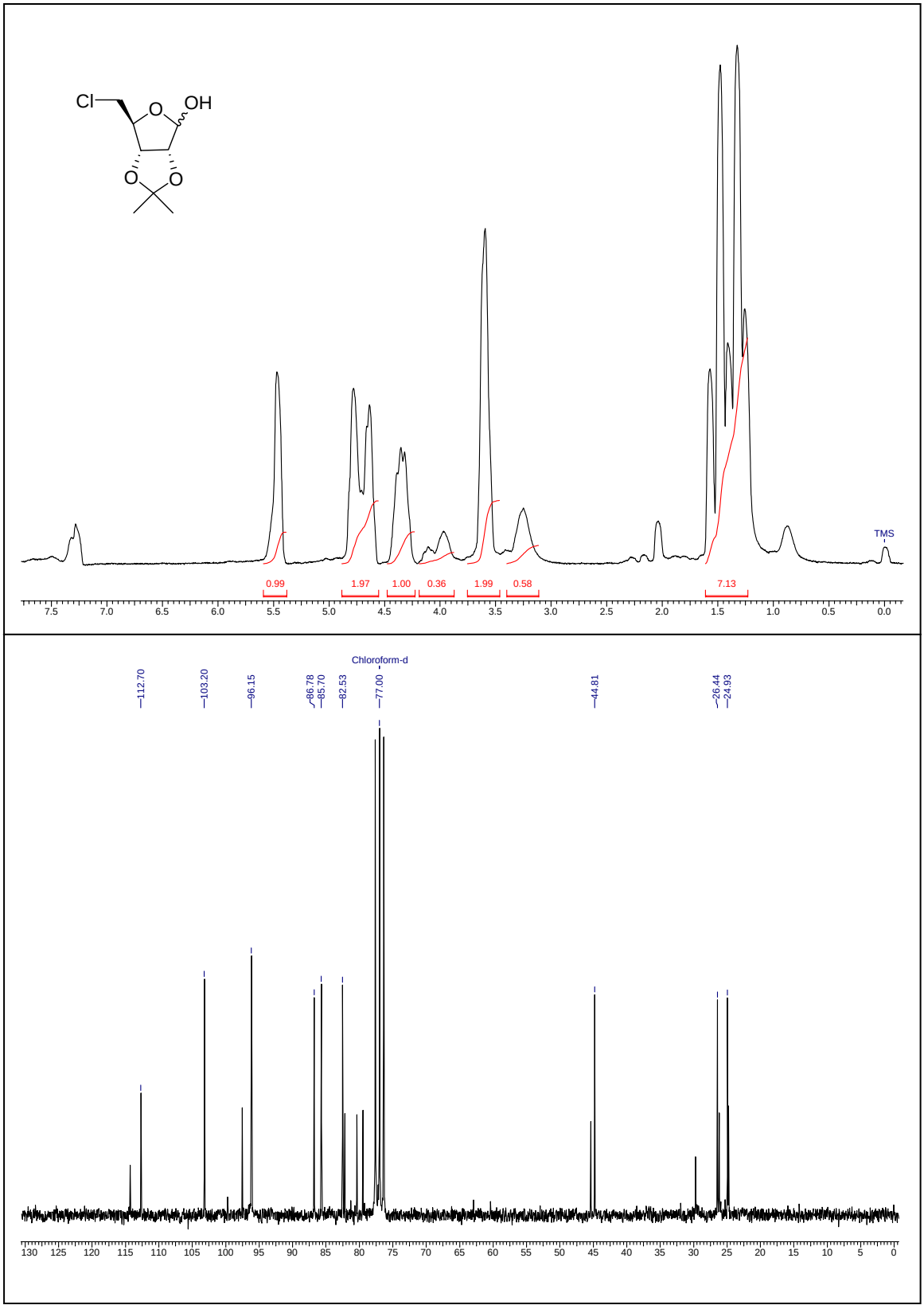
Anal : Calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83; Found: C, 67.60; H, 6.60%.

Spectroscopic Data

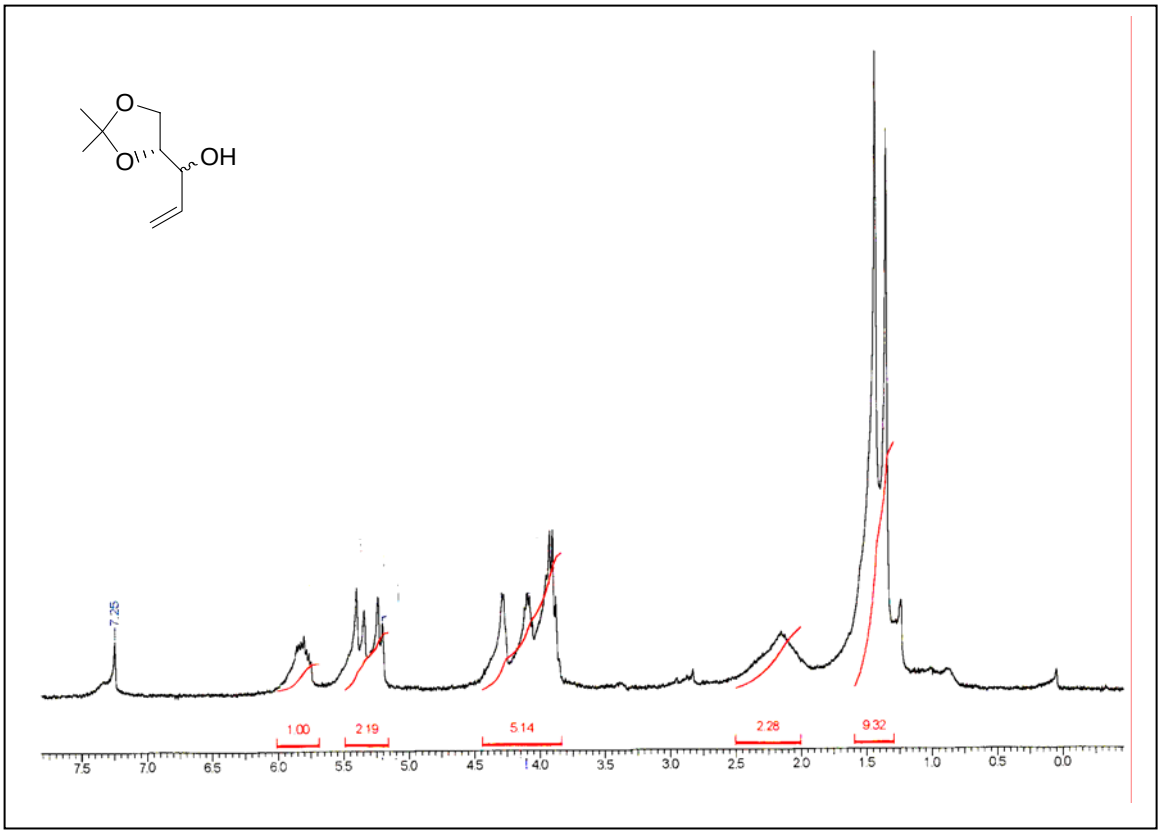
^{1}H and ^{13}C NMR spectra of compound 17 in $CDCl_3$



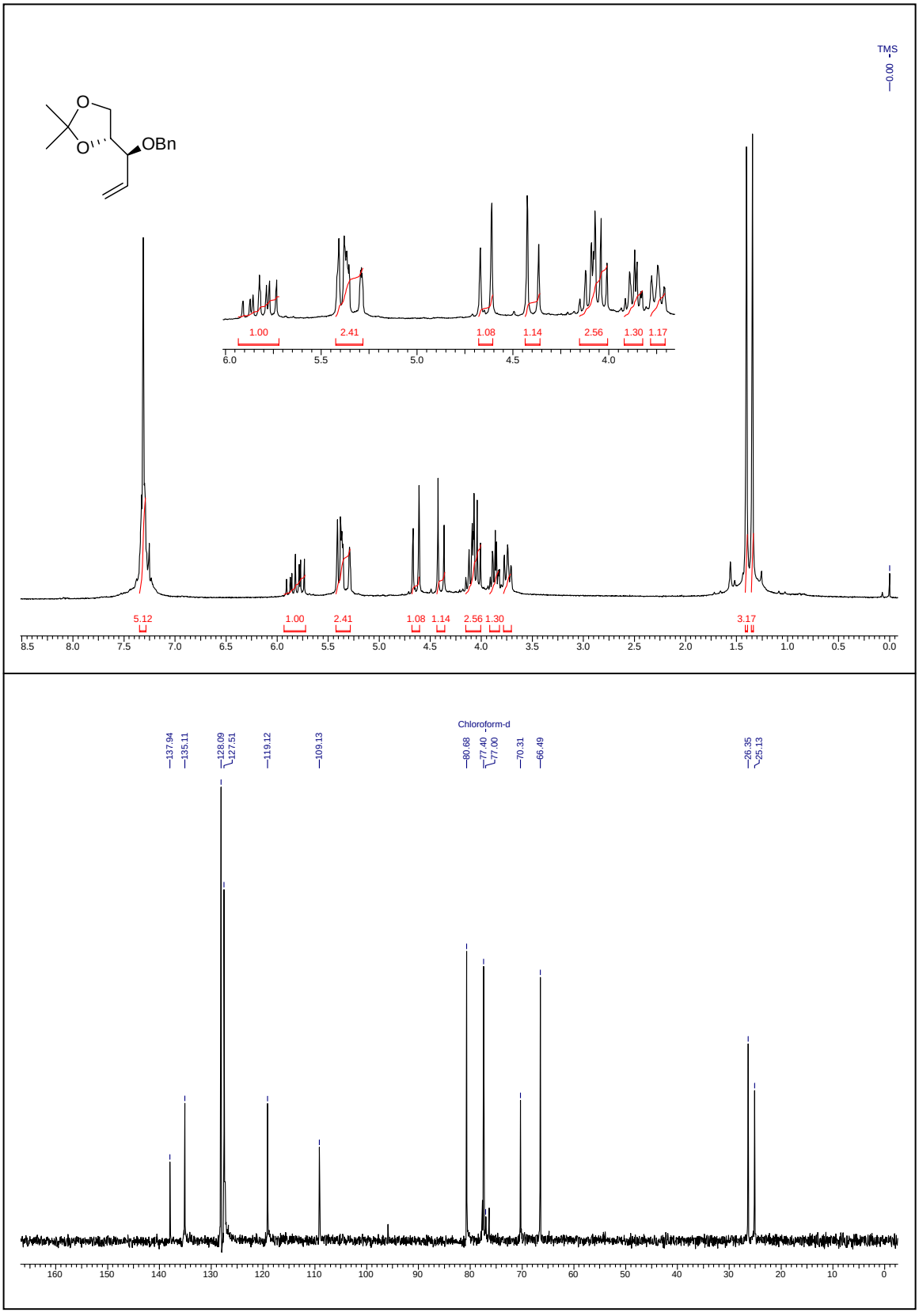
^{1}H and ^{13}C NMR spectra of compound 19 in $CDCl_3$



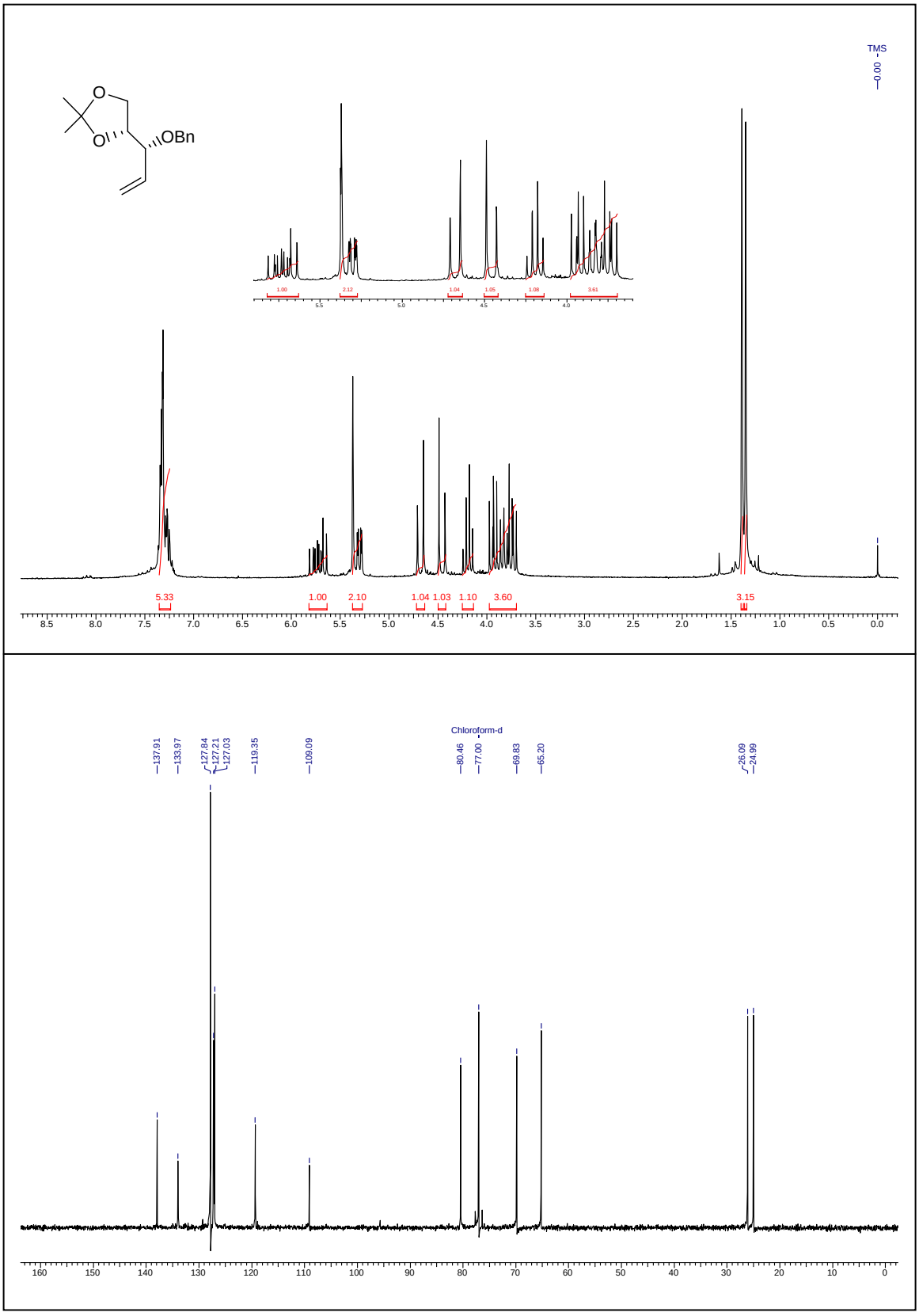
^{1}H NMR spectrum of compound 21 in $CDCl_3$



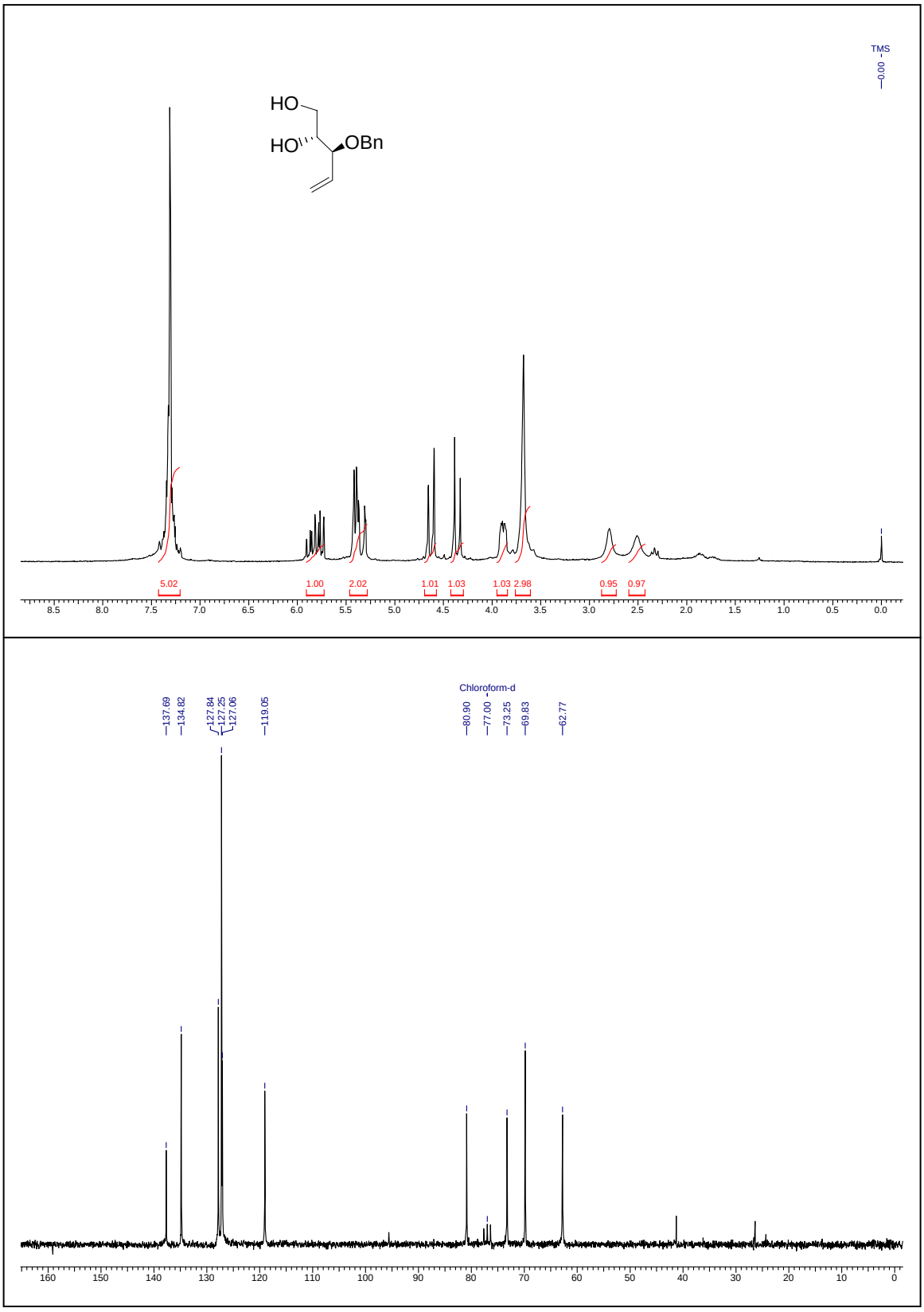
^{1}H and ^{13}C NMR spectra of compound 22 in $CDCl_3$



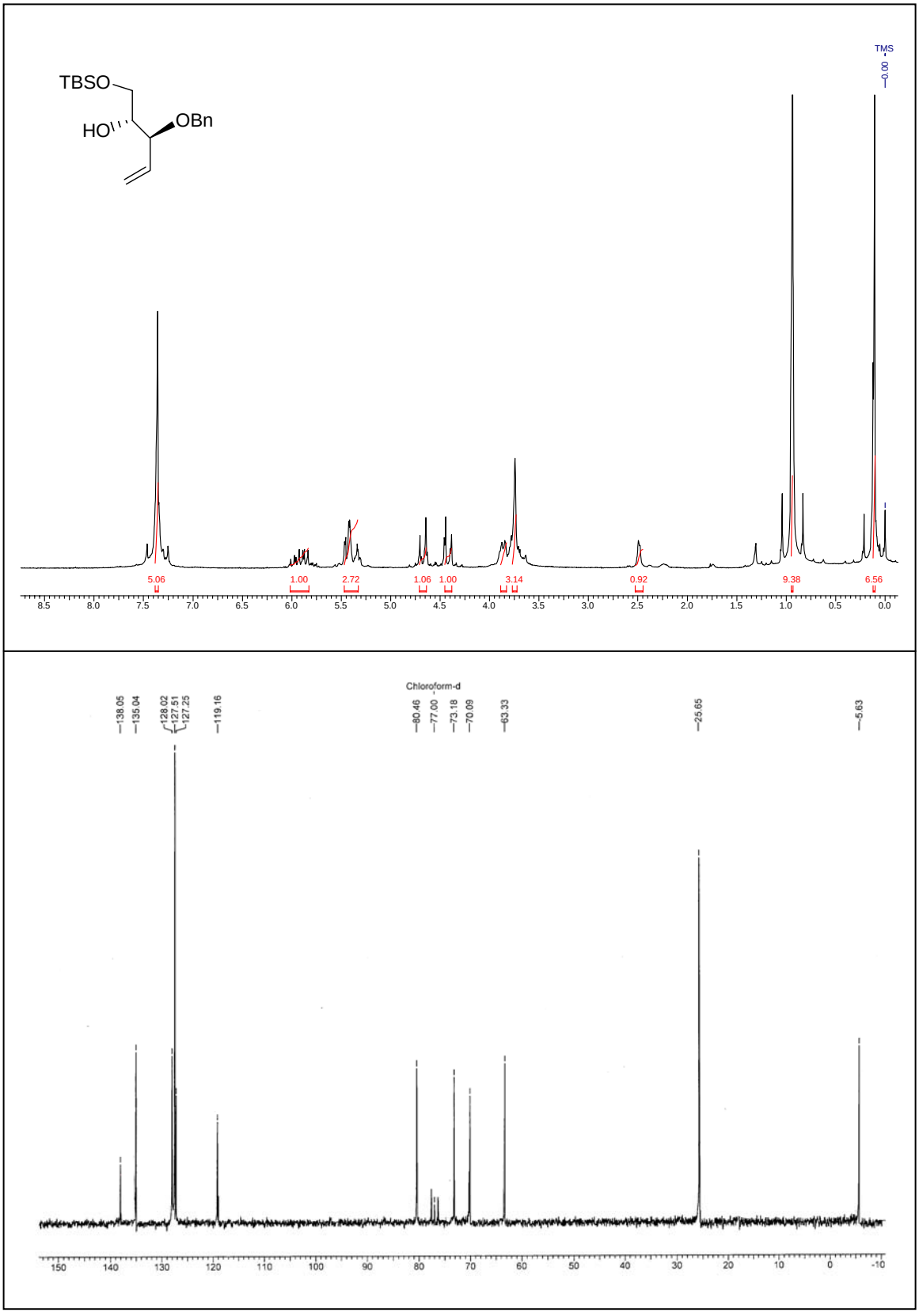
^{1}H and ^{13}C NMR spectra of compound 23 in $CDCl_3$



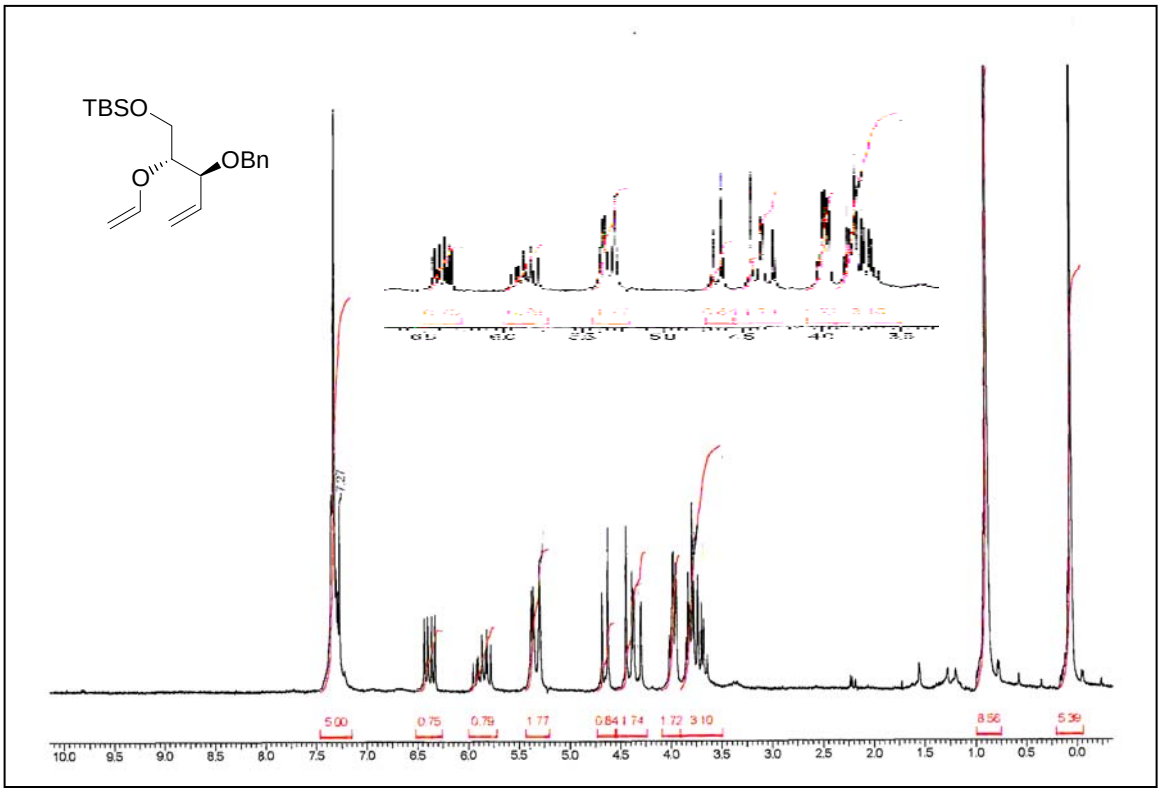
^{1}H and ^{13}C NMR spectra of compound 24 in $CDCl_3$



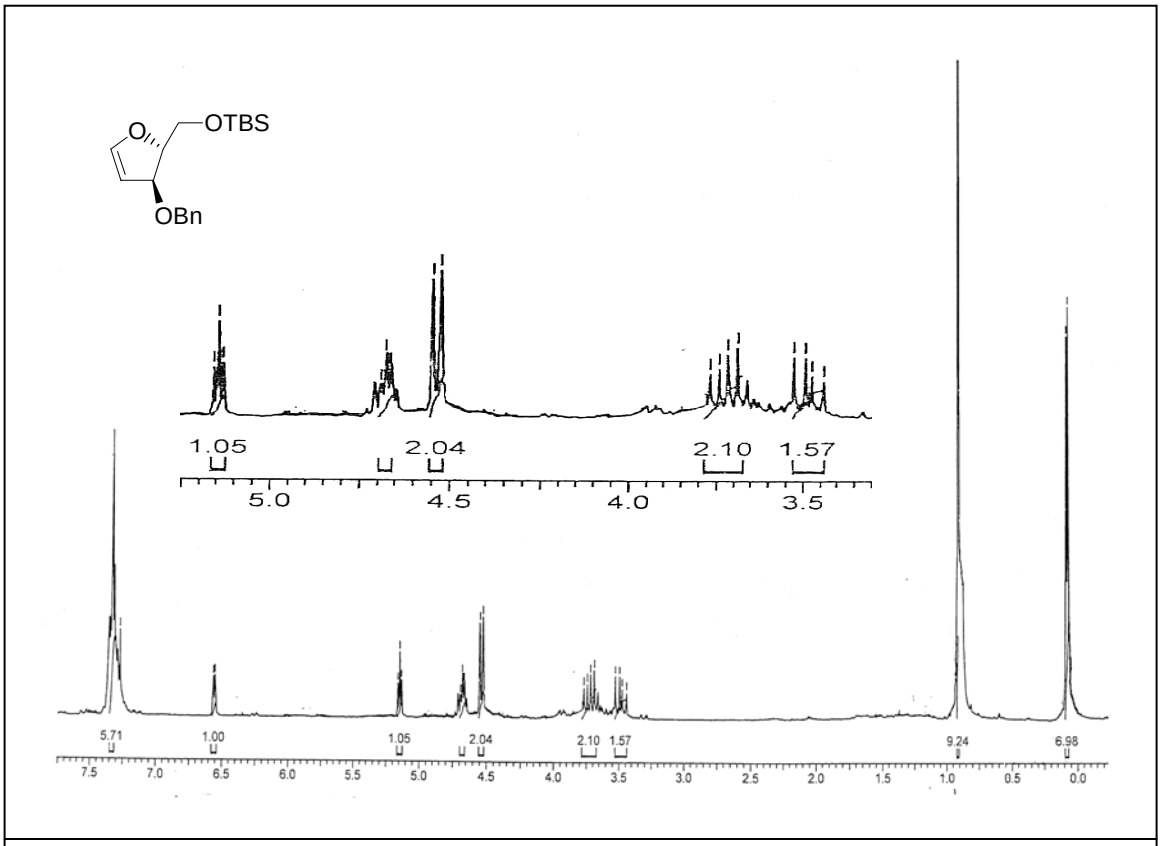
^{1}H and ^{13}C NMR spectra of compound 25 in $CDCl_3$

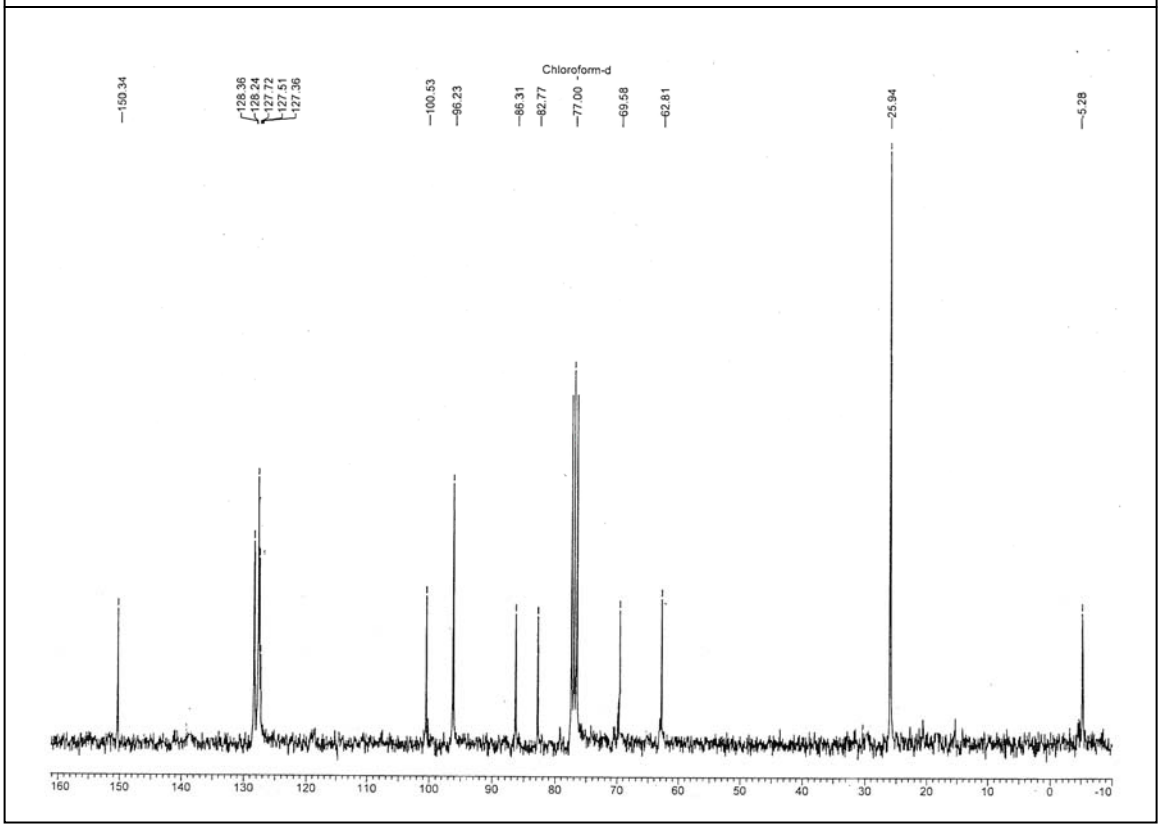


^{1}H NMR spectrum of compound 26 in $CDCl_3$

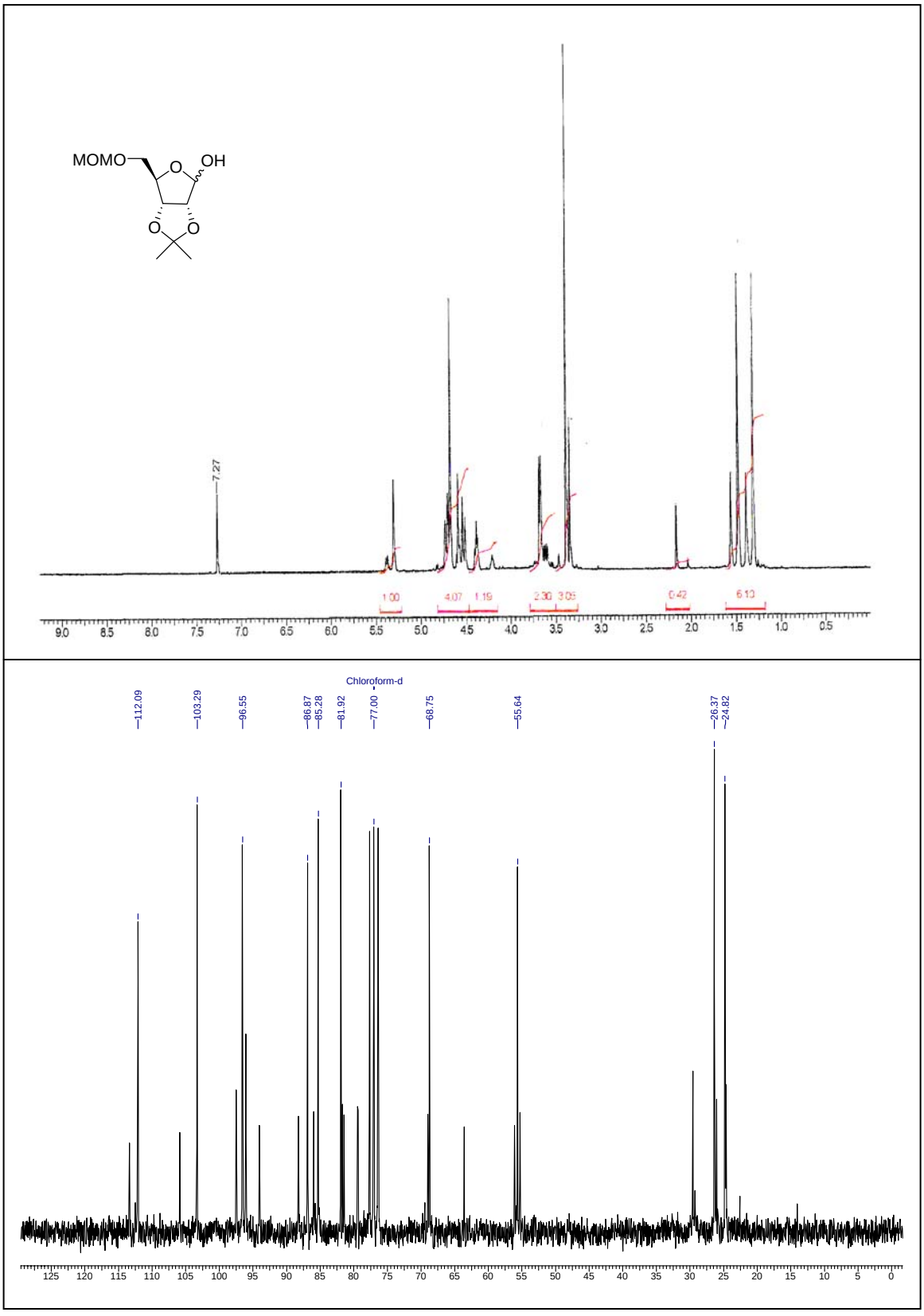


^{1}H and ^{13}C NMR spectra of compound 27 in $CDCl_3$

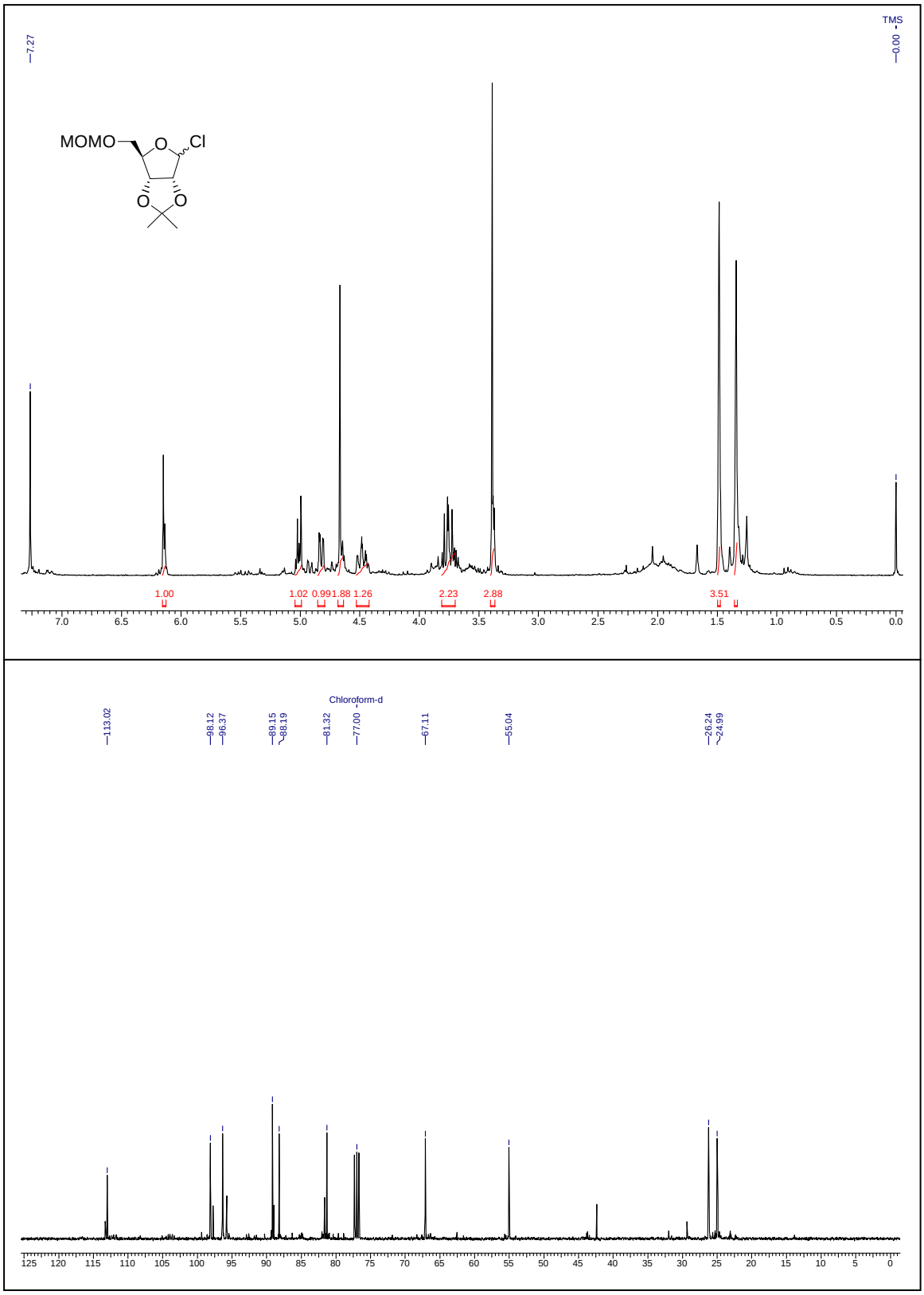




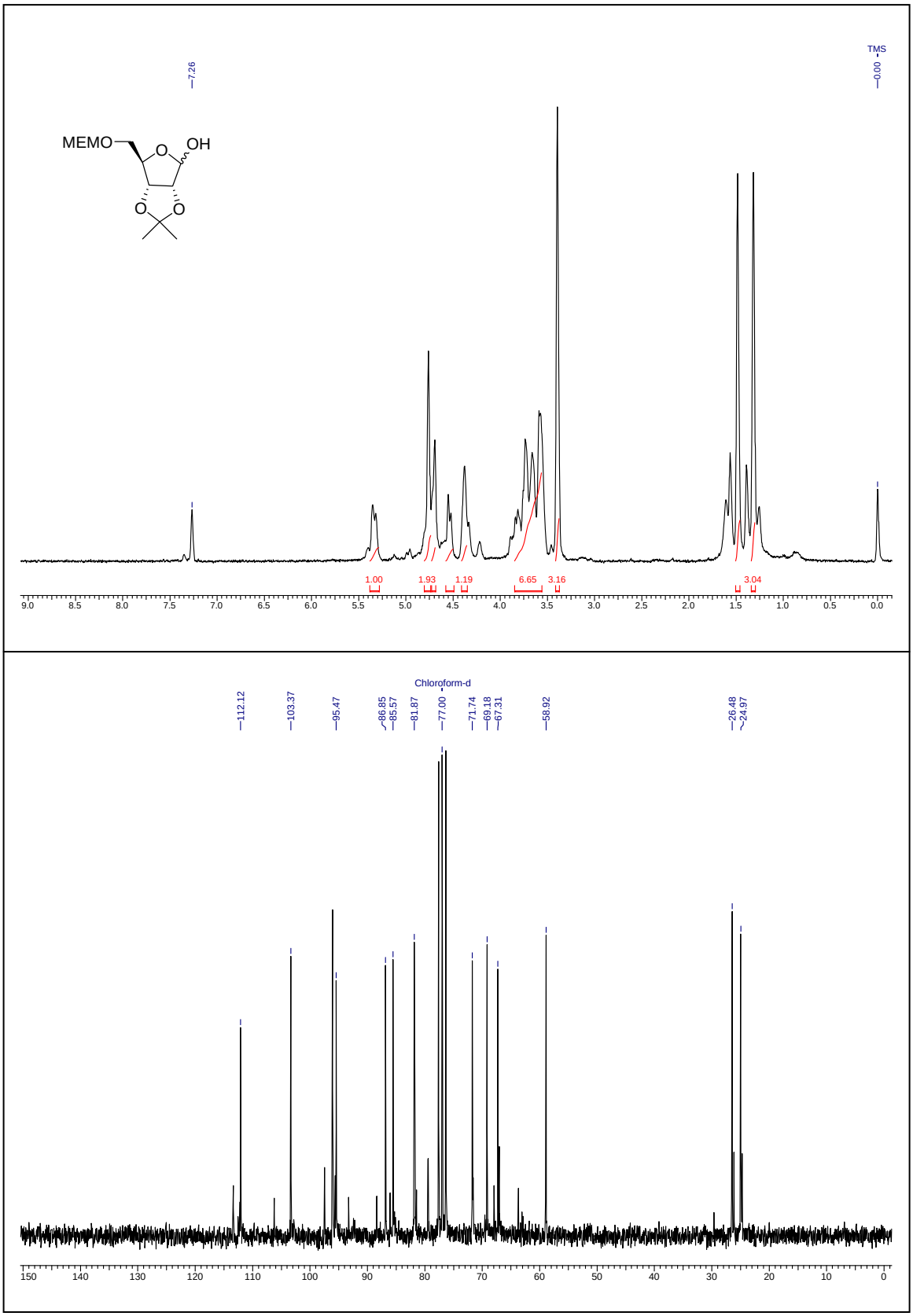
^{1}H and ^{13}C NMR spectra of compound 28 in $CDCl_3$



