Synthetic studies toward Multiplolides and Crocacins

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PUNE - 411 008
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DECLARATION

The research work embodied in this thesis entitled ***"Synthetic studies toward Multiplolides and Crocacins"*** 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**. 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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Dr. Homi Bhabha Road, PUNE - 411 008(INDIA).

CERTIFICATE

The research work presented in this thesis entitled ***"Synthetic studies toward Multiplolides and Crocacins"*** has been carried out under my supervision and is bonafide work of **Mr. Khaladkar Tushar P.** This work is original and has not been submitted for any other degree or diploma to this or any other University.

Pune - 411 008 **Dr. M. K. Gurjar**

Date: (Research Guide)

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Finally I thank Director, NCL, Pune for providing infrastructural facilities and UGC, New Delhi for the financial assistance.

Tushar P. Khaladkar

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.
- Molecular weights of the compounds and *m/z* values in the mass spectra are corrected to nearest integers.

Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	Azoisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
9-BBN	-	9-Borabicyclo[3,3,1]nonane dimer
n-BuLi	-	*n*-Butyl lithium
^{t}BuOH	-	*tert*-Butanol
TBS	-	*tert*-Butyldimethylsilyl
CCl_4	-	Carbontetrachloride
DCM	-	Dichloromethane
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	-	Dess-Martin periodinane
2,2-DMP	-	2,2-Dimethoxy propane
Et	-	Ethyl
EtOAc	-	Ethyl acetate
Et_2O	-	Diethylether
EtOH	-	Ethanol
$HgCl_2$	-	Mercuric chloride
HgO	-	Mercuric oxide
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
MeOH	-	Methanol
MeI	-	Mehyl iodide
NaH	-	Sodium hydride
$NaNH_2$	-	Sodamide

NEt_3	-	Triethyl amine
Pd/C	-	Palladium on carbon
PDC	-	Pyridiniumdichromate
PMB	-	*para*-Methoxy benzyl
*p*TSA	-	*para*-Toluenesulfonic acid
Py	-	Pyridine
rt	-	Room temperature
TBAF	-	Tetra-n-butylammonium fluoride
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TMS	-	Trimethyl silyl
TPP	-	Triphenylphosphine

Contents

Abstract

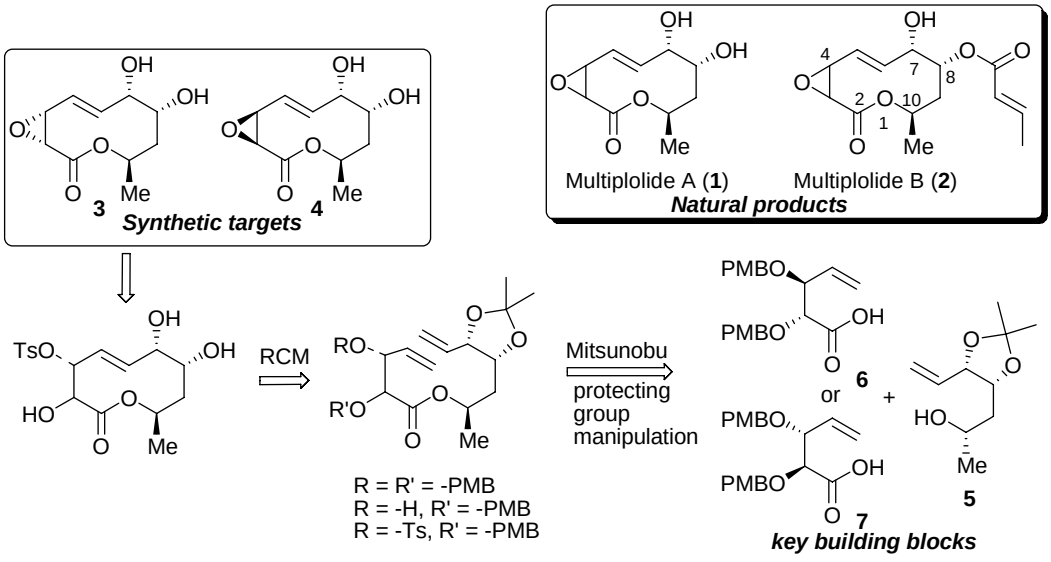
Abstract

The thesis entitled "Synthetic studies toward Multiplolides and Crocacins" consists of two chapters. Each chapter is further subdivided into following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter I describes the first total synthesis of multiplolide A and its diastereomer employing RCM. Second chapter deals with the synthesis of common intermediate for crocacin family of natural products featuring the Heck reaction of carbohydrate derived olefin.

Chapter I: Total synthesis of multiplolide A and its diastereomer

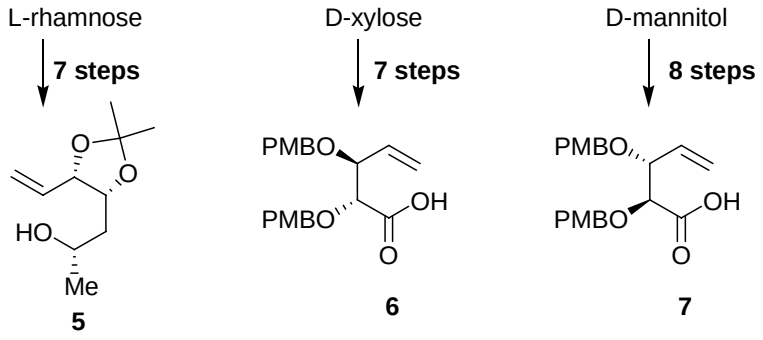
Multiplolides A (**1**) and B (**2**) were isolated in 2001 from the crude ethyl acetate extract of the culture broth of *Xylaria multiplex*. Multiplolides A (**1**) and B (**2**) exhibited antifungal activity against *Candida albicans* with IC_{50} values of 7 and 2 μg/mL, respectively. As a result of detailed structural investigations the constitution and partial relative stereochemistry were elucidated leaving behind the relative stereochemistry of the oxirane ring for both the natural products. To establish the absolute and relative stereochemistry of the oxirane ring beyond ambiguity it was decided to synthesize both the possible diastereomers of multiplolide A [3*R*, 4*R* (**3**) and 3*S*, 4*S* (**4**)].

Figure 1 *Chemical structures of multiplolide A, B and retrosynthetic strategy for both the possible diastereomers of multiplolide A*



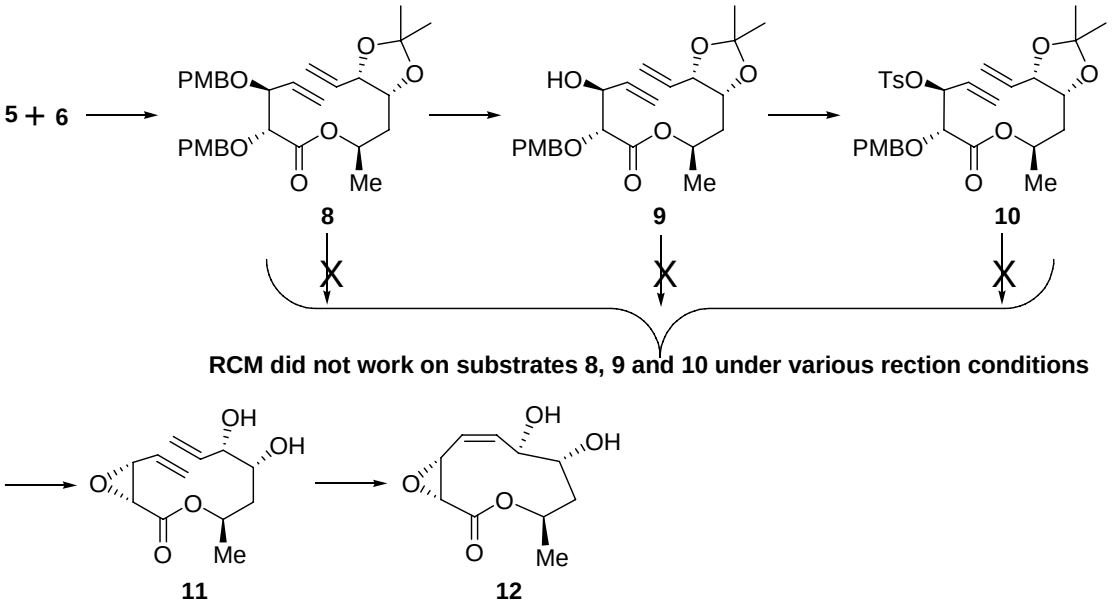
Retrosynthetic strategy for both the diastereomers is depicted in figure 1. RCM reaction for formation of *E* configured macrocycle and Mitsunobu reaction were envisaged as the key steps. The syntheses of the alcohol **5** and the enantiomeric acids **6** and **7** were achieved (Scheme 1) through straightforward functional group manipulations on corresponding sugar building blocks keeping the requisite stereochemical information intact.

Scheme 1



After preparation of coupling partners the next job was to proceed with one of the acids (**6** or **7**) and try the further sequence of reactions as per the retrosynthetic plan. The fact that there was no clue whatsoever to speculate which of the isomers of multiplolide A (**3** or **4**) was more plausible to be the natural product had made the choice entirely capricious.

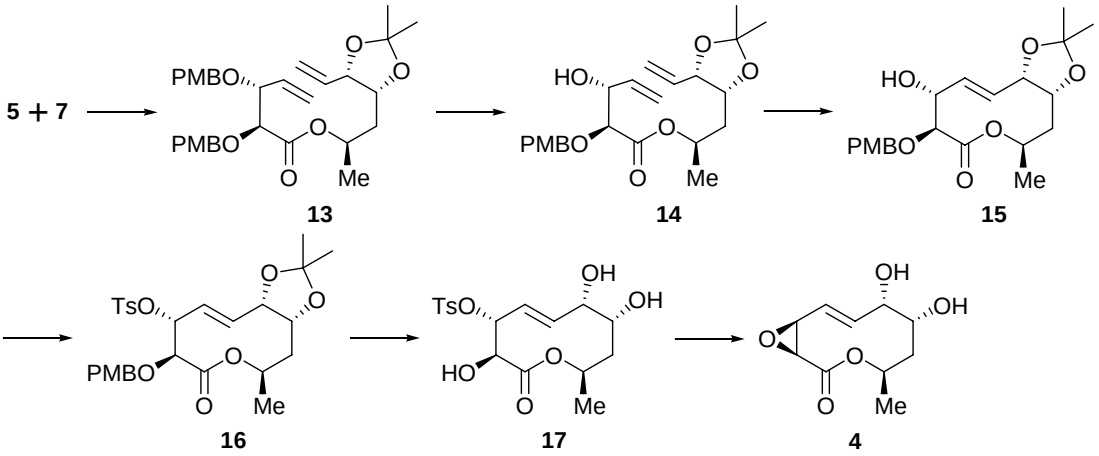
Scheme 2



It was chosen to proceed first with acid **6**, to evaluate the proposed route (Scheme 2). Mitsunobu reaction between the alcohol **5** and acid **6** proceeded with exclusive inversion of configuration at C-10 to give the di-PMB ester **8,** which was converted to mono-PMB derivative **9** and the free hydroxyl generated was tosylated to furnish **10**. Attempts for ring closure employing RCM reactions on compounds **8**, **9** and **10** under various reaction conditions ended into failures. The global deprotection was carried out by the employment of TFA in DCM and basification of reaction mixture using di-isopropylethylamine furnished the oxirane **11**. Though the RCM reaction of **11** in refluxing DCM employing Grubbs' second-generation catalyst was successful in ring closure, the olefin it furnished possessed the *cis* geometry (compound **12**).

Esterification of acid **7** with alcohol **5** produced ester **13** with exclusive inversion of configuration at C-10 as in the earlier case. However the RCM reaction failed with ester **13**. Selective deprotection of allylic PMB ether furnished the diene **14**. Fortunately RCM reaction at this stage with Grubbs' second-generation catalyst in refluxing benzene was successful and yielded required *trans* olefin **15** exclusively. Compound **15** was converted into mulitplolide A (**4**) in three steps (scheme 3).

Scheme 3

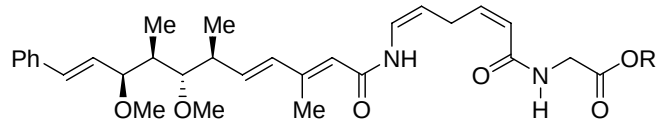


Despite the optical rotation {$[\alpha]_D$ +22.6 (c 0.3, $CHCl_3$)} of synthetic 3-*S*, 4-*S* multiplolide A (**4**) was higher than the reported value {$[\alpha]_D$ +6.7 (c 0.18 $CHCl_3$)}, the spectroscopic data of **4** was in excellent agreement with that of reported for the natural product, thus establishing the absolute stereochemistry of multiplolide A as (3*S*, 4*S*, 7*S*, 8*R*, and 10*R*).

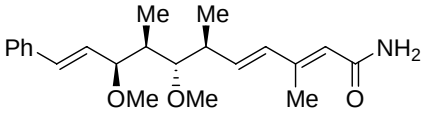
Chapter II: Synthetic studies toward crocacins A-D

Crocacins A–D (**1**–**4**) (Figure 1) possess antifungal and cytotoxic activities and are isolated from the extracts of *Chondromyces crocactus* and *Chondromyces pediculatus*. Synthetic efforts towards crocacins A–D have been significantly influenced by the synthesis of the advanced intermediate **5** (Figure 1) which is then elaborated to install variable side chains. The Evans aldol reaction based synthetic protocols appear to be the most commonly used strategy for crocacin synthesis. Carbohydrate based protocols seem to be missing from the artillery eventhough chiral centers in D-glucose can be ostensibly transformed to produce the crocacin skeleton. We have investigated for the first time a carbohydrate-based synthesis of **5**.

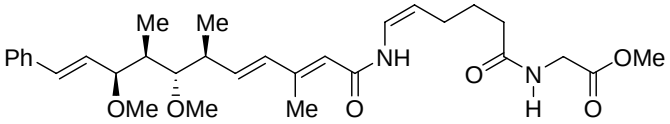
Figure 1 *Chemical structures of crocacins A-D*



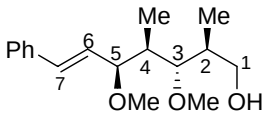
1 Crocacin A; R = Me
2 Crocacin B; R = H



3 Crocacin C



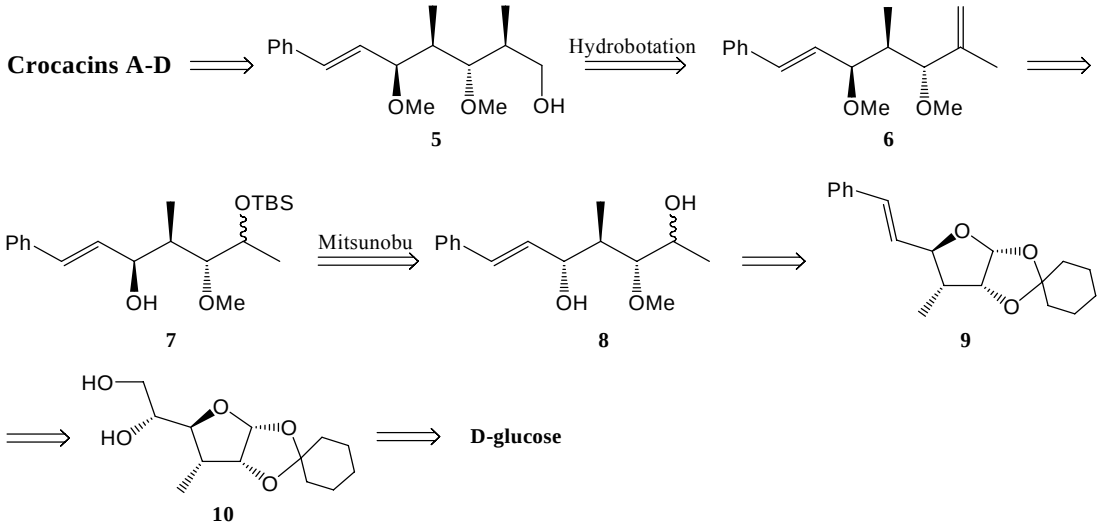
4 Crocacin D



5

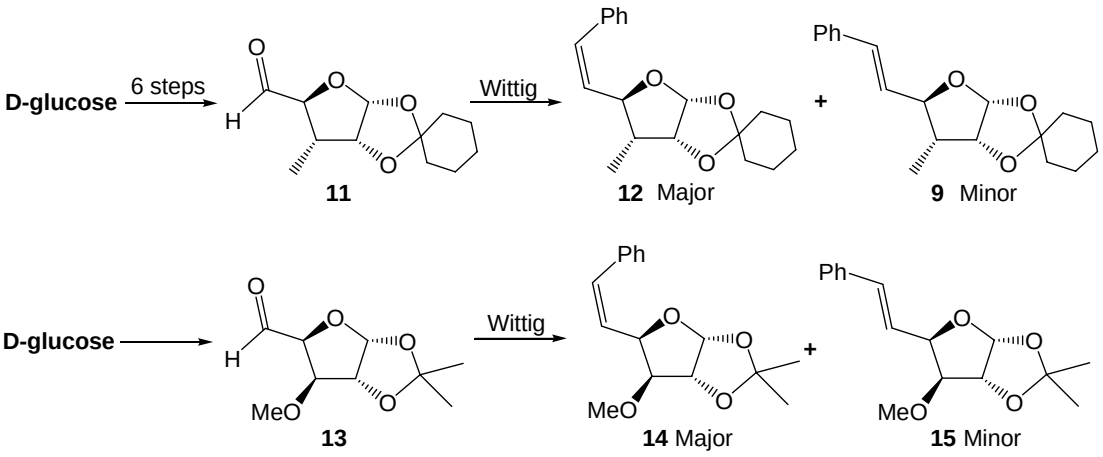
Retrosynthetic analysis for the common intermediate **5** is depicted in figure 2. Stereochemistry of the methyl at C-2 could be fixed by the stereoselective hydroboration-oxidation of the olefin **6**. Synthesis of olefin **6** was thought to be a matter of few functional group transformations from the alcohol **7**. Mitsunobu reaction of the suitably protected alcohol, to be derived from diol **8,** was the key for manipulation of stereochemistry at C-5. Diol **8** would be a consequence of a methyl grignard on the lactol, to be obtained from the compound **9**. Installation of *E*-styene moiety on the aptly substituted carbohydrate residue was planned using the Wittig reaction. Precursor for the Wittig reaction was the diol **10**, which was to be obtained from D-glucose.