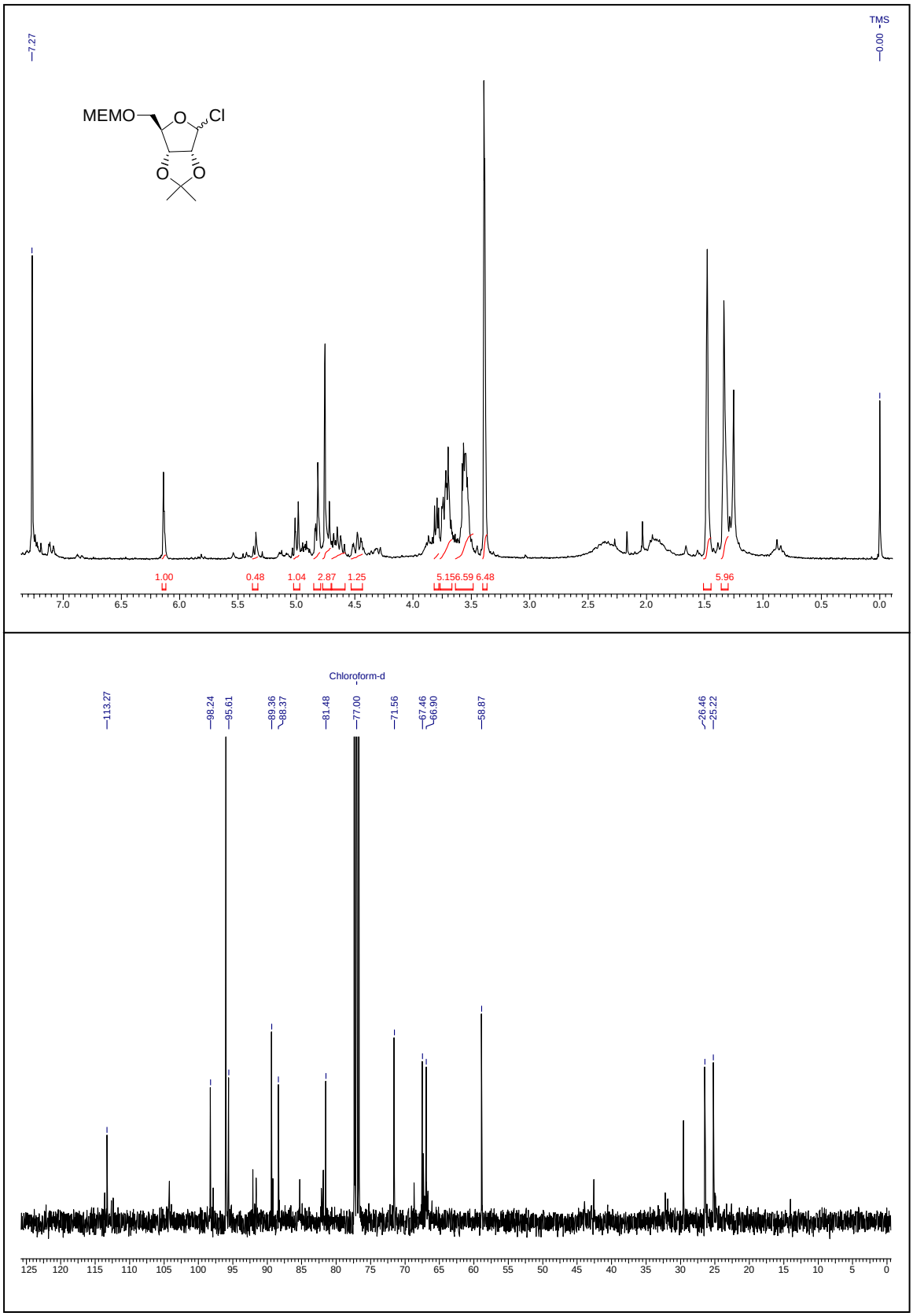
^{1}H and ^{13}C NMR spectra of compound 29 in $CDCl_3$



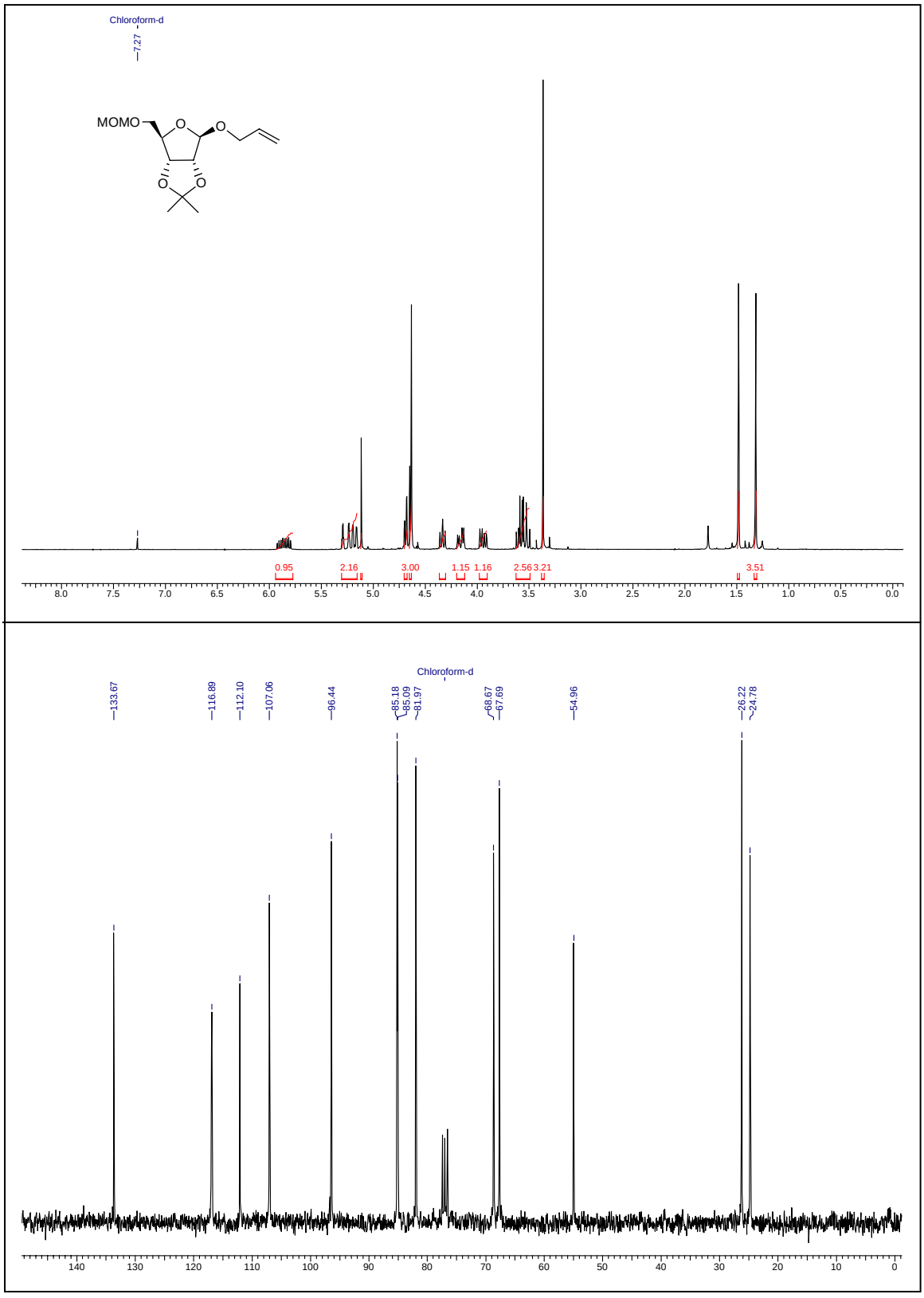
^{1}H and ^{13}C NMR spectra of compound 30 in $CDCl_3$



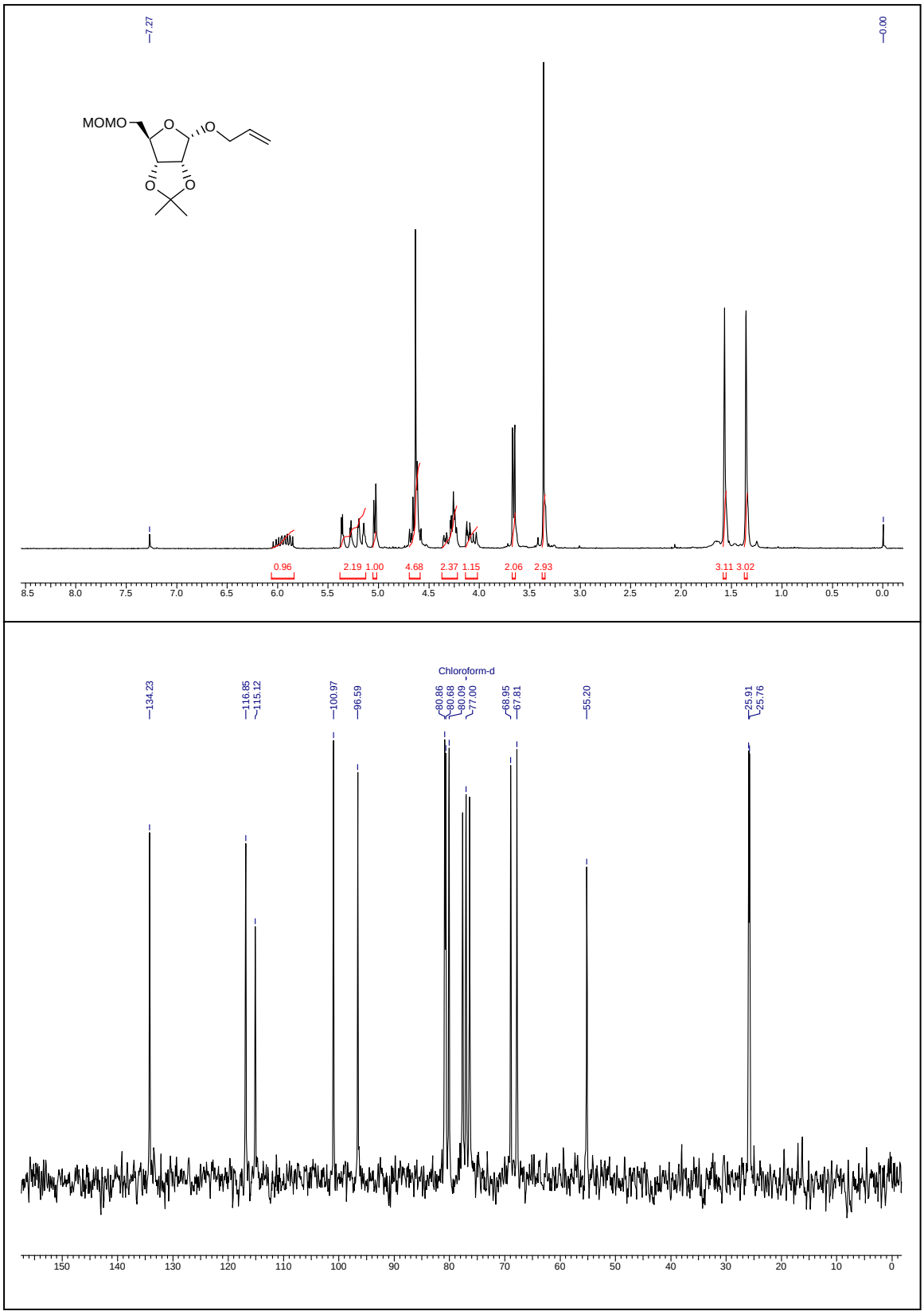
^{1}H and ^{13}C NMR spectra of compound 31 in $CDCl_3$



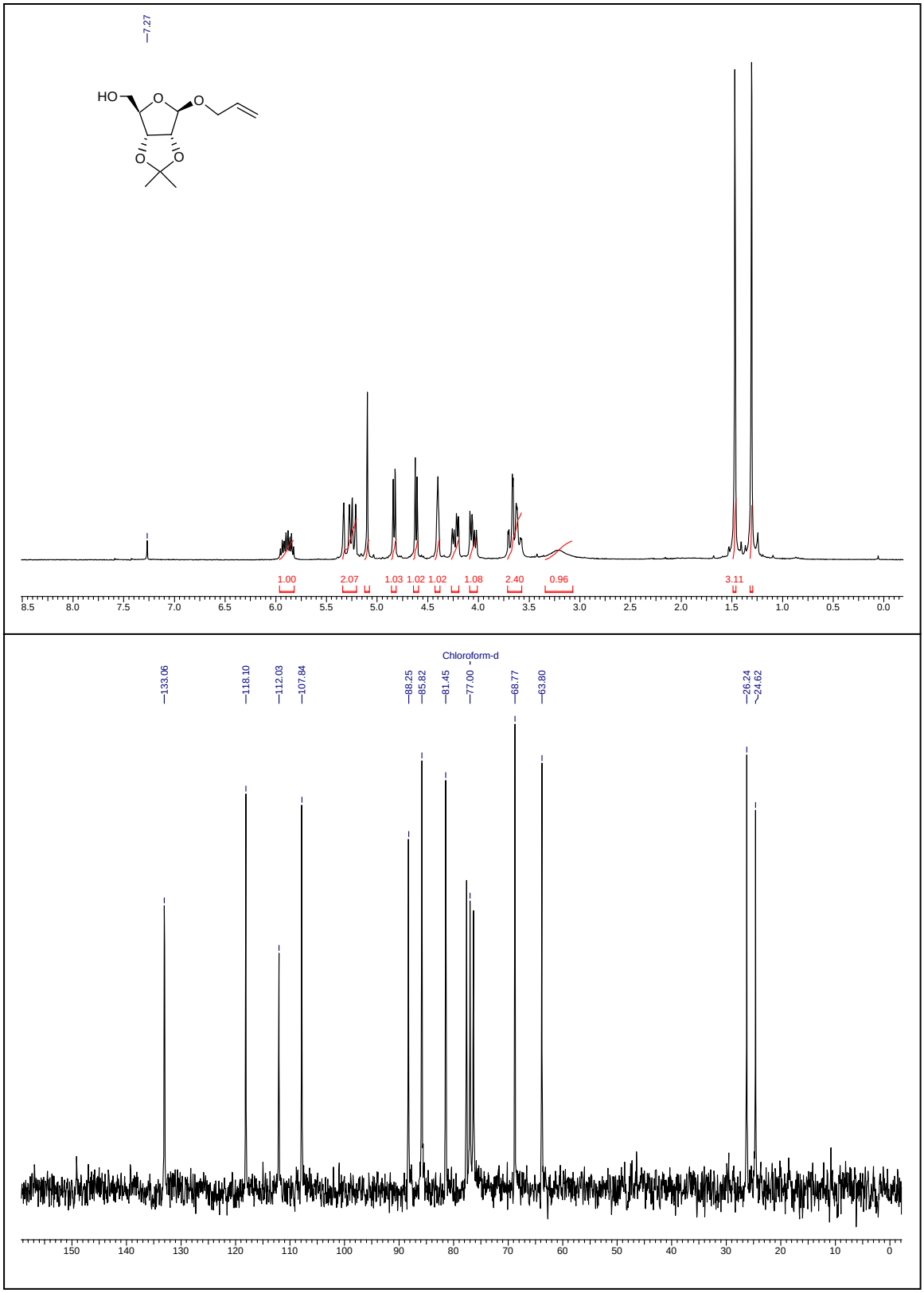
^{1}H and ^{13}C NMR spectra of compound 32 in $CDCl_3$



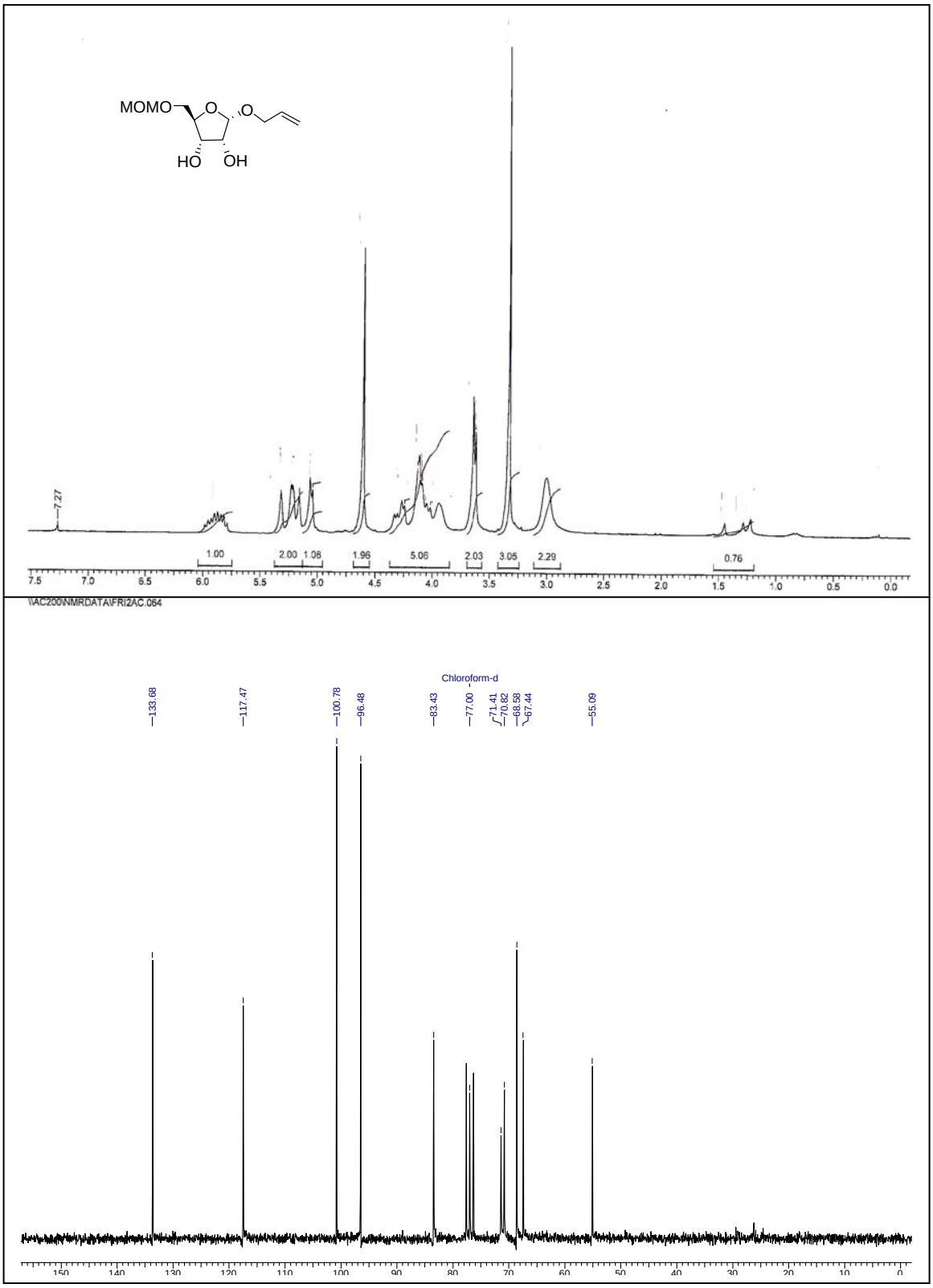
^{1}H and ^{13}C NMR spectra of compound 33 in $CDCl_3$



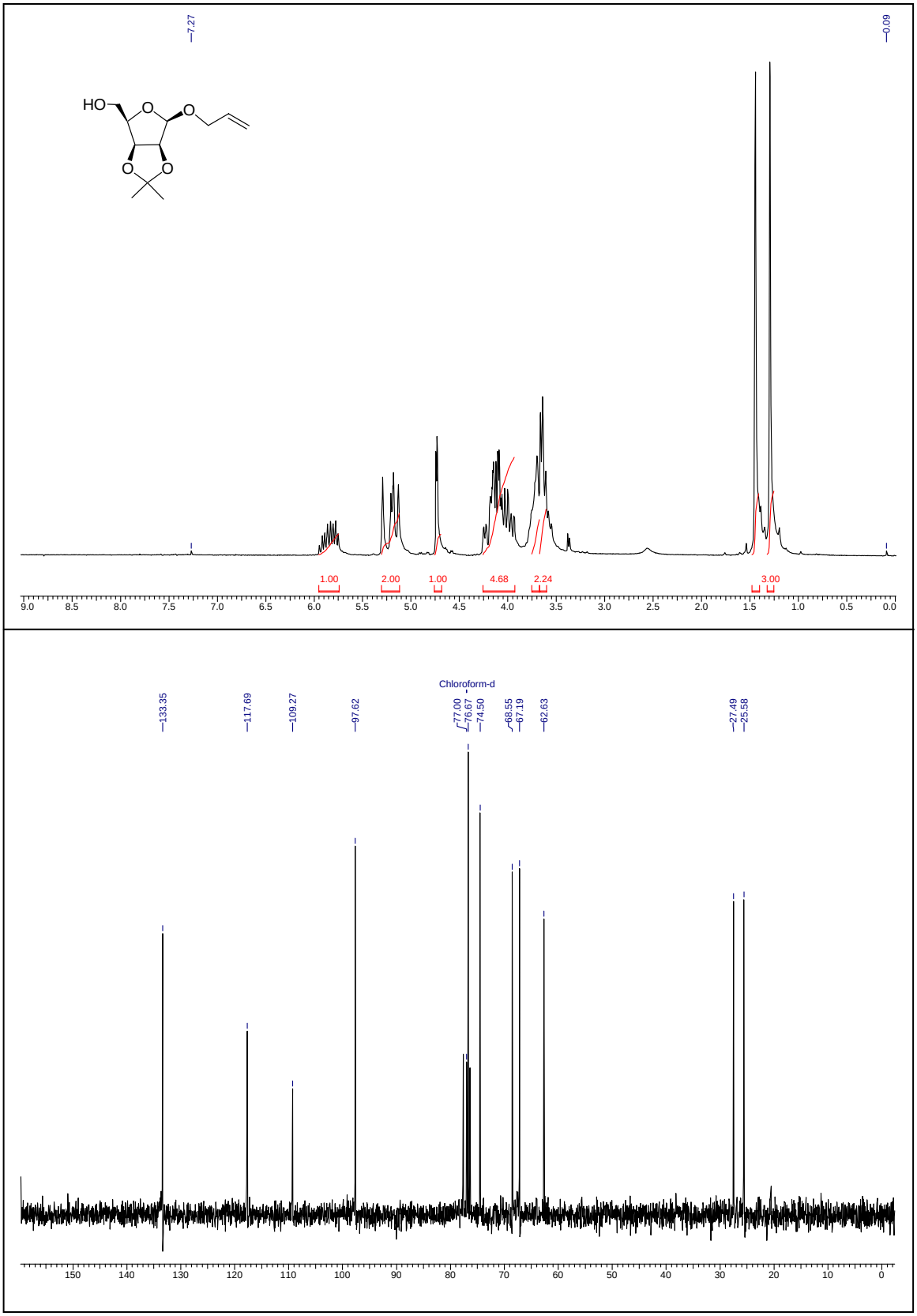
^{1}H and ^{13}C NMR spectra of compound 34 in $CDCl_3$



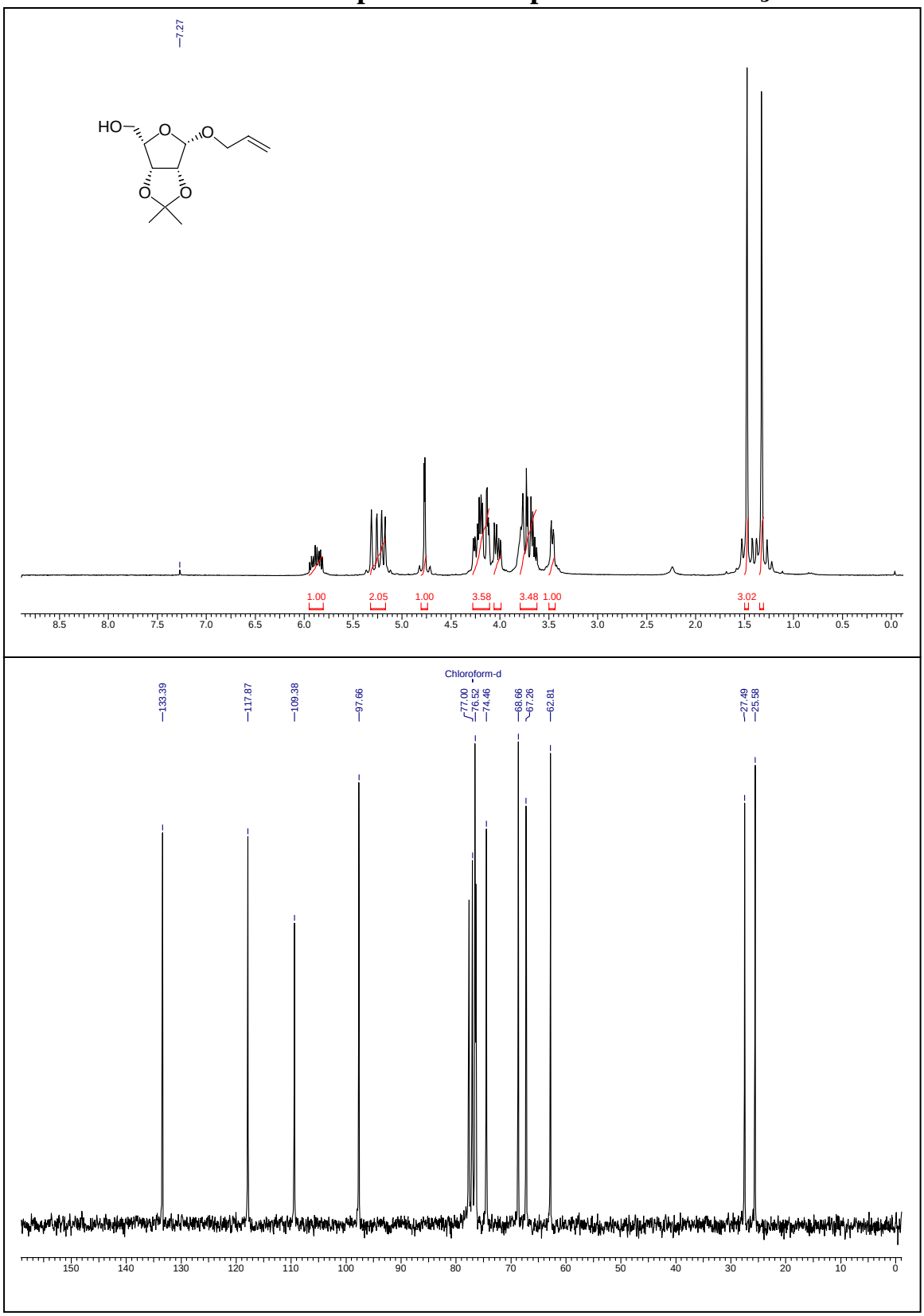
^{1}H and ^{13}C NMR spectra of compound 35 in $CDCl_3$



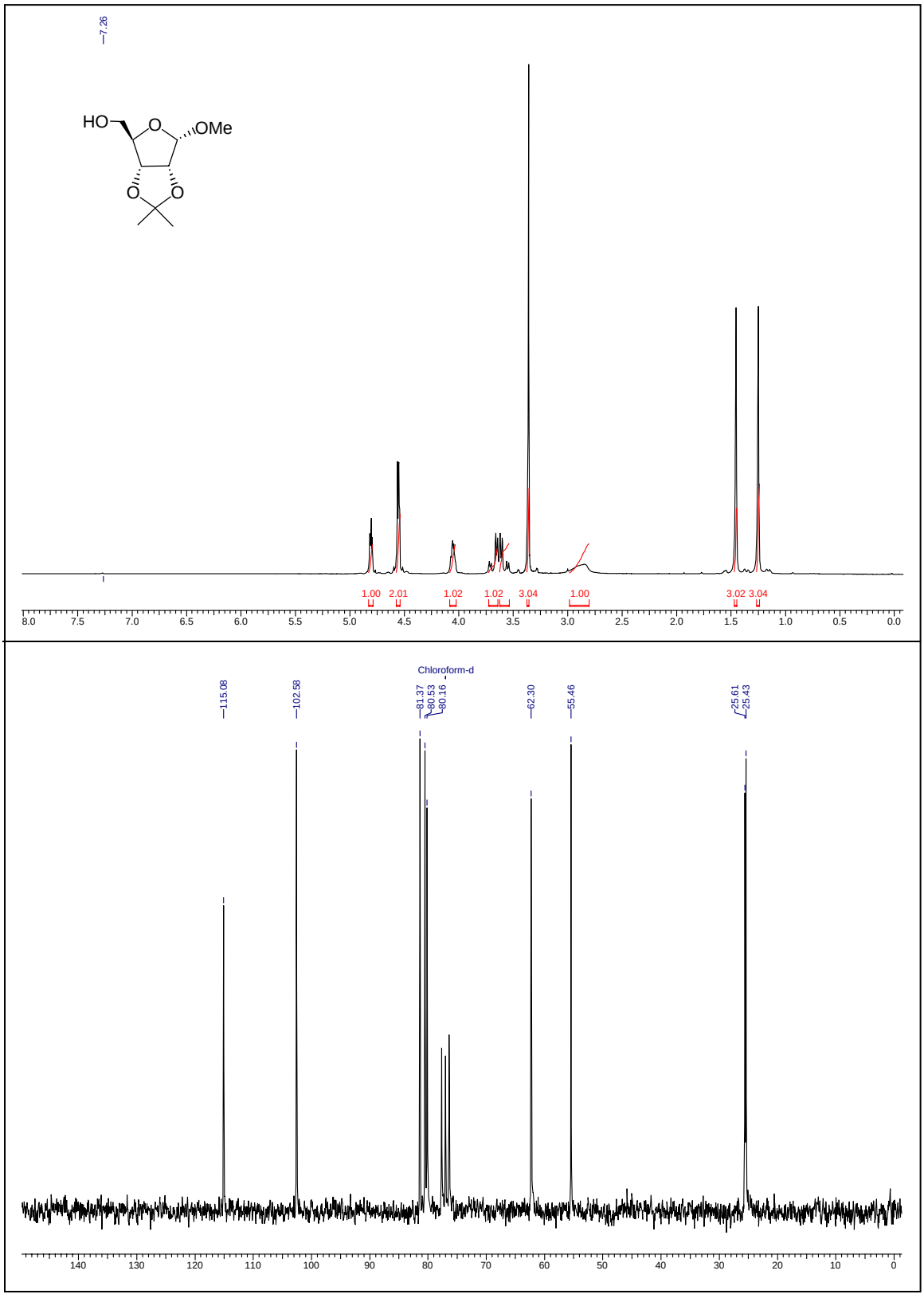
^{1}H and ^{13}C NMR spectra of compound 36 in $CDCl_3$



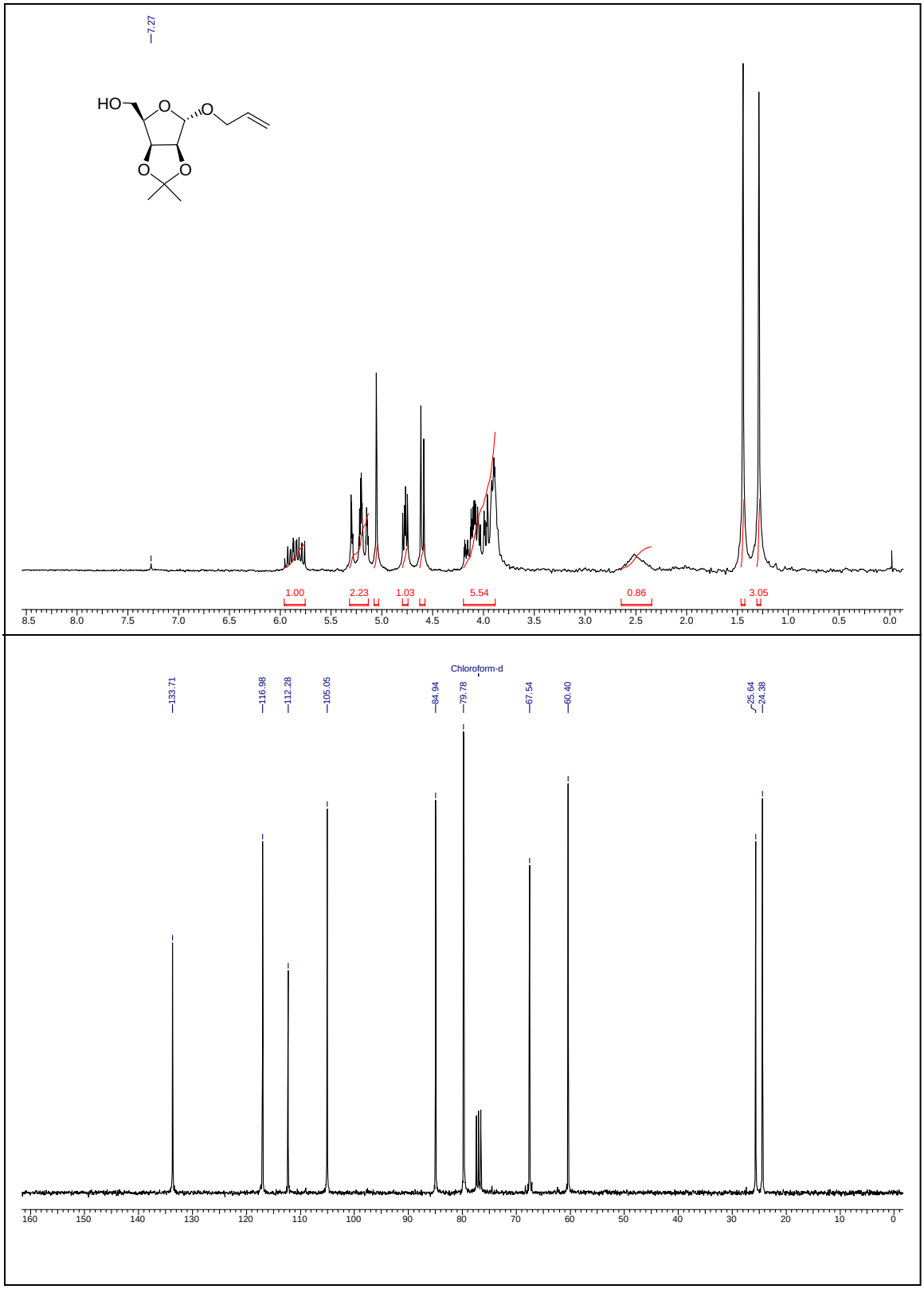
^{1}H and ^{13}C NMR spectra of compound 37 in $CDCl_3$



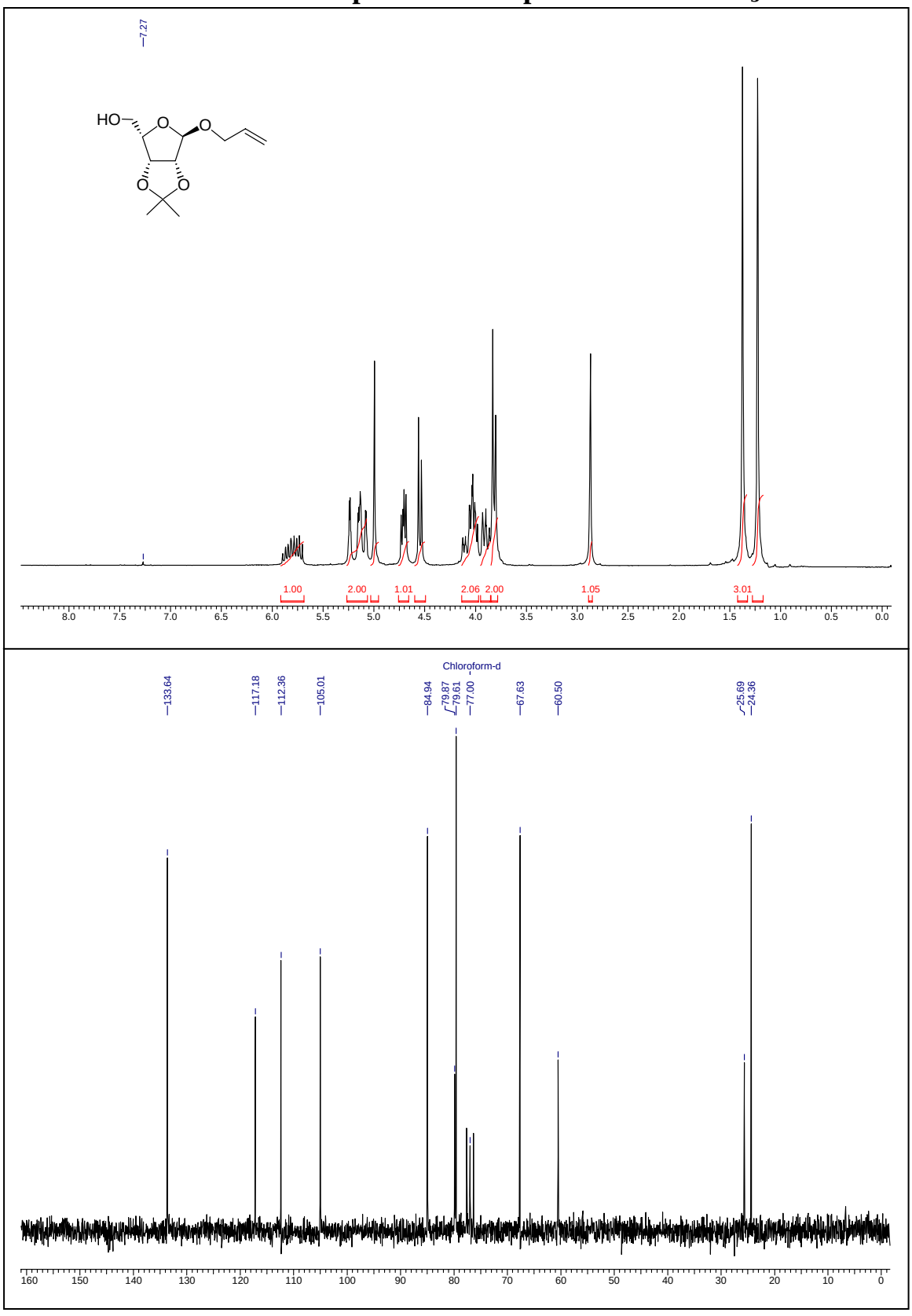
^{1}H and ^{13}C NMR spectra of compound 38 in $CDCl_3$



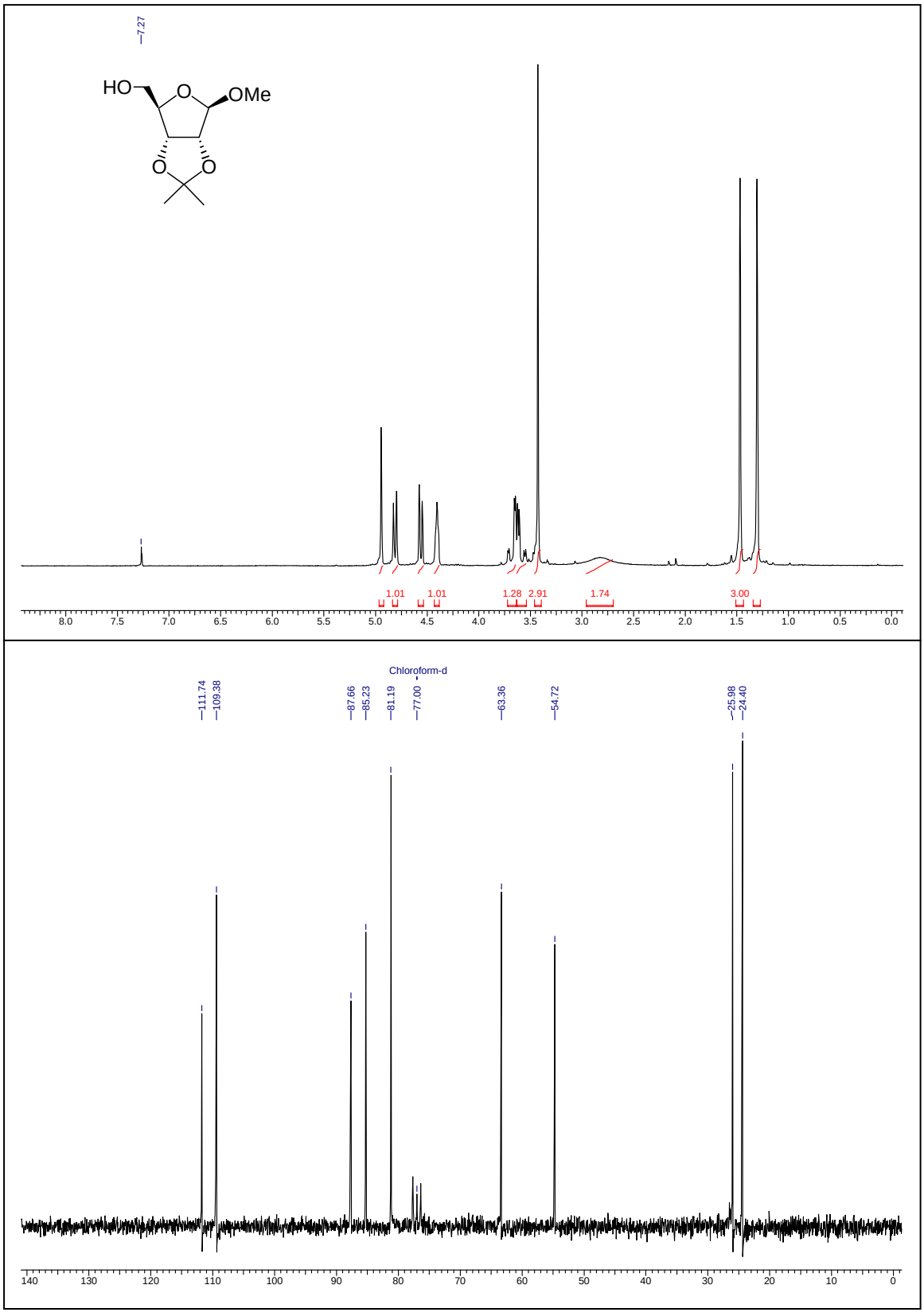
^{1}H and ^{13}C NMR spectra of compound 39 in $CDCl_3$



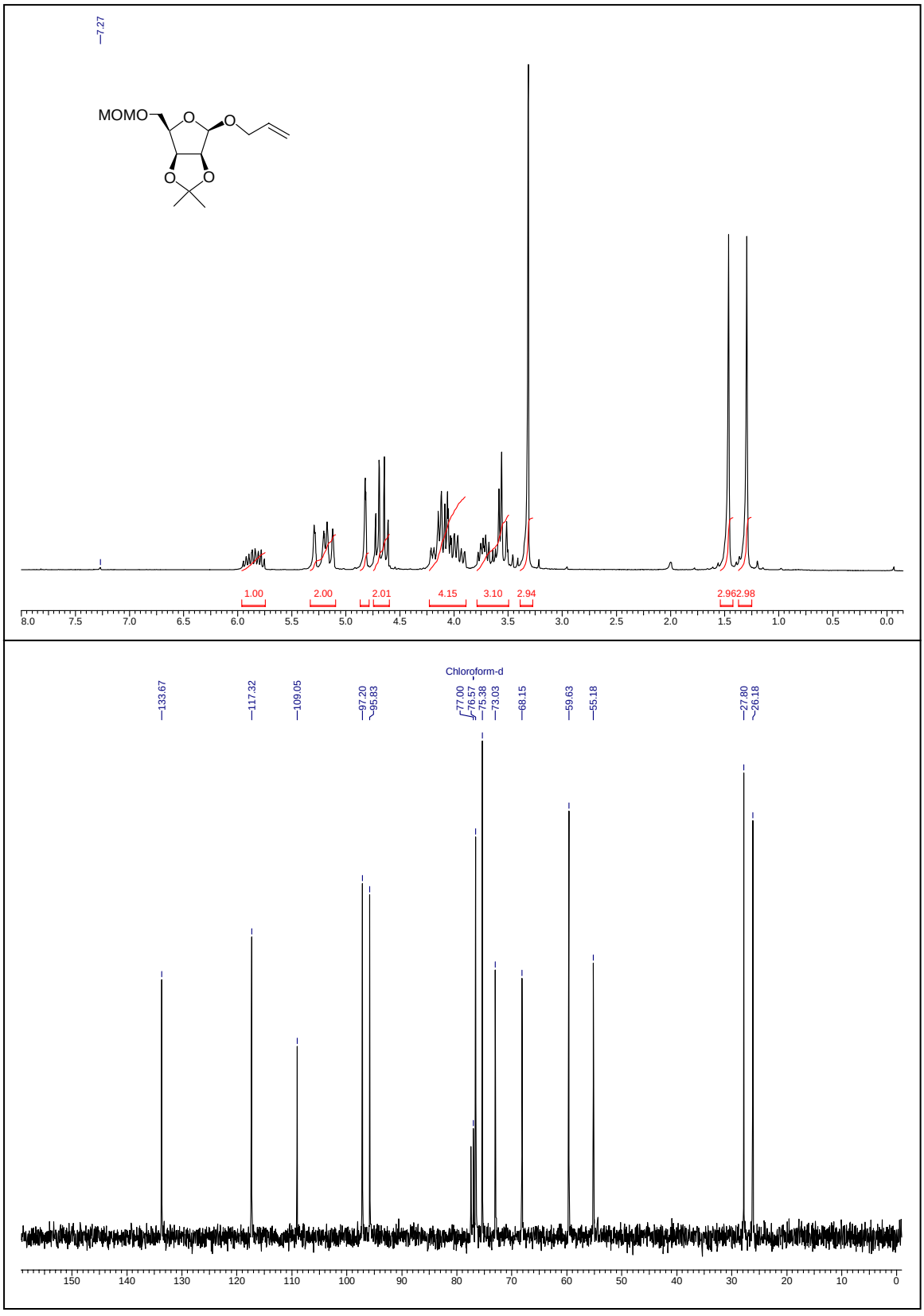
^{1}H and ^{13}C NMR spectra of compound 40 in $CDCl_3$



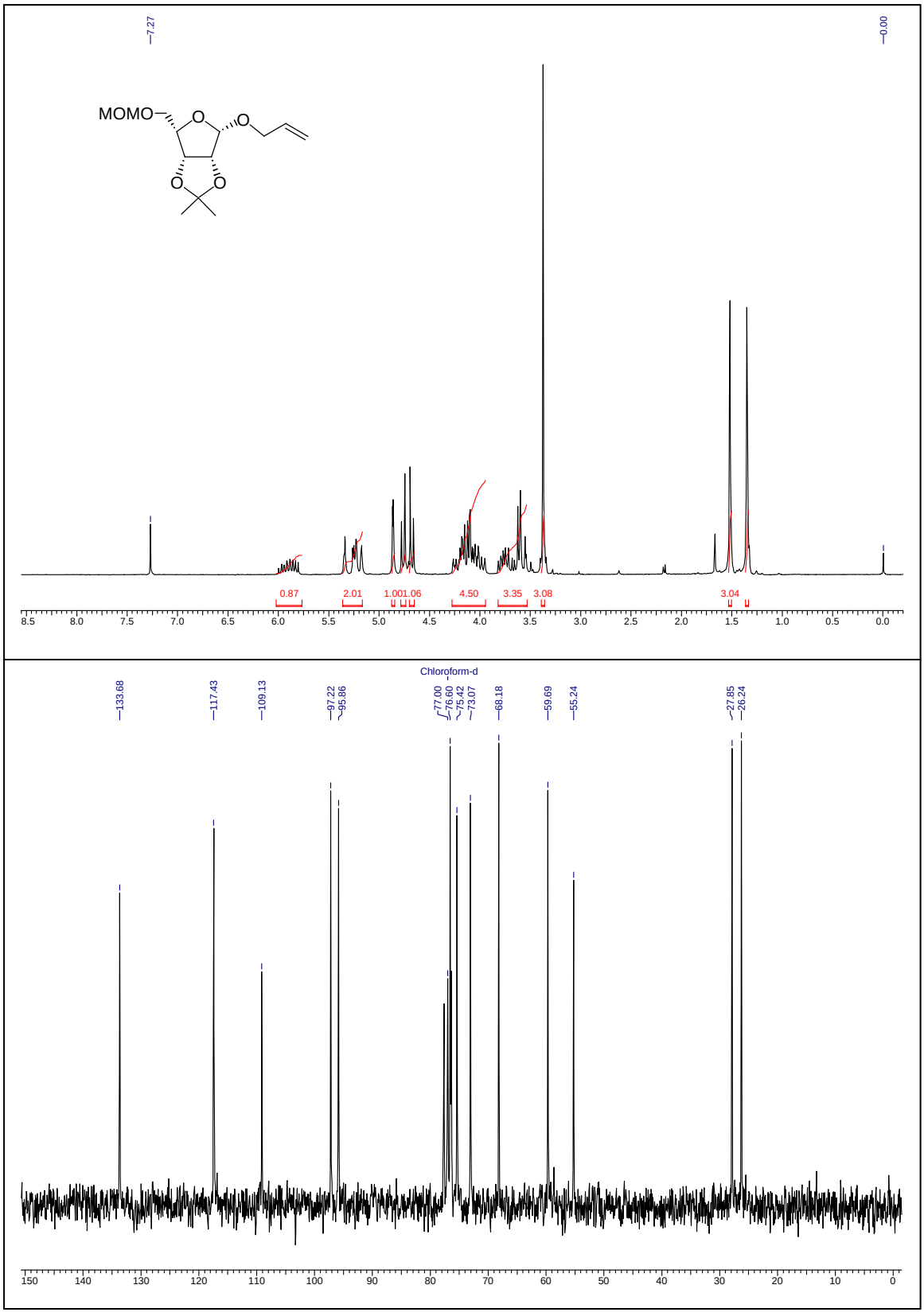
^{1}H and ^{13}C NMR spectra of compound 41 in $CDCl_3$



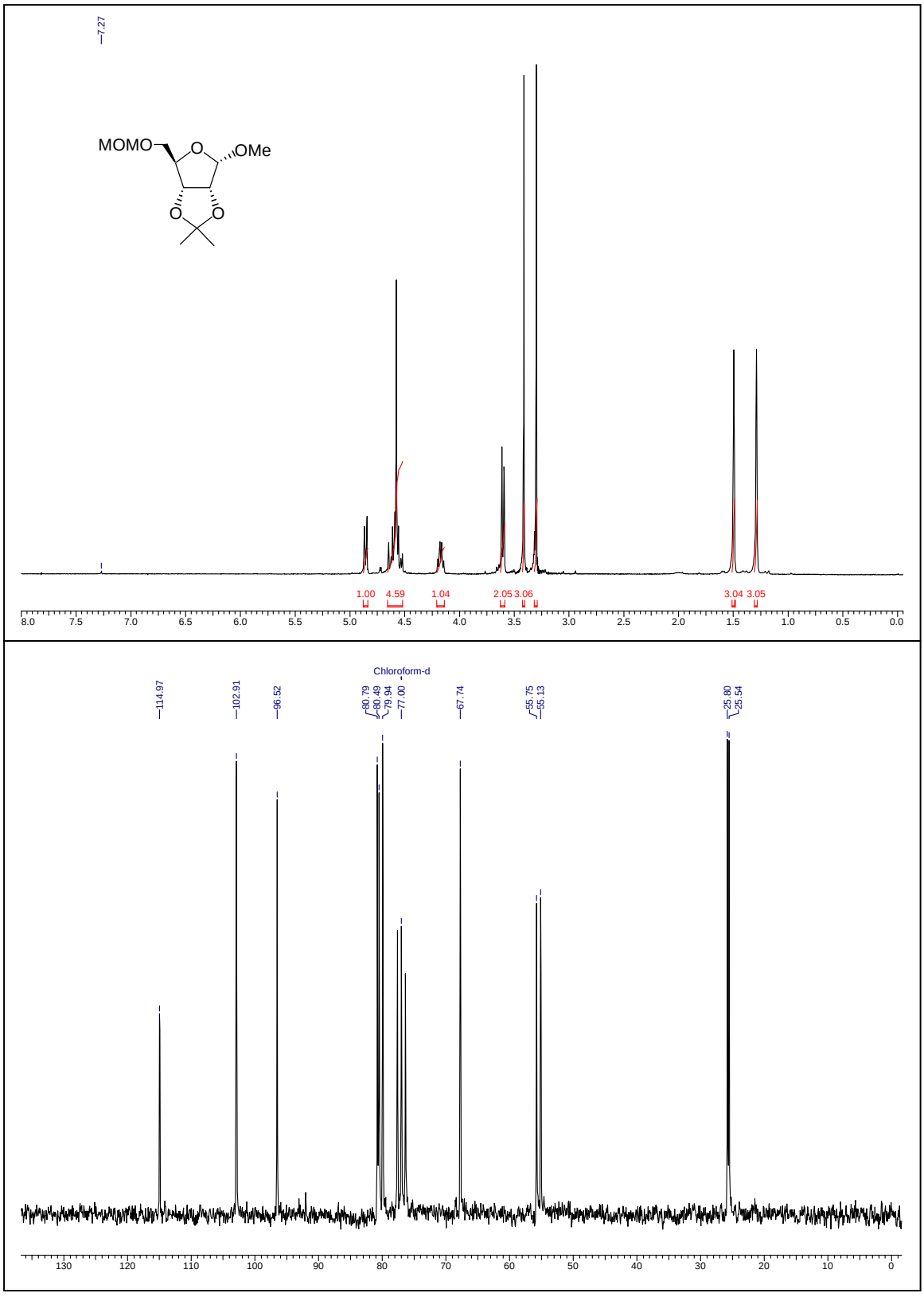
^{1}H and ^{13}C NMR spectra of compound 42 in $CDCl_3$



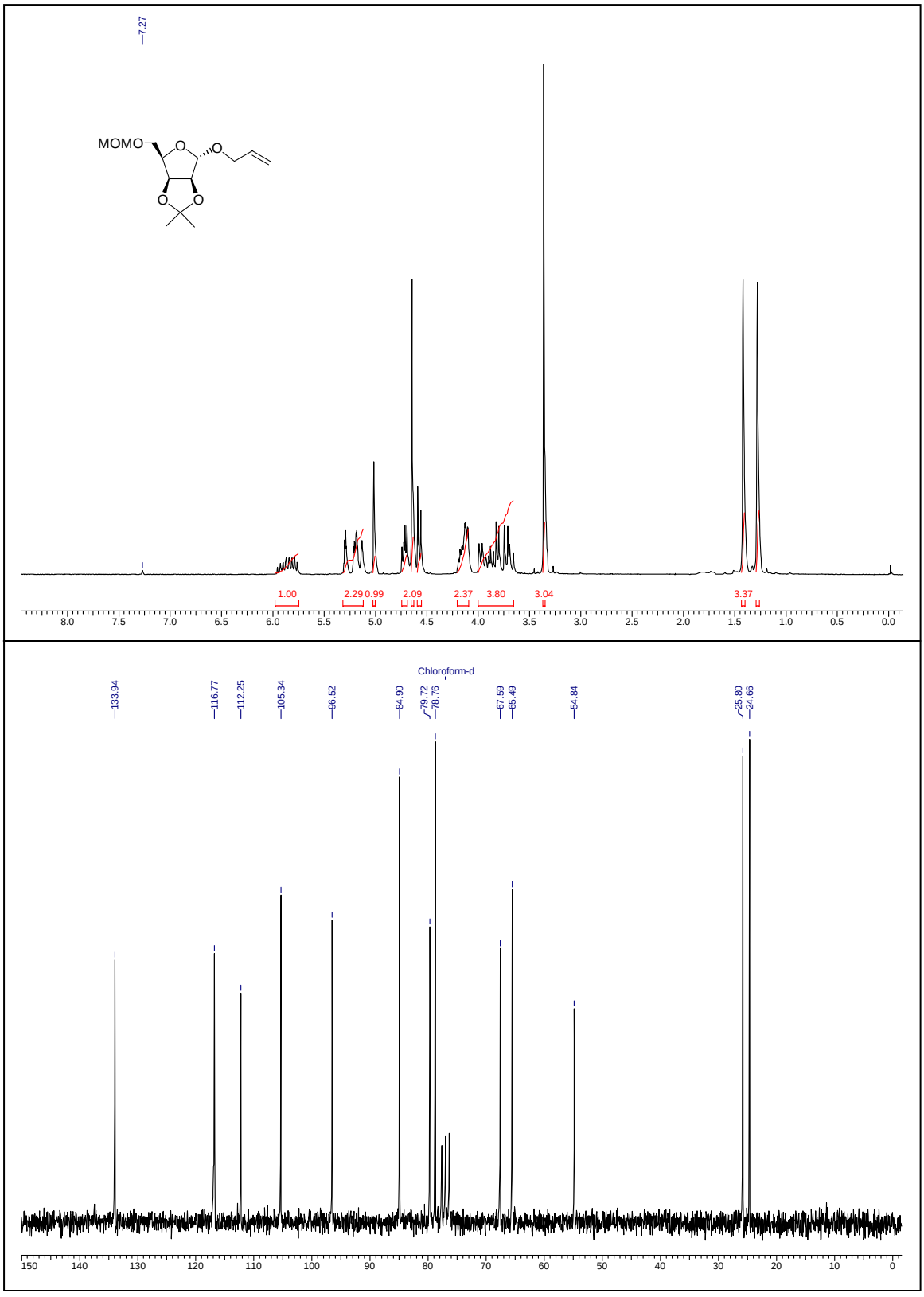
^{1}H and ^{13}C NMR spectra of compound 43 in $CDCl_3$



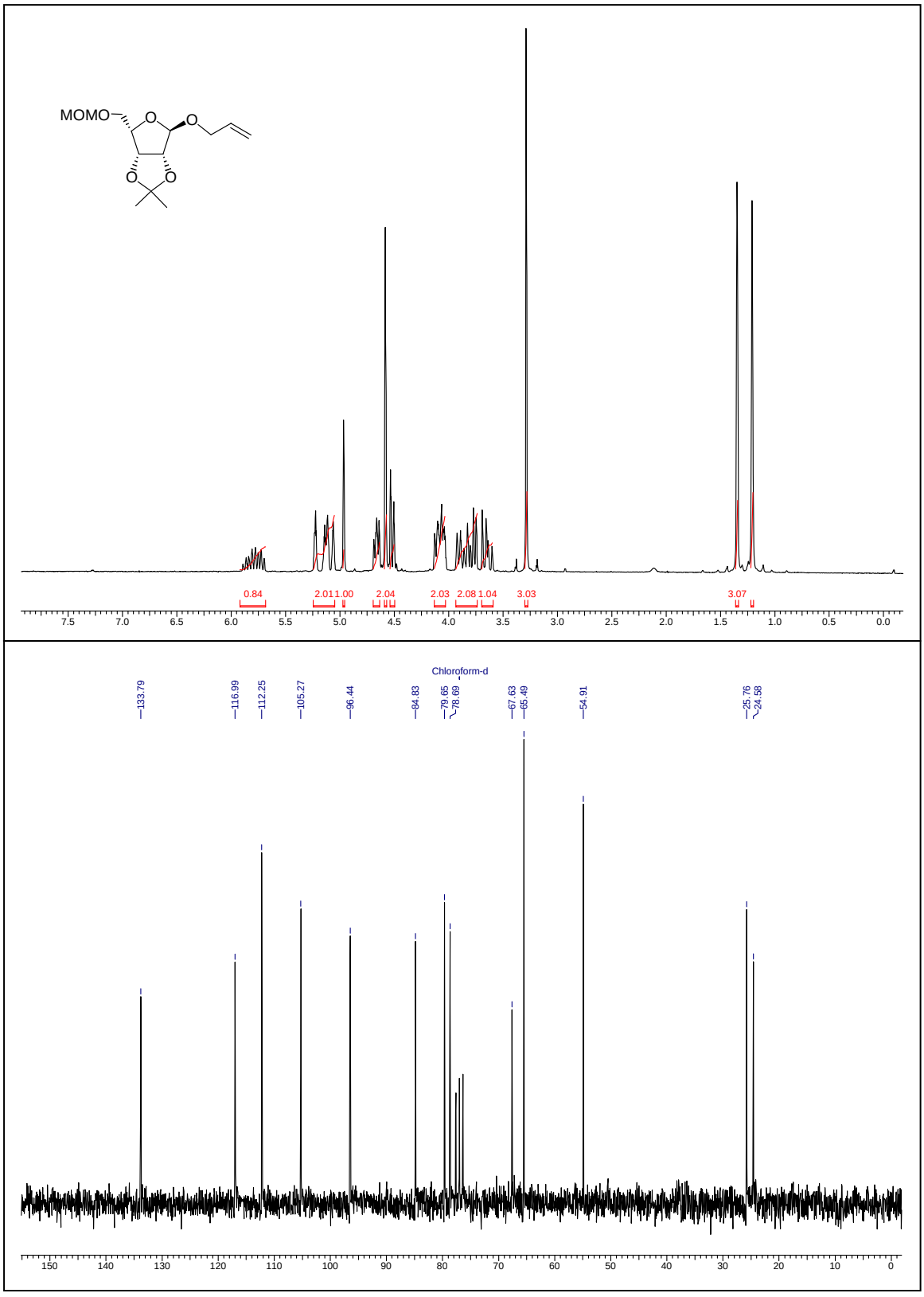
^{1}H and ^{13}C NMR spectra of compound 44 in $CDCl_3$



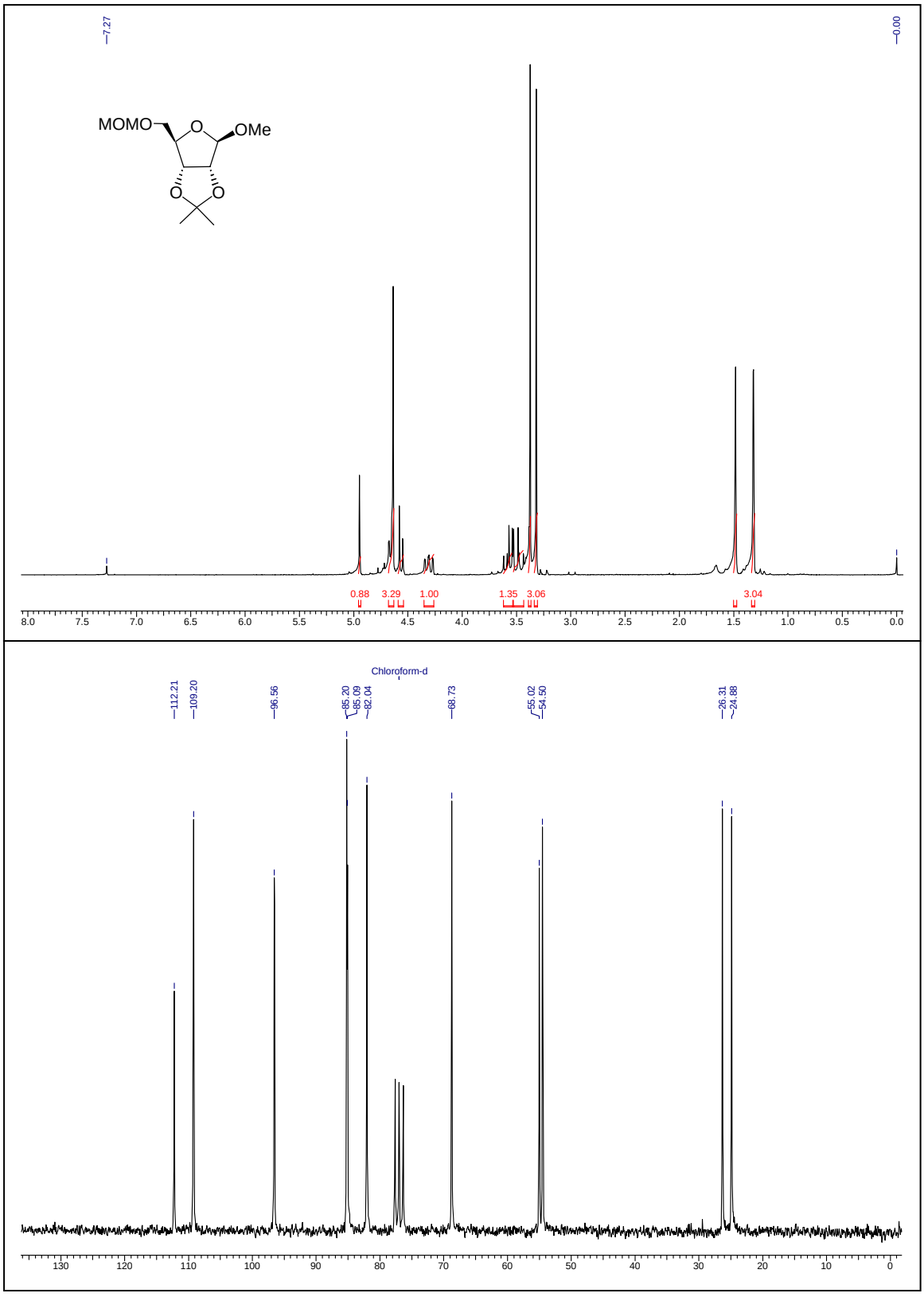
^{1}H and ^{13}C NMR spectra of compound 45 in $CDCl_3$



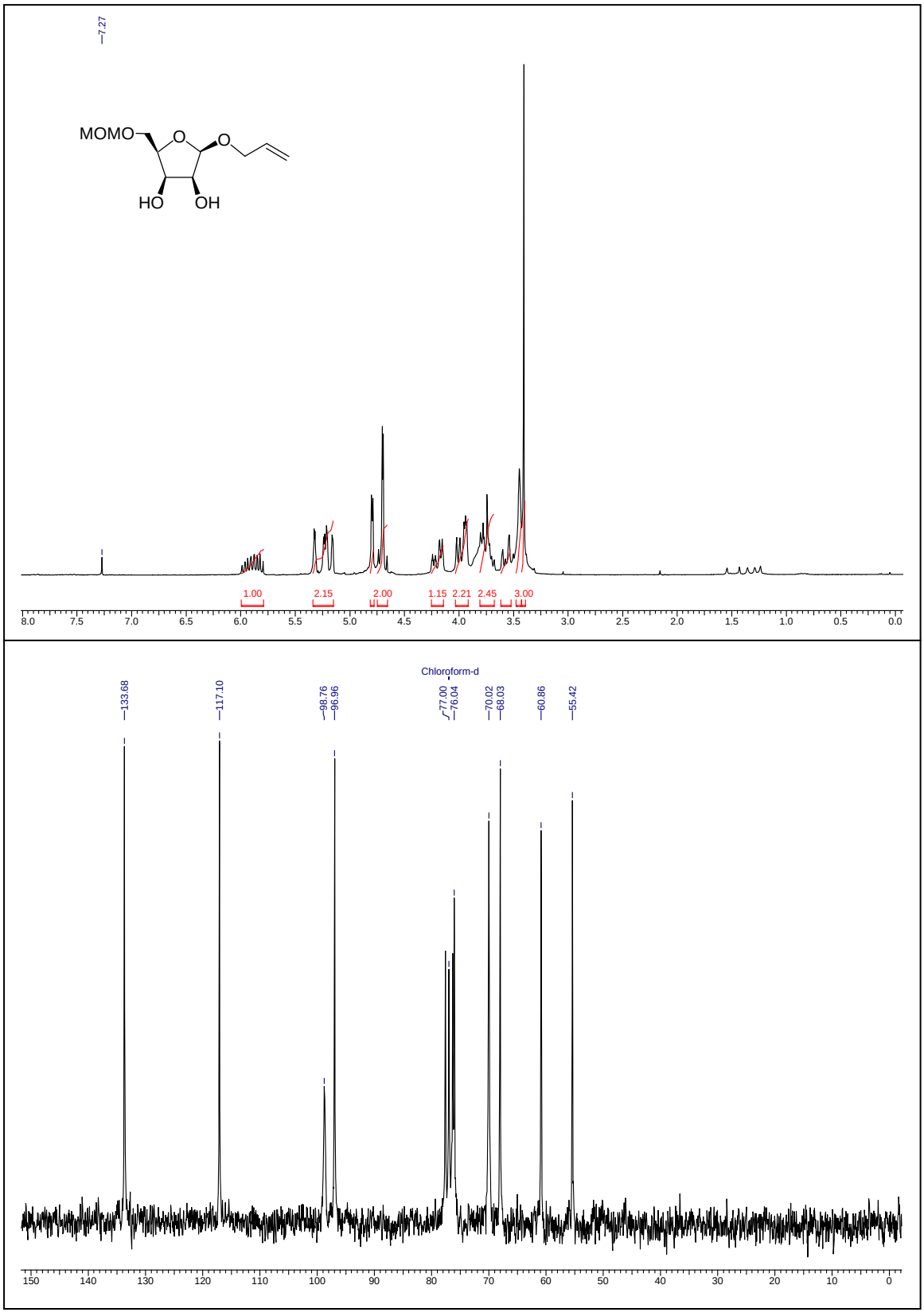
^{1}H and ^{13}C NMR spectra of compound 46 in $CDCl_3$