Figure 2 *Retrosynthetic analysis for crocacins A-D*



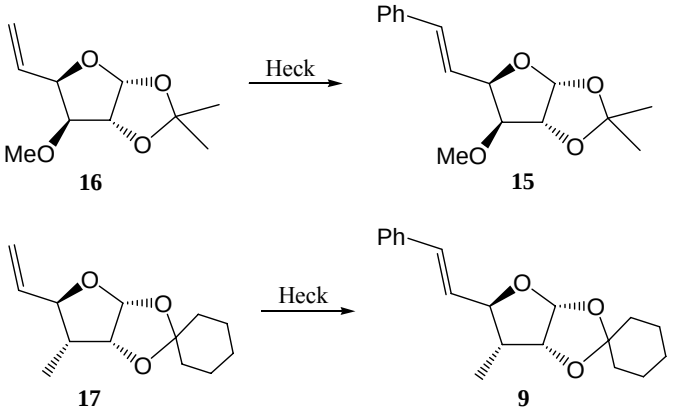
Aldehyde **11** was prepared from D-glucose over 6 steps but all our attempts to procure the desired *E*-styrene derivative **9** in acceptable yield and selectivity through Wittig protocol turned out to be failures and the *Z*-styrene derivative **12** was the major product under all the conditions. To understand whether this was a special case pertaining to our current substrate, the same transformation was carried out on the commonly used sugar derived aldehyde **13** under various reaction conditions but the result was similar (Scheme 1). Looking for a viable alternative for **9** we next turned our attention to the Heck reaction. However, the application of this reaction to 5,6-ene derivatives of sugar substrates was not reported.

Scheme 1



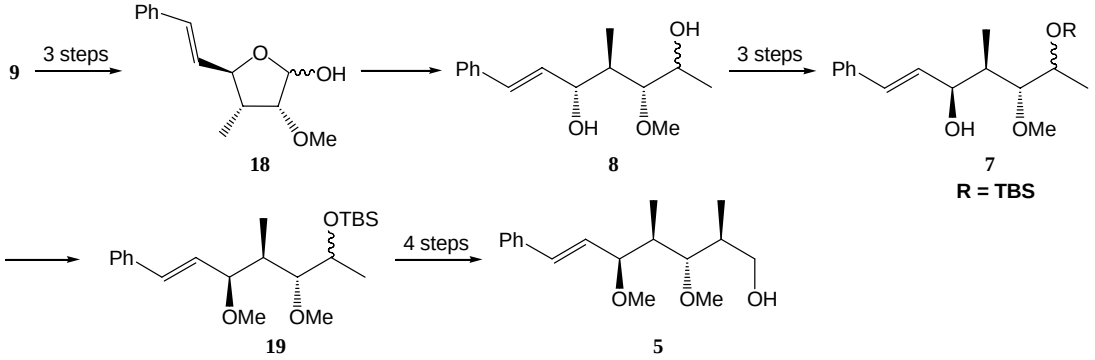
Prior to its employment in main synthetic sequence, the Heck reaction was carried out between a trial substrate **16** and iodobenzene, which worked well to produce the *E*-styrene derivative **15** as a sole product (scheme 2). Heck reactions carried out by changing either of coupling partners, sugar derived olefin and iodoarene also worked well resulting into the corresponding *E*-styrene derivative as the only product. After generalizing this observation, the Heck reaction between the olefin **17** and iodobenzene was effected to furnish the required *E*-styrene derivative **9** (scheme 2).

Scheme 2



Lactol **18** was prepared from compound **9** in three steps. Treatment of lactol **18** with mehylmagnesium chloride was followed by selective TBS protection, Mitsunobu reaction and hydrolysis of benzoate ester to procure alohol **7**. Masking of the free hydroxyl in **7** provided compound **19**, which was converted into target molecule **5** in four steps. (scheme 3).

Scheme 3



Chapter I

Total Synthesis of Multiplolide-A and its Diastereomer

Introduction

Introduction

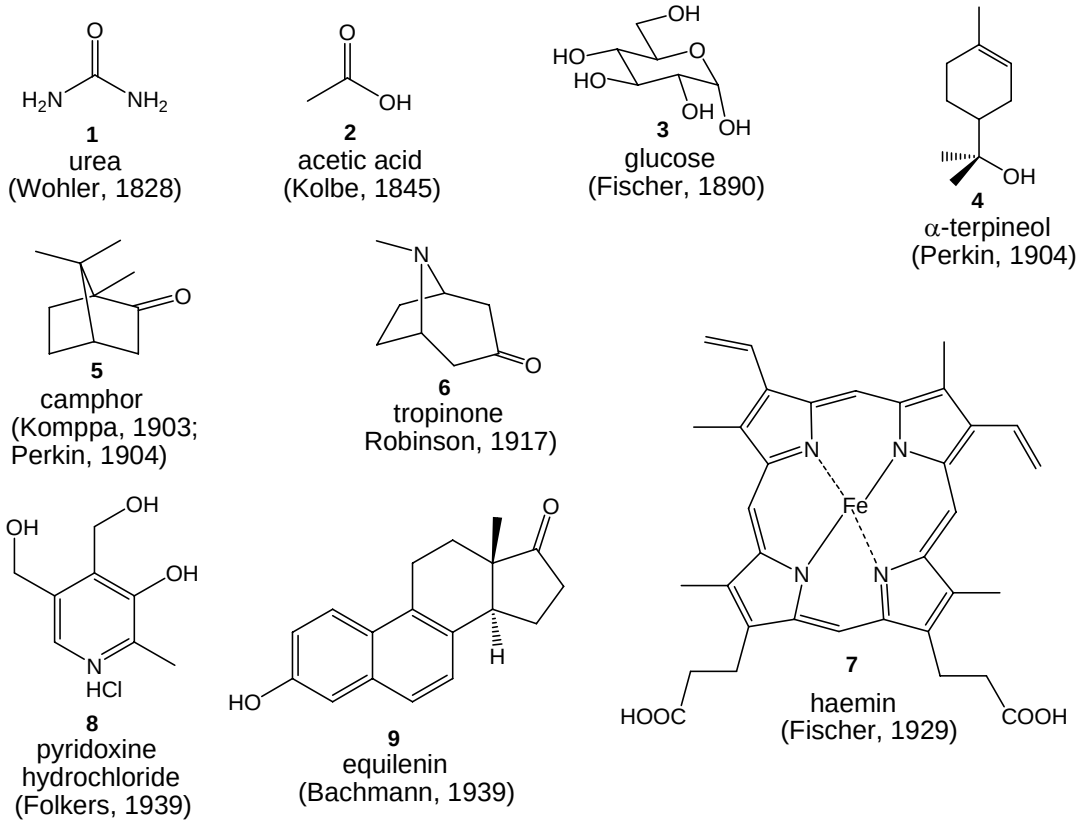
Nature has bestowed her most beloved creation, off-course the human being, by arranging all the resources needed for healthy and comfortable life around him in the form of various natural products. More importantly she has blessed human race by gifting it with the most developed brain. Doing justice to nature's reward, mankind has discovered and utilized the potential hidden in various natural prodcuts to make a healthy, happy and comfertable life. In addition to their utility for the fulfilment of basic needs, man has used these resources for several other purposes. It wont be unjust to say that, before the origin of modern science and industrial revolution, the progress of a society could be measured in terms of its efficiency and effectiveness to use the natural resources for the enhancement of the quality of life. If one has to restrict the discussion to only one facet of life, the '*Ayurveda'* is a classic paradigm to illustrate how man has been using natural products for the quality enhancement of life. Being practised for more than 5000 years, *Ayurveda* is an ancient system of health care that is native to the Indian subcontinent. Herbs and other naturally occuring substances contribute a major share of medicines discribed in ayurveda.

With the origin and development of modern science our understanding about the constitution of any given material has improved immensely, natural products not being an exception. With the advancements in the area of natural product isolation and characterization, it has become possible to isolate and identify the active compound responsible for the observed biological activity. As they are contained in very small quantities, often it is not practicable to isolate these natural products form their original resources for the commercial purposes. The solution for this problem is to synthesize them in laboratory by means of chemical synthesis. Accurate knowledge of the structure of the natural product is a prerequisite for its synthesis.

Nature synthesizes enumerable organic compounds using its own artillery. Understanding the structures of nature's creations and attempting to clone them in laboratory for aforementioned reasons, by means of chemical synthesis, has fascinated the generations of organic chemists. Wöhler's synthesis of urea[1] in 1828 is thought to be the origin of the science called modern organic synthesis. As is the case with almost all other branches of science, this branch has flourished immensely. Figure 1

displays some of the natural products synthesized in laboratory till the year 1939. The aspiration and efforts to understand the structures of natural products has always been of great aid to the advancement of the knowledge in the area of organic synthesis. At the same time the knowledge of chemical synthesis and ability to synthesize natural products in laboratory have had significant impact on the area of natural product structure elucidation. The way these two branches have complimented each other's progress is particularly astonishing.

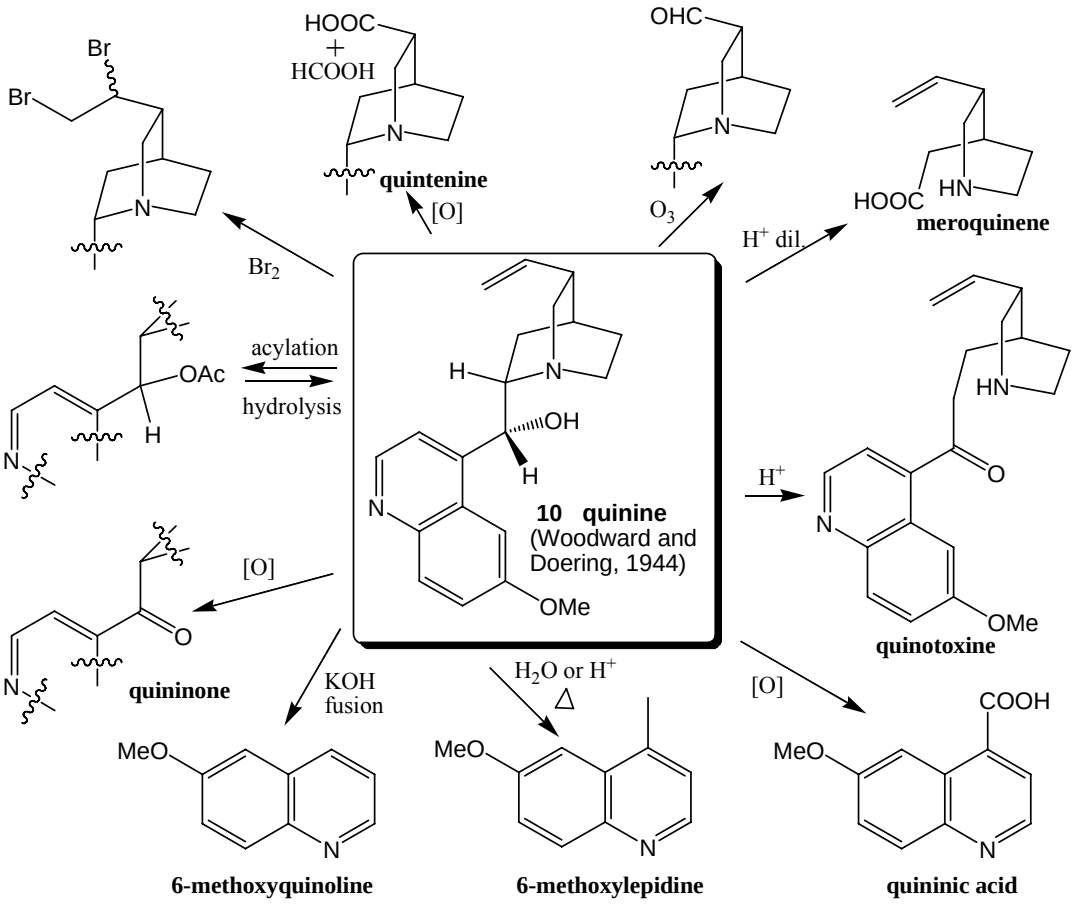
Figure 1 *Some natural products synthesized before world war II*



Almost until 1950s, chemical synthesis was used as the most effective tool in the area of natural product structure elucidation by means of the degradation or derivatization processes, to reveal the architectural design of a molecule. Assuming both that gram quantities of the substance under investigation were available and that the chemical transformations employed proceeded along expected lines, researchers of that era might have expected to solve their molecular puzzles after a few years of painstaking effort. Strychnine[2], haemin[3] (**7**) and quinine[4] (**10**) are the few examples where the correct structures were assigned by the almost exclusive use of chemical synthesis. Just to have a glimpse how the structure elucidation used to be carried out

employing chemical degradation and derivatization, figure 2 summarizes the structure elucidation efforts for quinine. The assignment of absolute or relative configuration of a natural product using chemical degradation and derivatization was not possible in most cases. Needless to say, this intellectually difficult and physically tedious approach had its limitations, and was often attended with errors.

Figure 2 *Some degradation and derivatization reactions for structure elucidation of quinine*



The chances of encountering such errors during efforts towards structure elucidation decreased significantly by the late 1960s, as the "classical" chemical approach was gradually replaced by a set of far more accurate nondestructive methods, such as nuclear magnetic resonance (NMR), ultraviolet (UV), and infrared (IR) spectroscopy, circular dichroism (CD), and mass spectrometry (MS). One can obtain a complete structural assignment for a few milligrams of an unknown natural product using these advanced techniques. Far more complex molecules can be tackled in far less time, even when the compounds are isolated in very small amounts. Impact

of these techniques on the role of synthetic chemists and synthetic chemistry in the area of natural product structure elucidation was quiet obvious. The change in scenario was precisely foreseen and expressed in following words, just at the dawn of the new era,

While it is undeniable that organic chemistry will be deprived of one special and highly satisfying kind of opportunity for the exercise of intellectual élan and experimental skill when the tradition of purely chemical structure elucidation declines, it is true too that the not infrequent dross of such investigations will also be shed; nor is there any reason to suppose that the challenge for the hand and the intellect must be less, or the fruits less tantalizing, when chemistry begins at the advanced vantage point of an established structure.

R. B. Woodward (1963)[5]

The efficacy of these physical methods in the area of natural product structure elucidation and the revolution they have brought about in terms of time and efforts required for the same, is nicely reflected in the following statement

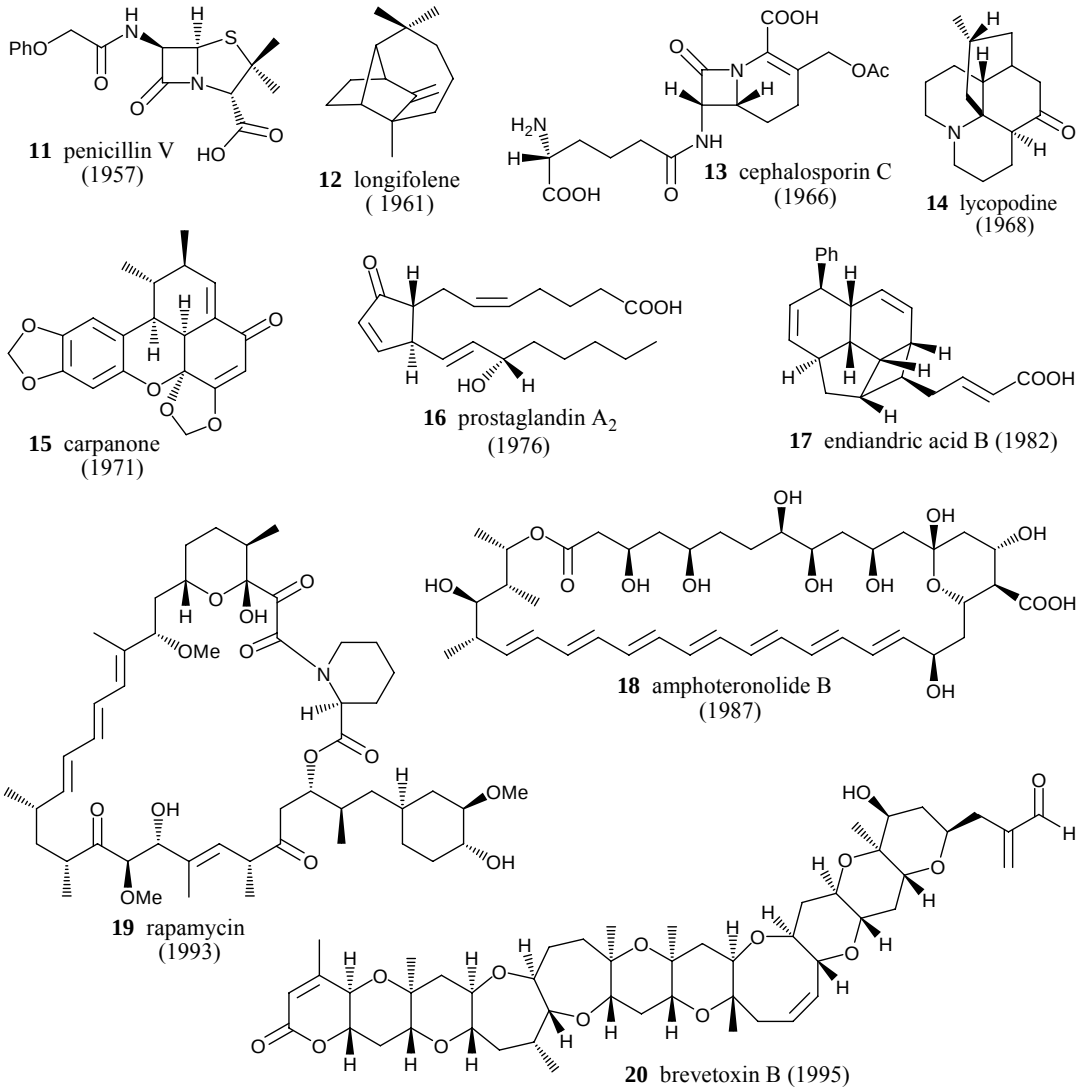
If penicillin were discovered today … the scientific problems of studying a pure crystalline compound with a molecular weight of about 350 would not have been nearly so difficult. The conclusion is that a good graduate student would probably work out the structure of penicillin in a day or so. Just a generation ago, that same scientific feat took the best of us years of intensive work.