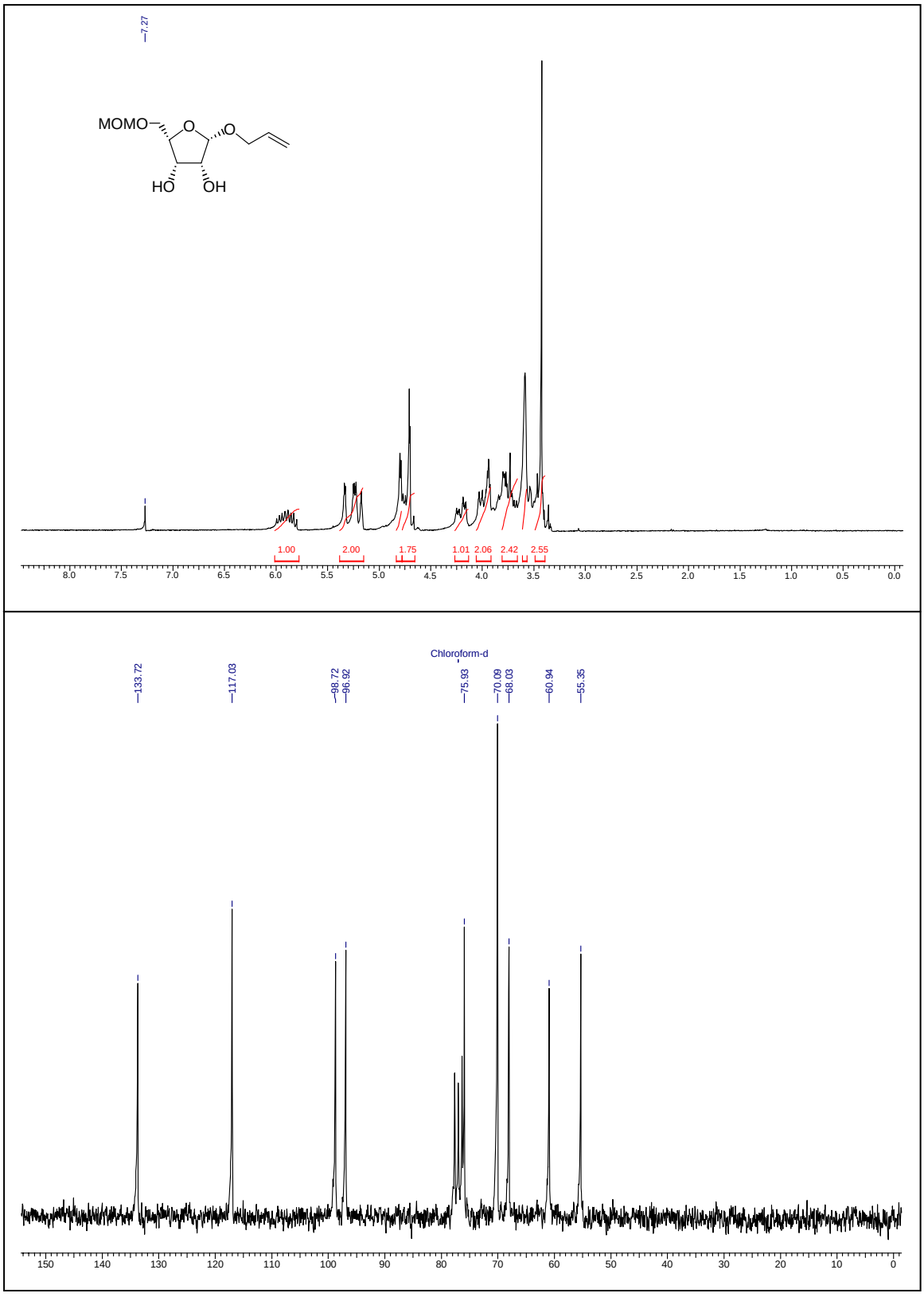
^{1}H and ^{13}C NMR spectra of compound 47 in $CDCl_3$



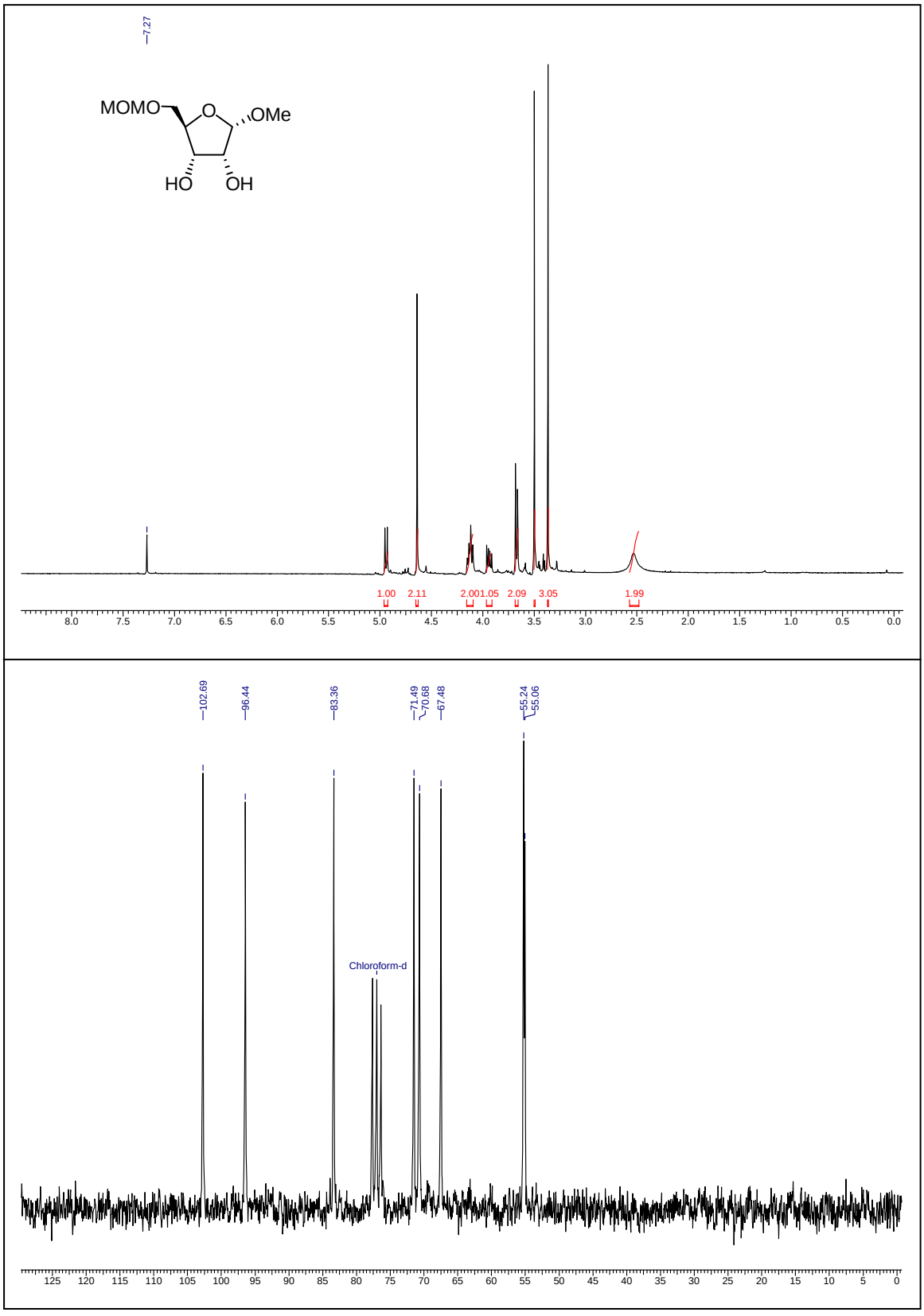
^{1}H and ^{13}C NMR spectra of compound 48 in $CDCl_3$



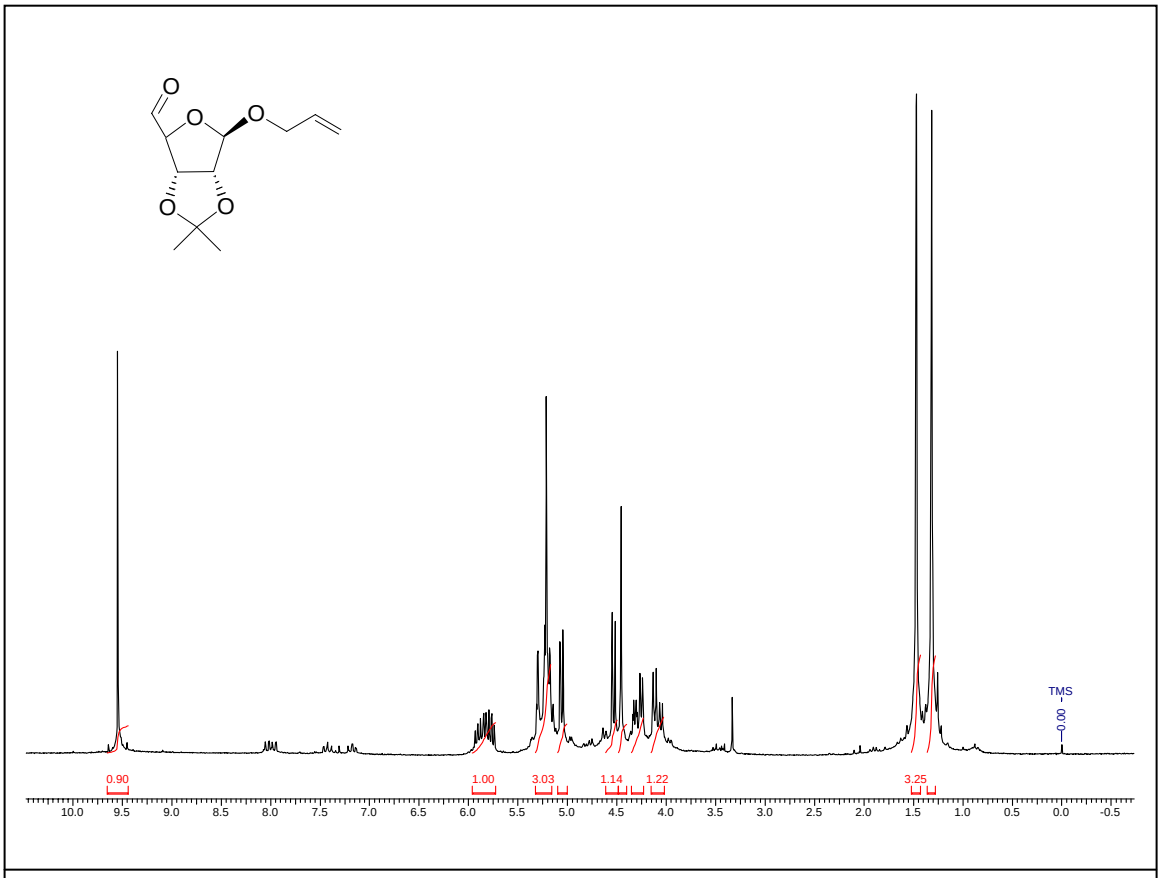
^{1}H and ^{13}C NMR spectra of compound 49 in $CDCl_3$

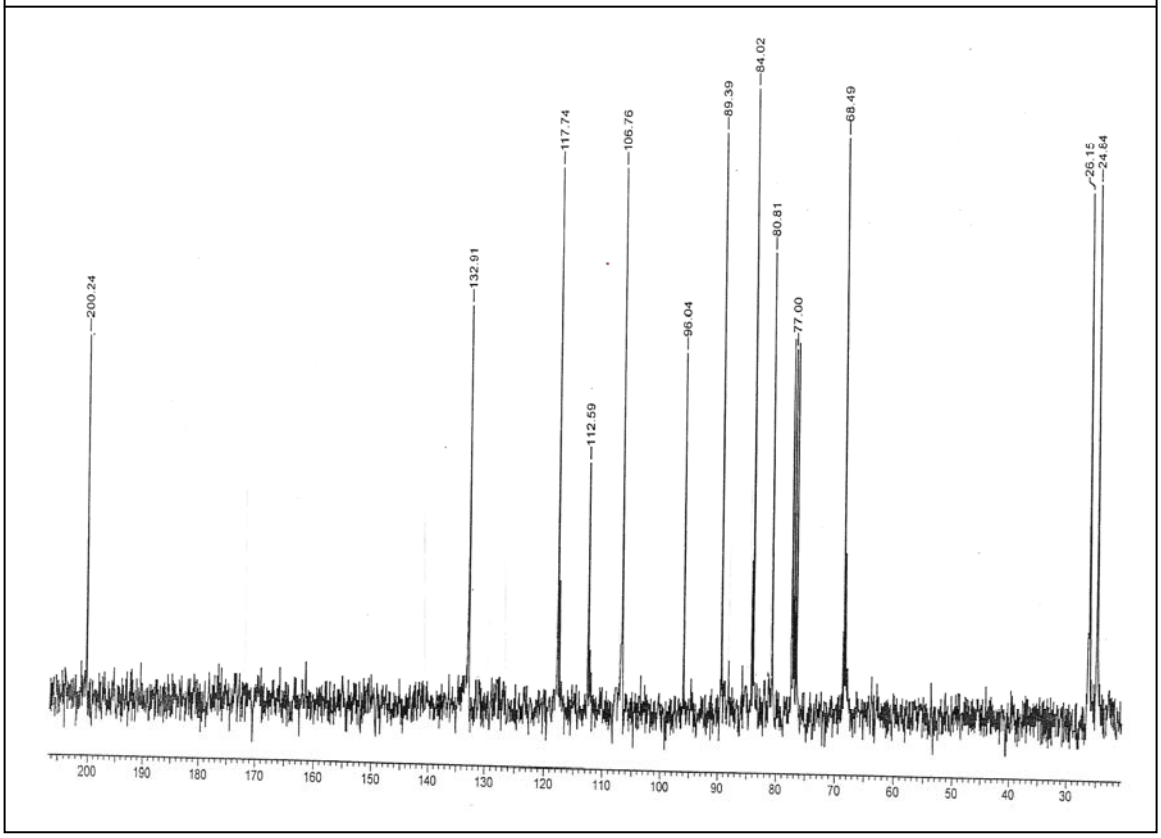


^{1}H and ^{13}C NMR spectra of compound 50 in $CDCl_3$

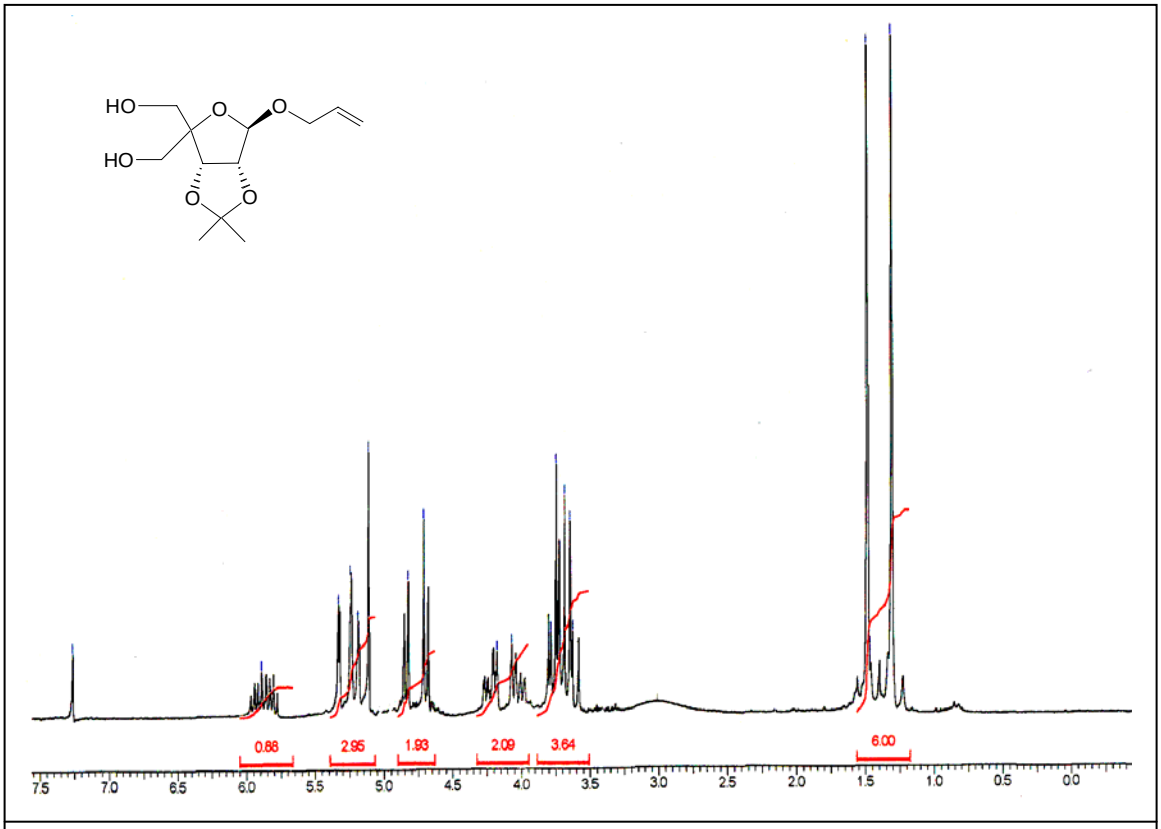


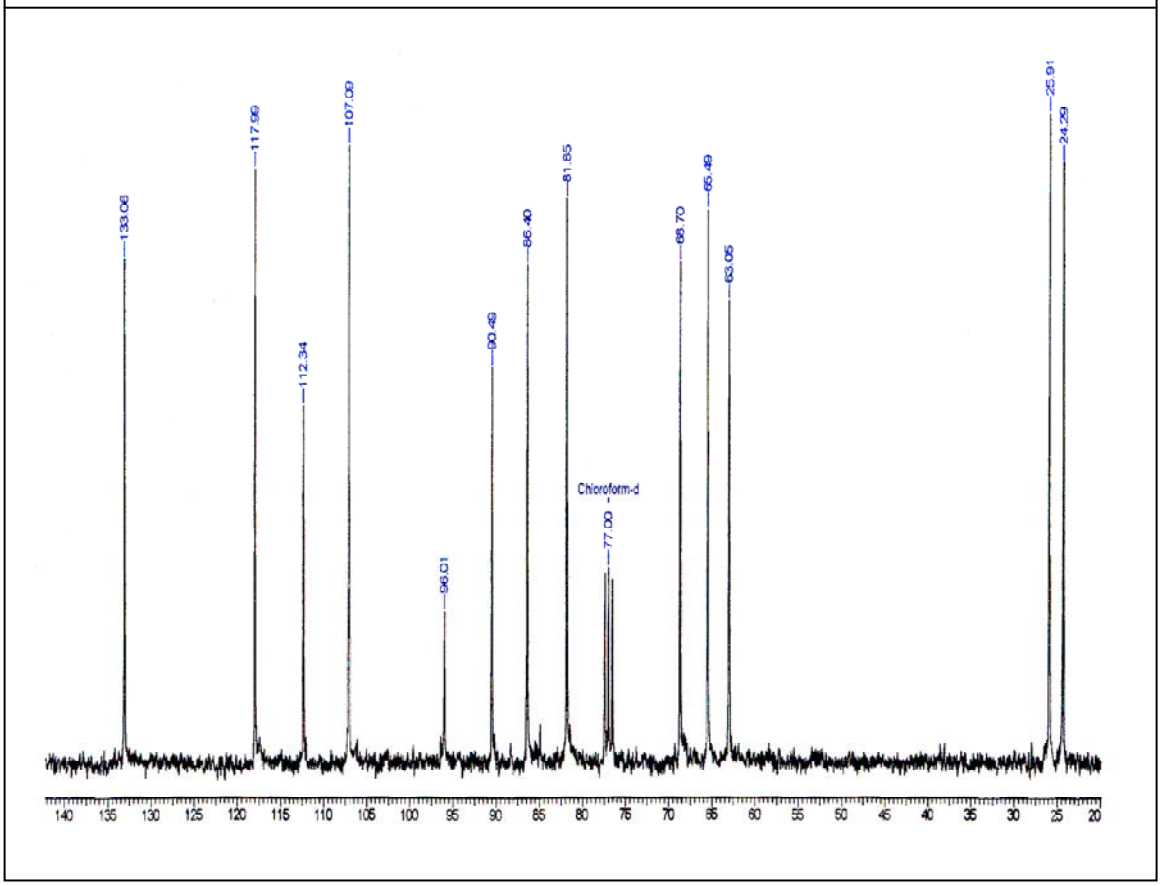
^{1}H and ^{13}C NMR spectra of compound 51 in $CDCl_3$



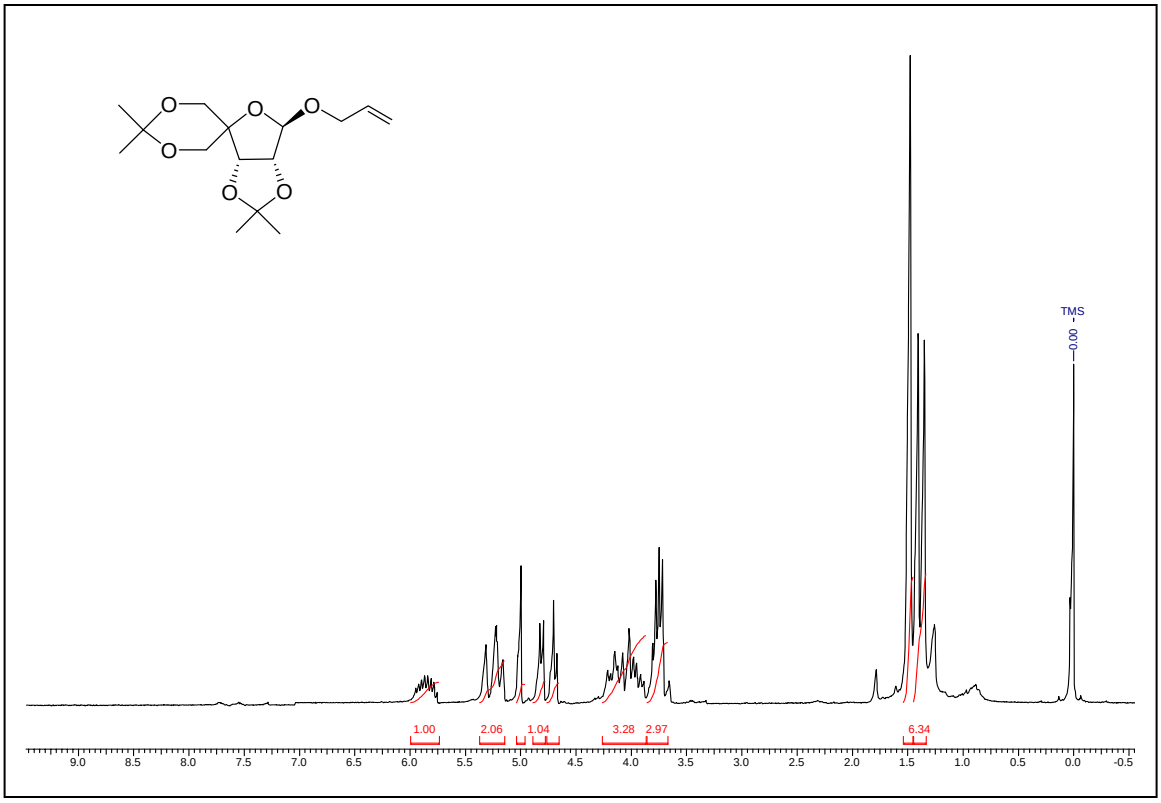


^{1}H and ^{13}C NMR spectra of compound 52 in $CDCl_3$

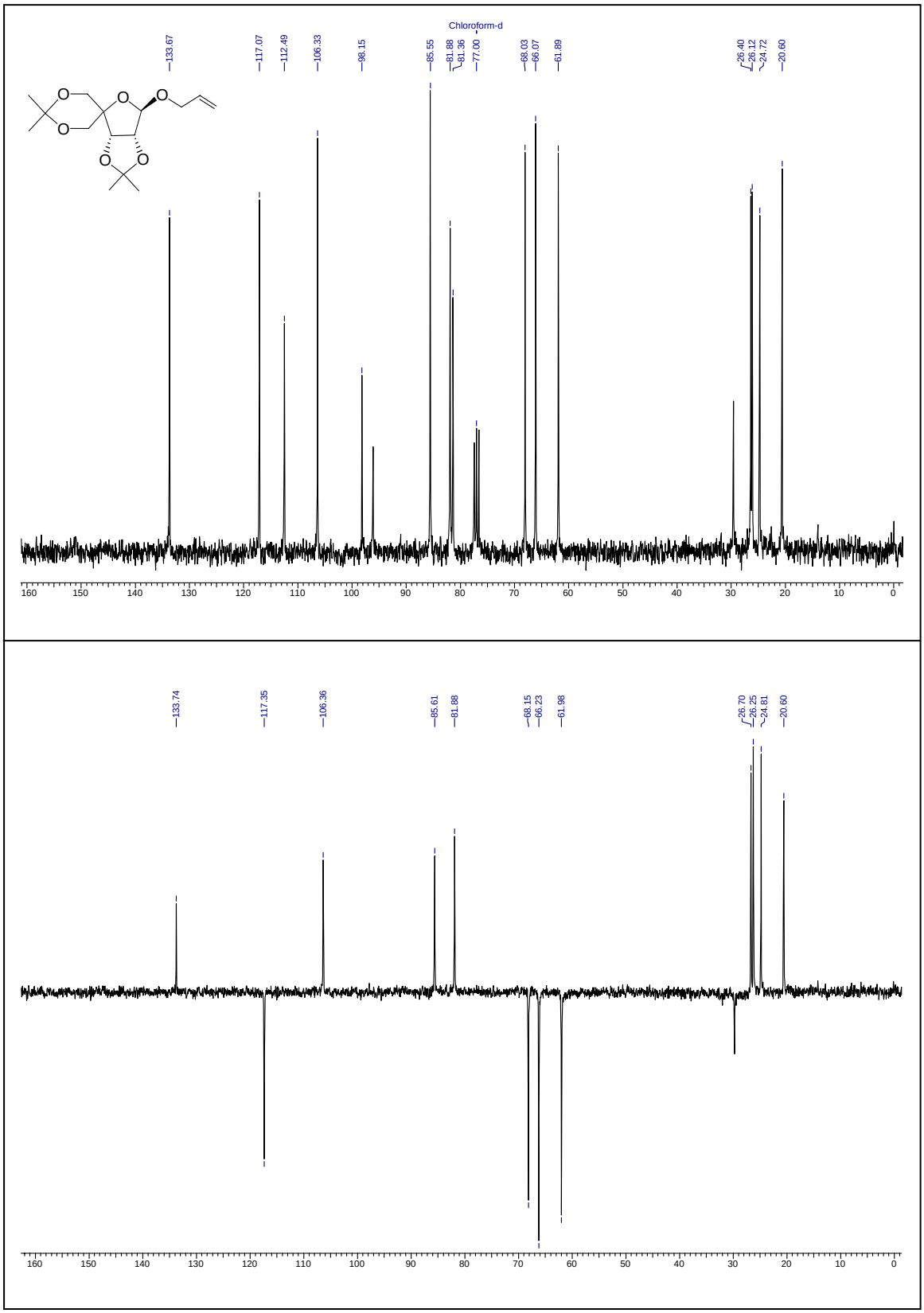




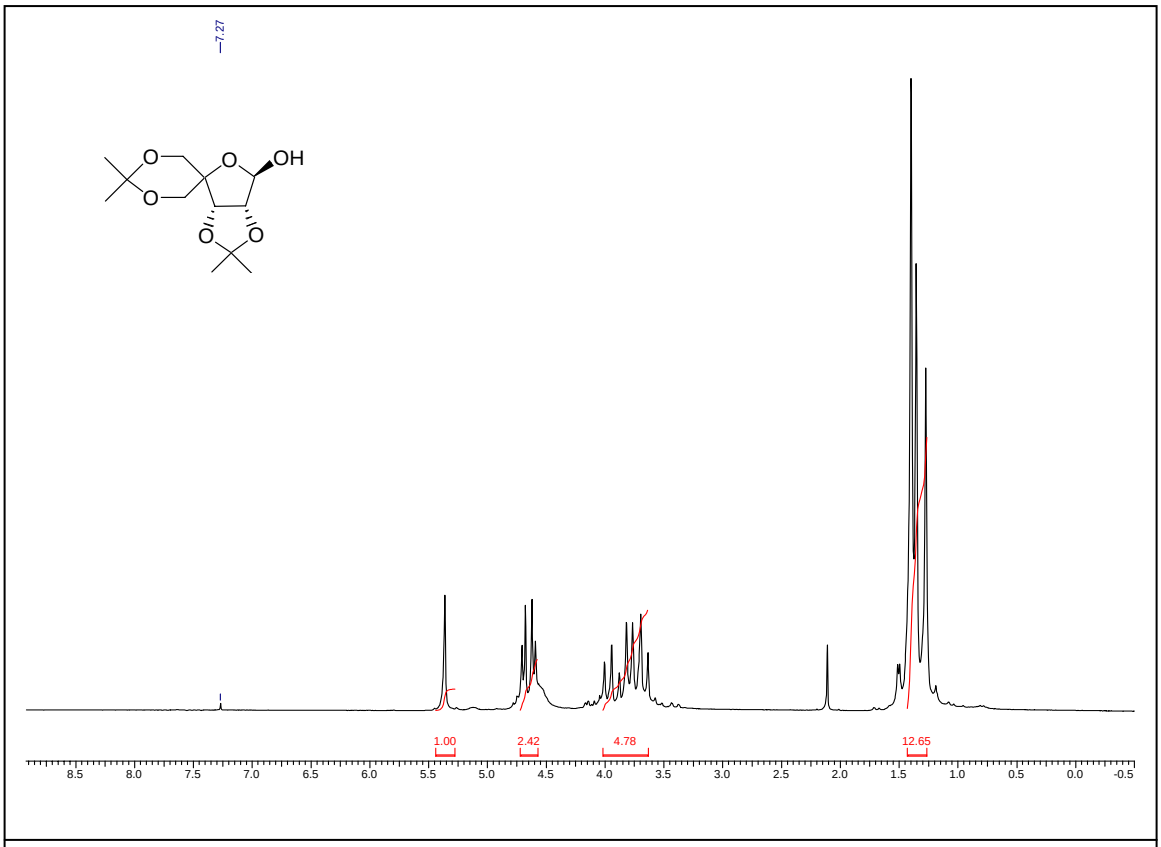
^{1}H NMR spectrum of compound 53 in $CDCl_3$

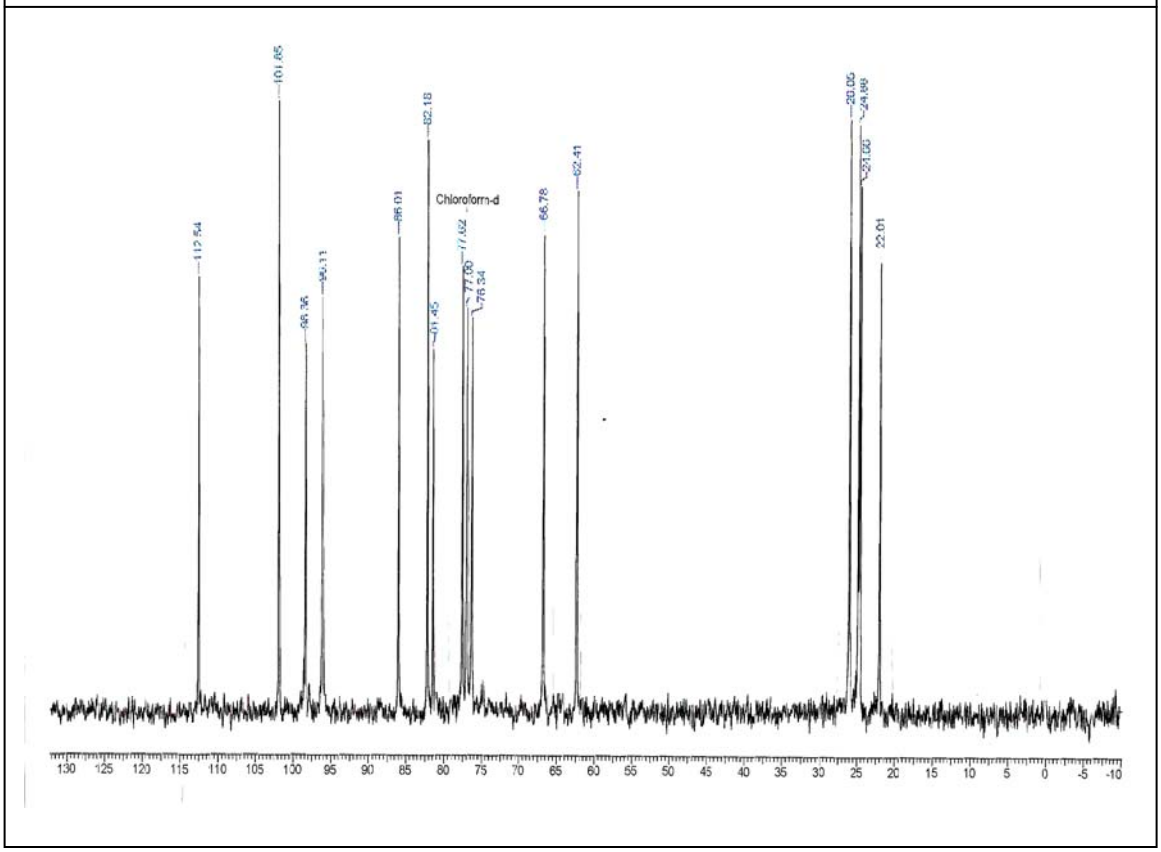


^{13}C NMR spectrum of compound 53 in $CDCl_3$

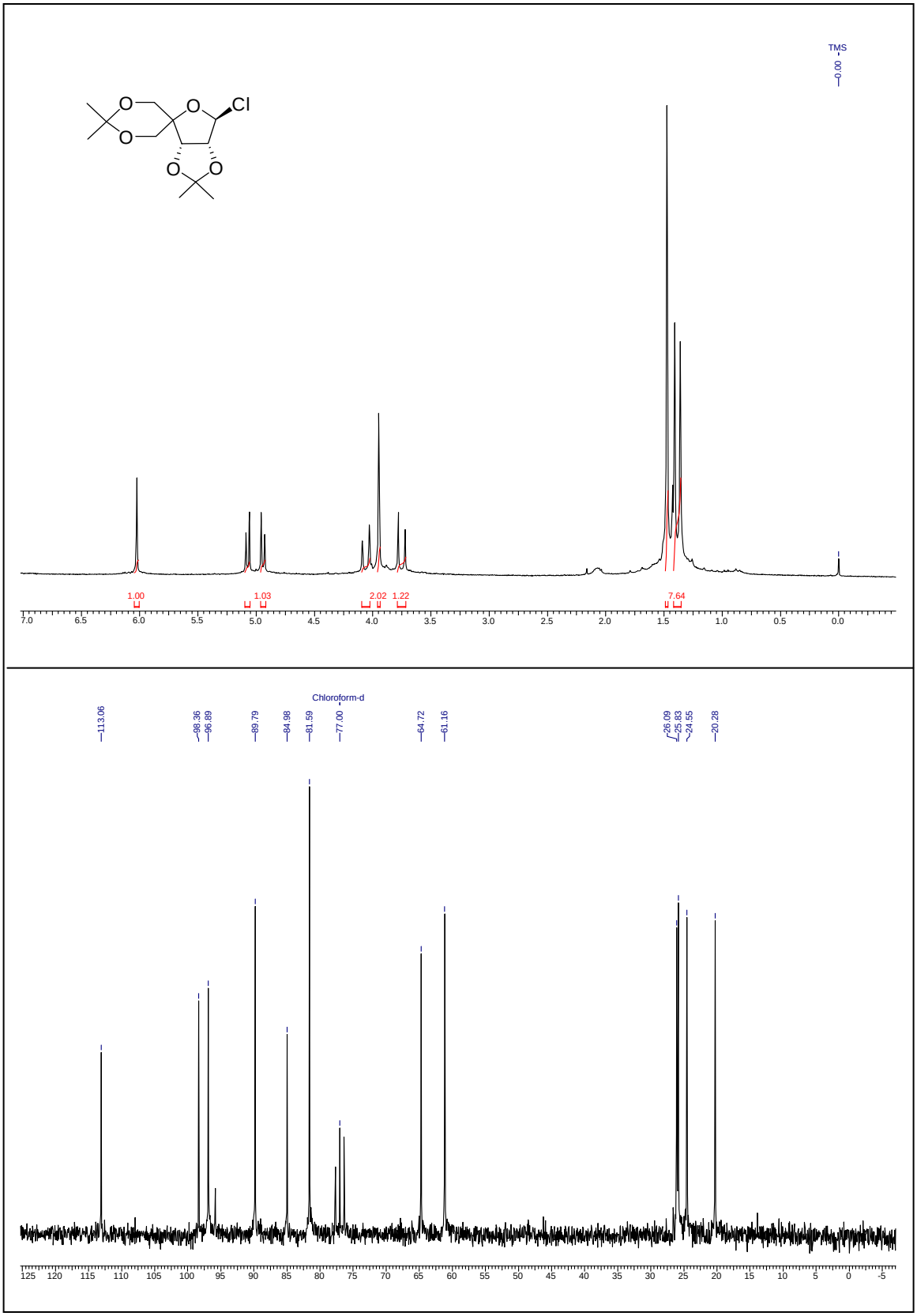


^{1}H and ^{13}C NMR spectra of compound 54 in $CDCl_3$

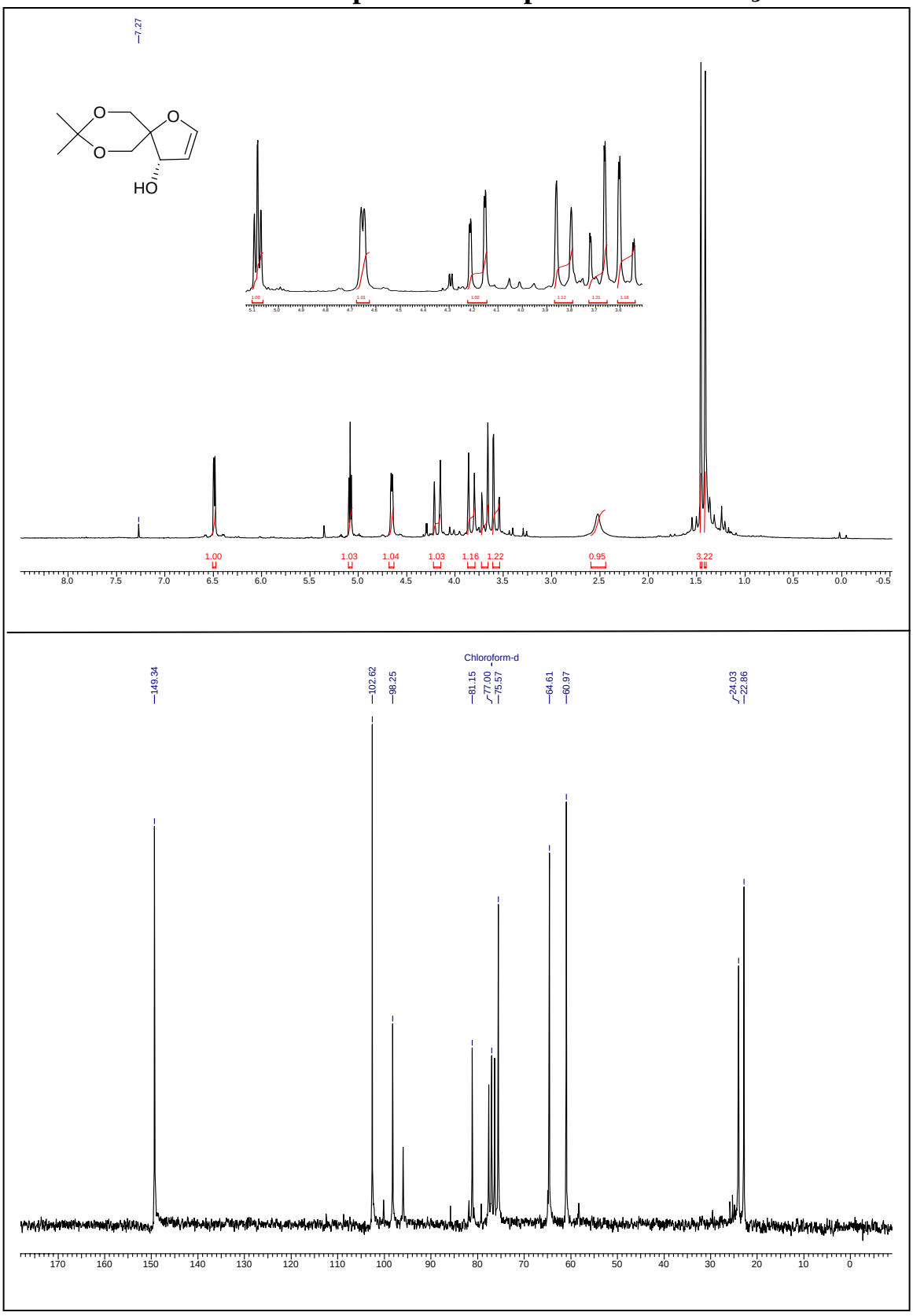




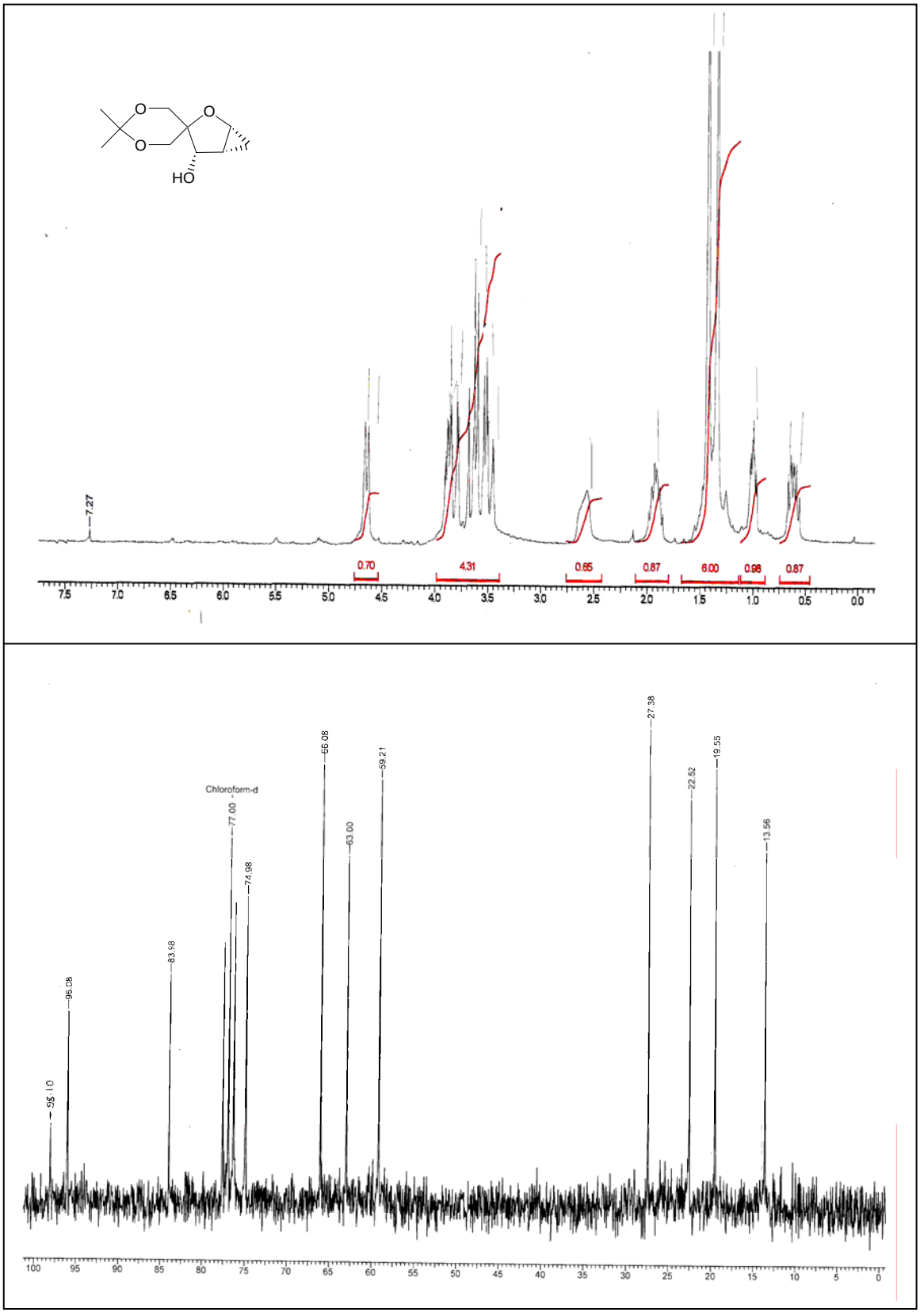
^{1}H and ^{13}C NMR spectra of compound 55 in $CDCl_3$



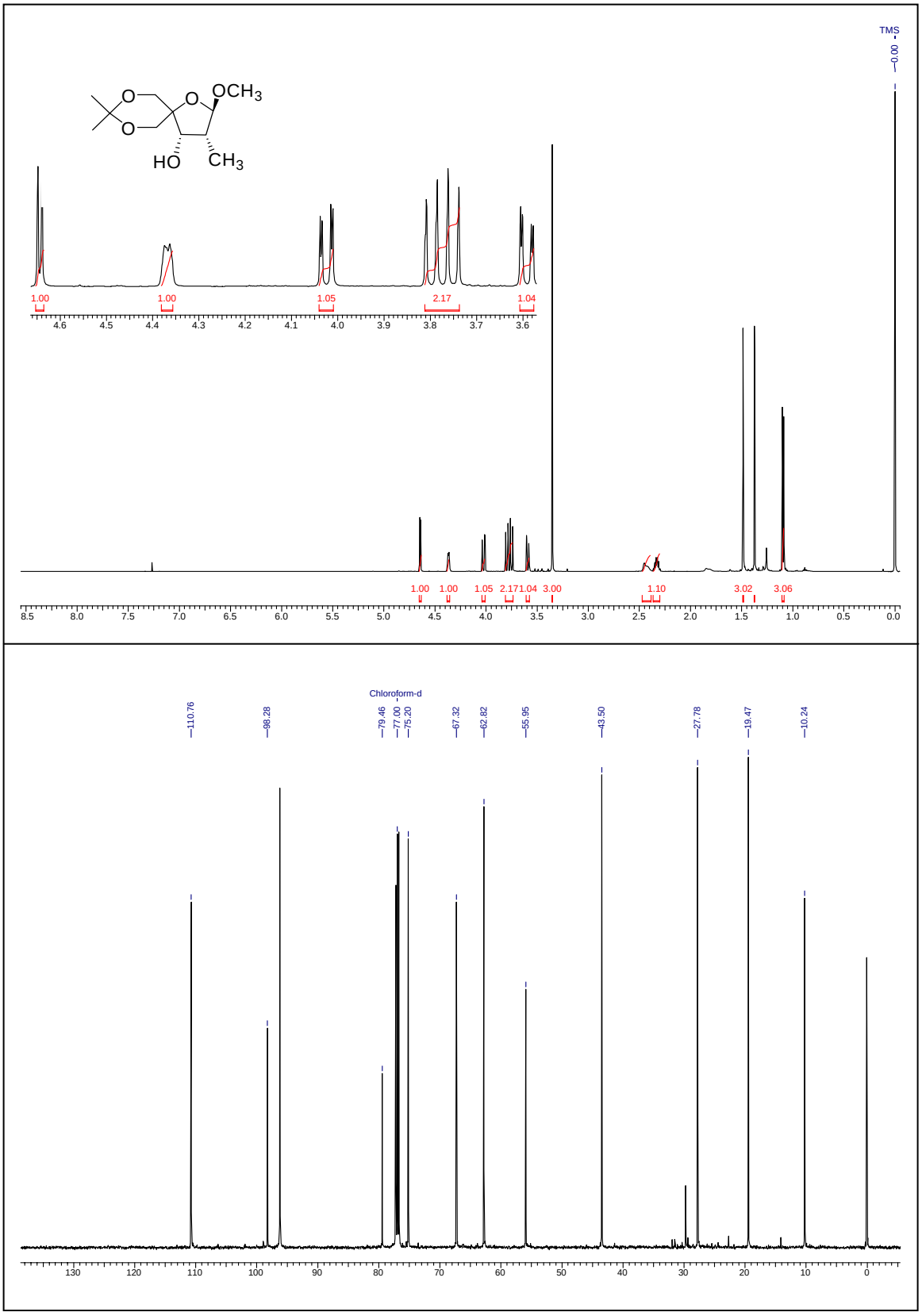
^{1}H and ^{13}C NMR spectra of compound 56 in $CDCl_3$



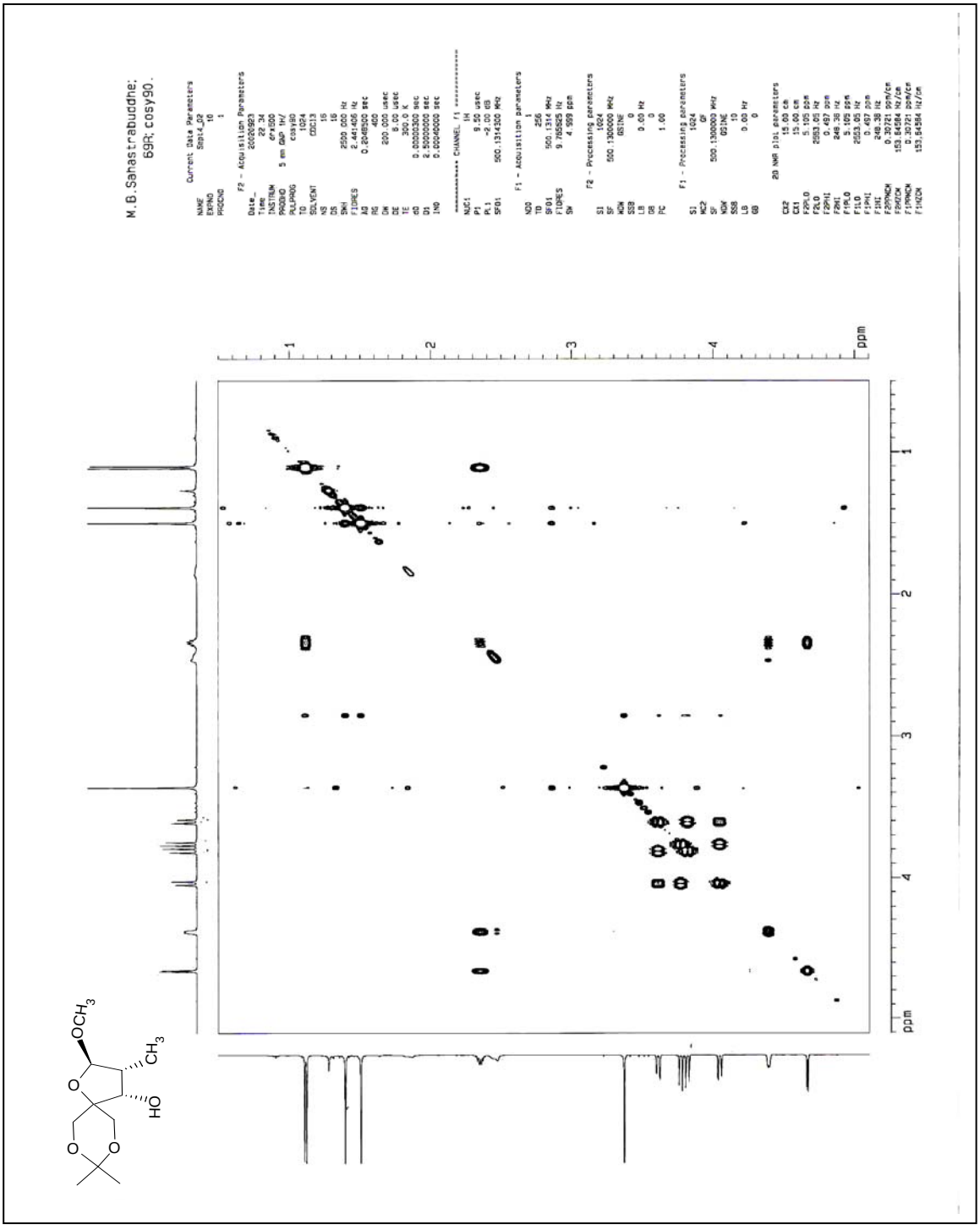
^{1}H and ^{13}C NMR spectra of compound 57 in $CDCl_3$



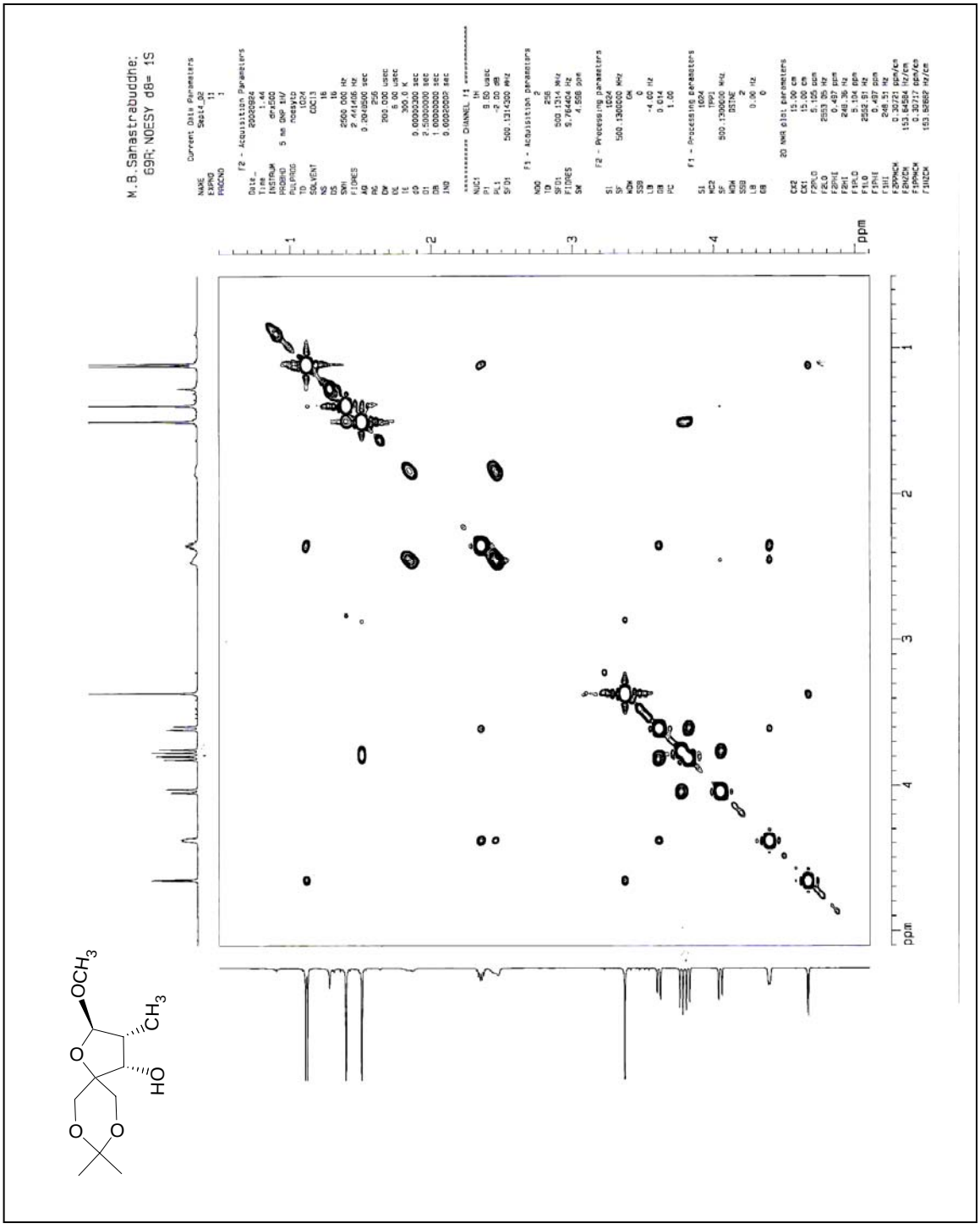
^{1}H and ^{13}C NMR spectra of compound 58 in $CDCl_3$



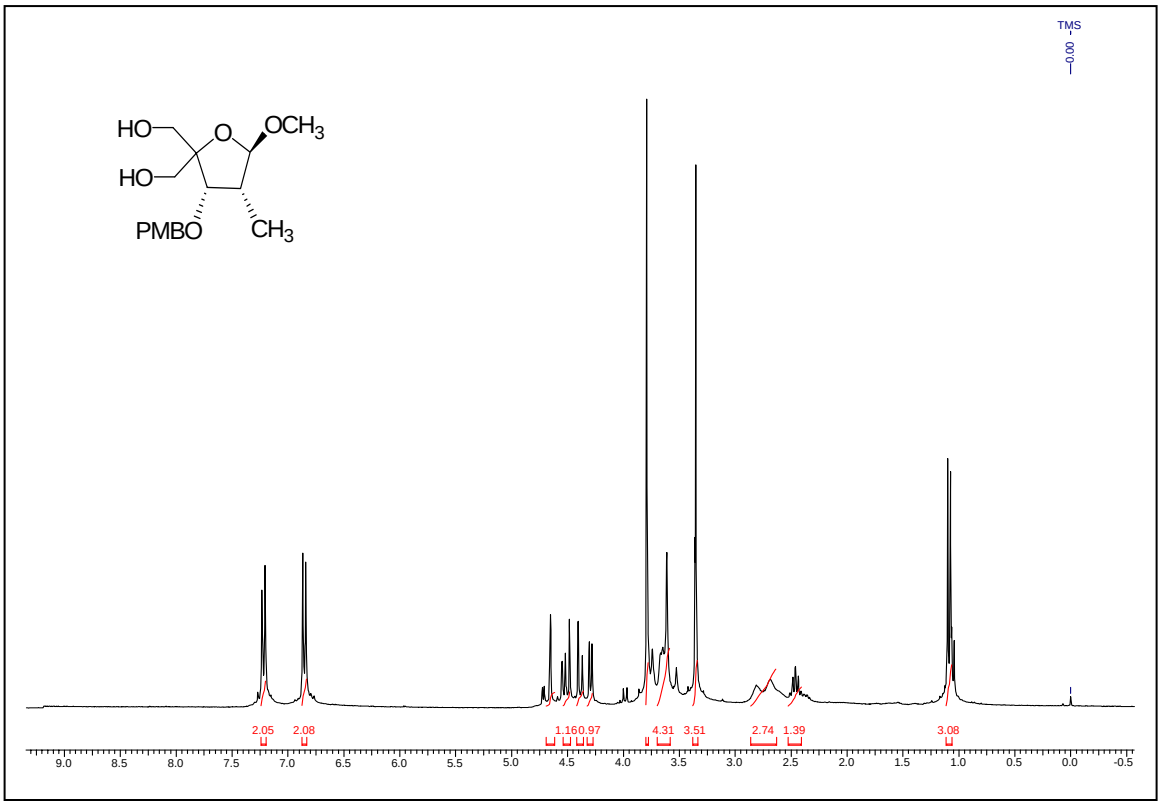
COSY of compound 58



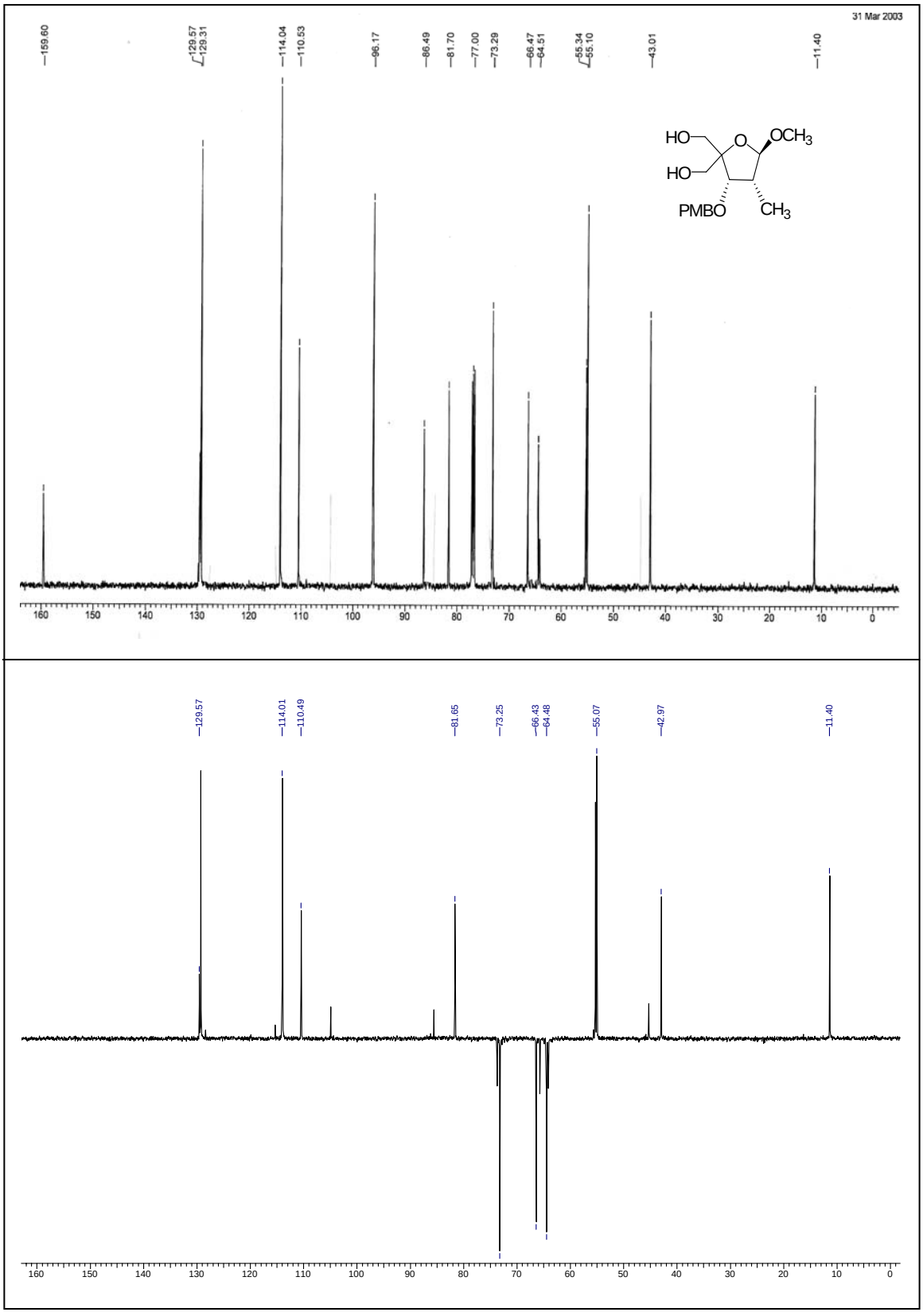
NOESY of compound 58



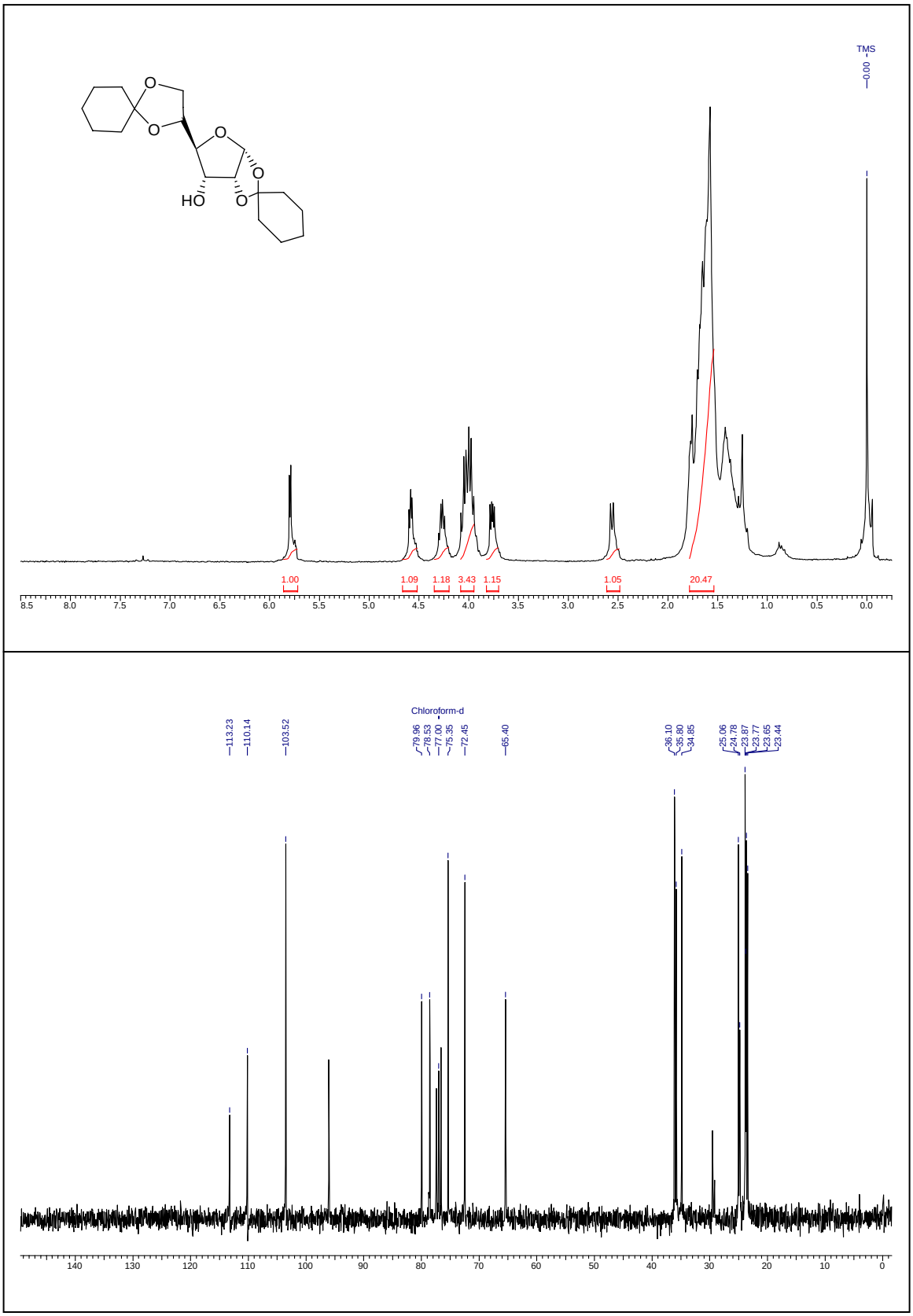
^{1}H NMR spectrum of compound 59 in $CDCl_3$



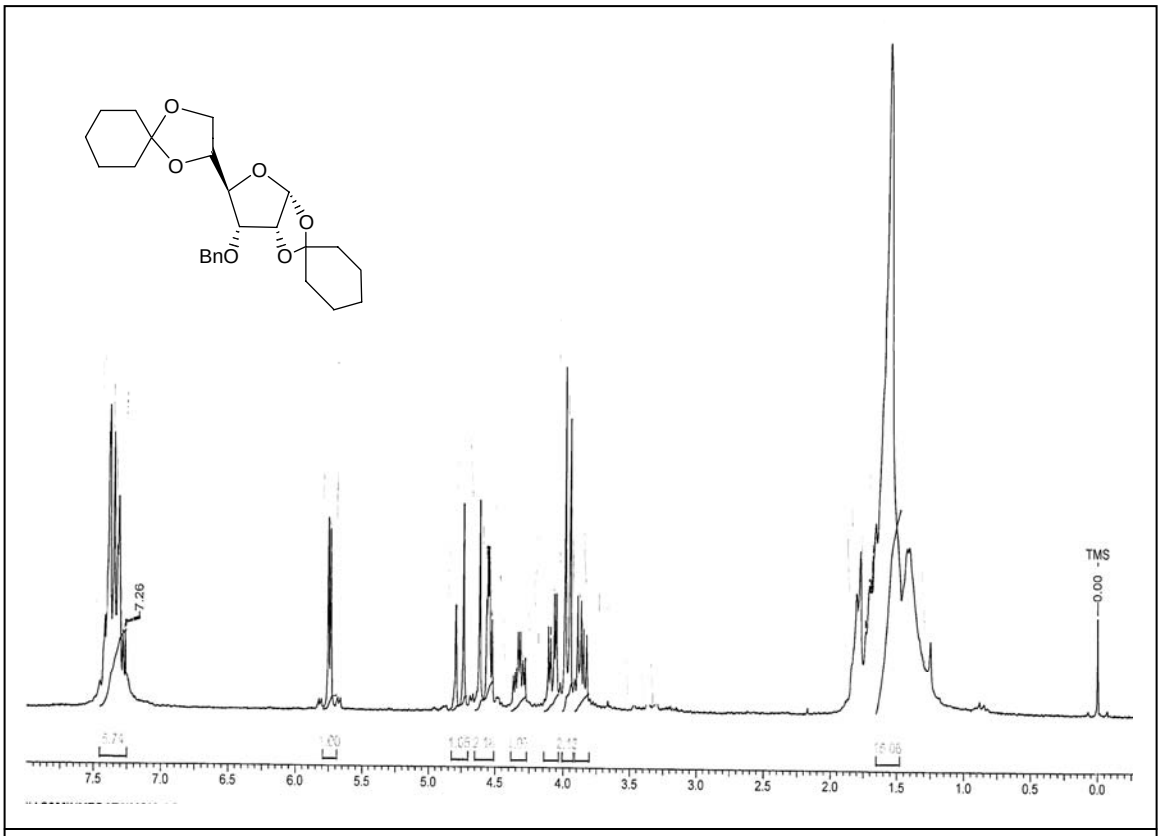
^{13}C NMR spectrum of compound 59 in $CDCl_3$

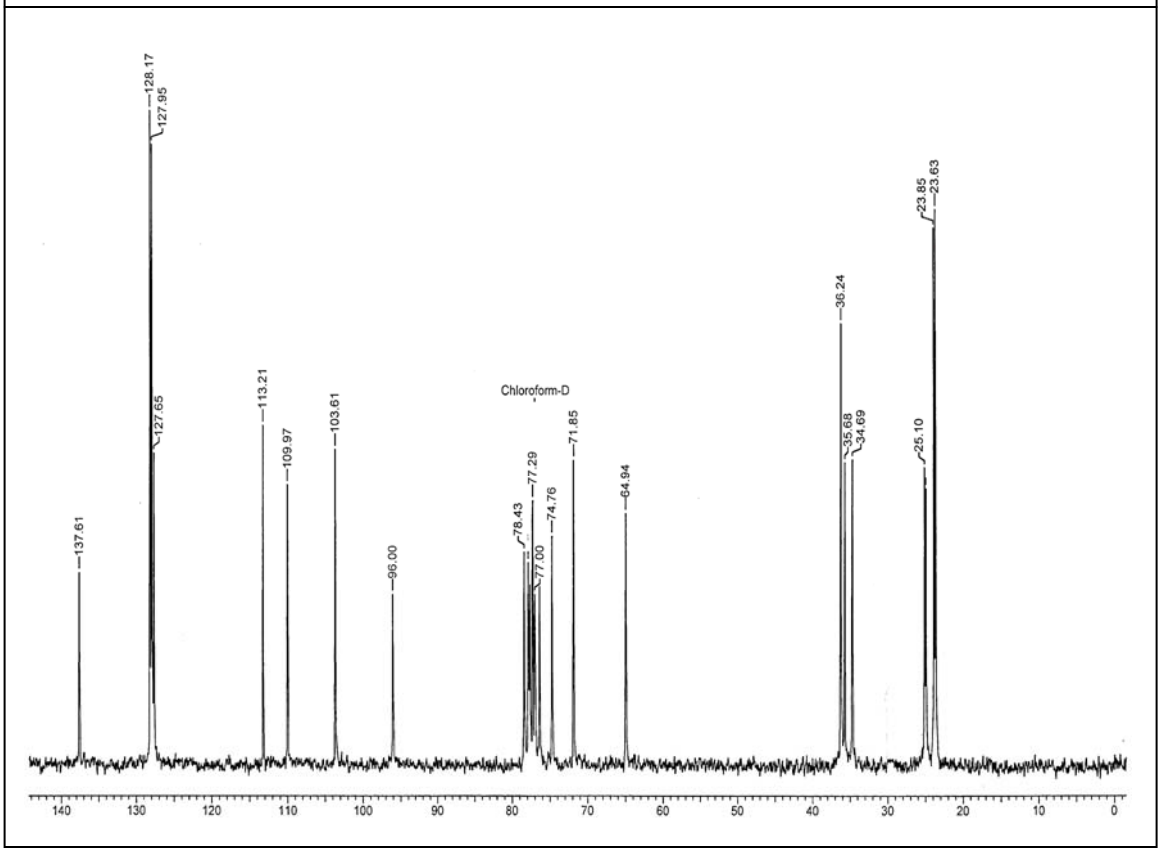


^{1}H and ^{13}C NMR spectra of compound 61 in $CDCl_3$

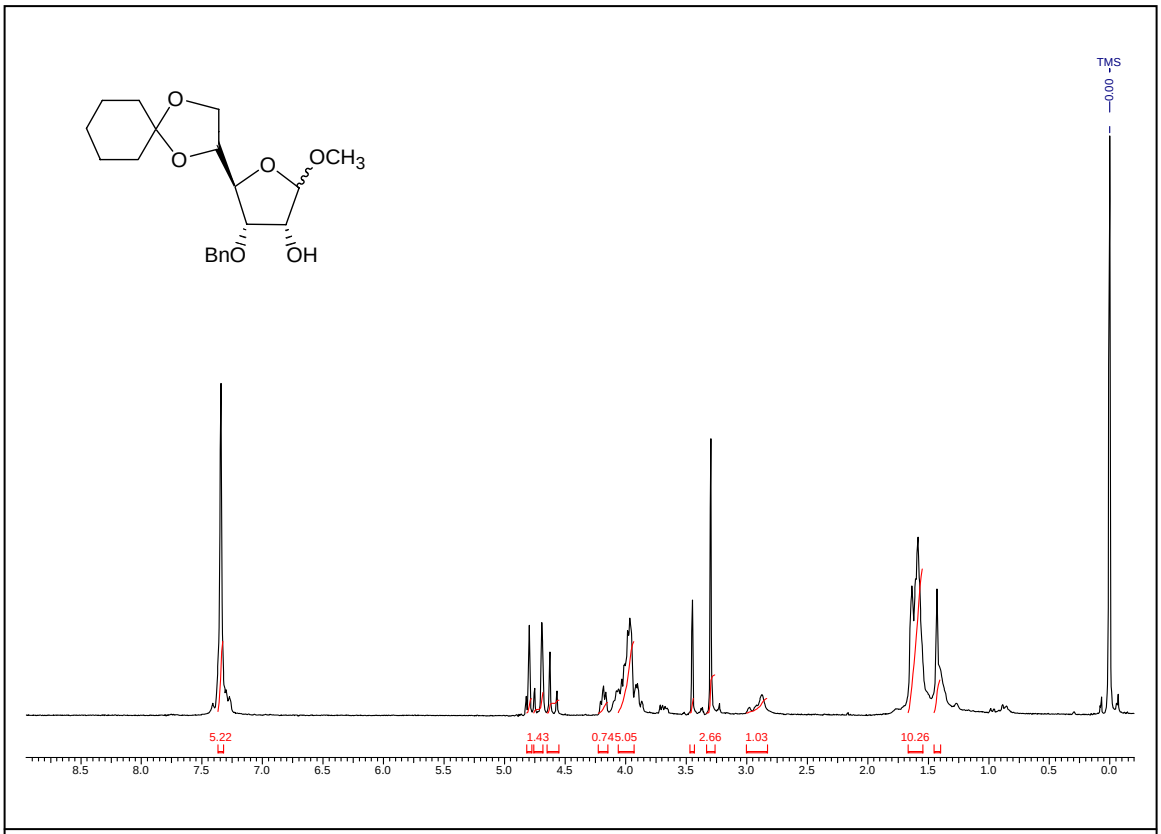


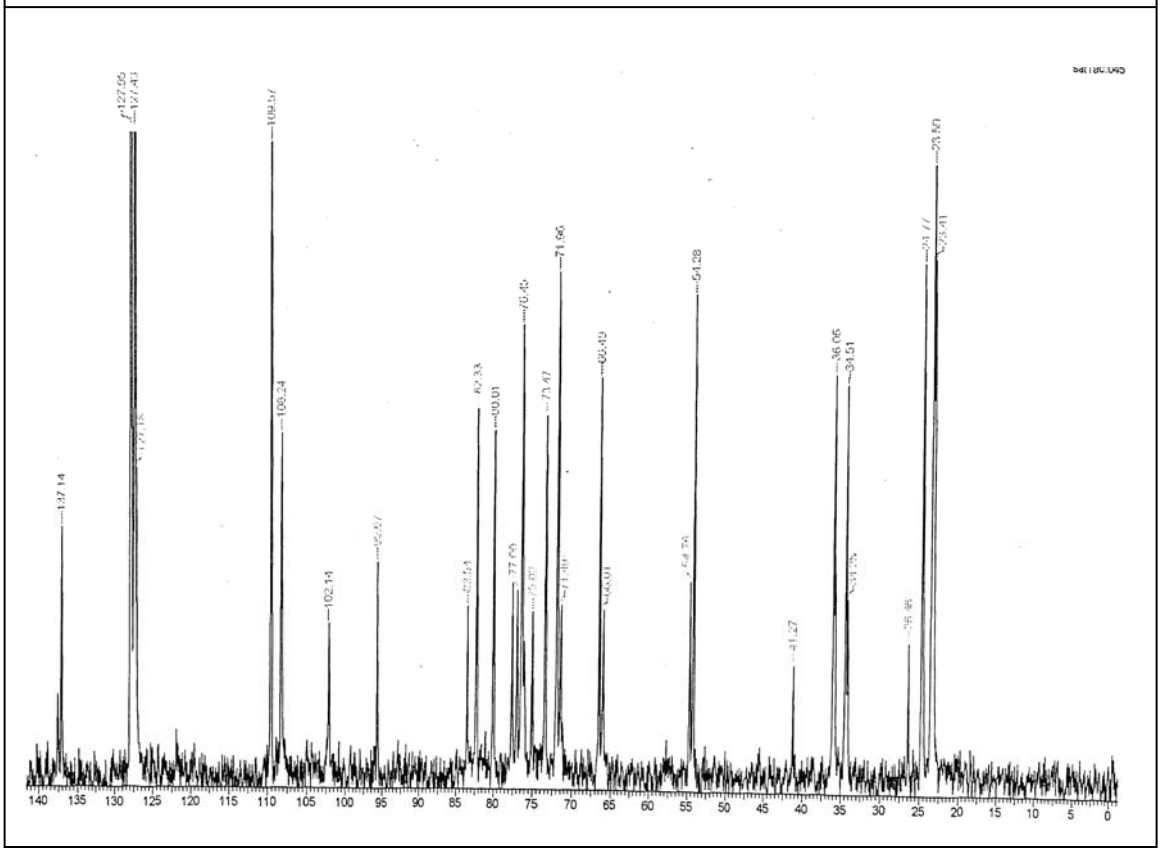
^{1}H and ^{13}C NMR spectra of compound 62 in $CDCl_3$