John C. Sheehan *(1982)*[6]

Thus due to their intrinsic superiorities, spectroscopic methods, by now, have almost entirely dislodged chemical methods from the area of natural product structure elucidation. The role of chemical synthesis is seen to be restricted to confirm the proposed structure by total synthesis. These techniques, no doubt, on the one hand have trimmed down the role of synthetic chemists in the area of natural product structural elucidation, by replacing the degradation and derivatization processes. But on the other hand they have stimulated the progress in the area of total synthesis of natural products as the supply of the '*target molecules*' is enriched both in terms of numbers and complexity. The fraternity of the synthetic organic chemists has responded to this change in a positive manner. They have not only achieved the synthesis of the complex targets put forth by the isolation chemists but in that process

have also advanced the knowledge in the area of synthetic organic chemistry by discovering novel methodologies as the tools to conquer their synthetic targets. The progress made in the area of synthetic organic chemistry is evident from the increasing complexity of the targets achieved with time (figure 3).

Figure 3 *Some natural products synthesized after 1955*



The situations those arise when one considers the natural product structure elucidation employing spectroscopic methods can be classified into three types;

i) Structure of the natural product under investigation is accurately solved using spectroscopic methods. In these cases role of synthetic chemists is limited to confirm the proposed structure by total synthesis.

ii) The spectroscopic data mislead the isolation chemists and the erroneous structure is proposed. In these cases synthetic chemists revise the proposed structure in the light of results obtained during the efforts to synthesize originally proposed structure.

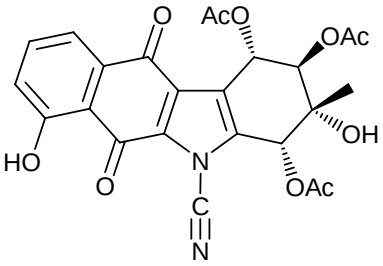
iii) Even with the aid of all the modern spectroscopic techniques, the isolation chemists find themselves in a position where they are unable to propose the complete structure. In most of the cases of this type, absolute and relative stereochemistry for one or more chiral centers can not be assigned. Synthetic chemists have to arrive at the correct structure by synthesizing the possible isomers and comparing them with natural product.

First type is of common occurrence and countless examples of this type can be seen if one goes through the journals devoted to the area of natural product isolation. The second and the third type of situations, though are not as abundant as the first one, nor are very infrequent too. Number of errors or the number of cases in which complete structure can not be elucidated simply reflects the fact that every method for assignment has its weaknesses, some of which can not be resolved even if every other tool for structural elucidation is also applied. Just to have a very brief idea, limitations of some of the modern physical techniques are discussed, in the context of the second type of situations where the erroneous structure was proposed.

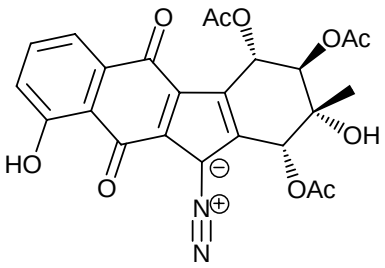
X-ray crystallography

The biggest limitation of this technique is that it can not be used for the natural products which are not or can not be converted to crystalline solids. Apart from that this technique may occasionally lead to miss-assignments because it does not reveal the positions of hydrogen atoms. Therefore it is sometimes difficult to distinguish between O atoms and -NH groups. X-ray crystallography can also confuse the identity of the atoms within certain functional groups devoid of hydrogen atoms. The assignment of a C atom instead of an N atom (cyano rather than diazo group) led to the incorrect structure for the kinamycins[7] (Figure 4).

Figure 4 *Proposed and revised structure for kinamycin-C*



21 kinamycin C
proposed structure
(1973)

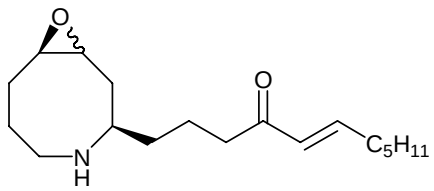


22 kinamycin C
revised structure
(1994)

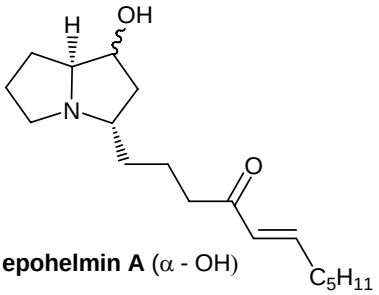
NMR spectroscopy

Though NMR spectroscopy can provide a great deal of overall information regarding the structure of the molecule under investigation, it suffers serious limitations when it comes to the more intricate issues such as absolute and relative stereochemistry. This drawback is more pronounced when the number of hydrogen atoms in the molecule is insufficient to obtain ^{1}H-^{13}C correlations, which are needed to assign the finer details about the structure. Many of the structural revisions fall into this category, even though a number of powerful two-dimensional techniques, such as INEPT, HMBC, HMQC, and TOCSY, are applied before the original structure is proposed. In some cases, even NMR spectroscopy is of little use as a tool despite its awesome power. The structures proposed for epohelmins A (**23**) and B (**24**) on the basis of spectral data, principally on NMR data, were revised later on the basis of chemical syntheses and comparison of analytical data for synthetic materials with natural products.[8]

Figure 5 *Proposed and revised structures for epohelmins*



23 epohelmin A (α - O, β – H)
24 epohelmin B (β - O, α – H)
proposed structures
(2004)

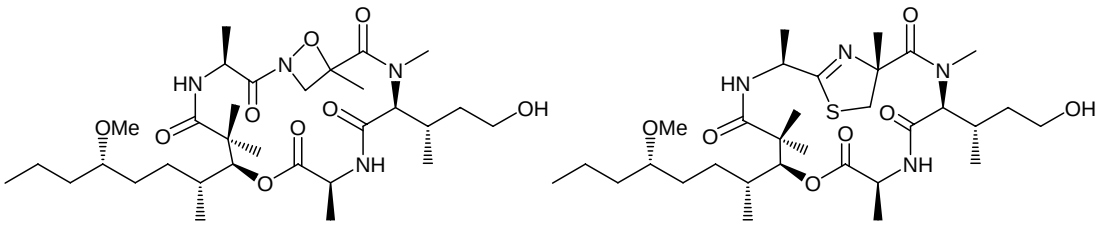


25 epohelmin A (α - OH)
26 epohelmin B (β - OH)
revised structures
(2005)

Mass spectrometry

Molecular formula suggested by a particular mass spectrometric technique is sometimes incorrect. This incorrect information when co-related with the information from other analytical techniques, such as NMR, leads to prediction of incorrect structures. For example, in case of halipeptin-A (Figure 6), the fast atom bombardment technique suggested the molecular formula to be $C_{31}H_{54}N_4O_9$. This information when coupled with information from NMR spectroscopy, led the researchers to propose the incorrect structure. However the same group corrected the structure in the light of data from electron-spray inonization (ESI) mass spectrometry, which suggested the molecular formula $C_{31}H_{54}N_4O_7S$, to be a far better match for the halipeptin-A.[9]

Figure 6 *Proposed and revised structure for halipeptin-A*



27 halipeptin A
proposed structure
(1991)

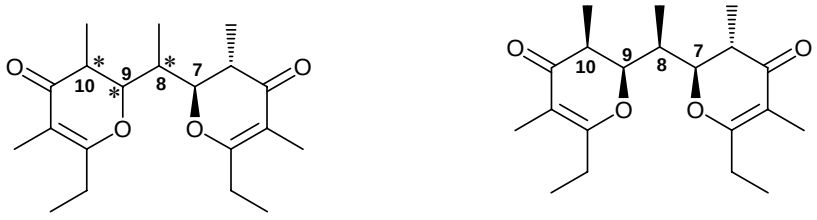
28 halipeptin A
revised structure
(1998)

In order to understand as to how frequently the errors occur in the business of structure elucidation, it would be relevant to cite an interesting observation by K. C. Nicolaou and S. A. Snyder.[10] While searching the scientific databases for the structural revisions, limiting their search to literature published form January 1990 to April 2004, they could find well over 300 examples of such revisions. Many of these included major and sometimes complete constitutional changes apart from simple stereochemical problems. Amazingly, the examples covered virtually every compound class, including steroids, terpenes, indole alkaloids, and peptides, and included molecules of all sizes and levels of stereochemical complexity. The detail study of 50 examples out of these, taken in no particular order, revealed that the chemical synthesis was required in 27 cases to reach the revised structure. In 22 cases out of 50, it was total synthesis, which indicated that there was a problem in originally proposed structure.

Apart from proposal of erroneous structures, isolation chemists sometimes can not elucidate the complete structure of the natural product, despite of having at hands, a bunch of all the modern analytical techniques. This, in one sense, can be viewed as the victory of the nature on human progress. But man is more than familiar with this kind of circumstances and all the human progress has made its way through such obstacles and resistances. As is the case with all other walks of life, a difficulty or inability for a particular branch is taken as a challenge or opportunity by the other one. The role of synthetic chemists becomes imperative in this kind of situations. The missing links are put in place by the synthetic chemists, by synthesizing various possible structures and comparing the data for each one of them with the natural product. There are abundant instances of this type where the challenge of nature was successfully faced by the harmonious efforts of *'synthetic'* and *'natural product isolation'* chemists.

Membrenone C (Figure 7) was isolated and the partial stereostructure **29** was proposed on the basis of NMR and other analytical data. Though the coupling constant between H-9 and H-10 suggested the *cis* relationship between them, the absolute stereochemistry at the C-9 and C-10 stereocenters could not be determined. As the absolute configuration of C-8 methyl was also unknown, four diastereomeric structures were possible for membrenones. The correct absolute stereostructure was established by the synthesis of three of four possible diastereomers. As the spectral and analytical data for none of the three was in agreement with that of natural product, the fourth possible stereostructure **30** was assigned to the natural product.[11]

Figure 7 *Partial and total stereostructure for membrenone-C*



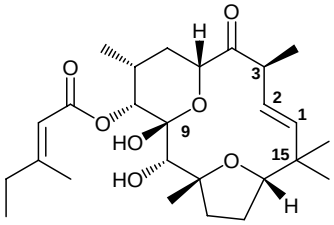
29 membrenone-C
partial stereostructure
(1993)

30 membrenone-C
total stereostructure
(2001)

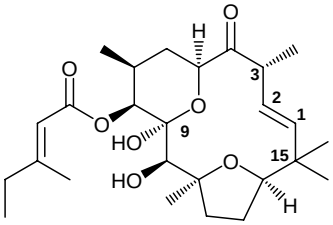
Similar was the case with tonantzitlolone (Figure 8), which was isolated in 1997 and the relative stereochemistry was proposed as represented by structure **31**. However, the absolute stereostructure could not be determined at that time. This was

achieved by the synthesis of the enantiomer **32** in the year 2005. All the spectral and analytical data for **32** was in excellent agreement with natural product, except for optical rotation (authentic natural product, $[\alpha]^{20}_D$ = +134° (*c* 0.25, $CHCl_3$); found, $[\alpha]^{20}_D$ = -119° (*c* 0.06, $CHCl_3$)). This clearly established **31** as the correct absolute stereostructure for tonantzitlolone.[12]

Figure 8 *Partial and total stereostructure for tonantzitlolone-1*



31 tonantzitlolone-1
proposed relative stereostructure
(1997)

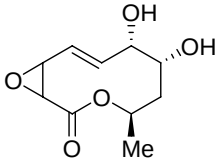


32 tonantzitlolone-1
31 was proved to be relative and absolute stereostructure by sythesis of enantiomer **32**
(2005)

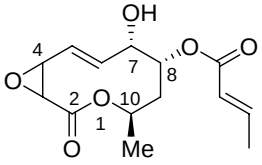
The case of multiplolides A (**33**) and B (**34**) was another story of partial structure elucidation.[13] In 2001, Kttakoop and co-workers reported isolation of two new antifungal compounds from the crude ethyl acetate extract of the culture broth of *Xylaria multiplex* BCC 1111. Multiplolides A (**33**) and B (**34**) exhibited antifungal activity against *Candida albicans* with IC_{50} values of 7 and 2 μg/mL, respectively.

Figure 9 *Chemical structures of multiplolide A, B and both possible diastereomers of multiplolide A*

Natural Products:



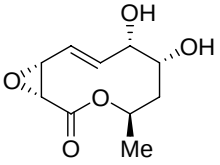
Multiplolide A (**33**)



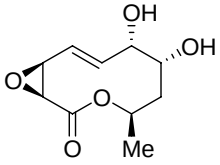
Multiplolide B (**34**)

proposed partial stereostructures for multiplolides A and B
(2001)

Synthetic Targets:



35



36

structures of possible diastereomers of multiplolide-A

As is the case with every natural product, the structures of multiplolides A and B were elucidated on the basis of their spectral data. The ESI-TOF mass spectrum of multiplolide A (**33**) gave an accurate mass of *m*/*z* 215.0923 [$(M + H)^+$, Δ +0.5 mmu], establishing the molecular formula of **33** as $C_{10}H_{14}O_5$. The IR spectrum of multiplolide A (**33**) exhibited an absorption peak at 1721 cm^{-1}, characteristic of an ester carbonyl. The ^1H NMR ($CDCl_3$) spectrum of multiplolide A (**33**) showed a

methyl doublet at δ 1.30, a nonequivalent methylene (at δ 1.21 and 2.21), five oxy protons (at δ 3.60, 3.75, 3.95, 4.50, and 5.25), and two olefinic protons (at δ 5.72 and 5.88). The $J_{H\text{-}5,H\text{-}6}$ value of 15.0 Hz revealed a *trans*-configuration of the olefinic protons in **33**. The ^{13}C NMR ($CDCl_3$) spectrum of multiplolide A (**33**) showed 10 signals, attributable to one methyl, one methylene, seven methine, and one quaternary carbon, as determined by DEPT experiments. The ^{1}H-^{1}H COSY spectrum of multiplolide A (**33**) conclusively demonstrated the connectivity from H-3 to H-11. The epoxide moiety at carbons 3 and 4 in **33** was evident from the HMBC spectrum, in which the ^{13}C-^{1}H one-bond coupling constant ($^{1}J_{C\text{-}H}$) of 167 Hz (for C-3 and C-4) was observed. The HMBC spectrum also showed the correlation of both H-3 and H-10 to the carbonyl carbon (C-2), H-4 to C-6, H-5 to C-7, and H-9 to both C-7 and C-11. The NOESY spectrum of **33** revealed correlations of the methyl group to H-9ax, and H-9ax to both H-8 and H-7, suggesting that the methyl, H-9ax, H-7, and H-8 were coplanar. Owing to the *trans*-configurated C_5-C_6 double bond, a *cis*-configuration of H-3 and H-4 of the oxirane moiety is a prerequisite for the formation of the 10-membered lactone ring in **33**. The $J_{H\text{-}3,H\text{-}4}$ of 4.5 Hz also suggested a *cis*-relationship of the epoxide protons in **33**.

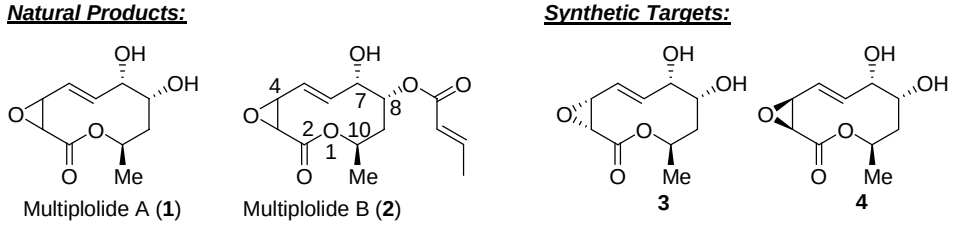
Similarly the structure of multiplolide B was elucidated on the basis of its spectral data. The absolute configuration at C-7 of **34** was determined as *S* by the application of the Mosher method which indirectly established the absolute configurations of both C-8 and C-10 centers as *R, R*. By taking into account the positive optical rotation shown by both **33** and **34**, a similar absolute configurations at C-7, C-8 and C-10 were proposed for multiplolide A (**33**). The relative configuration of epoxide moiety could not be assigned for both **33** and **34**, from the available spectral data. This was another classic case illustrating the limitations of the modern analytical techniques. Total synthesis deemed necessary for the establishment of the relative stereochemistry of the oxirane ring. The fact that the absolute configurations at C-7, C-8 and C-10 for **33** were proposed on the basis of similar sign of rotation as that of **34** and were not directly determined by Mosher method, naturally made **33** even more attractive synthetic target as compared to **34**. It was planned to synthesize both possible diastereomers (**35** and **36**) of multiplolide A to unambiguously establish the relative stereochemistry of oxirane ring.

Present Work

Medium ring compounds (those having a ring size in the range of 8 to 11)[14] are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of natural products. These compounds have specific characteristics which had been recognized by at the beginning of this century,[15] and it was soon observed that they were much more difficult to synthesize by cyclization methods than other cyclic compounds including macrocyclic compounds (ring sizes >12). These difficulties are caused by the fact that the formation of these cyclic compounds are disfavoured by entropy as well as enthalpy[15] (vide infra).

Natural products containing a medium ring lactone framework are found in plants, insects (pheromones) and bacteria (antibiotics); they can have a terrestrial, fungal or a marine origin. In 2001, multiplolides A (**1**) and B (**2**),[13] the two new antifungal 10-membered lactones were isolated from the crude ethyl acetate extract of the culture broth of *Xylaria multiplex* BCC 1111. Multiplolides A (**1**) and B (**2**) exhibited antifungal activity against *Candida albicans* with IC_{50} values of 7 and 2 μg/mL, respectively.

Figure 1 *Chemical structures of multiplolide A, B and both possible diastereomers of multiplolide A*

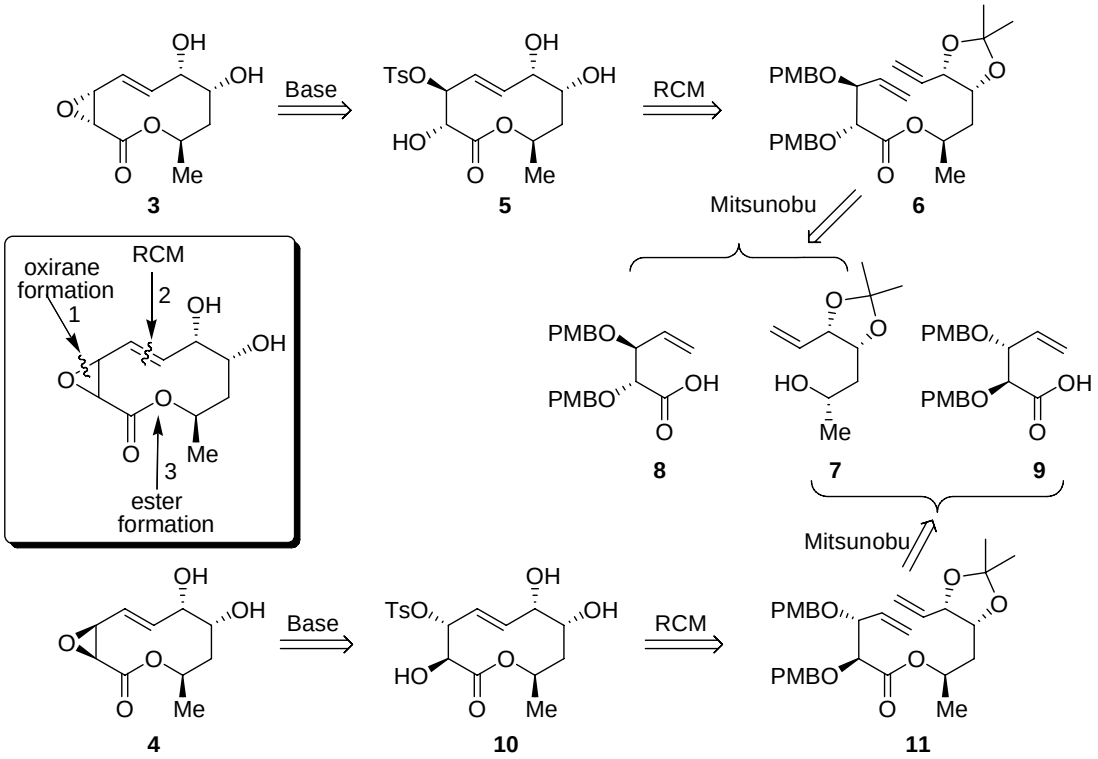


Chemical structures of **1** and **2** were elucidated on the basis of their spectral data. The most striking structural feature from synthetic point of view is the epoxide functionality embedded between lactone carbonyl and ring olefin. The absolute configuration at C-7 of **2** was determined as *S* by the application of the Mosher method which indirectly established the absolute configurations of both C-8 and C-10 centers as *R, R*. By taking into account the positive optical rotation shown by both **1** and **2**, a similar absolute configurations at C-7, C-8 and C-10 were proposed for multiplolide A (**1**). Eventhough the latest analytical techniques including various 2D-NMR experiments were employed, the relative stereochemistry of the oxirane ring

could not be elucidated owing to its specific position on the macrocycle. The lactone carbonyl on one side and *E*-configured ring olefin on the other must have resulted in the spacial isolation of epoxide protons (H-3 and H-4) from the protons on other chiral centers (H-7, H-8 and H-10) and hence was the failure in elucidation of relative stereochemistry at C-3 and C-4.

The fact that the assignment of absolute stereochemistry at C-7, C-8 and C-10 of multiplolide A (**1**) was merely a hypothesis based on the same sign of optical rotation as that of multiplolide B (**2**), made the former an automatic choice, as our synthetic target. Moreover to establish the absolute and relative stereochemistry of the oxirane ring beyond ambiguity it was decided to synthesize both the possible diastereomers of multiplolide A [3-*R*, 4-*R* (**3**) and 3-*S*, 4-*S* (**4**)]. Comparison of the analytical data for both the isomers with that of natural product would enable us to determine the stereochemistry at C-3 and C-4 for multiplolide A. Success in synthesizing multiplolide A would leave synthesis of multiplolide B as a matter of few straight forward potection-deprotections.

Figure 2 *Retrosynthetic analysis for both possible diastereomers of multiplolide A*



Retrosynthetic strategy for both the isomers is depicted in figure 2. Three major disconnections were visualized; one at the oxirane ring, other at ring olefin and

the final one at the ester linkage. Since the oxirane functionality is positioned alpha to carbonyl it would be wise to install it in the end, therefore priority was given to the disconnection at the oxirane ring. It would require a leaving group on one of the carbons and the free hydroxyl on the other to install the oxirane. The leaving group was envisaged at allylic position since the selective protections and deprotections at allylic positions are very well established. The knowledge of the position of leaving group (C-4) and the absolute stereochemistry at that center would enable us to state the absolute stereochemistry of the oxirane ring beyond any ambiguity and hence fix the missing link in its structure elucidation.

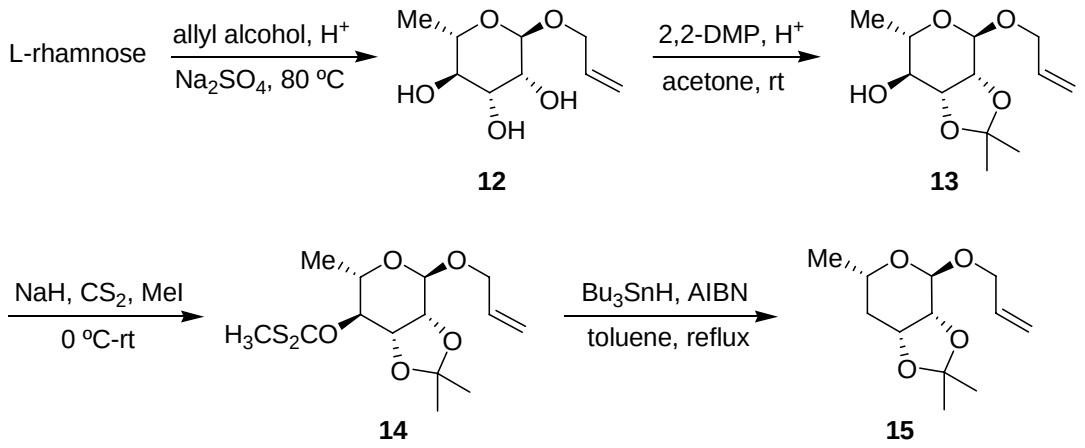
In line with the practice of our group to use the RCM reaction for the synthesis of various natural products and synthetically important intermediates,[16,17] the construction of the ring olefin of multiplolide A and consequently the macrocycle formation was planned by employing the RCM reaction on a suitable diene-ester. It is observed that the outcome of the RCM reaction is highly dependent on substrate and reaction conditions. The situation becomes complex and the prediction difficult when the olefins involved in the ring closure reaction are surrounded by multiple chiral centers. Oxygen functions on these centers, their stereochemistry and nature of the protections all contribute towards the stereochemical outcome of reaction leaving behind very less space for prediction. Keeping this in mind the path was chosen so as to offer enough flexibility with the substrates for RCM. As many as three substrates could be tried under RCM conditions to suit the requirement of *trans* olefin.

In view of the chances of epimerization at C-3 under the reaction conditions where base needs to be employed for ester formation (eg. DCC or Yamaguchi), the di-PMB ester **6** was visualized from the Mitsunobu reaction between the alcohol **7** and acid **8**. Remaining pertinent to the practice of using cheaply available sugars for total synthesis, D-xylose and L-rhamnose were chosen as precursors for acid **8** and alcohol **7** respectively after careful stereochemical investigations. The other diastereomer **4** of the multiplolide A could be similarly synthesized from the same alcohol **7** and the acid **9**, D-mannitol being the precursor for the later.

Synthesis of fragment 7

Synthesis of the alcohol **7** (Scheme 1) began with the preparation of the known[18] deoxy derivative **15** from L-rhamnose in four steps. L-Rhamnose was converted into its allyl glycoside by treatment with allyl alcohol in presence of acid and sodium sulfate at 80 ºC. The crude glycoside was then converted into the 2,3-*O*-isopropylidene derivative **13** using 2,2-dimethoxypropane in acetone and in the presence of catalytic acid. The ^{1}H and ^{13}C NMR spectra of **13** revealed the presence of only one anomer. The anomeric proton appeared as a singlet at 4.99 ppm in the ^{1}H NMR spectrum whereas the C-1 resonated at δ 96.1 in the ^{13}C NMR spectrum indicating α-anomer. Two singlets at δ 1.35 and 1.52 in the ^{1}H NMR spectrum integrating for three protons each were assigned to methyl groups of isopropylidene protection, which was further supported by presence of a peak for quaternary carbon at 109.3 ppm in the ^{13}C NMR spectrum. Results from mass spectrum, IR, and elemental analysis were in accordance with the structure **13**.

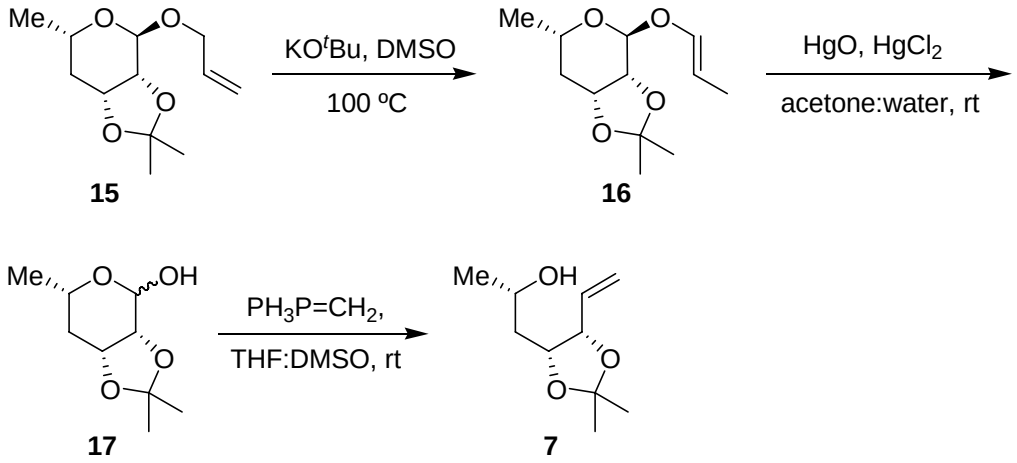
Scheme 1



The free hydroxyl at C-4 was deoxygenated using the Barton's protocol.[18c] The xanthate derivative **14** was prepared by treating **13** with NaH, CS_2 and MeI. Subsequently the xanthate derivative **14** was treated with *n*-Bu_3SnH and catalytic AIBN in refluxing toluene to obtain the deoxy derivative **15**. The structure **15** was well supported by ^{1}H NMR, ^{13}C NMR, mass spectrum and elemental analysis. In the ^{1}H NMR spectrum of **15**, two signals for C-4 methylene protons were located in the upfield region (1.35-1.42 ppm as a multiplet and at 1.80 ppm as a doublet of a double

doublet). In the partially decoupled ^{13}C NMR spectrum C-4 resonated at δ 36.1 as a triplet confirming the presence of methylene group.

Scheme 2



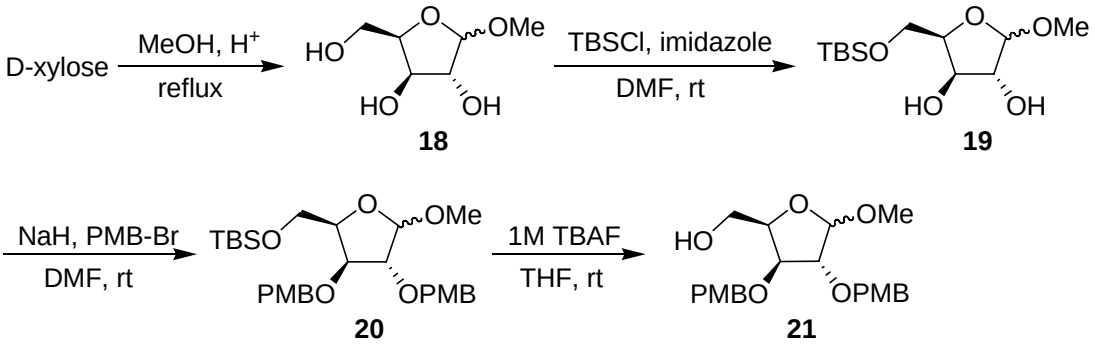
Deallylation of **15** was carried out in a two step sequence (Scheme 2),[19] first step being the isomerisation to the vinyl ether **16** by treatment with KO^{t}Bu in DMSO at 100 ºC. The crude vinyl ether **16** was treated with HgO to afford the lactol **17** as an inseparable anomeric mixture. Signals for the anomeric protons of the two anomers appeared at 4.89 and 5.42 ppm in the ^1H NMR spectrum whereas the anomeric carbons resonated at 92.5 and 93.0 ppm in the ^{13}C NMR spectrum. One carbon Wittig homologation of **17** by treatment with methyltriphenylphosphorane in THF:DMSO mixture furnished the required alcohol fragment **7**. The three signals for the olefinic protons integrating for one proton each, appeared at 5.23, 5.30, 5.78 ppm in the ^1H NMR spectrum. The presence of two olefinic carbons at δ 117.9 (triplet) and δ 134.2 (doublet) in the DEPT spectrum along with other analytical data such as mass spectrum, elemental analysis and IR spectrum supported the proposed structure **7**.

Synthesis of fragment 8

Methyl glycosidation of D-xylose was carried out as per reported procedure[20] and the primary hydroxyl group of the crude methyl glycoside **18** was selectively protected as its silyl ether[21] to afford compound **19** (Scheme 3). The presence of the characteristic peaks of TBS-group in the ^1H NMR spectrum [δ 0.09 (s, 6H) and 0.89 (s, 9H)] indicated the structure **19**. This was further supported by the mass spectrum with the highest mass peak at *m/z* 301 $[M+Na]^+$. Other analytical data was also found

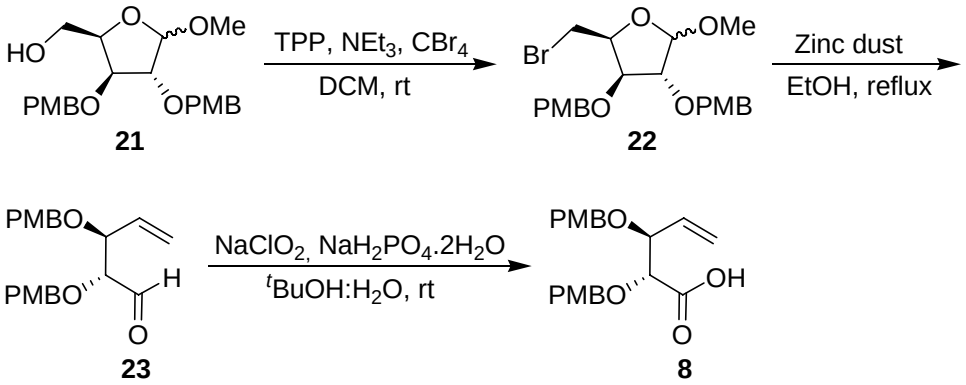
in accordance with the proposed structure. The 2,3-diol segment of **19** was converted to its *bis*-PMB ether derivative **20** on teatment with sodium hydride followed by PMB-Br[22]. Subsequently the TBS-ether at C-5 of crude **20** was removed using 1 molar TBAF[23] solution in THF at rt. Both the anomers of compound **21** could be seen separately on TLC. They were separated by column chromatography and characterized separately. Signals due to TBS-ether were absent in the ^{1}H NMR and the ^{13}C NMR spectra of both the anomers. For the non-polar anomer of the two, the H-1 appeared at δ 4.87 as a doublet with J = 1.8 Hz and C-1 appeared at δ 107.8 whereas H-1 was observed at δ 4.77 as a doublet with J = 4.2 Hz and C-1 at δ 100.1 for the polar anomer. These signals clearly indicated the non-polar isomer to be the β anomer and the polar one to be α anomer.

Scheme 3



The bromination of **21** was carried out using TPP and CBr_4[24] to furnish the bromo derivative **22** (Scheme 4). In this case too, the anomers could be characterized separately. On treatment with activated zinc dust[25] in refluxing ethanol the bromo derivative **22** furnished the aldehyde **23**, which was used as such for the next reaction. The aldehyde **23** was oxidized to acid **8** on treatment with $NaClO_2$ and $NaH_2PO_4.2H_2O$ in presence of 2-methyl-2-butene.[26] The presence of acid functionality was confirmed by the IR spectrum of **8** with O-H stretching at 3394 cm^{-1} and the C=O at 1726 cm^{-1}. In the ^{13}C NMR spectrum the carbonyl carbon was seen at 173.8 ppm. The proton alpha to acid carbonyl resonated as a doublet at δ 3.96 with J = 3.5 Hz and the olefinic protons appeared between δ 5.29-5.34 and at δ 5.87. The mass spectrum and elemental analysis also supported the proposed structure **8**.