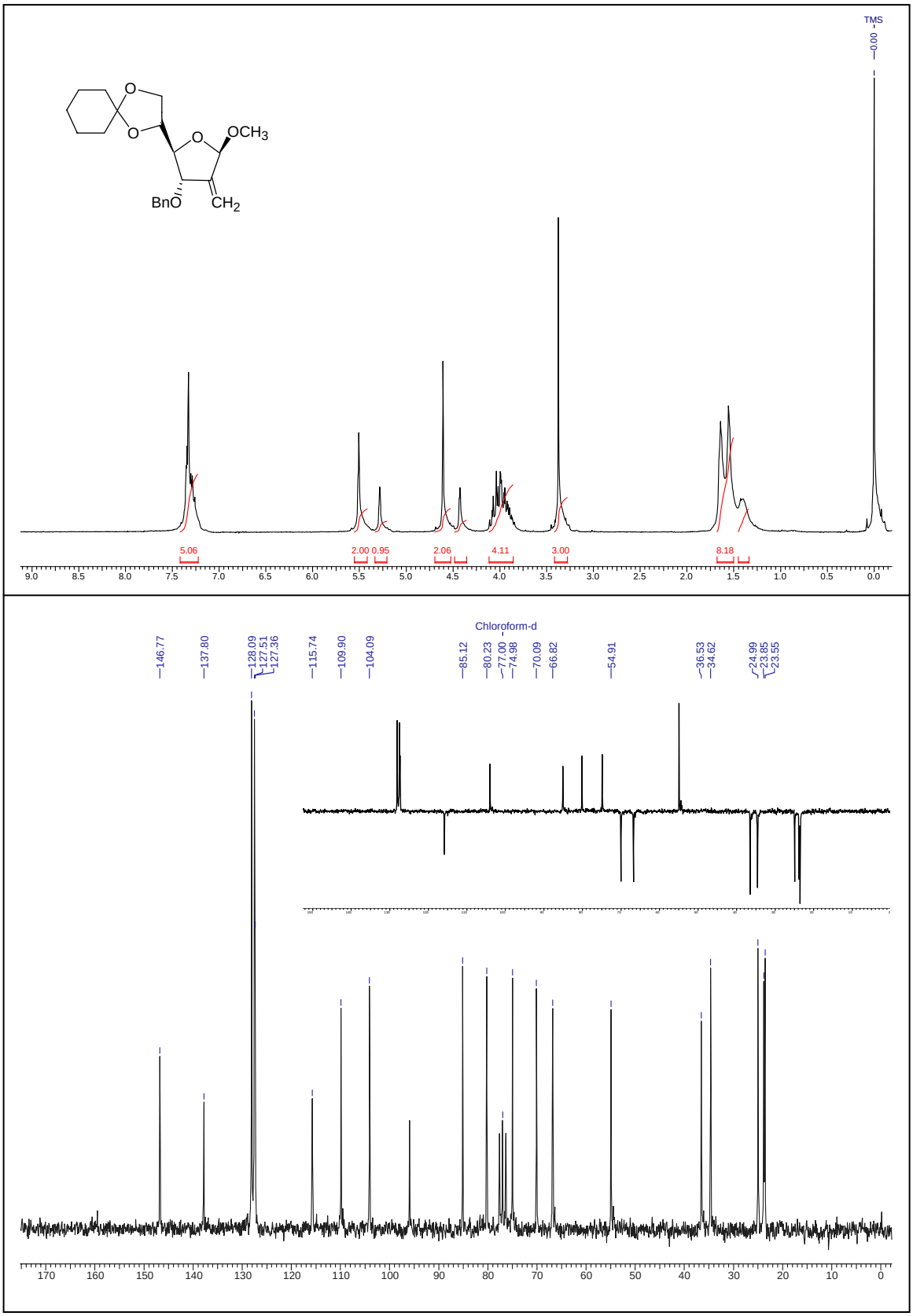


^{1}H and ^{13}C NMR spectra of compound 63 in $CDCl_3$

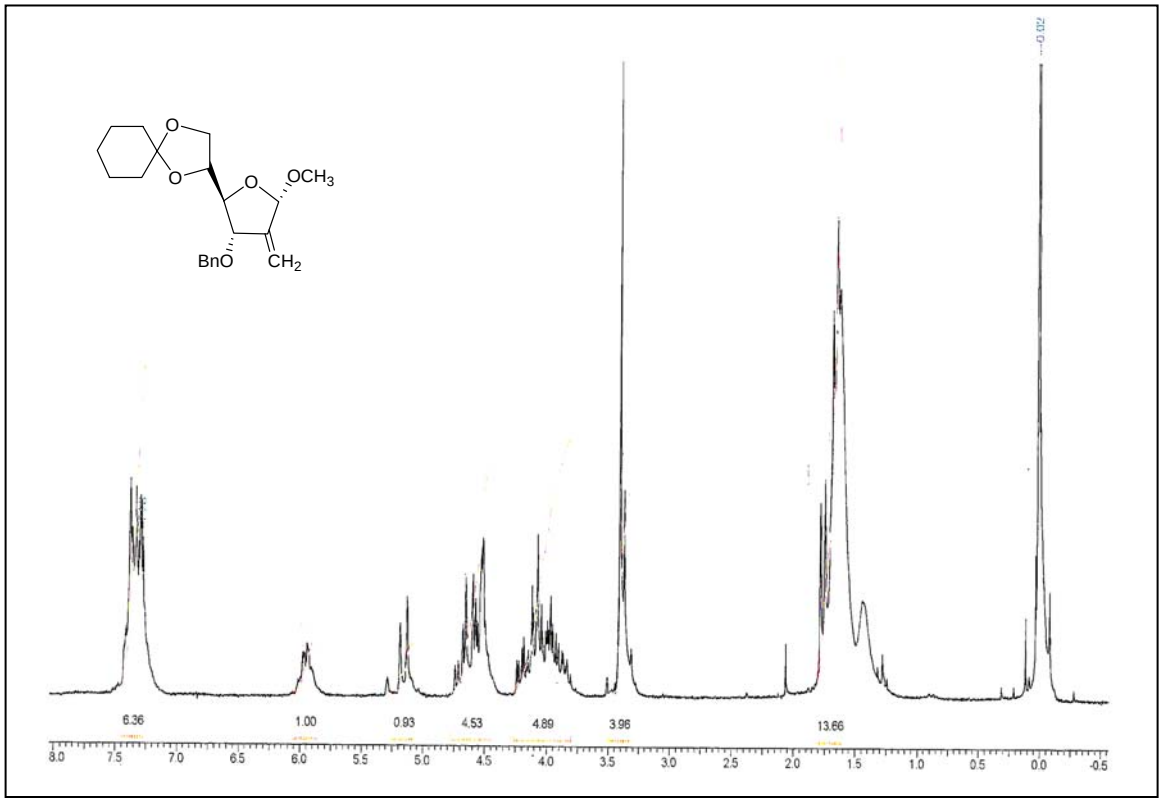




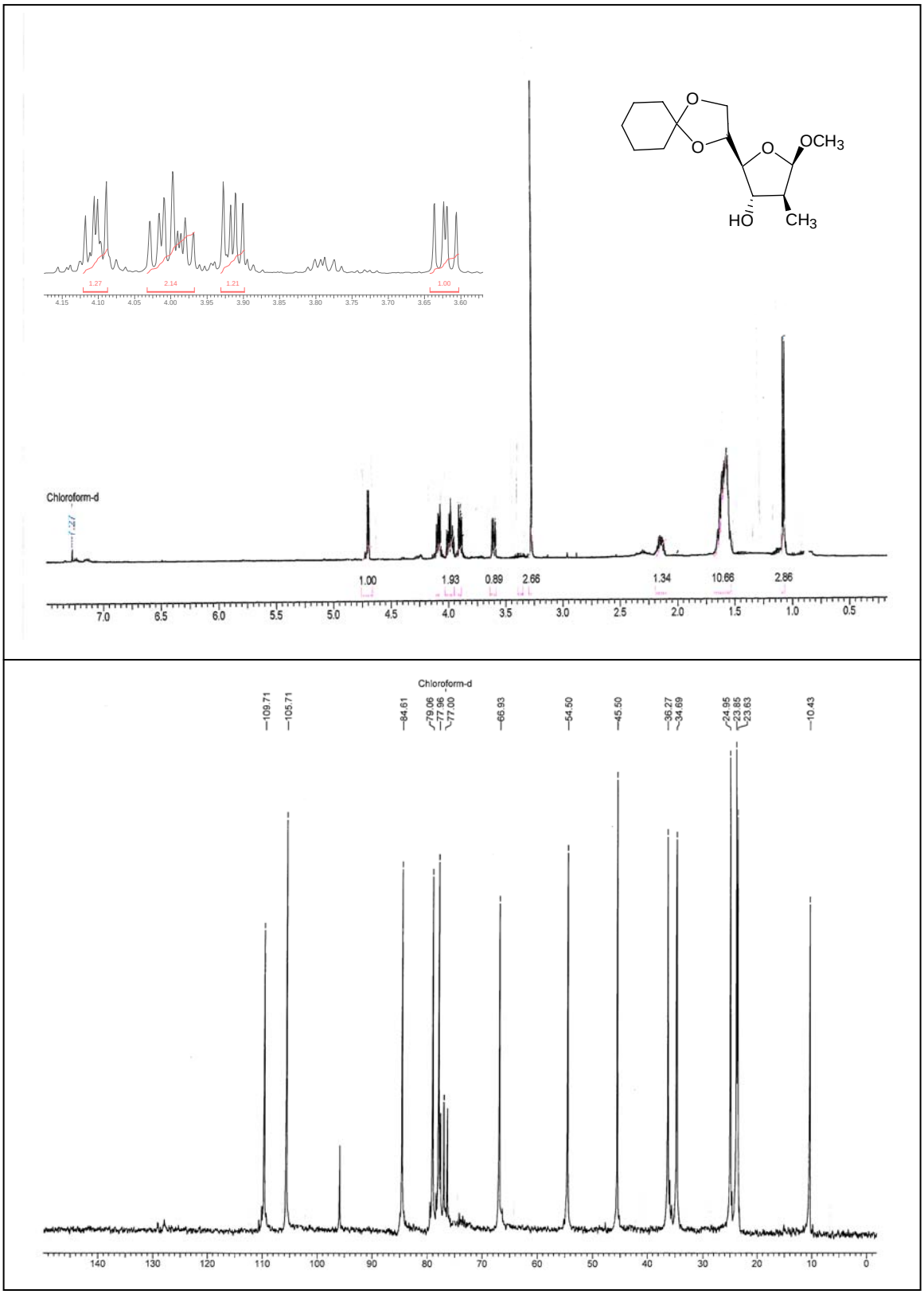
^{1}H and ^{13}C NMR spectra of compound 64 in $CDCl_3$



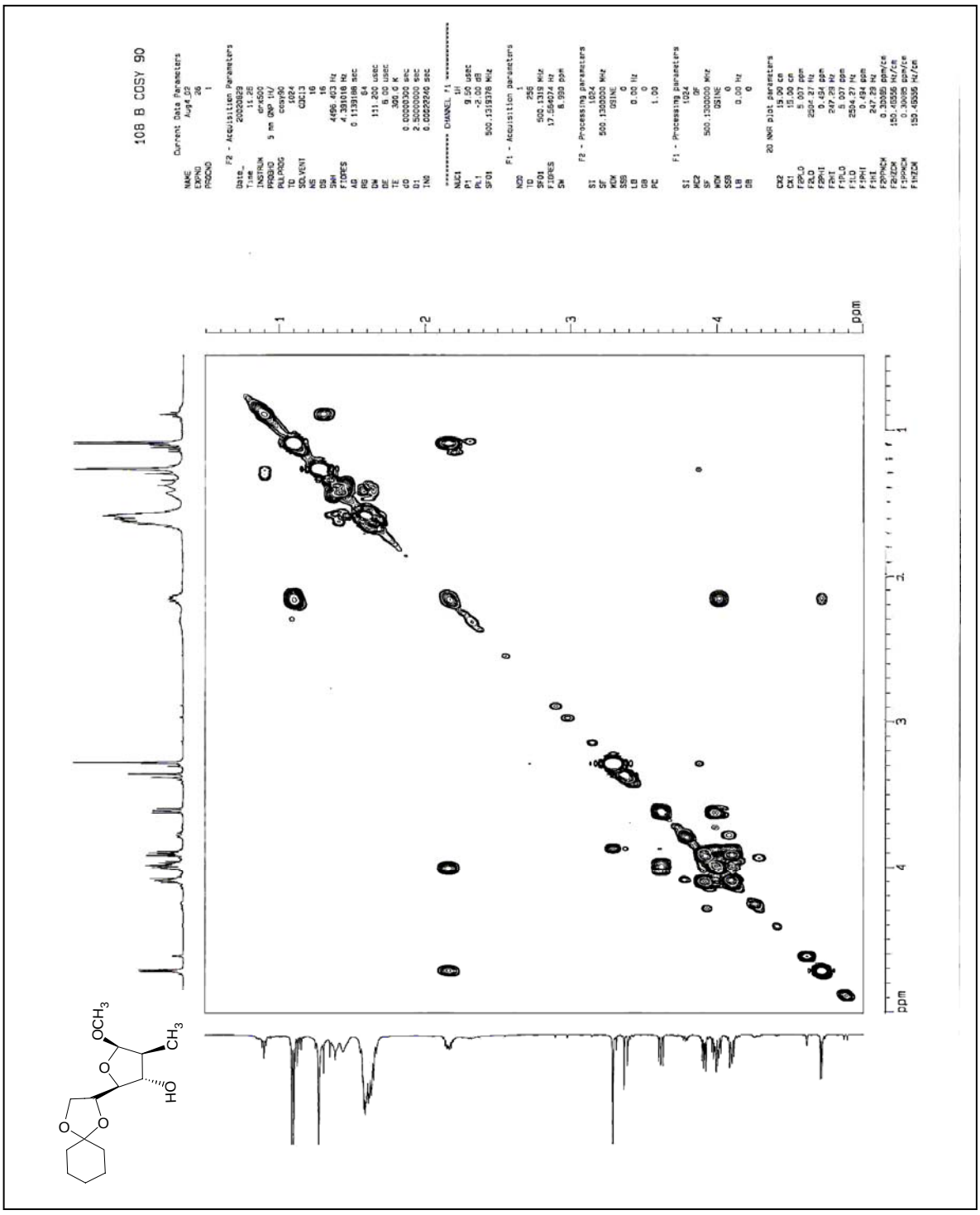
^{1}H NMR spectrum of compound 65 in $CDCl_3$



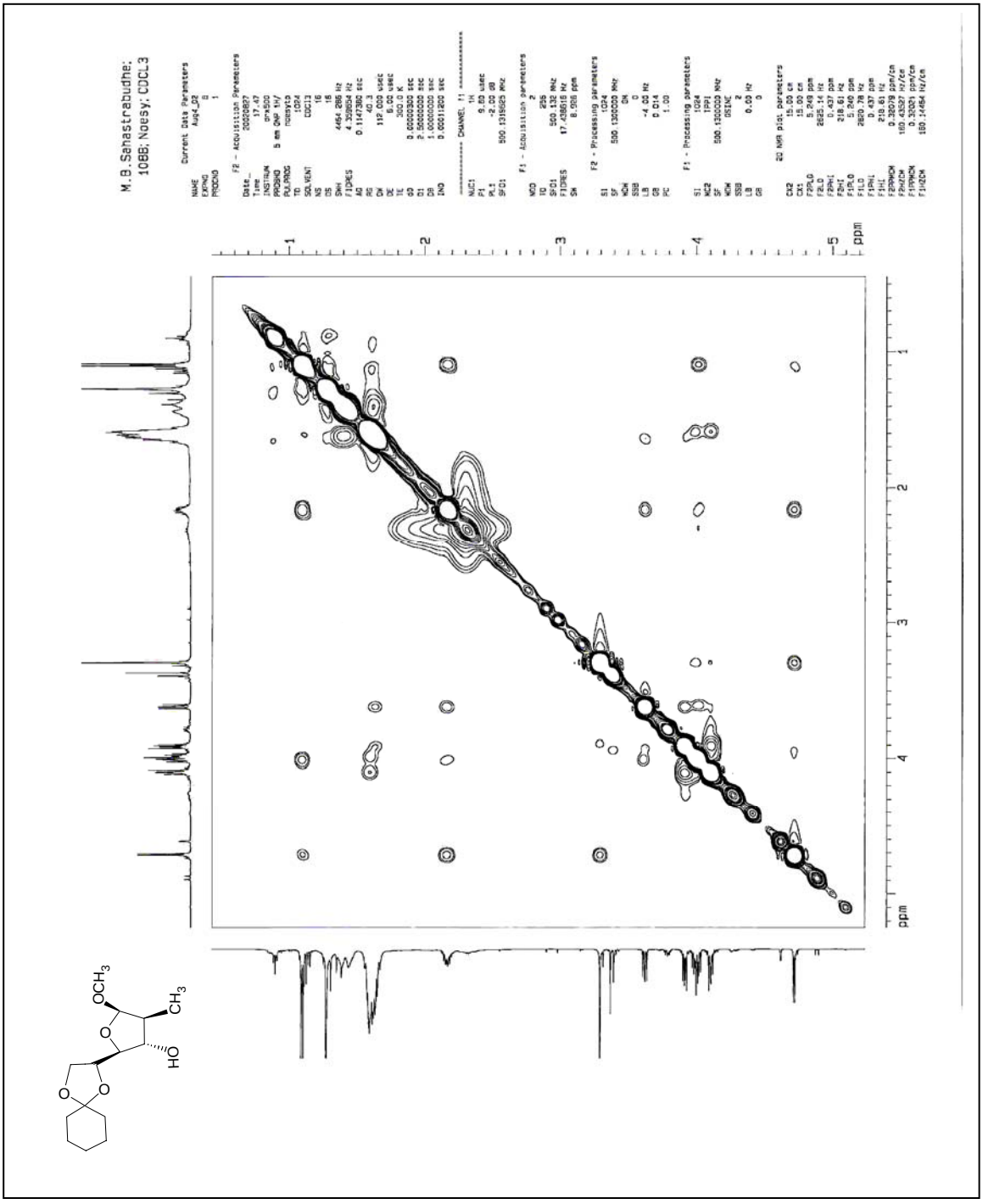
^{1}H and ^{13}C NMR spectra of compound 66 in $CDCl_3$