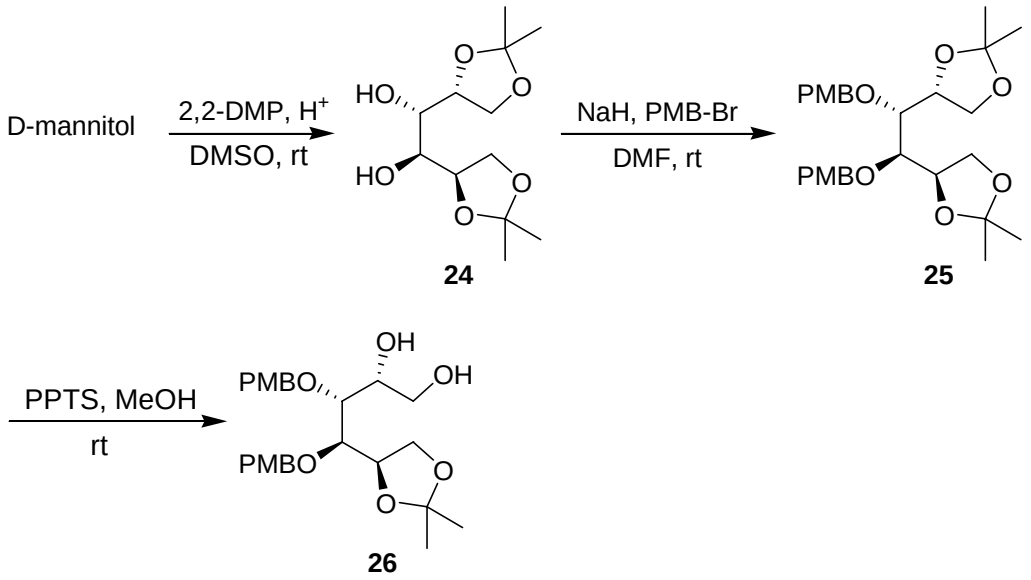
Scheme 4



Synthesis of fragment 9

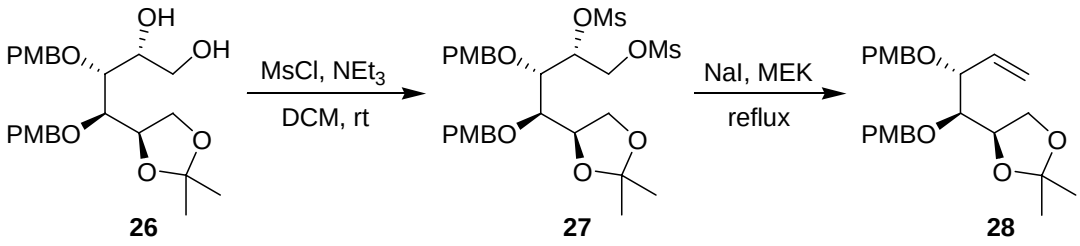
The preparation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**24**) was carried out employing literature procedure (Scheme 5).[27] The free hydroxyl functions at C-3 and C-4 in the isopropylidene derivative **24** were protected as PMB-ethers by treatment with NaH and PMB-Br[22] in DMF to afford the di-PMB derivative **25**. The isopropylidene groups of **25** resonated at δ 1.33 and 1.41 in the ^{1}H NMR spectrum. The benzylic methylene groups appeared as a singlet at δ 4.60 and the aromatic protons at δ 6.83 and 7.22. In the ^{13}C NMR spectrum and the DEPT spectrum the methylene groups were observed at 66.7 and 74.0 ppm. The highest peak at *m/z* 525 $[M+Na]^+$ in the mass spectrum and the elemental analysis supported the structure **25**. The next job was to remove one of the isopropylidene groups of C_2-symmetric **25** keeping the other one intact. This was achieved employing PPTS[28] in MeOH at rt. After running the reaction for various time intervals it was noted that 12 h was the optimum reaction time. At this time even though some starting material remained unreacted, the yields of the required diol **26** were maximum. The starting material could be easily separated on a silica gel column and recycled. The loss of one of the isopropylidene groups was evident from the ^{1}H NMR spectrum where signals due to isopropylidene group at δ 1.34 and 1.43 integrated for three protons each as compared to the signals due to benzylic protons at δ 4.50, 4.57, 4.60, 4.67 which integrated for four protons. In the mass spectrum the peak was seen at *m/z* 485 $[M+Na]^+$ confirming proposed structure. The ^{13}C NMR spectrum and elemental analysis were also found to match the proposed structure **26**.

Scheme 5



Conversion of the vicinal diol unit in **26** into the terminal olefin **28** was effected using a two step procedure (Scheme 6).[29] In the first step the diol **26** was converted to its dimesyl derivative **27** by treatment with MsCl in presence of triethylamine in DCM. The crude dimesylate was treated with NaI in refluxing MEK to procure the olefin **28**. The terminal olefinic protons were seen between δ 5.13-5.38 as a multiplet and the internal proton as a doublet of a double doublet at δ 5.85 in the ^{1}H NMR spectrum. A triplet in the partially decoupled ^{13}C NMR spectrum at 118.1 ppm confirmed the presence of SP^2 methylene in the compound. Other analytical data was found in accordance with the structure.

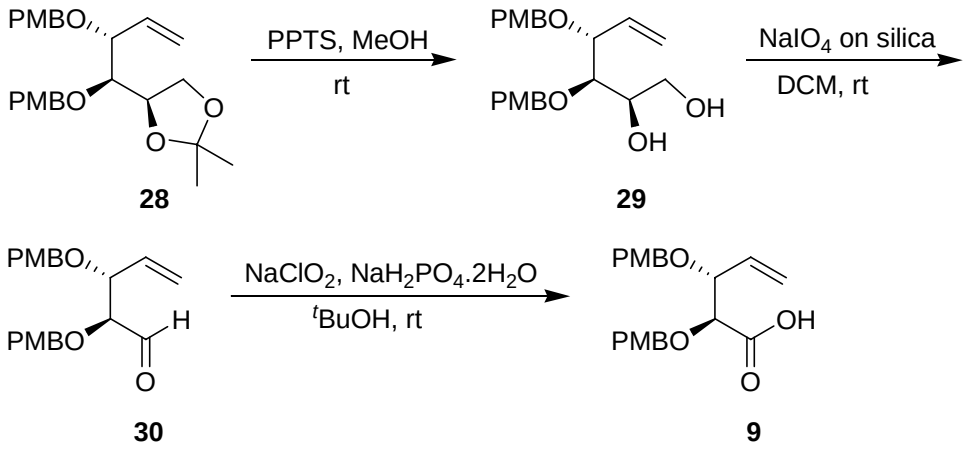
Scheme 6



The isopropylidene protection in **28** was cleaved using PPTS in methanol to furnish the diol **29**. The absence of peaks due to isopropylidene group in the ^{1}H and the ^{13}C NMR spectra was evident for the successful removal of the protecting group.

The structure was further supported by the IR spectrum with absorption corresponding to free hydroxyl at 3436 cm^{-1} and elemental analysis (Scheme 7).

Scheme 7



The diol **29** was cleaved by using sodium metaperiodate adsorbed on silica gel[30] to afford the aldehyde **30**, which was oxidized to the acid **9** on treatment with $NaClO_2$ and $NaH_2PO_4.2H_2O$ in the presence of 2-methyl-2-butene.[26] In the IR spectrum the O-H stretching was observed at 3394 cm^{-1} and the C=O stretching at 1724 cm^{-1}. The carbonyl carbon was observed at 173.4 ppm in the ^{13}C NMR spectrum. Other analytical data such as the ^{1}H NMR spectrum, mass spectrum, and elemental analysis of **9** were in accordance with the proposed structure. The specific rotations of **9** $\{[\alpha]_D^{25} = -46.8$ (*c* 0.9, $CHCl_3)\}$ and acid **8** (from xylose) $\{[\alpha]_D^{25} = +52.7$ (*c* = 0.7, $CHCl_3)\}$ confirmed the enantiomeric relationship between them.

Thus the fragment **7** was synthesized from L-rhamnose and the enantiomeric acids **8** and **9** were synthesized from D-xylose and D-mannitol respectively. Having successfully prepared the requisite coupling partners for the syntheses of both the isomers of multiplolide A, the next step was to proceed with one of the acids (**8** or **9**) and try the further sequence of reactions as per the retrosynthetic plan. The fact that there was no clue whatsoever to speculate which of the isomers of multiplolide A (**3** or **4**) was more plausible to be a natural product, had made the choice entirely capricious. It was chosen to proceed with the acid **8** first to evaluate the proposed route. The key step in the proposed route was of-course the macrocyclization using RCM. The literature survey revealed that the prediction of the stereochemical outcome of the reaction, particularly for the medium (8-11membered) ring size was

far from straight forward. Keeping this in mind the strategy was designed in such a way to offer at least three diene substrates to suit the requirement of *E* configured olefin.

A brief overview of factors affecting the stereochemical outcome of RCM in case of medium size rings

The fact that the Nobel prize in chemistry for the year 2005 was awarded to Grubbs, Chauvin and Schrock for their contributions in the area of metathesis, explains by itself the utility of the transformation and hence its wide applicability towards the synthesis of materials which are used in different walks of life. The awesome impact of this transformation in the area of *total synthesis of natural products* is clearly evident from the literature. This transformation offers various merits such as tolerance to various functional and protecting groups, easy and non-hazardous experimental procedures and reproducibility, which are of the particular interest to synthetic organic chemist. The development of new catalysts, which make previously impossible transformations possible and in some cases complement each other in stereochemical outcome, has made this tool even more effective and attractive.

Coupled with all these advantages this transformation still poses considerable challenges, still holds areas to be conquered and that is what fascinates synthetic chemists to employ it in their synthetic endeavors. One of such areas is synthesis of medium sized rings (8 – 11membered) using RCM and the prediction of the stereochemical outcome for the same. Ring strain predisposes cycloalkenes of 8-11 ring atoms for the reverse process, that is, for ring-opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP). Therefore, the number of successful applications of RCM to this series is still rather limited.

One approach to circumvent this problem is to incorporate control elements that force the cyclization precursors to adopt conformations suitable for ring closure.[31] Hydroxyl protecting groups are sometimes employed spanning hydroxyl groups in vicinity of the olefin with the anticipation that they should exert this function by aligning the olefinic side chains in a cyclization-friendly conformation. The extent of bias, if any, conferred by such a group on the stereochemistry of the newly formed

double bond is much less understandable and cannot be predicted with certainty. In general, RCM reactions in the macrocyclic series tend to give mixtures of the (*E*) and (*Z*)-configured cyclic olefins, and a reliable and general method of controlling the geometry of the newly formed double bond has yet to be found.[32, 33]

The results of RCM reactions employed in the various syntheses of Microcarpalide are summarized below in table 1, as a representative example. It nicely illustrates as to how it is difficult to correlate the effect of a set of protecting groups on the stereochemical outcome of RCM and hence it explains that it is still more difficult to predict the outcome of a reaction with a given set of protecting groups.

Figure 3 *Effect of protecting groups and reaction conditions on the stereochemical outcome of RCM reactions: Syntheses of Microcarpalide.*

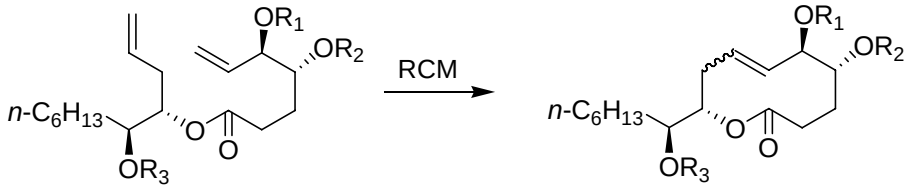


Table 1

No.	Protecting groups	Reaction conditions	Catalyst	*E:Z* ratio	Ref.
1.	$R_1 = R_2 =$ Bn, $R_3 =$ MEM	DCM, reflux	1st gen.	10:1	17c
2.	$R_1 = R_2 =$ Bn, $R_3 =$ MEM	DCM, reflux	1st gen.	10:1	34
3.	$R_1 = R_2 = R_3 =$ Bn	DCM, reflux	1st gen.	*E* only	35
4.	$R_1 = R_2 = R_3 =$ Bn	DCM, rt	1st gen.	*E* only	36
5.	$R_1 = R_2 =$ acetonide, $R_3 =$ MOM	DCM, reflux	1st gen.	2:1	37
6.	$R_1 = R_2 =$ acetonide, $R_3 =$ MOM	DCM, reflux	1st gen.	2:1	38
7.	$R_1 = R_2 =$ acetonide, $R_3 =$ Bn	DCM, reflux	1st gen.	2:1	39
8.	$R_1 = R_2 = R_3 =$ Bn	Not mentioned	2nd gen.	*E:Z* mixt.	36
9.	$R_1 = R_2 =$ acetonide, $R_3 =$ MOM	DCM, reflux	2nd gen.	Major *Z*	37

Recently the effect of protecting groups on the stereochemical outcome of RCM was studied by our group druing the synthesis of an anti-malarial nonenolide[40] (Figure 4). All the reactions were conducted in 0.001M solution of substrate in DCM, in presence of 10 mol% of Grubbs' second generation catalyst at the reflux temperature. Uniformity in reaction conditions was maintained with a view to understand the effect of protecting groups around the reaction centers on the geometry of the double bond under construction.

Figure 4 *Effect of protecting groups on the stereochemical outcome of RCM reactions: Syntheses of an anti-malarial nonenolide*

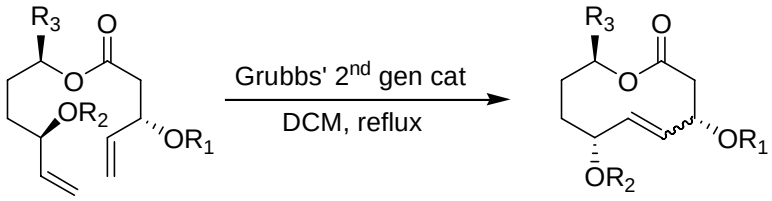


Table 2

No.	Protecting groups	*E*:*Z* ratio
1.	$R_1 = R_2 =$ PMB, $R_3 =$ Methyl	9:1
2.	$R_1 = R_2 = H$, $R_3 =$ Methyl	*Z* exclusively
3.	$R_1 = R_2 =$ PMB, $R_3 = H$	*E* exclusively
4.	$R_1 = R_2 = R_3 = H$	*Z* exclusively

Though in this particular case it is seen that the presence of PMB protecting groups favors formation of *E* isomer and free hydroxyl groups favor formation of *Z* isomer, these are preliminary results and the detailed investigations are still in progress in our laboratory. It is pertinent to mention that the results must be seen in the context of the system under consideration, and a lot more work is yet to be done, on the substrates bearing different substitution patterns, to arrive at a generalization for 10 membered macrocyclization using RCM.

The other factor that affects the stereochemical outcome of the reaction is the choice of catalyst. Grubbs' first generation catalyst often produces mixture of *E* and *Z* cycloalkens as a result of kinetic control. The congeners of first generation catalyst with increase in activity due to structural modification cause the competition between thermodynamic and kinetic control on the reaction, which is evident from the

presence of products due to thermodynamic control in the product mixtures. The more superior second generation catalyst and its congeners are shown to favor the thermodynamically stable products due to their higher overall activity. They are able to isomerize the cycloalkenes formed during the course of the reaction (secondary metathesis) and hence enrich the mixture in the thermodynamically favored product.[33] The reversible nature of metathesis reaction was demonstrated and exploited to a good effect to bring about the desired stereoslectivity by Grubbs,[41a] Smith, [42] Fürstner[43] and many others.

For this purpose the energies of both *E* and *Z* isomers are calculated to determine which of them is the thermodynamically stable product. Depending upon the requirement (product of thermodynamic control or kinetic control) the catalyst activity is tuned. More active the catalyst more effective it is to cause secondary metathesis and hence to produce thermodynamically more stable stereoisomer.

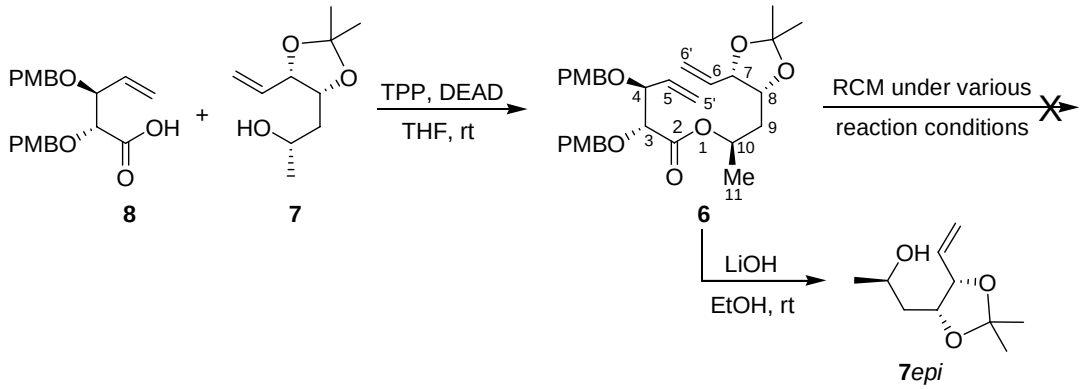
In the context of present work we could not avail the advantage of semi-empirical calculations to determine at which stage of the synthesis our desired *E* isomer was a thermodynamically stable product compared to corresponding *Z* isomer. This constraint blocked us from a systematic choice of catalyst leading to an obligation to go for a trial and error method using both possible catalysts (first and second generation Grubbs' catalysts) and all possible diene substrates along the way of synthesis, to suit the requirement of *E* olefin as the product of RCM reaction.

Coupling of alcohol 7 and acid 8

The coupling reaction between the alcohol fragment **7** and the acid fragment **8** was carried out under Mitsunobu[44] conditions (Scheme 8). To a mixture of alcohol **7**, acid **8** and TPP in THF was added DEAD to afford the ester **6** in 73% yield. The ^{1}H NMR spectrum of the ester **6** was found to be matching with the proposed structure. The proton at position C-10 appeared as a multiplet between δ 5.01-5.17 whereas the signals for olefinic protons were observed as multiplets between δ 5.20-5.35 and δ 5.65-5.96 integrating for six protons. In the ^{13}C NMR spectrum the carbonyl carbon was observed at δ 169.6. Two triplets in the DEPT spectrum in aromatic/olefinic region at δ 118.5 and 119.3 confirmed the presence of two SP^2 methylene groups.

Absorption due to ester carbonyl functionality was seen in the IR spectrum at 1736 cm^{-1}. In the mass spectrum the peak observed at *m/z* 563 corresponding to $[M+Na]^+$. Elemental analysis was also found to match with the calculated values. Inversion of the configuration at the alcohol center during the Mitsunobu reaction was confirmed by hydrolysis of ester **6**, which produced the epimeric alcohol (**7**-*epi*). The next critical step was the RCM reaction to build the ring structure. However several attempts for macrocyclization employing various RCM conditions on diene-ester **6** turned out to be a difficult proposition.

Scheme 8

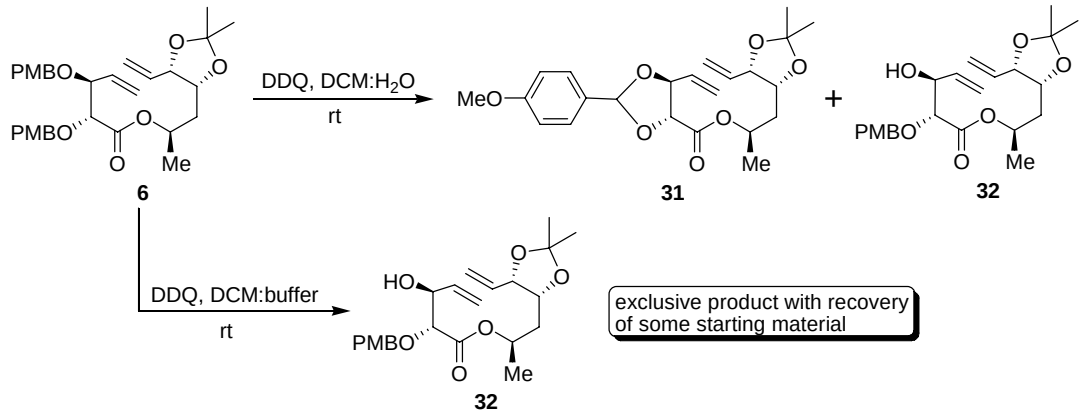


Having met with failure in the ring closure reaction of diene **6**, it was decided to go for deprotection of PMB ethers and then try the RCM reaction. As we wanted to preserve the isopropylidene protection during removal of PMB-ethers, the use of different reagents such as AcOH, TFA, $AlCl_3$, 1M HCl, was not suitable. The presence of diene functionality in the molecule has blocked the use hydrogenation reaction conditions employing catalysts such as Pd, Pt, Raney Nickel etc. Taking into consideration these facets the choice of reagents was restricted to either CAN or DDQ.

On treatment with two equivalents of DDQ in DCM:H_2O mixture[45] (Scheme 9), compound **6** gave a product with the highest mass peak at *m/z* 441 $[M+Na]^+$ in the mass spectrum suggesting the formation of benzylidene acetal **31**. The second product isolated from the reaction mixture showed the highest mass peak at *m/z* 443 $[M+Na]^+$, which corresponded with mono-PMB ether. It was established from the ^1H NMR and ^{13}C NMR spectra that the product was not the mixture of two mono-deprotected ethers present at C-3 and C-4.

To circumvent the formation of benzylidene acetal we used a buffer system of pH 7 (phosphate buffer).[46] Much to our delight the desired mono-deprotected compound formed exclusively along with some starting material remaining unreacted.

Scheme 9

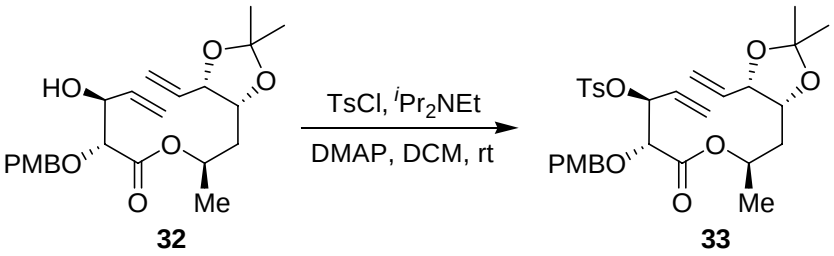


The next protocol was to find out which of the PMB-ethers (C-3 or C-4) was obtained. By the conventional procedure the free hydroxyl was tosylated with a view to make either (3*R*, 4*R*) or (3*S*, 4*S*) stereoisomer of multiplolide A. Tosylation proceeded smoothly in DCM using Hunig's base and tosyl chloride[47] (Scheme 10). The ^{1}H NMR spectrum of the tosyl derivative revealed that the initial deprotection and subsequent tosylation had occurred at allylic position i.e. at C-4, thus suggesting the structure of the tosyl derivative to be **33** and hence that of the precursor alcohol to be **32**. The conclusion was based on the comparison of chemical shift values for H-3 and H-4 for compounds **6**, **32** and **33** (Table 3). The H-3 was easy to locate and it appeared as a sharp doublet in all the three spectra without much deviation in its chemical shift or coupling constant as shown in table. This indicated that there was no major change in the electronic environment in the intimate vicinity of H-3. Whereas the significant change in the chemical shifts of H-4 clearly indicated the presence of tosyl group on C-4.

Table 3

Compund no.	Signal for H-3 in ^{1}H NMR	Signal for H-4 in ^{1}H NMR
6	3.93 (d, *J* = 4.8 Hz, 1H)	4.11 (dd, *J* = 4.8, 7.7 Hz, 1H)
32	3.88 (d, *J* = 4.5 Hz, 1H)	4.36-4.40 (br. m, 1H)
33	3.95 (d, *J* = 5.3 Hz, 1H)	5.17-5.36 (m, 5H)

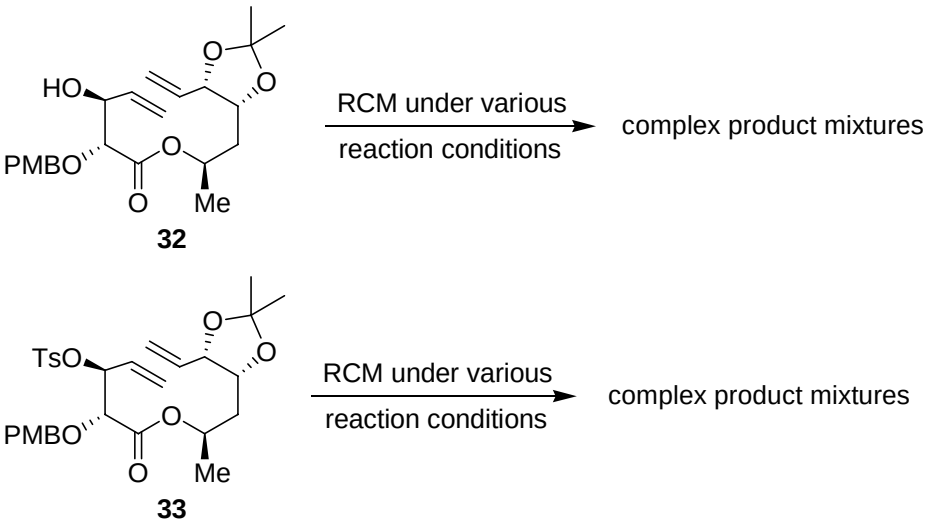
Scheme 10



32 **33**

Compound **32** and **33** were subjected to RCM reaction (Scheme 11) under various reaction conditions but all the attempts resulted into the complex product mixtures.

Scheme 11

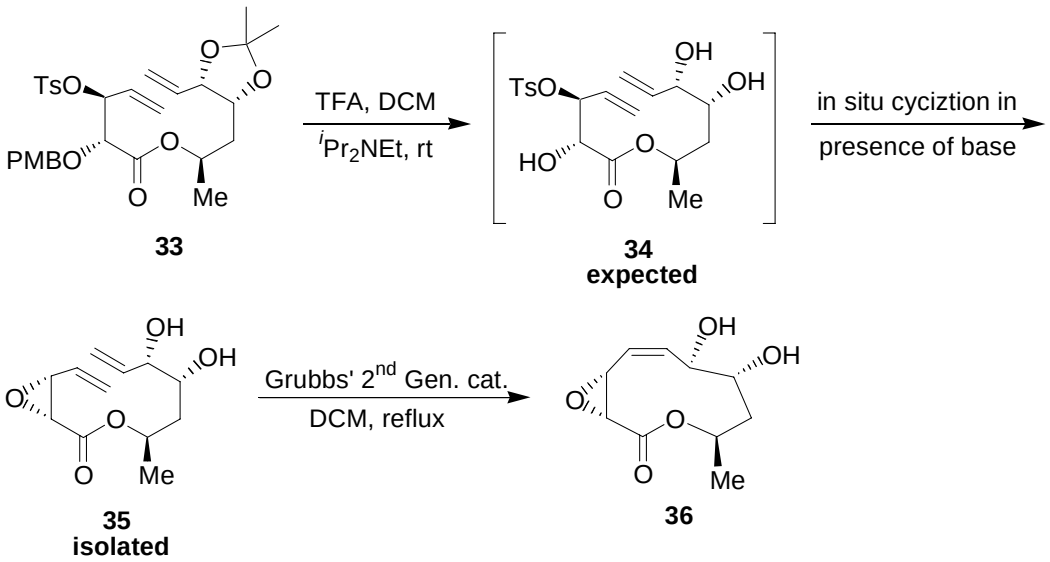


32

33

The RCM reactions on substrates **6**, **32** and **33** failed to take place. Therefore the final choice for us to try RCM reaction was the epoxide substrate **35** in which the isopropylidene group was also absent. With a plan to prepare **34,** compound **33** was treated with TFA[48] in DCM at rt (Scheme 12) and progress of reaction was closely monitered by TLC. The newly formed product showed the mass peak at m/z 265 $[M+Na]^+$ which corresponded to **35** instead of tosyl triol **34**. The treatment with Hunig's base during the neutralization had caused the transformation of **34** into **35** in situ. In the ^{1}H NMR spectrum the signal for H-3 was observed at δ 3.65 as a doublet with J = 4.6 Hz and H-4 at δ 3.62 as a double-doublet with J = 4.6, 7.8 Hz.

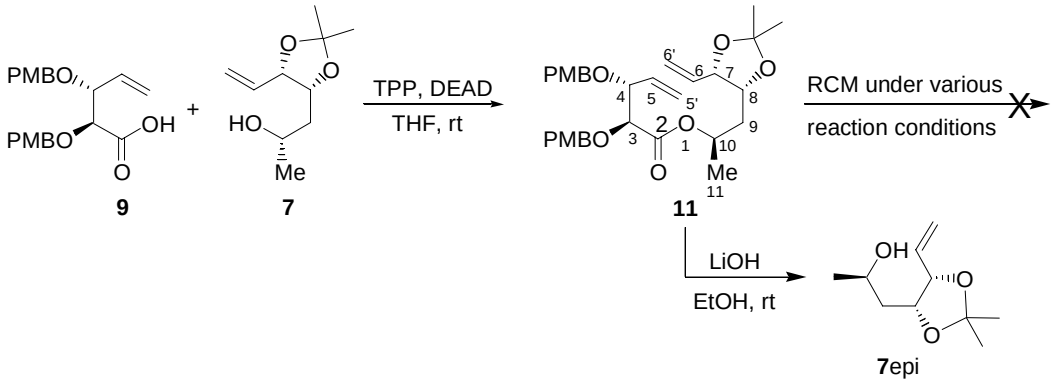
Scheme 12



The RCM reaction of epoxide-diene **35** in refluxing DCM using Grubbs' second- generation catalyst proceeded smoothly to produce a slower moving compound **36** on TLC with complete consumption of starting material. The mass spectrum of the product displayed the peak at *m/z* 237 corresponding to $[M+Na]^+$ for the product after ring closure. The ^1H NMR or ^{13}C NMR of the synthetic product did not match with the spectral data of natural product. In the ^1H NMR spectrum singnals corresponding to both the olefin protons overlappeed on each other resulting into a multiplet whereas in the ^{13}C NMR spectum the olefinic carbons were observed at δ 126.2 and δ 131.3. The difference in chemical shifts was 5 ppm, which was indicative of the *cis* geometry at the newly formed double bond. However unambiguous assignment of the geometry of the double bond was hampered due to inability in calculating the coupling constants of the olefinic protons from the ^1H NMR spectrum in $CDCl_3$. It was gratifying to note that the ^1H NMR spectrum of **36** in CD_3COCD_3 resolved the olefinic protons clearly. They appeared at δ 4.75 and δ 4.93 in the ^1H NMR spectrum. The proton at δ 4.75 appeared as a doublet with J = 11.5 Hz and the proton at δ 4.93 appeared as a doublet of a triplet with J = 1.8, 11.5 Hz. The coupling constant of 11.5 Hz between the olefinic protons provided the proof for the *cis* geometry of the double bond.

As the outcome of RCM is largely dependent on substrate including its stereochemistry, there existed a strong possibility of synthesizing the other isomer of multiplolide A (**4**), with the enantionmeric acid **9** in our hand. There also existed a strong possibility of synthesizing the multiplolide A (**3**) if RCM was successful before installation of leaving group on the substrate. In such case the position of leaving group could be altered by some manipulations and **3** could be synthesized to supersede the failure through the previous strategy.

Scheme 13



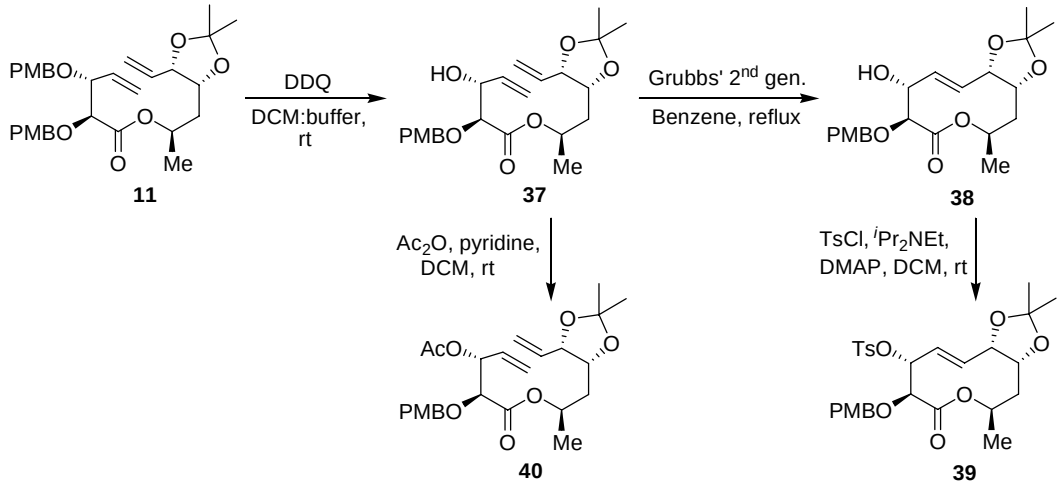
The Mitsunobu reaction between alcohol **7** and acid **9** proceeded smoothly to procure the ester **11** (Scheme 13). In the ^{1}H NMR spectrum the isopropylidene signals were observed at δ 1.32 and 1.47 as singlets whereas the signals due to PMB-methoxyl groups were observed at δ 3.77 and 3.78 as singlets, each integrating for three protons. The H-10 was observed at δ 5.10 as a quartet with J = 6.3 Hz. The structure was further supported by the IR spectrum, which revealed ester carbonyl at 1736 cm^{-1}. The ester carbonyl appeared at δ 169.6 in the ^{13}C NMR spectrum. The highest mass peak *m/z* 563 $[M+Na]^{+}$ and elemental analysis served as supporting evidences for structure **11**. The inversion of configuration at the alcohol center during the Mitsunobu reaction was confirmed in similar manner. However attempts for ring closure with compound **11** under various reaction conditions resulted in failures.

Compound **11** on treatment with DDQ under the conditions standardized for compound **6**, afforded compound **37** (Scheme 14). Cleavage of one of the PMB-ethers was evident from the ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum the presence of only one singlet at δ 3.79 integrating for three protons, two doublets at δ 4.39 and 4.69 integrating for two protons and aromatic protons integrating for four protons

clearly established that one of the PMB groups was cleaved. The presence of only one benzylic carbon at δ 72.5 and only one quaternary carbon at δ 159.6 in the ^{13}C NMR spectrum further cemented the conclusion. All other analytical data was also found in accordance. Without entirely depending on precedence, the acetate **40** was prepared from compound **37**. Which clearly indicated that the PMB group in allylic position, like in earlier case, had undergone cleavage to afford the monodeprotected derivative.

At this stage the RCM reaction of **37** was attempted in DCM with Grubbs' second- generation catalyst at reflux temperature. The reaction was sluggish with only 50% conversion after 36 h. Starting material and product were separated by column chromatography. To our delight the product showed the peak at 415 $[M+Na]^+$ in the mass spectrum corresponding to the ring closed product **38**.