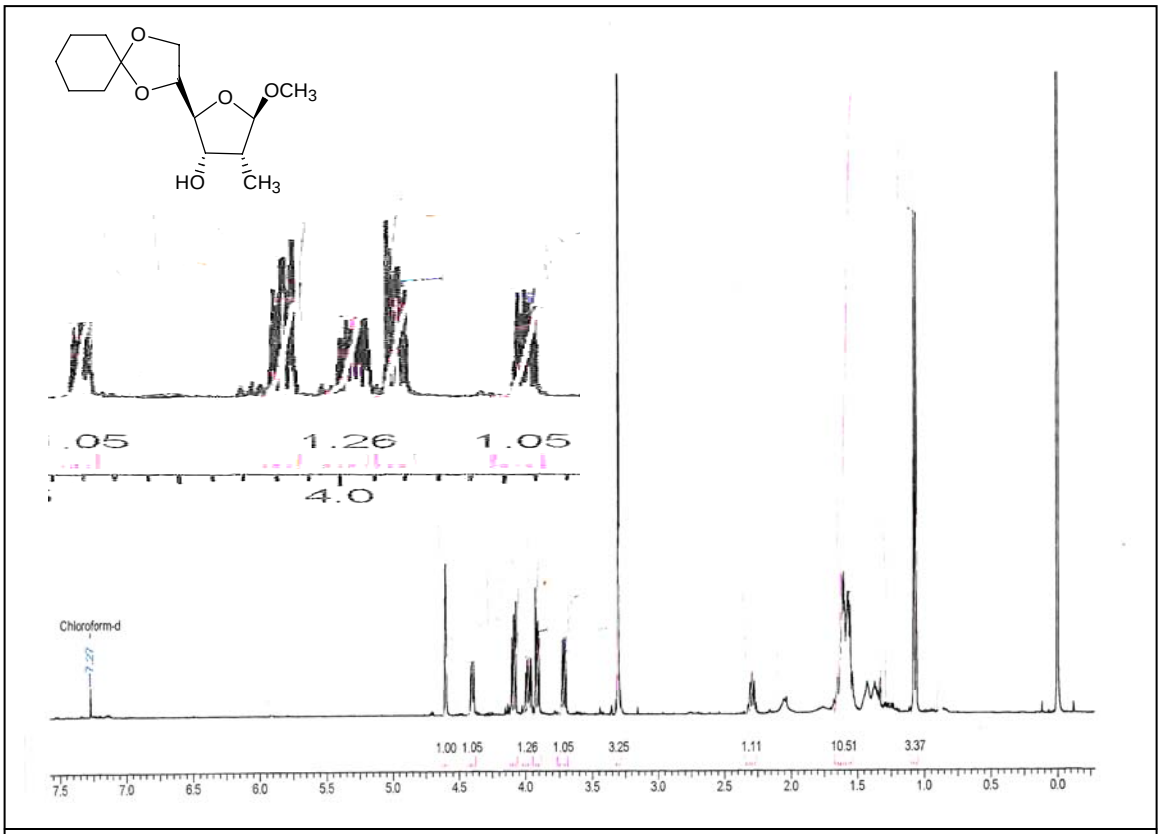
COSY of compound 66

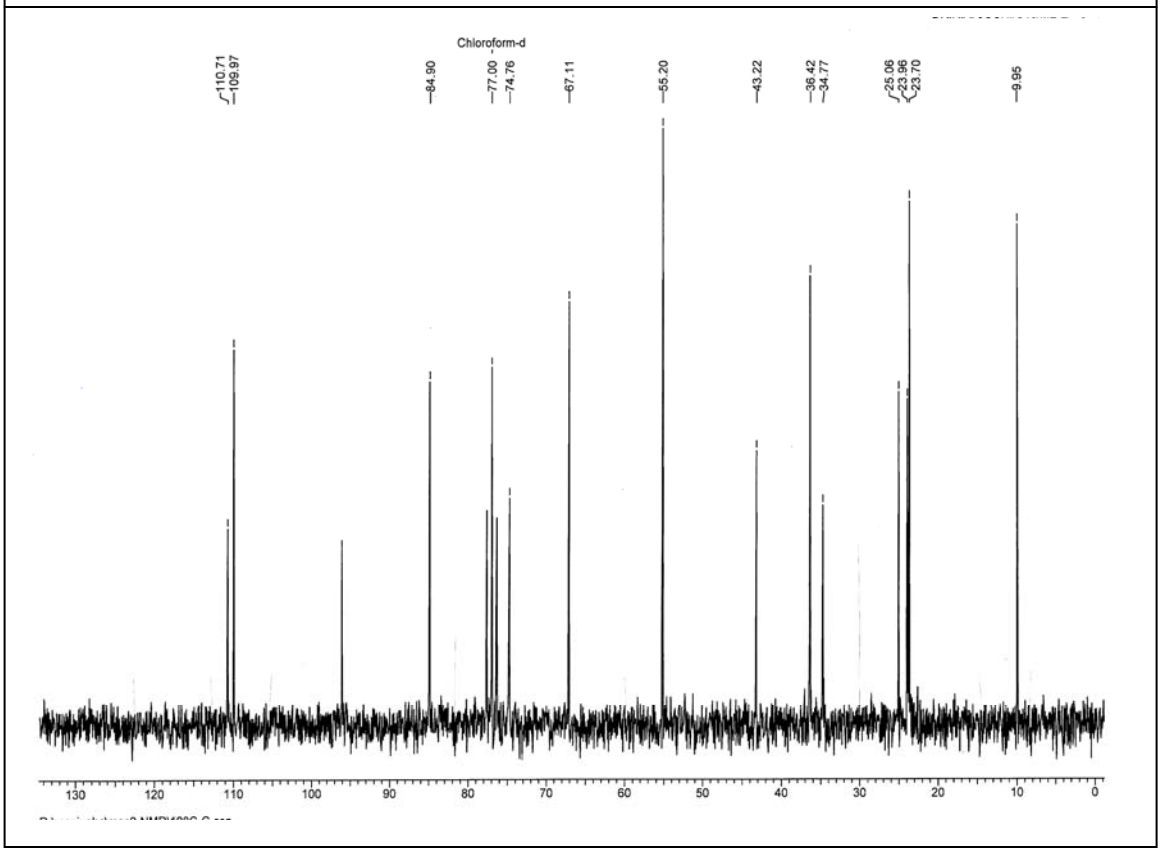


NOESY of compound 66

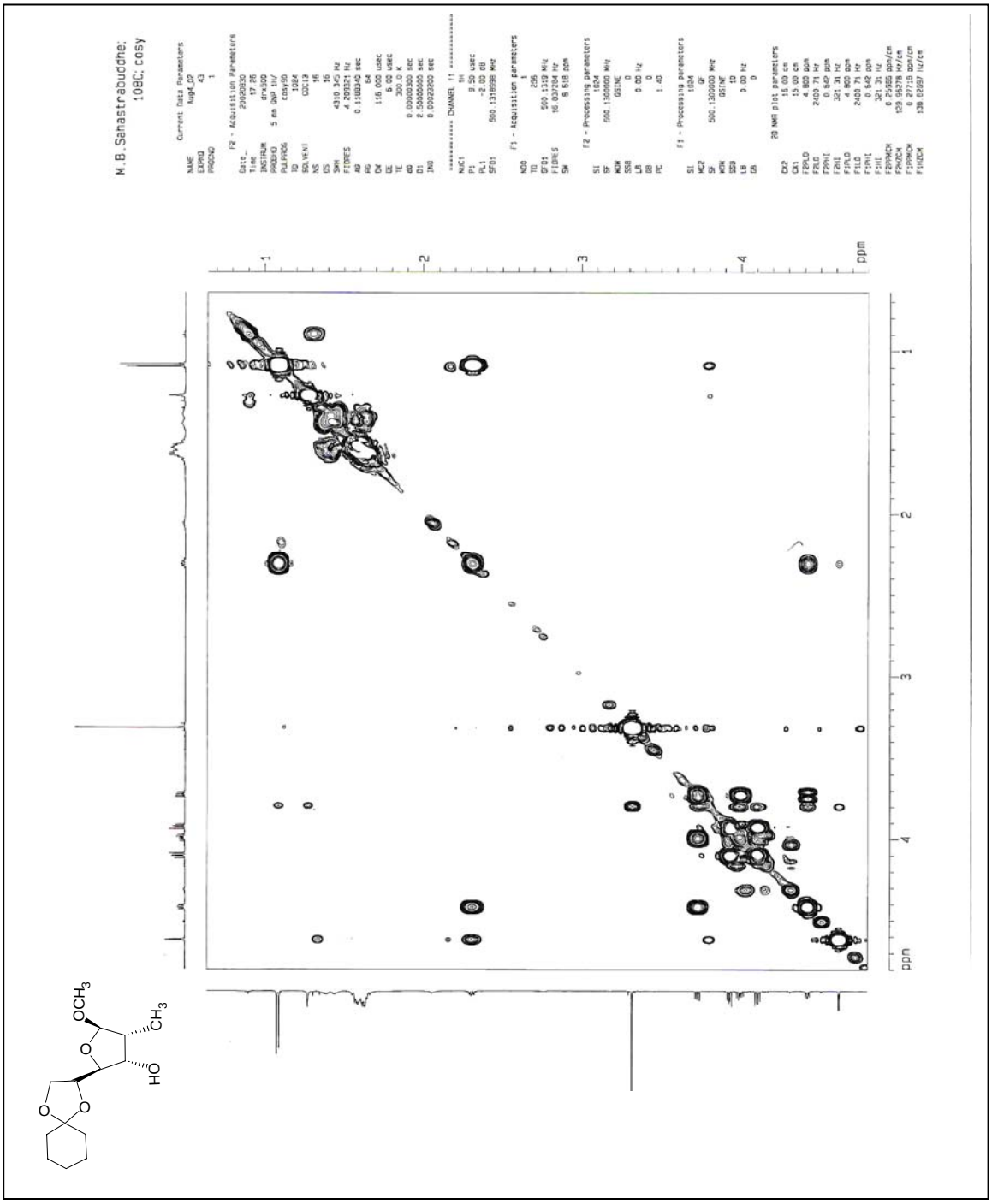


^{1}H and ^{13}C NMR spectra of compound 67 in $CDCl_3$

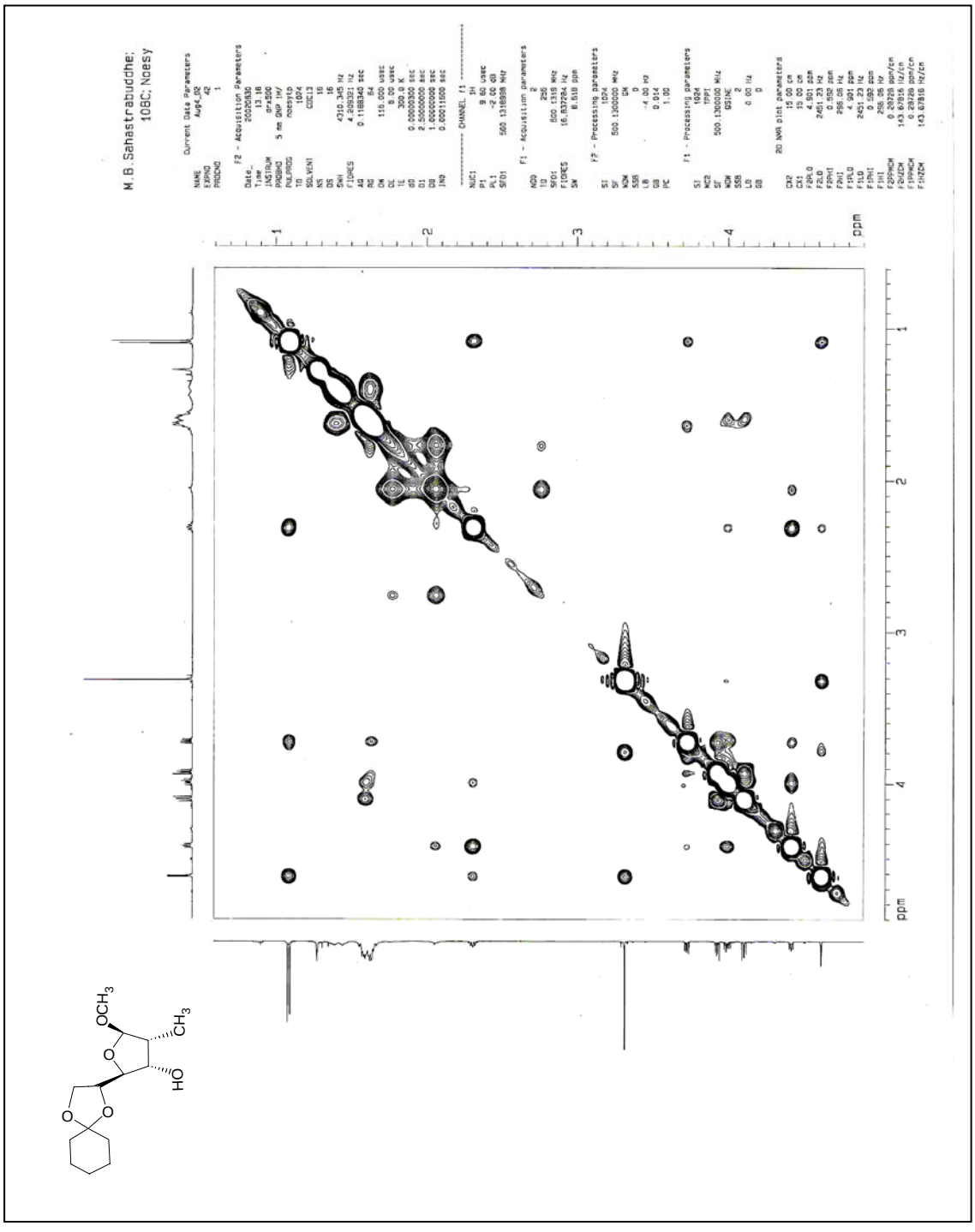




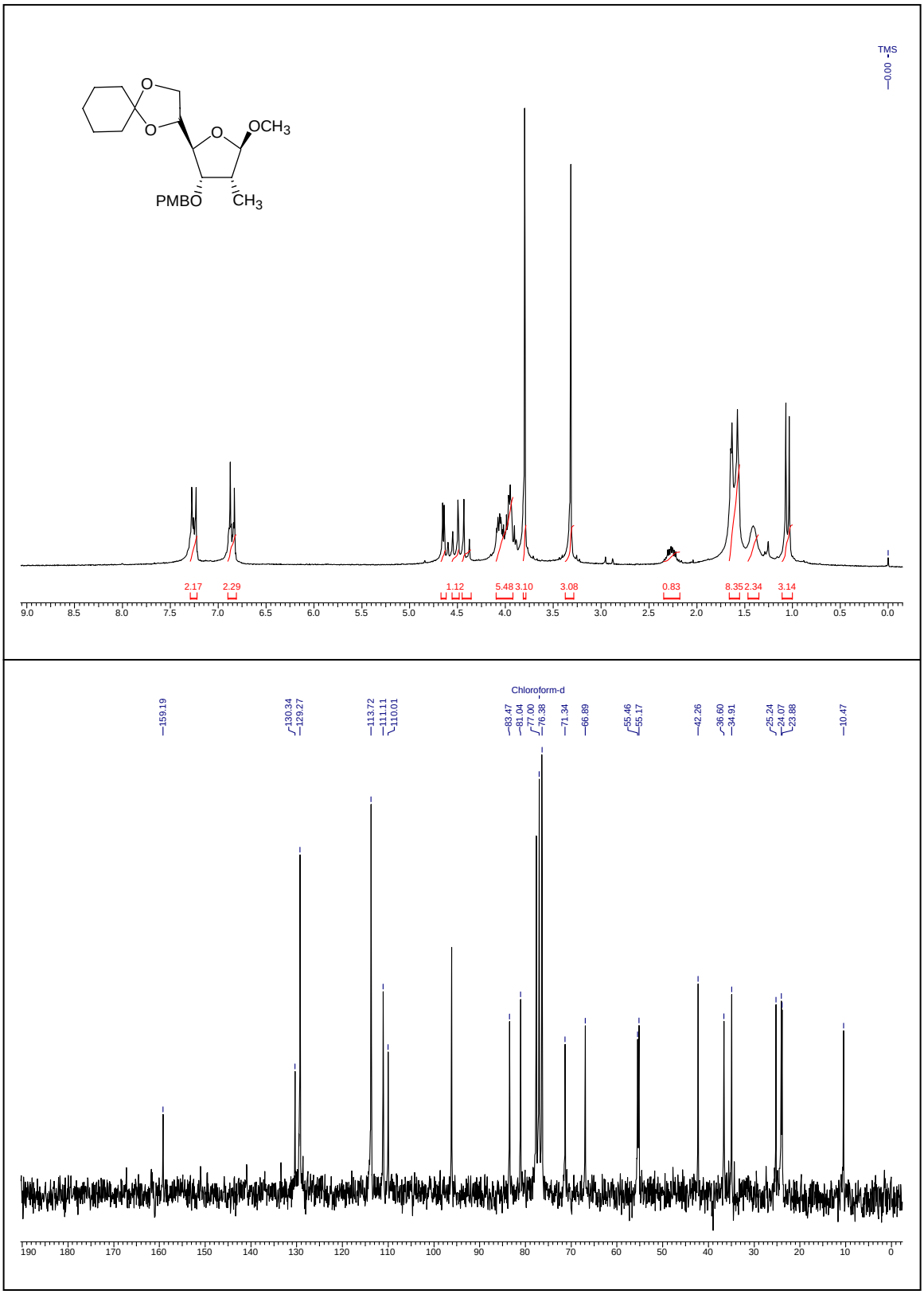
COSY of compound 67



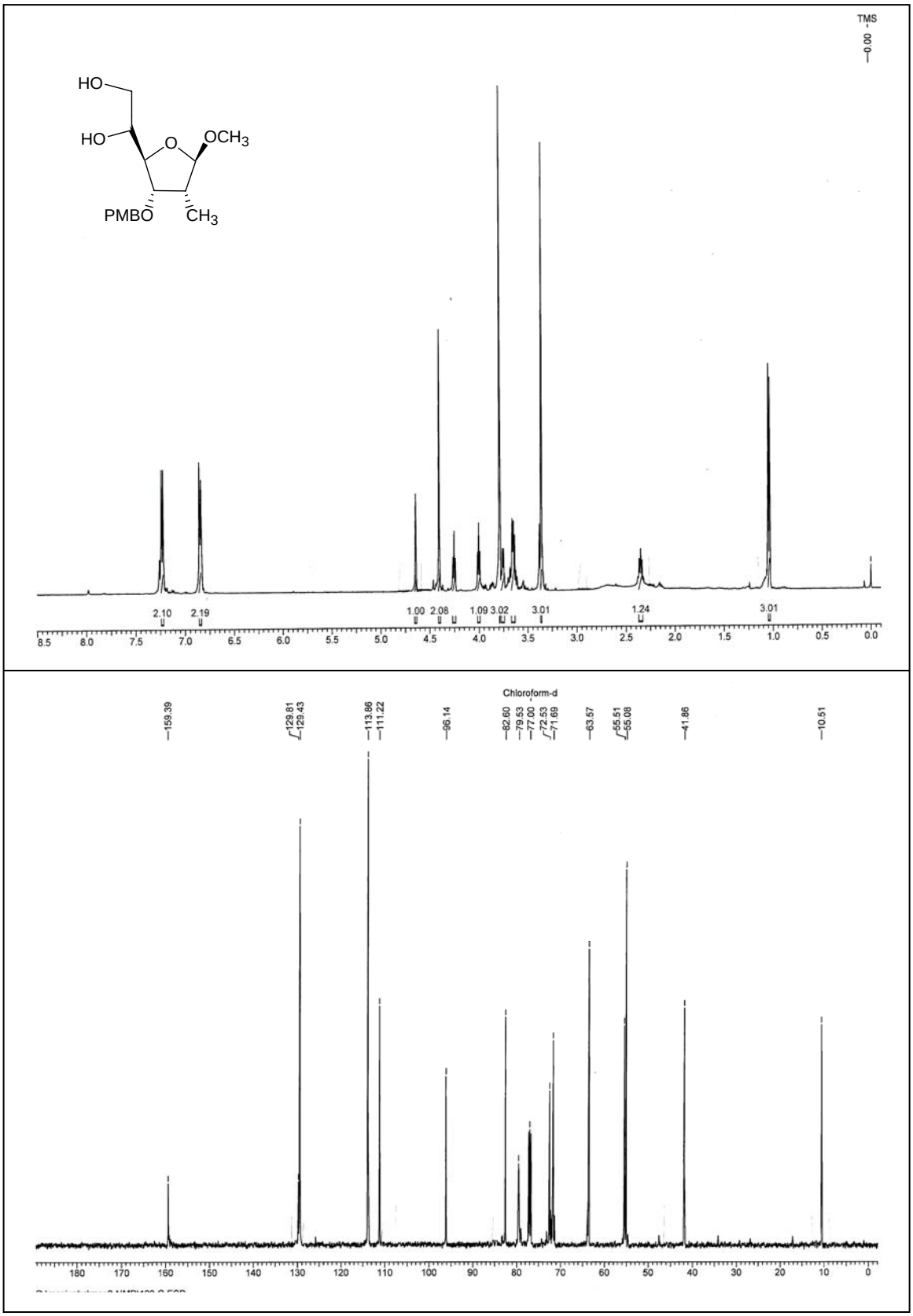
NOESY of compound 67



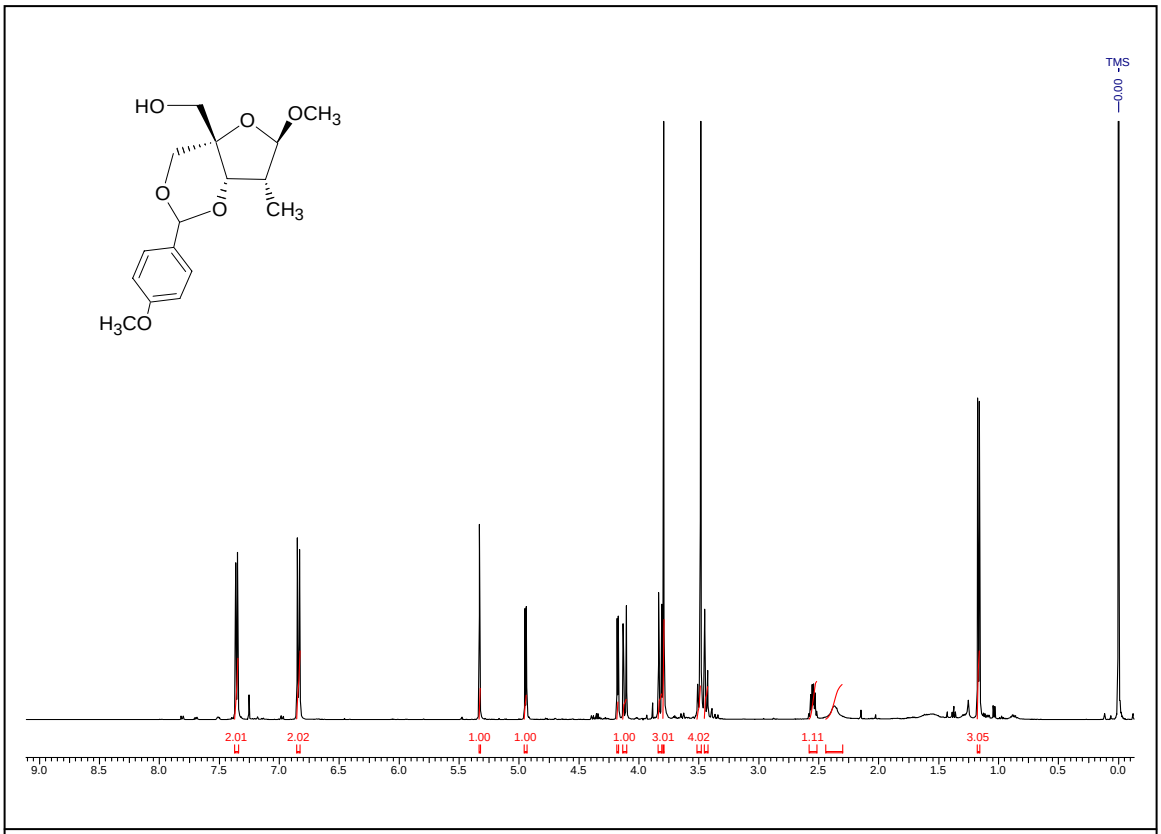
^{1}H and ^{13}C NMR spectra of compound 68 in $CDCl_3$

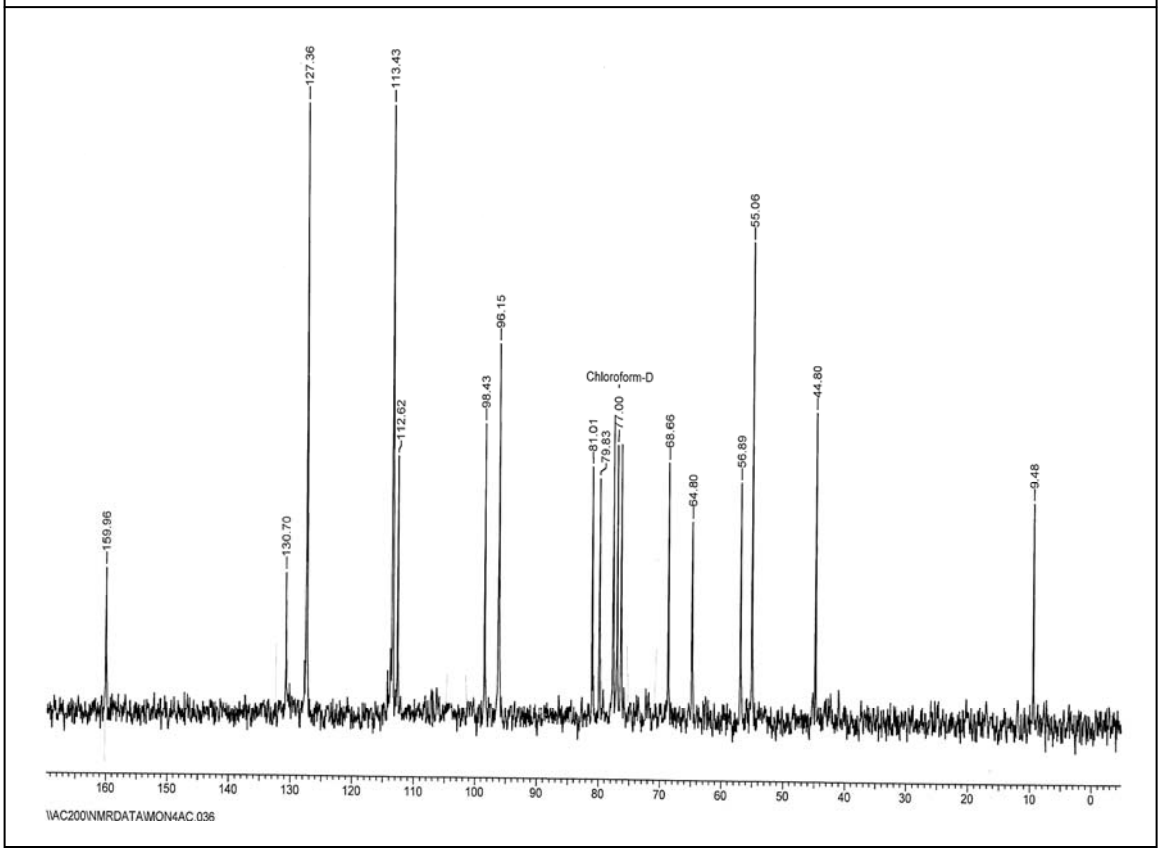


^{1}H and ^{13}C NMR spectra of compound 69 in $CDCl_3$

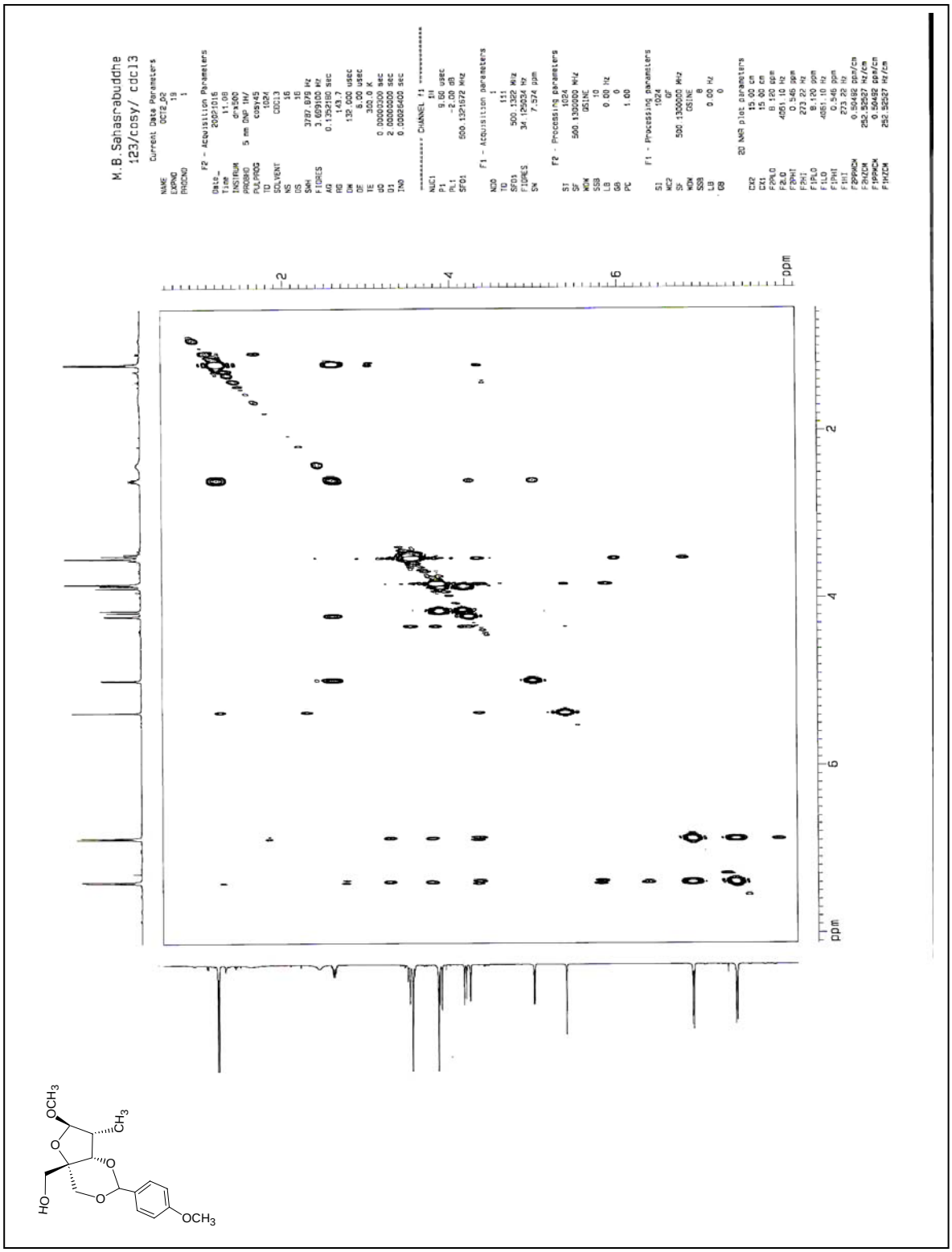


^{1}H and ^{13}C NMR spectra of compound 70 in $CDCl_3$

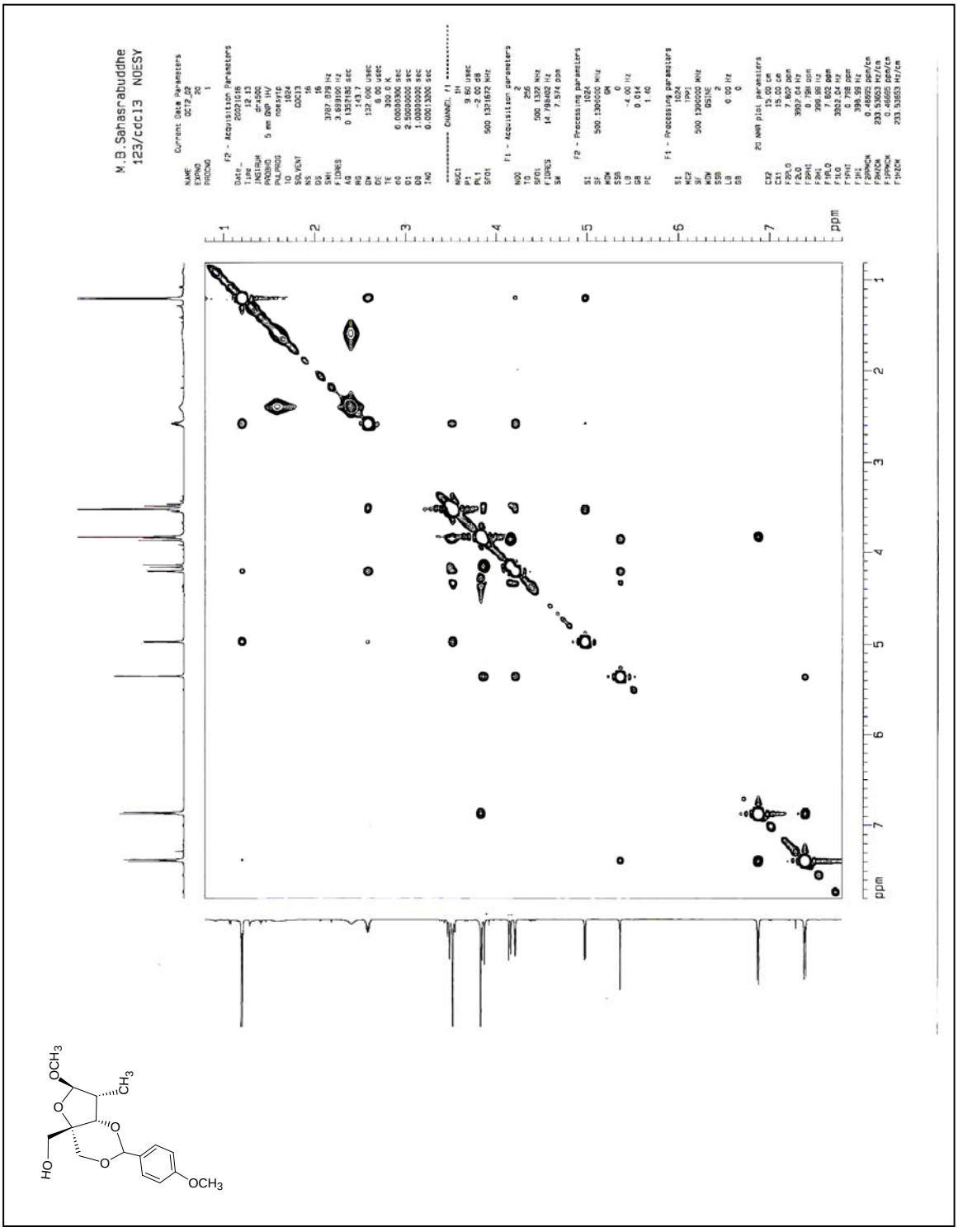




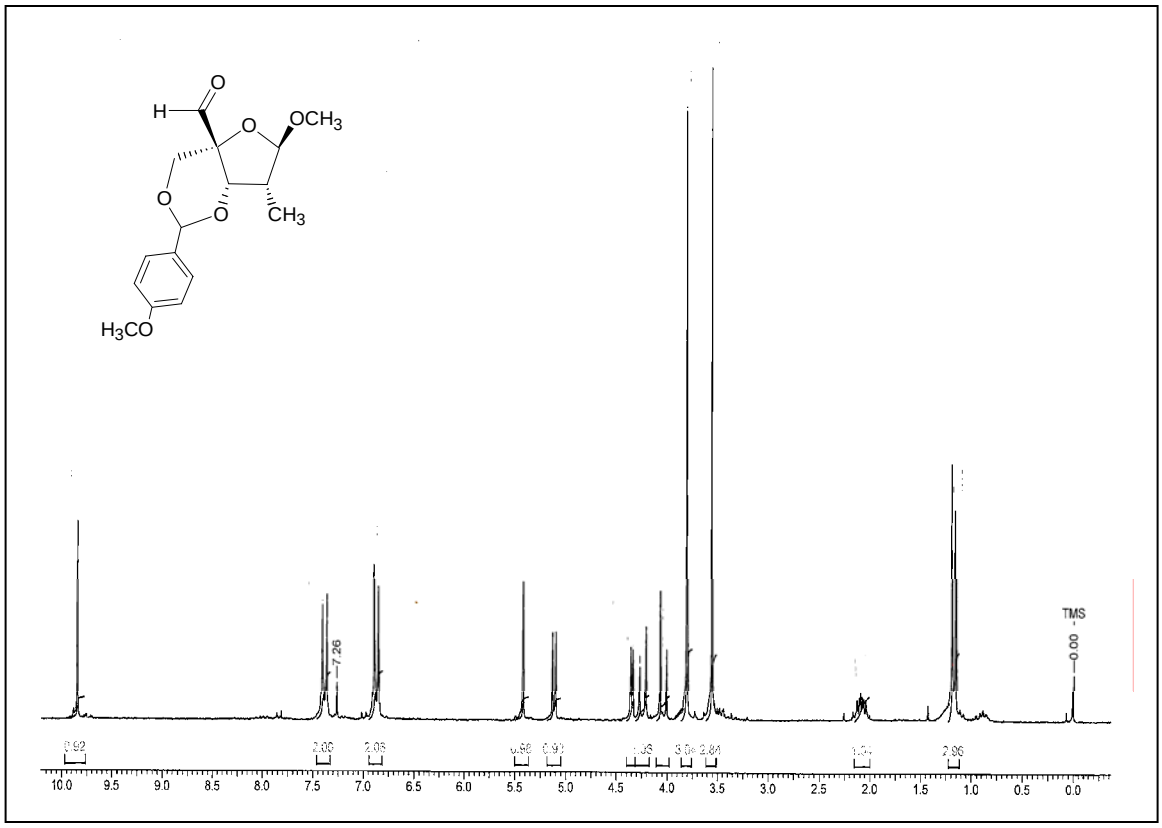
COSY of compound 70



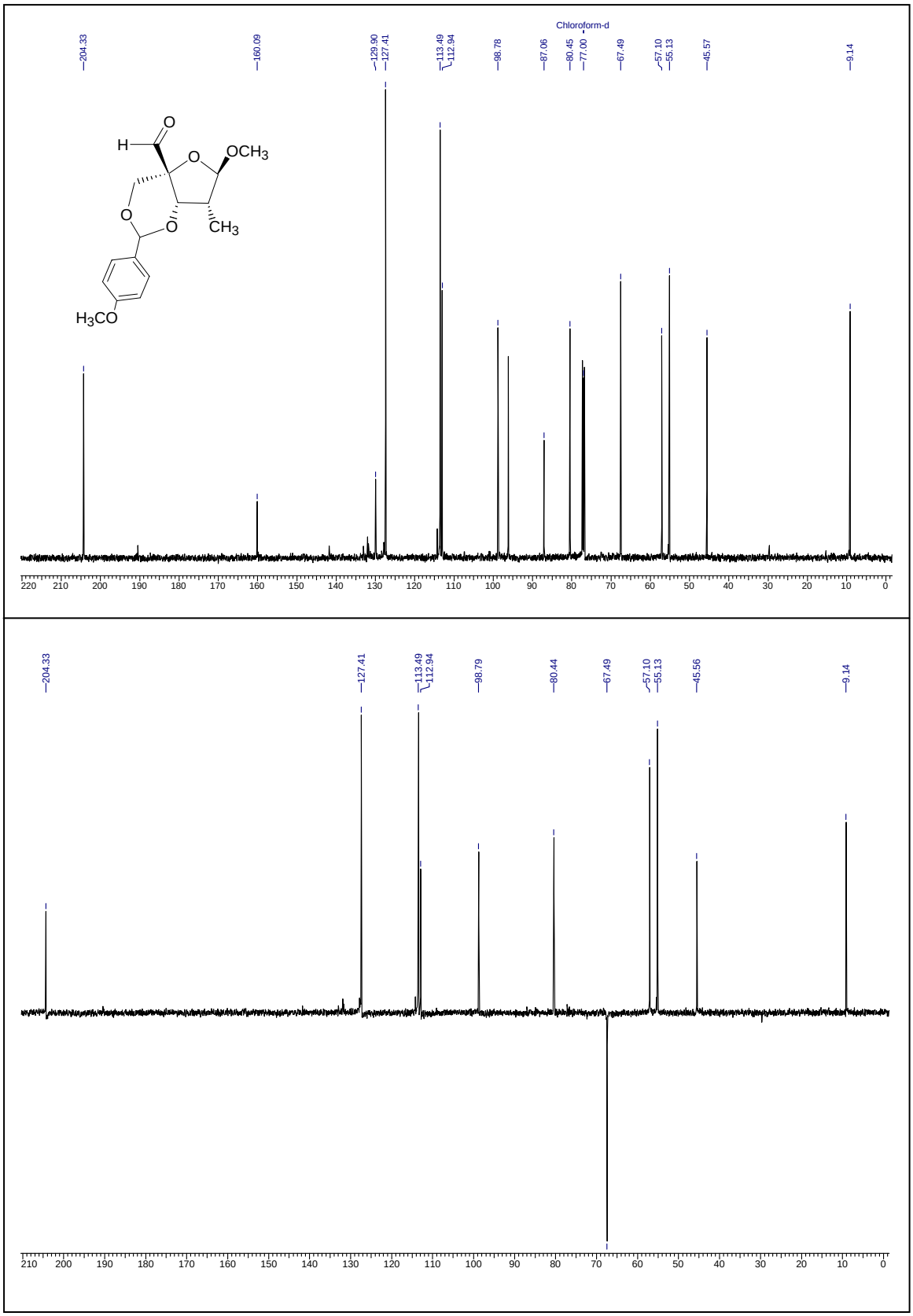
NOESY of compound 70



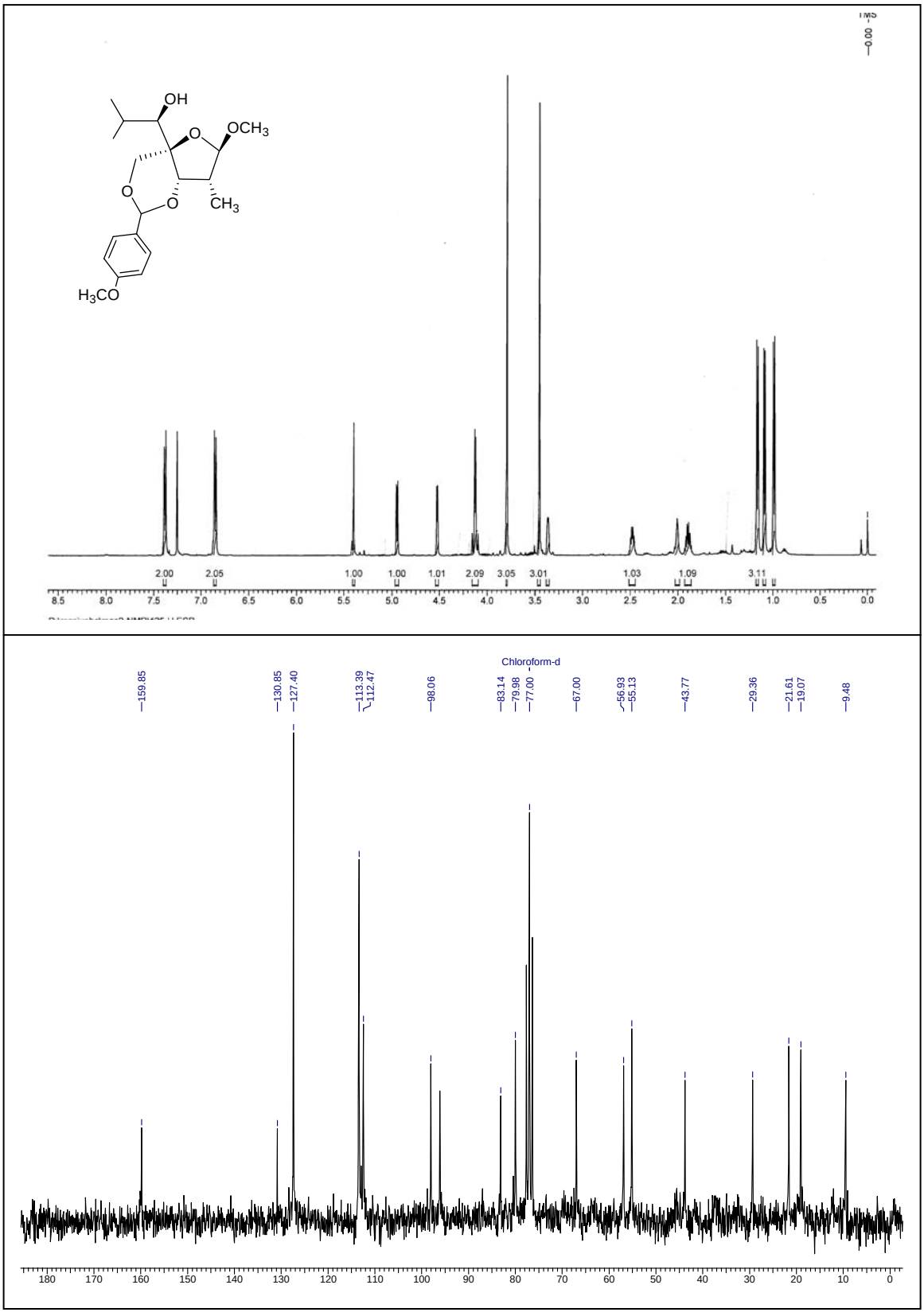
^{1}H NMR spectrum of compound 71 in $CDCl_3$



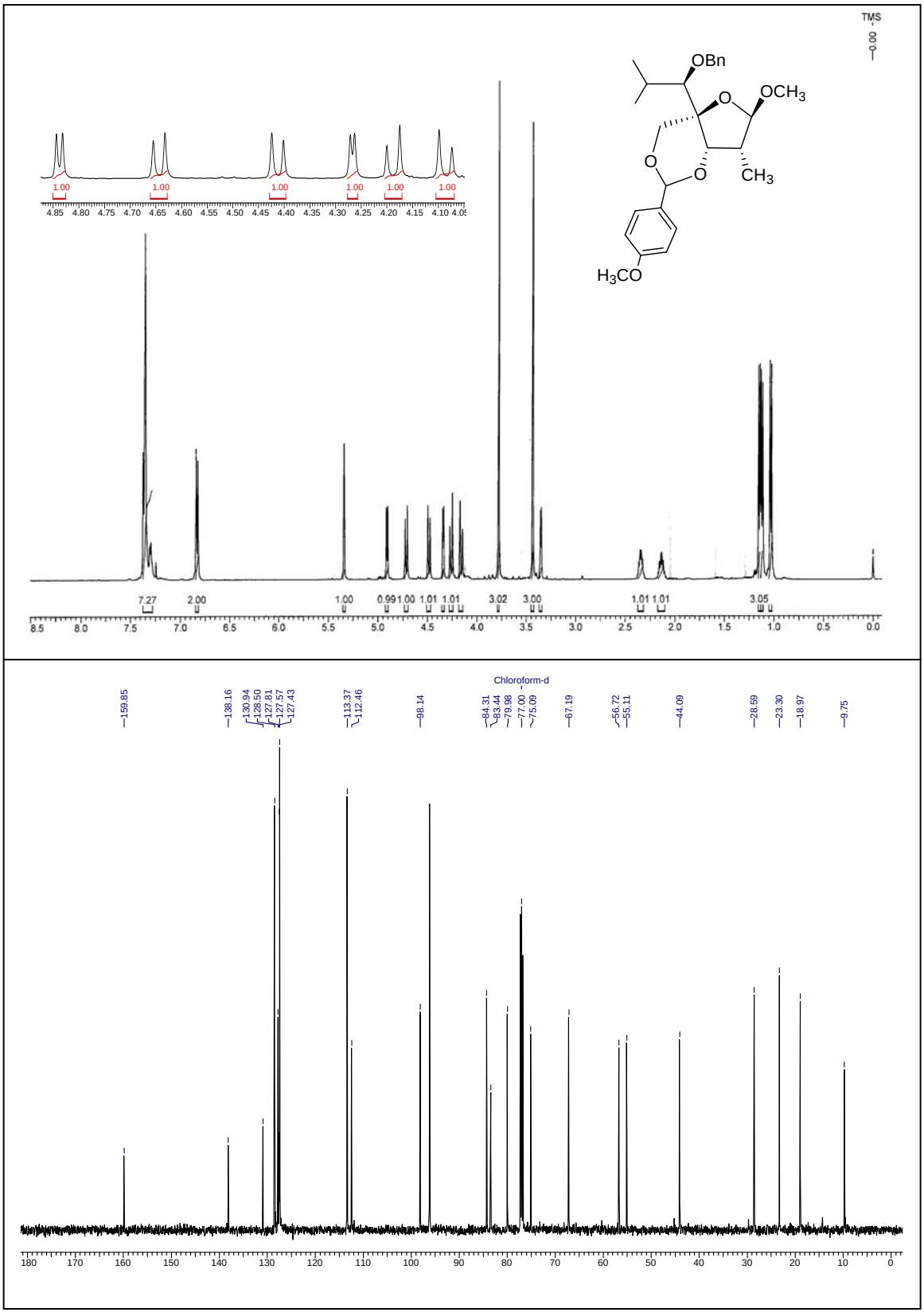
^{13}C NMR spectrum of compound 71 in $CDCl_3$



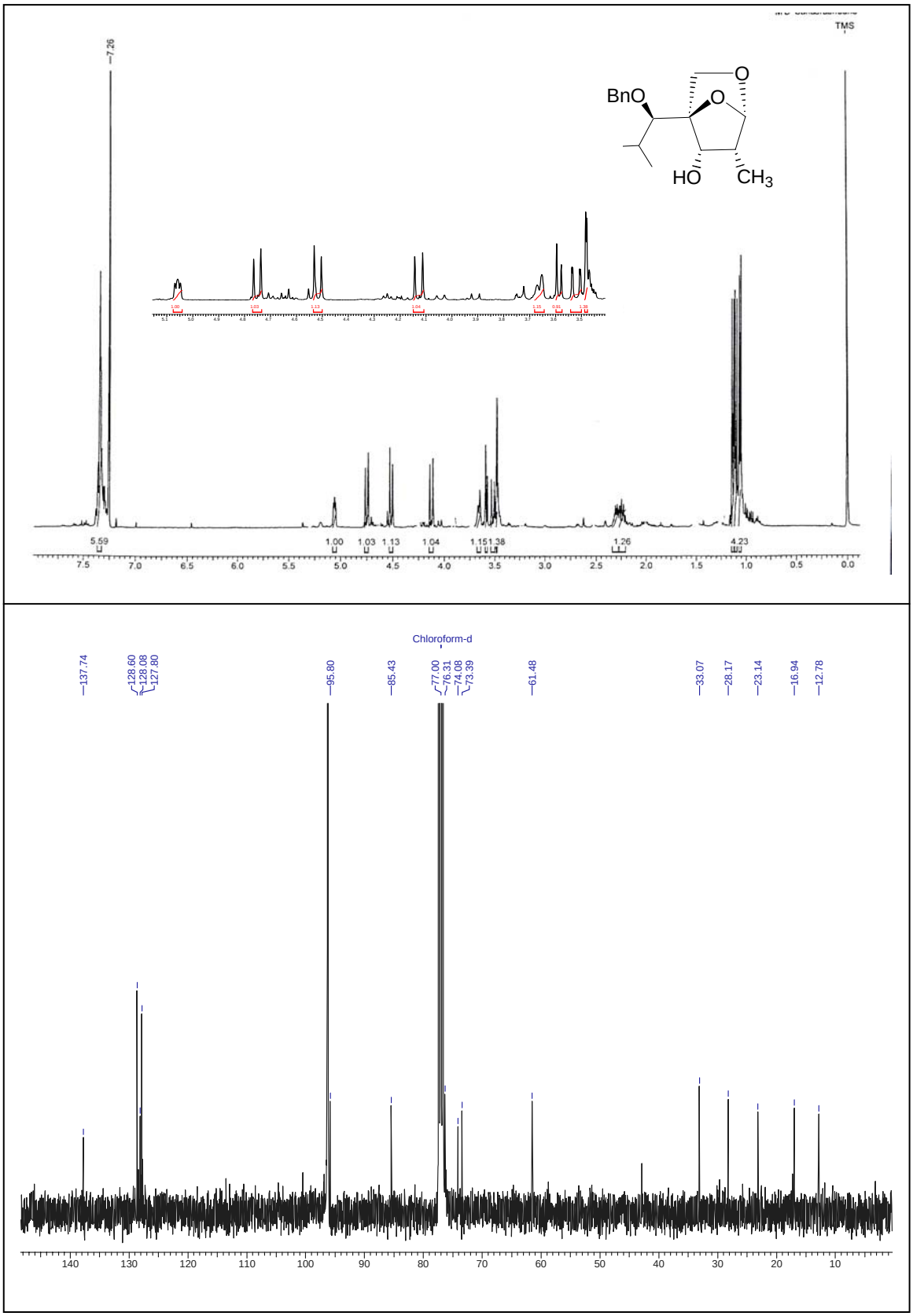
^{1}H and ^{13}C NMR spectra of compound 74 in $CDCl_3$



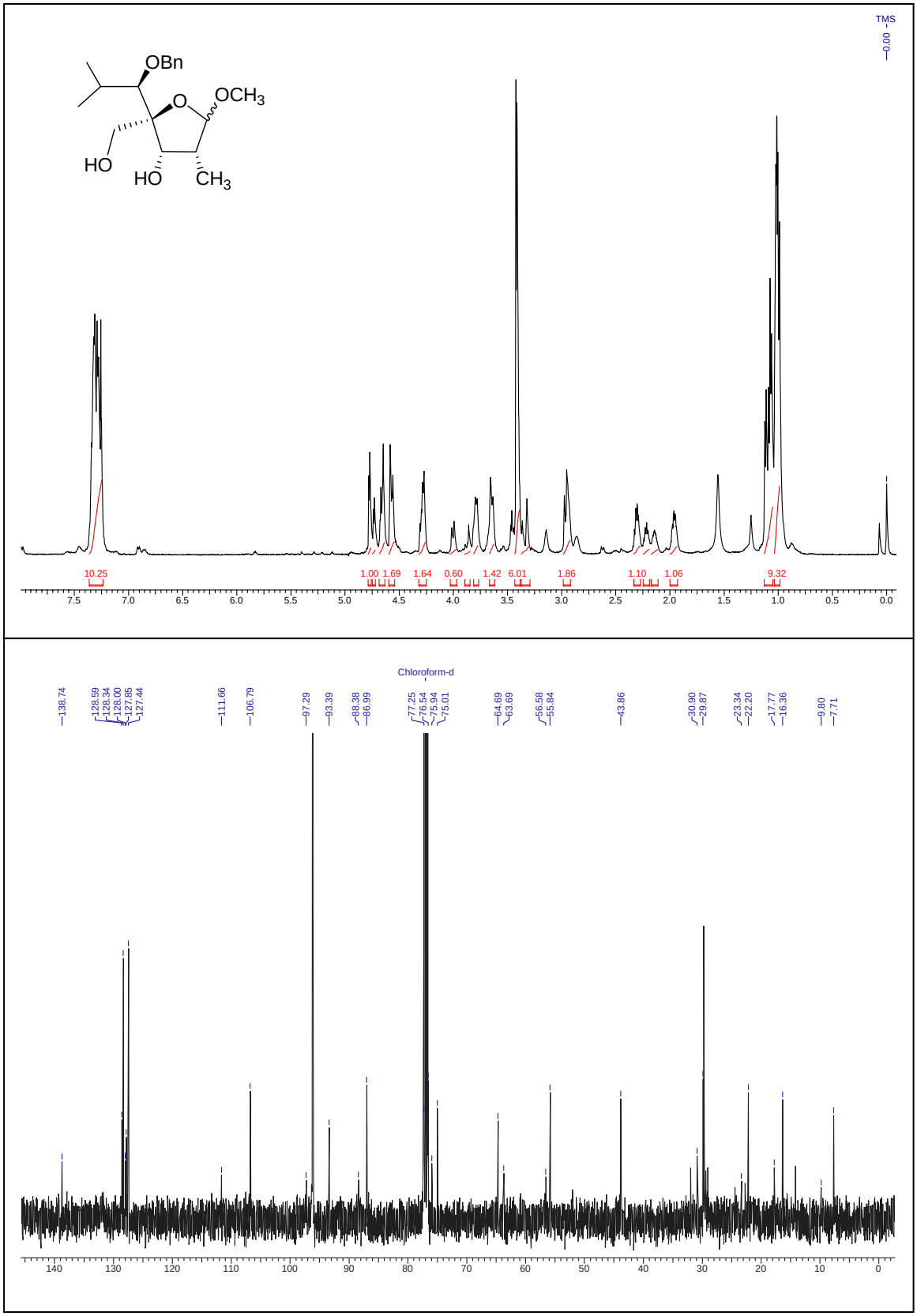
^{1}H and ^{13}C NMR spectra of compound 75 in $CDCl_3$



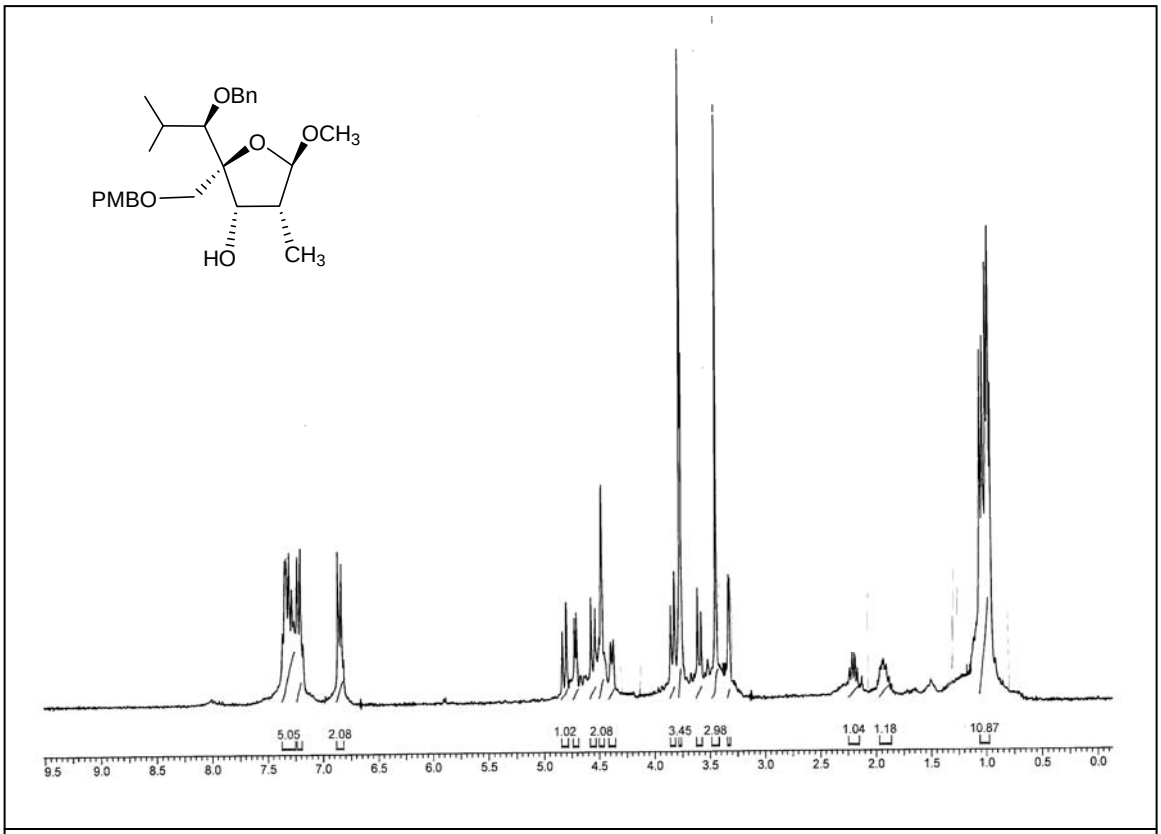
^{1}H and ^{13}C NMR spectra of compound 77 in $CDCl_3$

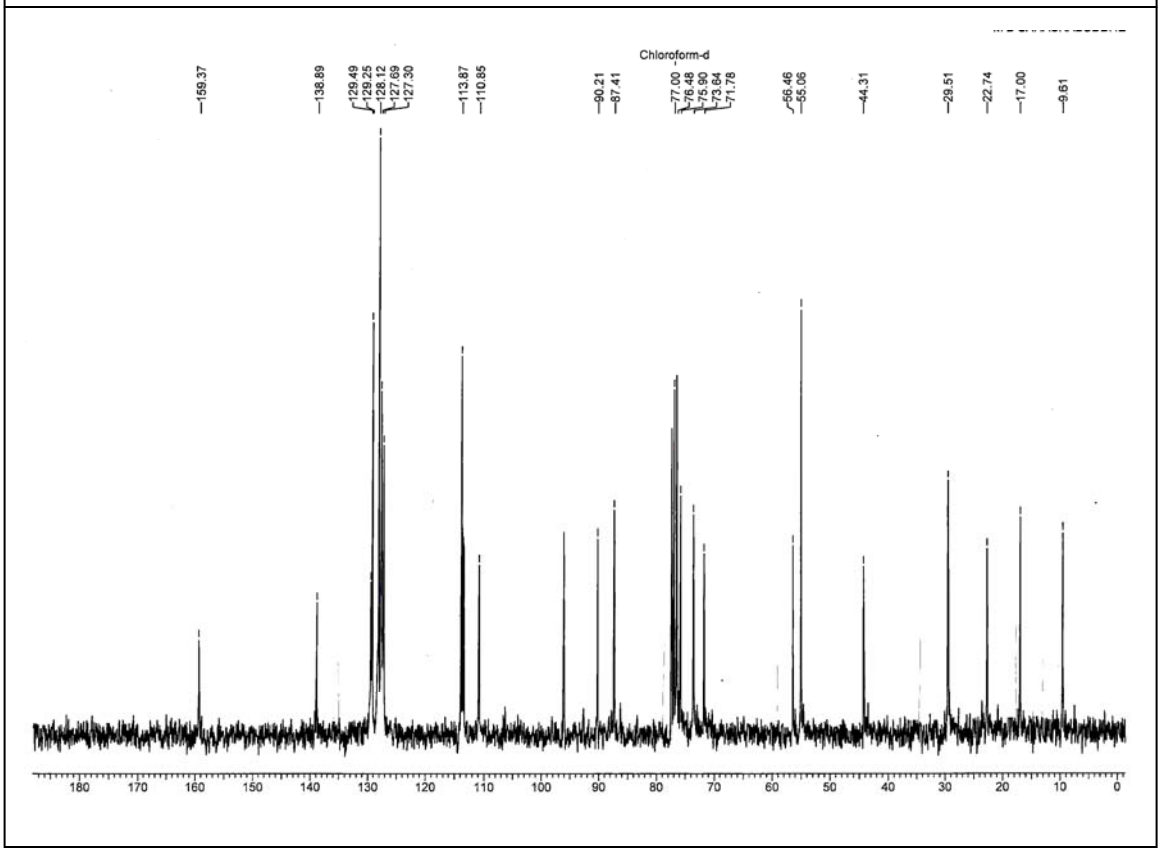


^{1}H and ^{13}C NMR spectra of compound 78 in $CDCl_3$

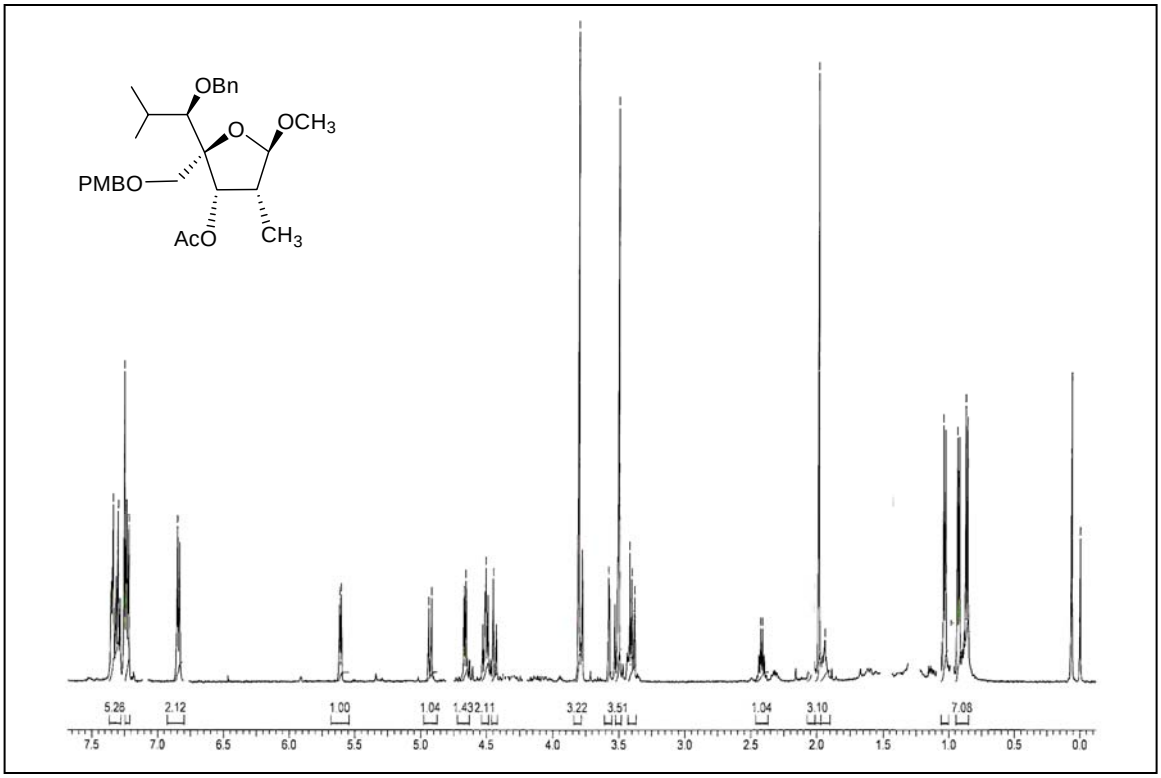


^{1}H and ^{13}C NMR spectra of compound 79 in $CDCl_3$

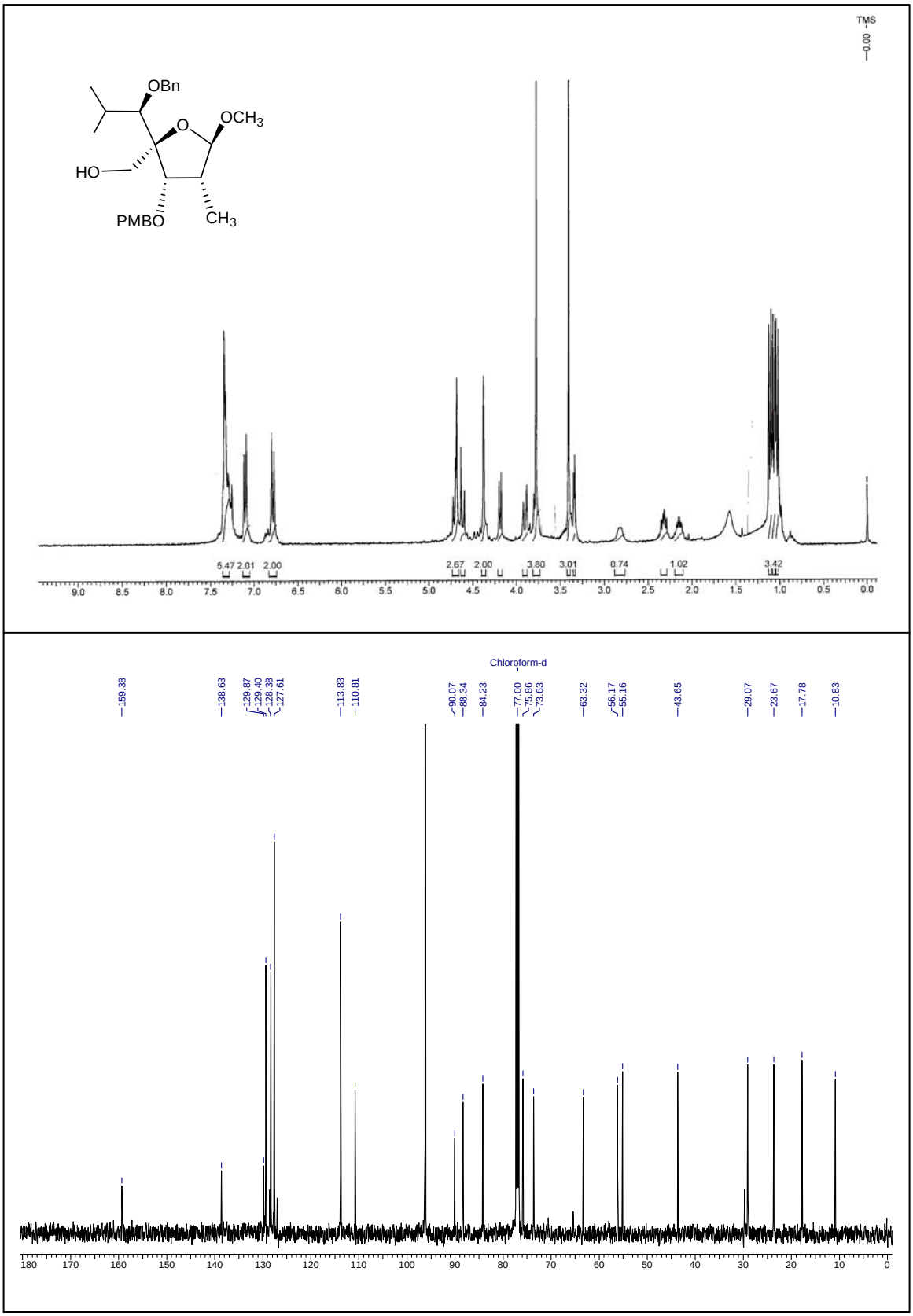




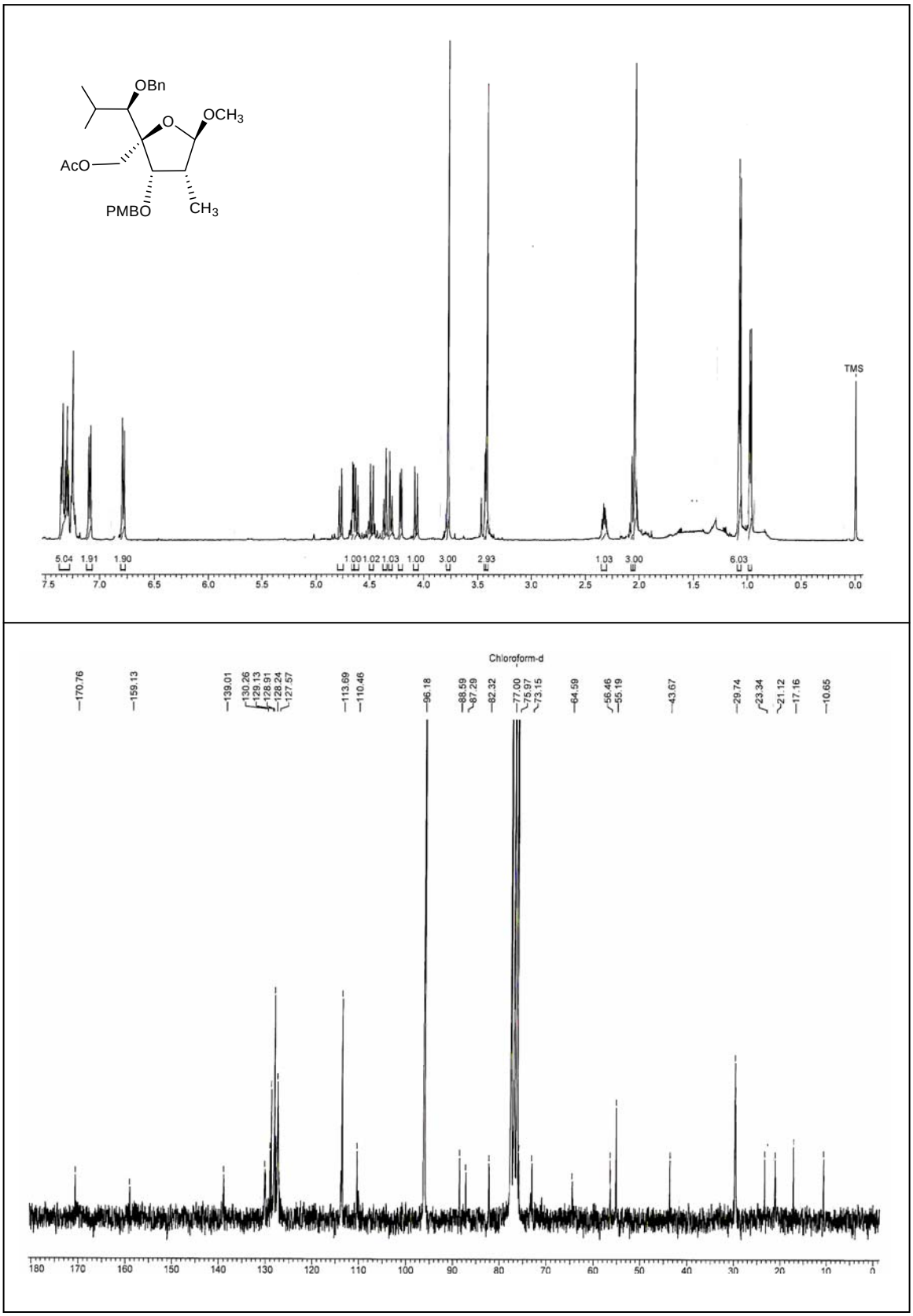
^{1}H NMR spectrum of compound 80 in $CDCl_3$



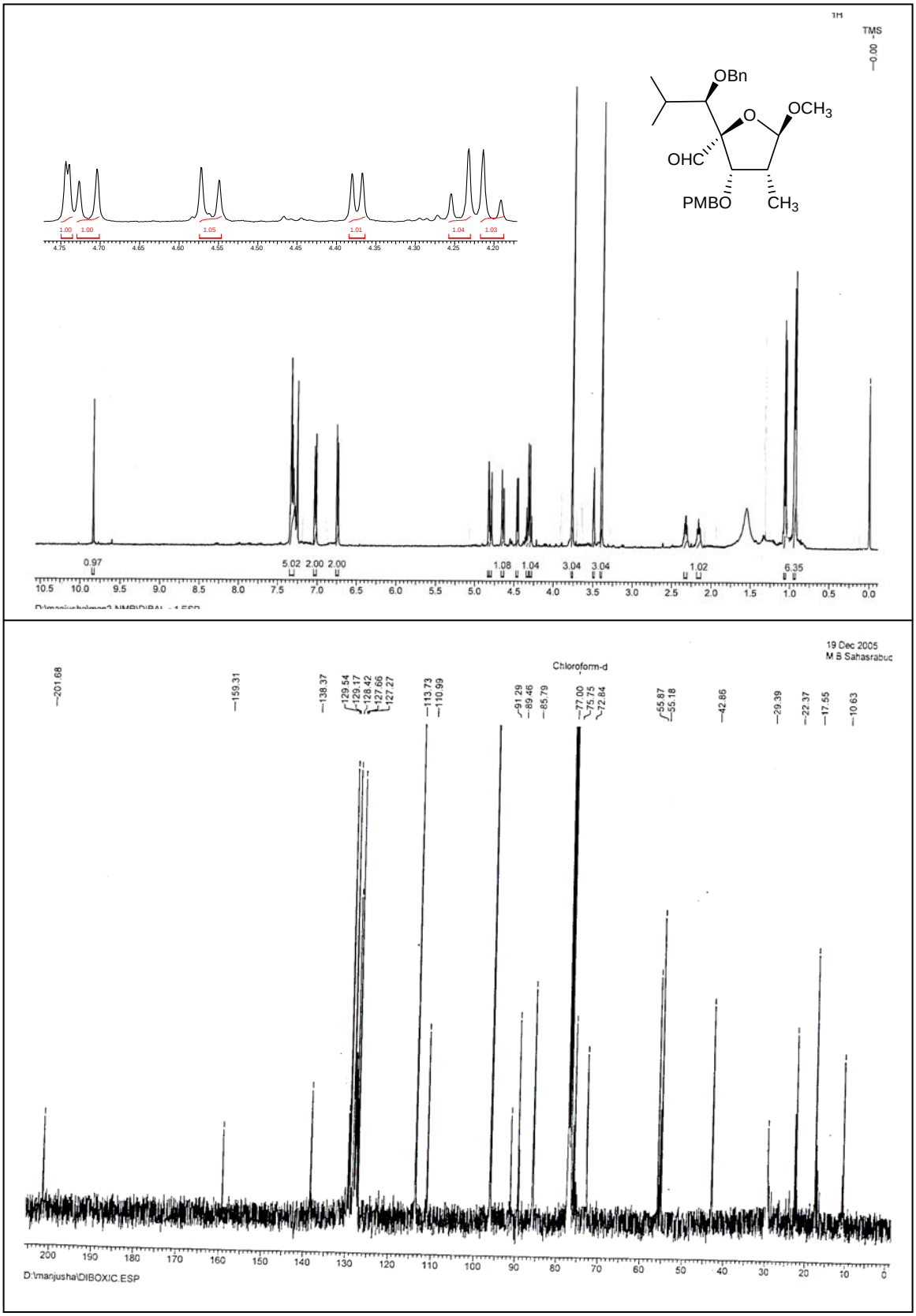
^{1}H and ^{13}C NMR spectra of compound 81 in $CDCl_3$



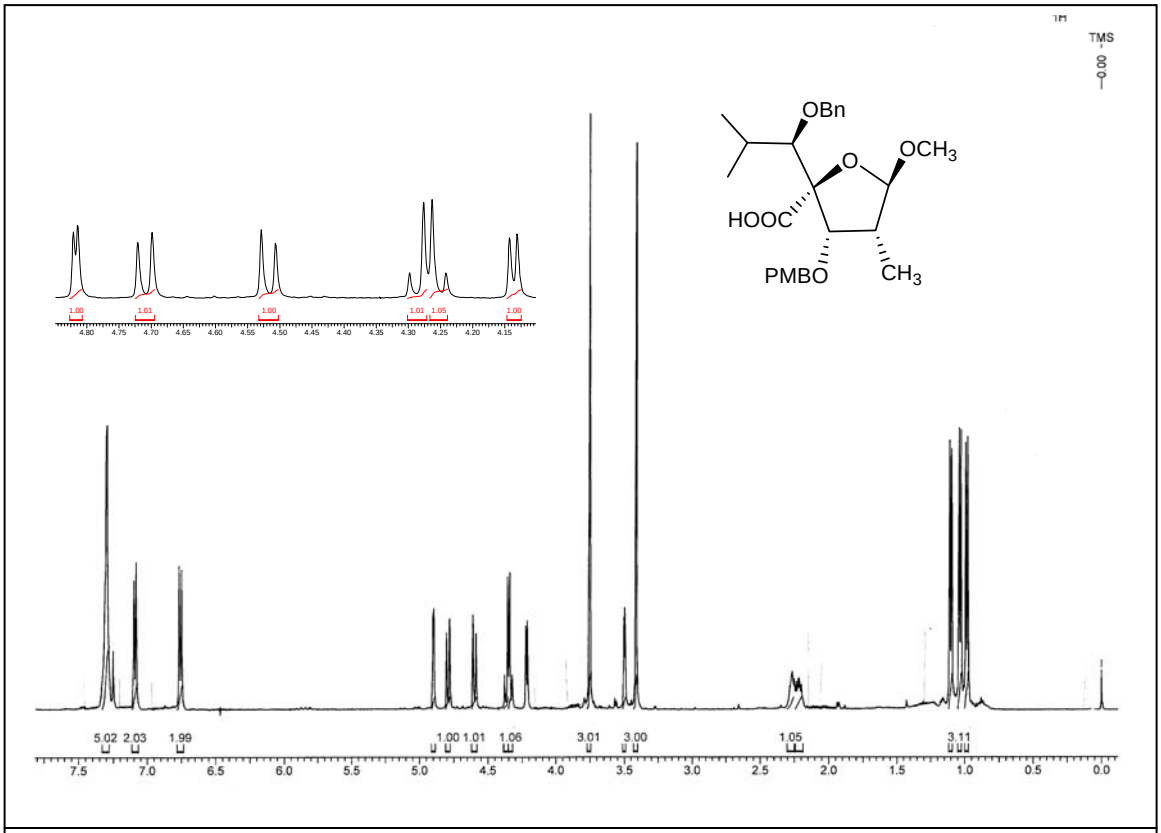
^{1}H and ^{13}C NMR spectra of compound 82 in $CDCl_3$

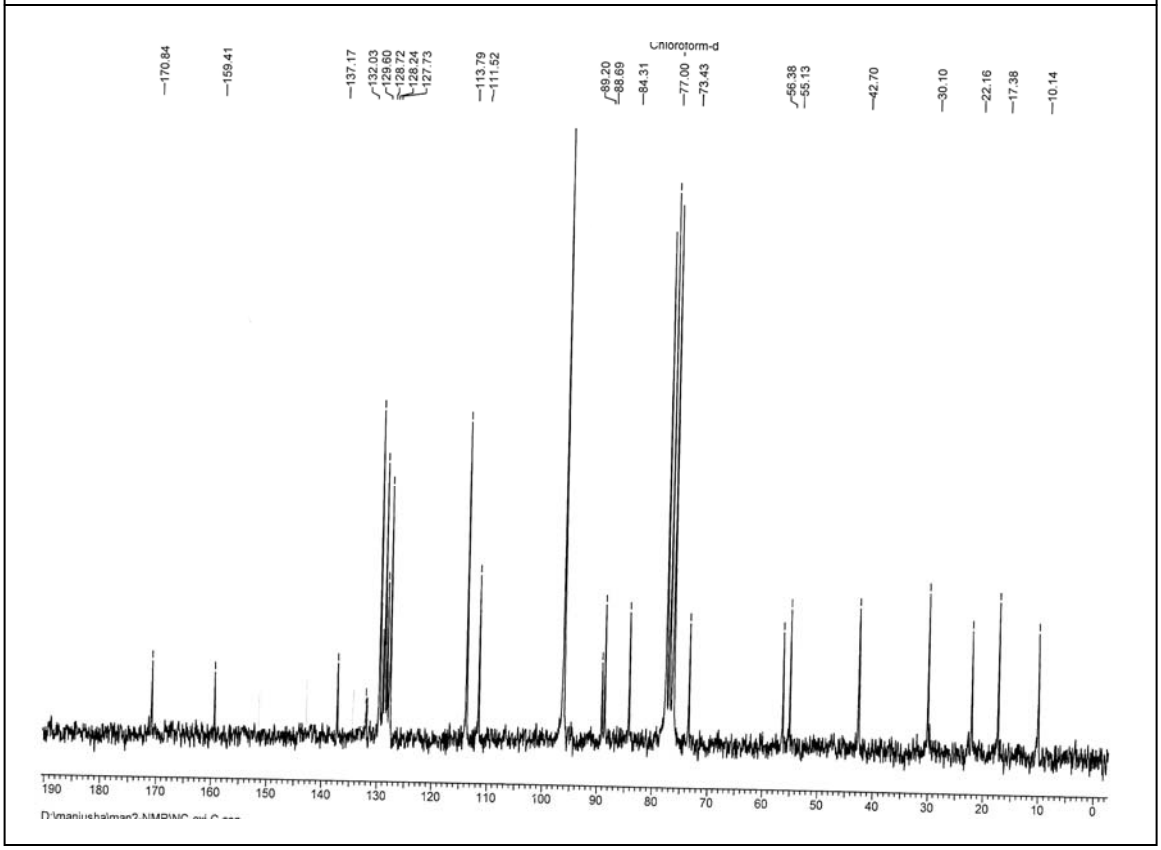


^{1}H and ^{13}C NMR spectra of compound 83 in $CDCl_3$

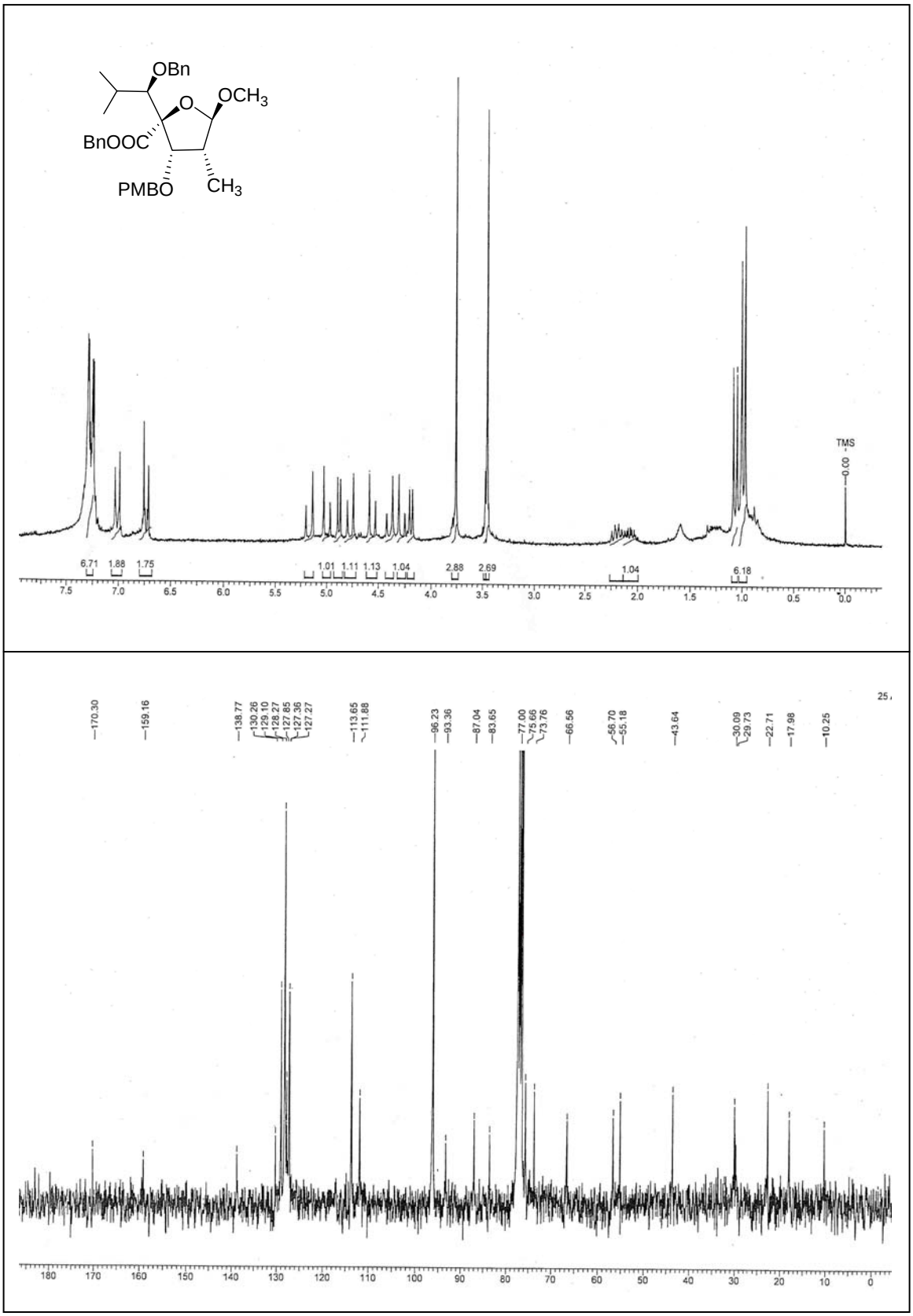


^{1}H and ^{13}C NMR spectra of compound 84 in $CDCl_3$

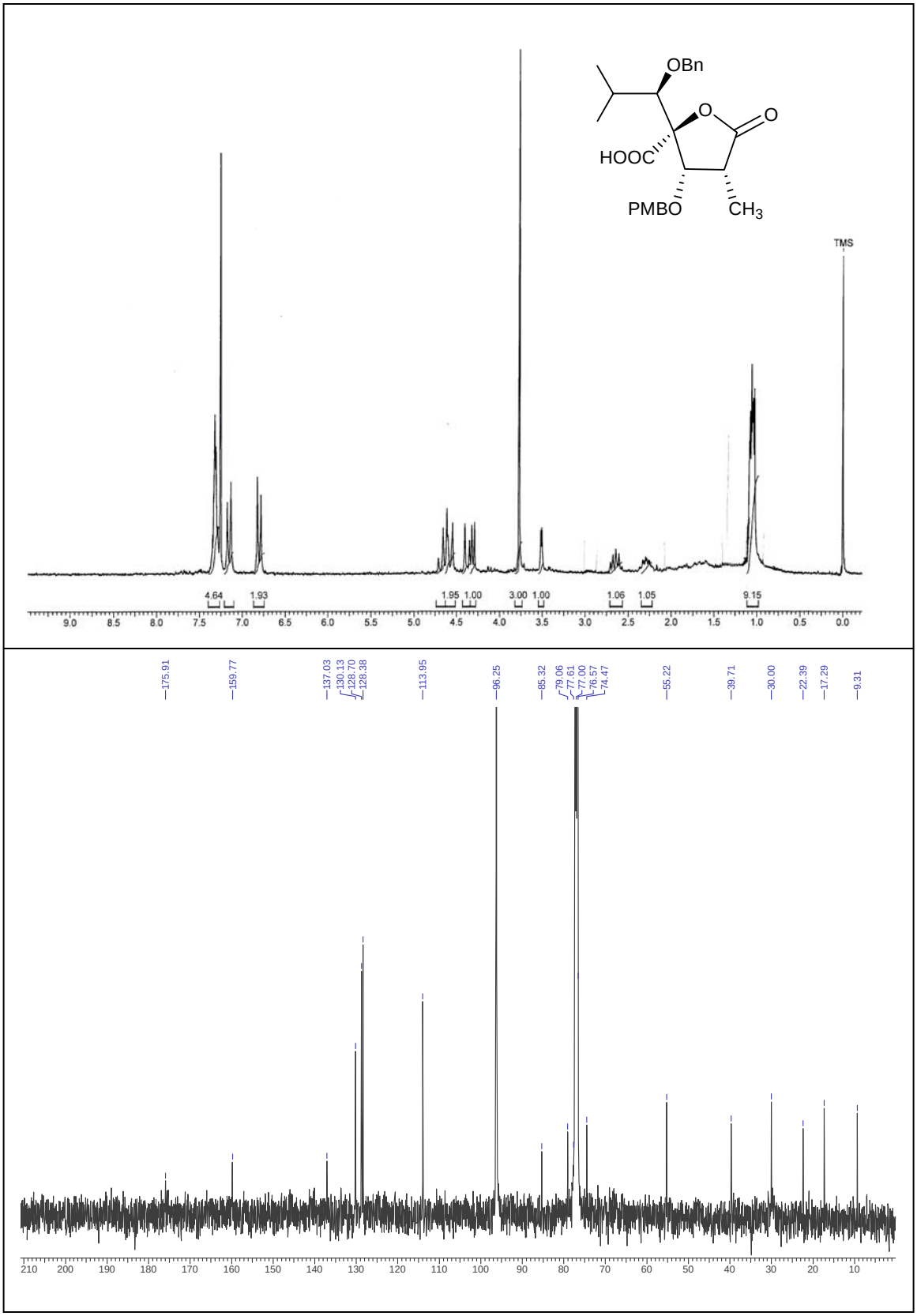




^{1}H and ^{13}C NMR spectra of compound 85 in $CDCl_3$



^{1}H and ^{13}C NMR spectra of compound 87 in $CDCl_3$



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Publications

1. "*Selective Cleavage of 2,3-O-Isopropylidene Group: A Case of Anchimeric Assistance from O-Glycoside*" Radhika D. Wakharkar, Manjusha B. Sahasrabuddhe, Hanumant B. Borate, Mukund K. Gurjar, *Synthesis*, **2004**, 11, 1830 – 1834.