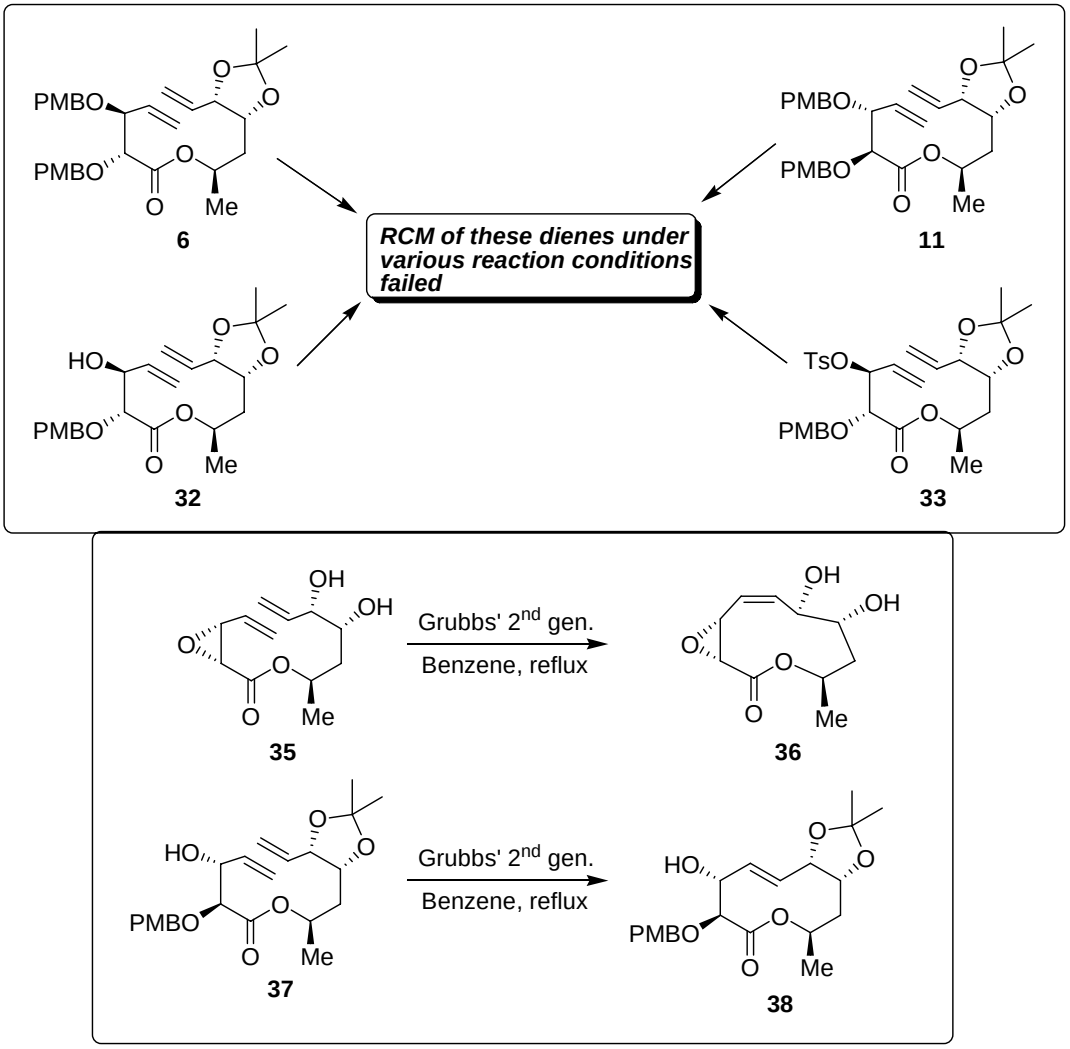
Scheme 14



The geometry of the newly formed double bond was *trans* as established by the coupling constant 16.5 Hz. As the reaction rate in DCM was very slow, benzene was substituted as a solvent and the reaction was conducted at the reflux temperature of benzene using Gubbs' second-generation catalyst. This proved to be extremely rewarding and complete conversion into the product **38** was achieved within 6 h. Structure of **38** was further supported by the absence of signals for olefinic methylenes in the ^{13}C NMR spectrum. Compound **38** was conventionally converted into its tosylate derivative **39**. In the ^{1}H NMR spectrum of **39**, H-4 resonated in the downfield region at δ 5.10. The structure of tosylate **39** was well supported by the

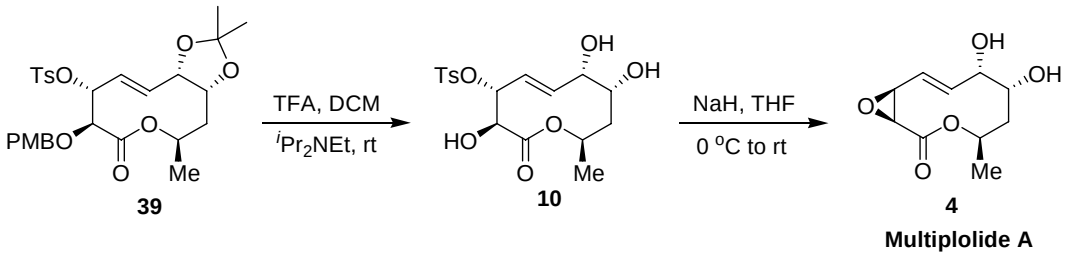
other analytical data. Figure 5 summarizes the attempts for RCM reaction of various dienes in the course of synthesis and their results.

Figure 5 *Summary of attempts for RCM of various dienes*



On treatment with TFA,[48] compound **39** produced a slower moving product **10** (Scheme 15), whose highest mass peak was observed at *m/z* 409. The oxirane was installed by treatment of crude **10** with excess of sodium hydride in THF to afford the compound **4**. All the analytical data was found to be perfectly matching with proposed structure and also with the reported data for natural product. The difference in specific rotation values {$[\alpha]_D^{25}$ *(synthetic)* = +22.6 (*c* 0.3, $CHCl_3$) $[\alpha]_D^{25}$ *(natural)* = +6.7 (*c* 0.18, $CHCl_3$)} was noted. This discrepancy may be due to the fact that the synthetic material was obtained in sufficient quantity whereas the natural product in minute quantity.

Scheme 15



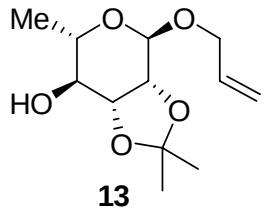
In context of the discrepancy between the magnitudes of specific rotations of the natural product and the synthetic material (**4**), the synthesis of the other possible diastereomer 3*R*, 4*R* multiplolide A (**3**) was felt even more important for the explicit establishment of relative and absolute configuration of the natural product. Synthesis of **3** was now planned from the advanced intermediate **38** and executed in our laboratory by my colleague. Comparison of the spectral and analytical data of **3** and **4** with the natural product unambiguously nominated **4** as the natural product.

Conclusion

Synthesis of Multiplolide A (**4**) was successfully achieved using RCM as a key reaction. Comparison of the spectral and analytical data of **4** and other possible diastereomer **3** with the natural product unequivocally designated **4** as the natural product and established the absolute stereochemistry of multiplolide A as 3*S*, 4*S*, 7*S*, 8*R*, and 10*R*. The attempts for RCM on substrates **6**, **11**, **32**, **33** proved to be failures and RCM of **35** produced undesired *cis* isomer (leading to the synthesis of diastereomer of **3**). Efforts to understand these results are in progress.

Experimental

Allyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (13)



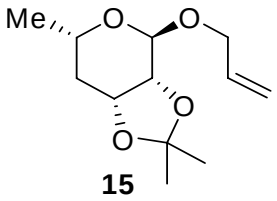
13

A mixture of L (–) rhamnose (10.0 g, 60.97 mmol), anhydrous sodium sulfate (20.0 g, 140.84 mmol), freshly distilled allyl alcohol (100 mL) and concentrated sulfuric acid (1 mL) was heated at 80 °C for 20 h. The reaction mixture was filtered through *Celite*, the filtrate passed through a bed of IR-400 resin and concentrated to afford the allyl pyranoside (11.2 g, 90%) as viscous oil (used for next step without further purification). The above product (11.2 g, 54.9 mmol), acetone (110 mL), 2,2-dimethoxypropane (22 mL, 179.38 mmol) and *p*-TSA (150 mg) were stirred at rt for 10 h, and triethylamine (4 mL) was introduced followed by concentration. The crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:5) to give **13** as colorless oil.

Yield	**:**	12.48 g, 84% (over two steps)
Mol. Formula	**:**	$C_{12}H_{20}O_5$
Mol. Weight	**:**	244
ESI-MS *m/z*	**:**	267 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 59.01; H, 8.20 % Found: C, 59.24; H, 8.05%
$[\alpha]_D^{25}$	**:**	–34.2 (*c* 1.3, $CHCl_3$); literature[18] $[\alpha]_D$ = –32
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3453, 2936, 1520, 1384, 1140, 1079, 1051, 929, 669 cm^{-1}
^{1}H NMR (200 MHz,	**:**	δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.35 (s, 3H), 1.52 (s, 3H),

$CDCl_3$)		3.38 (dd, *J* = 6.8, 9.2 Hz, 1H), 3.68 (dq, *J* = 6.2, 9.2 Hz, 1H), 4.0 (ddt, *J* = 1.4, 6.2, 12.8 Hz, 1H), 4.07 (br.d, *J* = 6.2 Hz, 1H), 4.14 (br.t, *J* = 5.6 Hz, 1H), 4.19 (ddt, *J* = 1.4, 5.2, 12.8 Hz, 1H), 4.99 (s, 1H), 5.21 (ddd, *J* = 1.4, 3.0, 10.3 Hz, 1H), 5.30 (ddd, *J* = 1.4, 3.0, 17.2 Hz,1H), 5.90 (dddd, *J* = 5.2, 6.2, 10.3, 17.2 Hz, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 17.3 (q), 26.1 (q), 27.9 (q), 65.7 (d), 67.8 (t), 74.3 (d), 75.8 (d), 78.5 (d), 96.1 (d), 109.3 (s), 117.6 (t), 133.6 (d)

Allyl 4,6-dideoxy-2,3-*O*-isopropylidene-*α*-L-*lyxo*-hexopyranoside (15)



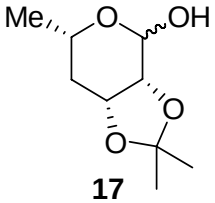
15

To a solution of **13** (5.0 g, 20.49 mmol) in dry THF (50 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 1.0 g, 25.0 mmol) followed by carbon disulfide (1.9 mL, 31.65 mmol) after 30 min. The stirring continued for 30 min and then methyl iodide (2.0 mL, 32.08 mmol) was introduced. After 2 h, reaction mixture was quenched by the addition of ice-water and repeatedly extracted with ethyl acetate. The combined organic extract was washed with water, dried over sodium sulfate and concentrated. The crude xanthate (6.5 g, 19.46 mmol) was dissolved in toluene (75 mL), degassed with Argon, AIBN (50 mg) and tri-*n*-butyltinhydirde (7.7 mL, 29.05 mmol) were added. The contents were heated under reflux for 10 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **15** as colorless oil.

Yield	**:**	3.8 g, 81% (over two steps)
Mol. Formula	**:**	$C_{12}H_{20}O_4$
Mol. Weight	**:**	228

ESI-MS *m/z*	**:**	251 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 63.16; H, 8.77% Found: C, 62.92; H, 8.49%
$[\alpha]_D^{25}$	**:**	–56.2 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3083, 2934, 1647, 1457, 1382, 1373, 1244, 1146, 1082, 997, 667 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.16 (d, *J* = 6.3 Hz, 3H), 1.28 (s, 3H), 1.35-1.42 (m, 1H), 1.46 (s, 3H), 1.80 (ddd, *J* = 2.3, 6.8, 13.1 Hz, 1H), 3.66-3.82 (m, 1H), 3.88 (br.d, *J* = 5.3 Hz, 1H), 3.94 (ddt, *J* = 1.4, 6.2, 12.9 Hz, 1H), 4.13 (ddt, *J* = 1.4, 5.2, 12.9 Hz, 1H), 4.25 (ddd, *J* = 5.5, 6.7, 12.2 Hz, 1H), 4.99 (s, 1H), 5.14 (ddd, *J* = 1.4, 3.0, 10.3 Hz, 1H), 5.23 (ddd, *J* = 1.4, 3.0, 17.2 Hz, 1H), 5.85 (dddd, *J* = 5.3, 6.2, 10.3, 17.2 Hz, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 21.2 (q), 26.3 (q), 28.2 (q), 36.1 (t), 62.1 (d), 67.8 (t), 70.9 (d), 72.7 (d), 96.8 (d), 108.6 (s), 117.3 (t), 134.0 (d)

4,6-Dideoxy-2,3-*O*-isopropylidene-α,β-L-*lyxo*-hexopyranose (17)



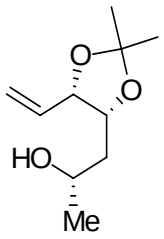
17

A mixture of **15** (2.5 g, 10.96 mmol), potassium *tert*-butoxide (1.6 g, 14.29 mmol) and DMSO (40 mL) was heated at 100 °C for 1 h, diluted with brine and repeatedly extracted with diethyl ether. The combined ether layer was washed with water, dried over sodium sulfate and concentrated. The residue (2.42 g, 10.61 mmol) was taken in acetone:water (9:1) mixture (50 mL) at 0 °C, yellow mercuric oxide (3.0

g, 13.89 mmol) and mercuric chloride (3.0 g, 11.07 mmol) were added over a period of 30 minutes. The stirring continued for 8 h at rt, filtered through *Celite* and the filtrate concentrated. The residue was partitioned between water and ethyl acetate and the organic layer was washed with saturated potassium iodide solution, brine, dried over sodium sulfate, filtered and concentrated. Purification of the crude on silica gel by eluting with ethyl acetate-light petroleum (1:6) furnished **17**.

Yield	**:**	1.32 g, 64% (over two steps)
Mol. Formula	**:**	$C_9H_{16}O_4$
Mol. Weight	**:**	188
ESI-MS *m/z*	**:**	211 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 57.45; H, 8.51% Found: C, 57.74; H, 8.37%
$[\alpha]_D^{25}$	**:**	+0.46 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3413, 2985, 2935, 1456, 1383, 1373, 1243, 1137, 1052, 668 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.21 (d, *J* = 6.3 Hz, 2.25H), 1.27 (d, *J* = 6.2 Hz, 0.75H), 1.35 (s, 2.25H), 1.37 (s, 0.75H), 1.42-1.50 (m, 1H), 1.52 (s, 2.25H), 1.54 (s, 0.75H), 1.82-1.93 (m, 1H), 3.44-3.60 (m, 0.25H), 3.74 (d, *J* = 3.4 Hz, 0.75H), 3.94-4.10 (m, 2H), 4.27-4.41 (m, 1H), 4.89 (dd, *J* = 2.3, 10.6 Hz, 0.25H), 5.42 (d, *J* = 3.2 Hz, 0.75H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 21.2 (q), 21.5 (q), 26.3 (q), 26.4 (q), 28.0 (q), 28.2 (q), 35.7 (t), 36.1 (t), 62.4 (d), 67.5 (d), 70.7 (d), 72.8 (d), 72.9 (d), 73.0 (d), 92.5 (d), 93.0 (d), 108.7 (s), 109.7 (s)

(2*S*,4*R*,5*S*)-4,5-*O*-isopropylidene-hept-6-ene-2-ol (7)



7

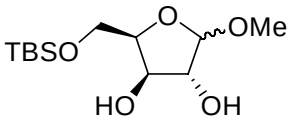
To a solution of **17** (1.0 g, 5.32 mmol) in THF: DMSO (4:1, 15 mL) at 0 ^{o}C was added methyltriphenylphosphorane ylide [generated by the action of *n*-butyllithium (8.49 mL, 20.21 mmol) with $Ph_3P^+CH_3I^-$ (8.60 g, 21.29 mmol) in anhydrous THF (40 mL) at 0 ^{o}C]. The reaction mixture was stirred at rt for 24 h, quenched with saturated ammonium chloride and filtered. The organic layer was separated and aqueous layer extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:6) to furnish **7**.

Yield	**:**	0.630 mg, 64%
Mol. Formula	**:**	$C_{10}H_{18}O_3$
Mol. Weight	**:**	186
ESI-MS *m/z*	**:**	209 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 64.52; H, 9.68% Found: C, 64.64; H, 9.82%
$[\alpha]_D^{25}$	**:**	+17.7 (*c* 0.8, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3436, 2988, 2935, 1645, 1456, 1381, 1372, 1166, 1040, 667 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.23 (d, *J* = 6.3 Hz, 3H), 1.38 (s, 3H), 1.42 (ddd, *J* = 3.0, 8.6, 14.3 Hz, 1H), 1.49 (s, 3H), 1.62 (ddd, *J* = 3.3, 9.8, 14.3 Hz, 1H), 2.08 (br. s, 1H), 3.93-4.12 (m, 1H), 4.43 (ddd, *J* = 3.3, 6.4, 9.8 Hz, 1H), 4.51-4.58 (m, 1H),

5.23 (ddd, *J* = 0.8, 1.7, 10.3 Hz, 1H), 5.30 (ddd, *J* = 1.0, 1.7, 17.2 Hz, 1H), 5.78 (ddd, *J* = 7.3, 10.3, 17.2 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 23.9 (q), 25.5 (q), 28.0 (q), 39.1 (t), 64.6 (d), 74.8 (d), 79.4 (d), 108.1 (s), 117.9 (t), 134.2 (d)

Methyl 5-*O*-tert-butyldimethylsilyl-α/β-D-xylofuranoside (19)



19

D-Xylose was converted to its methyl furanoside using literature procedure. To a solution of crude furanoside (10 g, 60.97 mmol), imidazole (4.97 g, 73.08 mmol) in DMF (60 mL) was added TBS-Cl (9.14 g, 60.93 mmol) in portions and the resulting mixture was stirred at room temperature for 36 h. The reaction mixture was poured on ice, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1) to furnish **19**.

Yield **:** 11.16 g, 66%

Mol. Formula **:** $C_{12}H_{26}O_5Si$

Mol. Weight **:** 278

ESI-MS *m/z* **:** 301 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 51.80; H, 9.35%

Found: C, 52.03; H, 9.17%

$[\alpha]_D^{25}$ **:** +11.8 (*c* 1.7, $CHCl_3$)

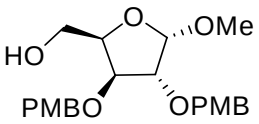
IR ($CHCl_3$) $\tilde{\nu}$ **:** 3422, 2931, 1255, 1099 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.09 (s, 6H), 0.89 (s, 9H), 2.57 (br. s, 1H), 3.37 (s, 1.8H), 3.46 (s, 1.2H), 3.79-4.32 (m, 5H), 4.80 (s, 0.6H),

4.89 (d, *J* = 4.3 Hz, 0.4H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ -5.7, -5.63, -5.58, -5.5, 18.0, 18.1, 25.6, 25.7, 55.1, 55.4, 62.7, 62.8, 76.9, 77.3, 77.6, 78.5, 80.1, 82.0, 101.5, 108.7

Methyl 2,3-di-*O*-(*p*-methoxybenzyl)-α-D-xylofuranoside (21α)



21α

To an ice-cooled solution of **19** (10 g, 35.97 mmol), in anhydrous DMF (75 mL) was added sodium hydride (60% dispersion in mineral oil, 4.31g, 107.75 mmol) in portion-wise manner. Stirring was continued at the same temperature for 1 h and then at rt for 3 h. The reaction mixture was cooled again to 0 °C and PMB-Br (18.3 mL, 126.18 mmol) was added in drop-wise manner. Reaction was allowed to attain room temperature and was stirred for 12 h. Reaction mixture was quenched by addition on ice, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude residue (16.6 g, 32.04 mmol) was taken in THF (150 mL) and treated with TBAF (1M solution in THF, 36.0 mL, 36.0 mmol). The reaction mixture was stirred for 16 h at rt and then concentrated under reduced pressure. The residue was chromatographed on silica gel by eluting with ethyl acetate-light petroleum (1:2) to afford both the anomers, **21α** and **21β**, which were characterized, and mixed for the next reaction (Yield: 10.35 g, 71% over two steps, after mixing both anomers).

Mol. Formula **:** $C_{22}H_{28}O_7$

Mol. Weight **:** 404

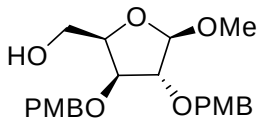
ESI-MS *m/z* **:** 427 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 65.35; H, 6.93%

Found: 65.62; H, 7.12%

$[\alpha]_D^{25}$	**:**	+42.4 (*c* 0.45, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3482, 2936, 1613, 1586, 1442, 1108, 1036 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 2.43 (br. s, 1H), 3.37 (s, 3H), 3.68-3.77 (br. m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.00 (dd, *J* = 4.3, 6.5 Hz, 1H), 4.13-4.21 (m, 1H), 4.39 (dd, *J* = 6.6, 7.6 Hz, 1H), 4.48, 4.65 (2d, *J* = 11.4 Hz, 2H), 4.51, 4.60 (2d, *J* =11.6 Hz, 2H), 4.77 (d, *J* = 4.2 Hz, 1H), 6.86, 6.88, 7.20, 7.30 (4d, *J* = 8.7Hz, 8H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 55.0 (q), 55.2 (q), 62.2 (t), 72.2 (t), 72.3 (t), 76.1 (d), 81.8 (d), 84.1 (d), 100.1 (d), 113.77 (d), 113.84 (d), 129.4 (d), 129.5 (s), 129.6 (s), 129.8 (d), 159.3 (s), 159.4 (s)

Methyl 2,3-di-*O*-(*p*-methoxybenzyl)-β-D-xylofuranoside (21β)



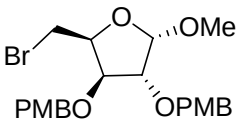
21β

Mol. Formula	**:**	$C_{22}H_{28}O_7$
Mol. Weight	**:**	404
ESI-MS *m/z*	**:**	427 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 65.35; H, 6.93% Found: C, 65.53; H, 7.09%
$[\alpha]_D^{25}$	**:**	-47.1 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3472, 2932, 1612, 1586, 1106, 1034 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 2.54 (br. s, 1H), 3.40 (s, 3H), 3.73-3.77 (br. m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.06 (dd, *J* = 1.8, 3.8 Hz, 1H), 4.14 (dd, *J* = 3.8, 6.7 Hz, 1H), 4.24-4.32 (m, 1H), 4.40, 4.57 (2d, *J* = 11.6Hz, 2H), 4.46, 4.51 (2d, *J* = 14.5 Hz, 2H), 4.87 (d, *J* = 1.8 Hz, 1H), 6.86, 6.89 (2d, *J* = 8.6 Hz, 4H), 7.21, 7.25 (2d, *J* = 8.2 Hz, 4H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 55.03 (q), 55.04 (q), 55.4 (q), 62.1 (t), 71.6 (t), 71.9 (t), 80.4 (d), 82.2 (d), 86.6 (d), 107.8 (d), 113.66 (d), 113.69 (d), 129.3 (d), 129.4 (s), 129.4 (d), 159.2 (s)

Methyl 5-deoxy-5-bromo-2,3-di-*O*-(4-methoxybenzyl)-α-D-xylofuranoside (22α)



22α

To a solution of **21** (5.2 g, 12.87 mmol), TPP (6.74 g, 25.73 mmol) and triethylamine (5.4 mL, 38.82 mmol) in dry DCM (65 mL) was added carbon tetrabromide (7.69 g, 23.16 mmol). The reaction mixture was stirred at rt for 40 h. DCM was evaporated under reduced pressure and the crude residue was partitioned between water and ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by column chromatography on silica gel using ethyl acetate-light petroleum (1:6) to furnish both the anomers **22α** and **22β**. These were characterized separately and again mixed for the next reaction. (Yield: 3.80 g, 63%, after mixing both anomers).

Mol. Formula **:** $C_{22}H_{27}BrO_6$

Mol. Weight **:** 466

ESI-MS *m/z* **:** 489 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 56.65; H, 5.79%

Found: C, 56.84; H, 6.01%

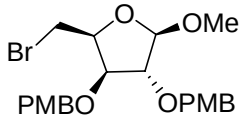
$[\alpha]_D^{25}$: +57.7 (*c* 0.4, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 2998, 1612, 1585, 1464 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.38 (dd, *J* = 7.3, 10.6 Hz, 1H) 3.41 (s, 3H), 3.55 (dd, *J* = 5.2, 10.6 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.96 (dd, *J* = 4.2, 5.2 Hz, 1H), 4.20 (dd, *J* = 5.3, 6.7 Hz, 1H), 4.35-4.45 (m, 1H), 4.50, 4.56 (2d, *J* = 11.9 Hz, 2H), 4.50, 4.59 (2d, *J* =11.6 Hz, 2H), 4.80 (d, *J* = 4.2 Hz, 1H), 6.87, 6.88, 7.22, 7.28 (4d, *J* = 8.7 Hz, 8H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 31.0 (t), 55.2 (q), 55.4 (q), 72.2 (t), 72.3 (t), 76.7 (d), 81.2 (d), 83.3 (d), 100.8 (d), 113.75 (d), 113.77 (d), 129.4 (d), 129.5 (s), 129.8 (d), 159.3 (s), 159.4 (s)

Methyl 5-deoxy-5-bromo-2,3-di-*O*-(4-methoxybenzyl)-β-D-xylofuranoside (22β)



22β

Mol. Formula : $C_{22}H_{27}BrO_6$

Mol. Weight : 466

ESI-MS *m/z* : 489 $[M+Na]^+$

Elemental Analysis : Calcd: C, 56.65; H, 5.79%

Found: C, 56.77; H, 5.58%

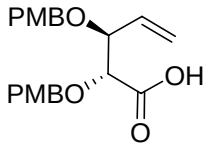
$[\alpha]_D^{25}$: -26.2 (*c* 0.45, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 2928, 1612, 1586 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 3.41 (s, 3H), 3.52 (dd, *J* = 7.2, 10.3 Hz, 1H), 3.60 (dd, *J* = 6.1, 10.2 Hz, 1H), 3.81 (s, 6H), 3.96 (dd, *J* = 1.1, 2.5 Hz, 1H), 4.04 (dd, *J* =2.7, 5.9 Hz, 1H), 4.40 (dd, *J* = 6.2, 7.2 Hz, 1H), 4.40, 4.53 (2d, *J* = 11.6 Hz, 2H), 4.43, 4.47 (2d, *J* =11.9 Hz, 2H), 4.90 (d, *J* = 1.0 Hz, 1H), 6.87, 6.88 (2d, *J* = 8.7Hz, 4H), 7.22, 7.24 (2d, *J* = 8.9 Hz, 4H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 31.6 (t), 55.2 (q), 55.7 (q), 71.7 (t), 72.2 (t), 81.2 (d), 81.5 (d), 86.3 (d), 108.2 (d), 113.77 (d), 113.82 (d), 129.3 (s), 129.4 (d), 129.6 (d), 159.4 (s)

(2*R*,3*S*)-2,3-bis(4-methoxybenzyloxy)pent-4-enoic acid (8)



8

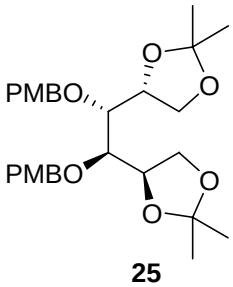
To a solution of **22** (2.0 g, 4.29 mmol) in ethanol (40 mL) was added excess of activated zinc dust (8 g) and the suspension was heated to reflux for 0.5 h. After cooling to rt, the suspension was filtered through the pad of *Celite* and the filtrate was concentrated under reduced pressure to afford the crude aldehyde (1.4 g), which was used as such for the next reaction. To a solution of aldehyde (1.4 g 3.93 mmol) in ^{t}BuOH:H_2O (3:1, 30 mL) was added successively $NaH_2PO_4.2H_2O$ (1.84 g, 11.79 mmol), 2-methy-2-butene (7 mL) and sodium chlorite (1.06 g, 11.78 mmol). The reaction was stirred for 1 h at rt and was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined extract was dried over sodium sulfate and concentrated to afford a crude product, which was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1.5) to afford **8** as colorless oil.

Yield **:** 1.14 g, 71% (over two steps)

Mol. Formula **:** $C_{21}H_{24}O_6$

Mol. Weight	**:**	372
ESI-MS *m/z*	**:**	395 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 67.74; H, 6.45% Found: C, 68.00; H, 6.30%
$[\alpha]_D^{25}$	**:**	+52.7 (*c* 0.7, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3394, 2936, 1726, 1612, 1586, 1249 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$)	**:**	δ 3.76 (s, 3H), 3.78 (s, 3H), 3.96 (d, *J* = 3.5 Hz, 1H), 4.13 (dd, *J* = 3.5, 7.5 Hz, 1H), 4.30, 4.46, 4.55, 4.68 (4d, *J* = 11.5 Hz, 4H), 5.29-5.34 (m, 2H), 5.87 (ddd, *J* = 7.5, 10.5, 17.3 Hz, 1H), 6.81, 6.84, 7.17, 7.23 (4d, *J* = 8.5 Hz, 8H)
^{13}C NMR (100 MHz, $CDCl_3$)	**:**	δ 55.07, 55.10, 70.4, 73.1, 79.7, 80.1, 113.7, 113.8, 119.7, 128.7, 129.4, 129.5, 129.9, 134.0, 159.2, 159.5, 173.8

1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-(4-methoxybenzyl)-D-mannitol (25)



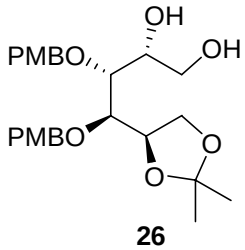
25

To a solution of 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**24)** (15.0 g, 57.25 mmol) in DMF (150 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 6.87 g, 171.75 mmol). After 1 h, 4-methoxybenzyl bromide (19.9 mL, 137.21 mmol) was added and stirring continued for 36 h at room temperature. The reaction mixture was decomposed with ice-water and repeatedly extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate

and concentrated to a syrup, which was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to furnish **25**.

Yield	**:**	25.3 g, 88%
Mol. Formula	**:**	$C_{28}H_{38}O_8$
Mol. Weight	**:**	502
ESI-MS *m/z*	**:**	525 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 66.93; H, 7.57 % Found: C, 67.12; H, 7.47 %
$[\alpha]_D^{25}$	**:**	+33.45 (*c* 1.5, $CHCl_3$); literature[27] $[\alpha]_D$ = +38 (*c* 0.5, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2936, 1612, 1514, 1382, 1372, 1249, 1070, 1036, 667 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.33 (s, 6H), 1.41 (s, 6H), 3.71-3.83 (m, 4H), 3.79 (s, 6H), 3.96 (dd, *J* = 6.2, 8.3 Hz, 2H), 4.13-4.23 (m, 2H), 4.60 (s, 4H), 6.83, 7.22 (2d, *J* = 8.7 Hz, 8H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 25.2 (q), 26.6 (q), 54.9 (q), 66.7 (t), 74.0 (t), 75.8 (d), 79.4 (d), 108.3 (s), 113.6 (d), 129.5 (d), 130.3 (s), 159.2 (s)

1,2-*O*-Isopropylidene-3,4-di-*O*-(4-methoxybenzyl)-D-mannitol (26)



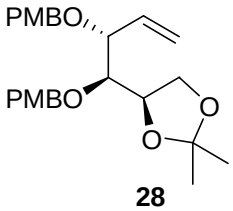
26

A solution of **25** (10.0 g, 19.92 mmol), PPTS (0.5 g) and methanol (100 mL) was stirred at room temperature for 12 h, basified with triethylamine and concentrated. The crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:2) to afford **26** and some of starting material **25** being recovered (3.2 g).

Yield	**:**	4.15 g, 66% (based on recovered starting material)
Mol. Formula	**:**	$C_{25}H_{34}O_8$
Mol. Weight	**:**	462
ESI-MS *m/z*	**:**	485 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 64.93; H, 7.35% Found: C, 64.63; H, 7.05%
$[\alpha]_D^{25}$	**:**	+9.2 (*c* 1, $CHCl_3$)
IR (Neat) $\tilde{\nu}$	**:**	3449, 2986, 2935, 1613, 1514, 1463, 1422, 1381, 1371, 1302, 1250, 921, 851, 823 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.34 (s, 3H), 1.43 (s, 3H), 3.55-3.75 (m, 4H), 3.78 (s, 6H), 3.80-3.92 (m, 2H), 4.02 (dd, *J* = 6.2, 8.3 Hz, 1H), 4.21-4.30 (m, 1H), 4.50, 4.57 (2d, *J* = 11.3 Hz, 2H), 4.60, 4.67 (2d, *J* = 11.4 Hz, 2H), 6.84, 6.85, 7.22, 7.23 (4d, *J* = 8.6 Hz, 8H)
^{13}C NMR (50 MHz,	**:**	δ 25.0 (q), 26.5 (q), 55.0 (q), 63.4 (t), 66.4 (t), 71.0 (d), 73.4 (t), 73.9 (t), 75.8 (d), 78.2 (d), 78.7 (d), 108.3 (s),

113.7 (d), 129.7 (d), 129.9 (s), 130.0 (s), 159.2 (s), 159.3 (s)

(3*R*,4*S*,5*R*)-2,3-bis(4-methoxybenzyloxy)-5,6-*O*-isopropylidene-hex-1-ene (28)



28

To a solution of **26** (5.0 g, 10.82 mmol) in DCM (50 mL) at 0 ^{o}C was added Et_3N (4.5 mL, 32.34 mmol) followed by methanesulfonyl chloride (2.1 mL, 27.20 mmol). After 1 h at rt, the reaction mixture was partitioned between water and DCM. The organic layer was dried over sodium sulfate and concentrated. The crude dimesylate **27** (5.81 g, 9.40 mmol) and NaI (14.10 g, 94.0 mmol) were refluxed in MEK (50 mL). After 10 h, the solvent was removed and the residue dissolved in ethyl acetate. The organic layer was washed with saturated sodium thiosulfate, water, dried over sodium sulphate, evaporated and the residue purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **28**.

Yield : 3.15 g, 68% (over two steps)

Mol. Formula : $C_{25}H_{32}O_6$

Mol. Weight : 428

ESI-MS *m/z* : 451 $[M+Na]^+$

Elemental Analysis : Calcd: C, 70.09; H, 7.48%

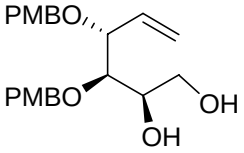
Found: C, 70.31; H, 7.20%

$[\alpha]_D^{25}$: +7.7 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 2987, 2935, 1612, 1586, 1464, 1442, 1380, 1370, 1302, 1218, 1173, 1036, 848, 823 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.32 (s, 3H), 1.40 (s, 3H), 3.69-3.73 (m, 1H), 3.79 (2s, 6H), 3.80-3.93 (m, 3H), 4.18 (ddd, *J* = 3.8, 6.3, 7.5 Hz, 1H), 4.27 (d, *J* = 11.5 Hz, 1H), 4.44-4.69 (m, 3H), 5.13-5.38 (m, 2H), 5.85 (ddd, *J* = 7.2, 9.9, 17.7 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 4H), 7.20, 7.23 (2d, *J* = 8.6 Hz, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 25.3 (q), 26.5 (q), 55.1 (q), 65.4 (t), 70.2 (t), 74.5 (t), 76.4 (d), 80.1 (d), 80.8 (d), 108.0 (s), 113.5 (d), 113.6 (d), 118.1 (t), 129.4 (d), 129.5 (d), 130.2 (s), 130.6 (s), 135.7 (d), 159.09 (s), 159.13 (s)

(2*R*,3*R*,4*R*)-3,4-bis(4-methoxybenzyloxy)hex-5-ene-1,2-diol (29)



29

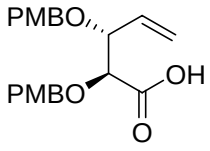
Compound **28** (3.5 g, 8.18 mmol), PPTS (0.2 g) and methanol (35 mL) were stirred for 36 h at rt and worked up as described above (see preparation of compound **26**) to give **29**.

Yield	**:**	2.52 g, 79%
Mol. Formula	**:**	$C_{22}H_{28}O_6$
Mol. Weight	**:**	388
Elemental Analysis	**:**	Calcd: C, 68.04; H, 7.22% Found: C, 67.77; H, 7.40%
$[\alpha]_D^{25}$	**:**	+9.5 (*c* 0.7, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3436, 3007, 2932, 1612, 1586, 1514, 1464, 1302, 1248, 1174, 1035, 823 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 3.57-3.79 (m, 5H), 3.80 (s, 3H), 3.81 (s, 3H), 3.97-4.17 (m, 2H), 4.30, 4.59 (2d, *J* = 11.5 Hz, 2H), 4.50, 4.60 (2d, *J* = 11.1 Hz, 2H), 5.30-5.45 (m, 2H), 5.93 (ddd, *J* = 7.1, 10.9, 16.8 Hz, 1H), 6.84, 6.86, 7.20, 7.21 (4d, *J* = 8.7 Hz, 8H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 55.0 (q), 63.1 (t), 70.3 (t), 71.1 (d), 73.4 (t), 79.6 (d), 79.8 (d), 113.6 (d), 113.7 (d), 118.8 (t), 129.4 (d), 129.6 (d), 129.9 (s), 134.5 (d), 159.2 (s)

(2*S*,3*R*)-2,3-bis(4-methoxybenzyloxy)pent-4-enoic acid (9)



9

A solution of **29** (1.4 g, 3.61 mmol), sodium metaperiodate adsorbed on silica gel (12 g containing 2.45 g of $NaIO_4$) in DCM (25 mL) was stirred at rt for 1 h, filtered and concentrated to afford aldehyde **30** (1.21 g, 3.4 mmol), which was dissolved in ^{t}BuOH:H_2O (3:1, 30 mL). To this solution were successively added $NaH_2PO_4.2H_2O$ (1.59 g, 10.19 mmol), 2-methy-2-butene (7 mL) and sodium chlorite (918 mg, 10.2 mmol). The reaction was stirred for 1 h at rt and was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined extract was dried over sodium sulfate and concentrated to afford a crude product, which was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1.5) to afford **9** as colorless oil.

Yield **:** 974 mg, 73% (over two steps)

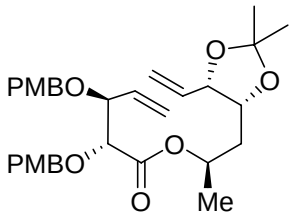
Mol. Formula **:** $C_{21}H_{24}O_6$

Mol. Weight **:** 372

ESI-MS *m/z* **:** 395 $[M+Na]^+$

Elemental Analysis	**:**	Calcd: C, 67.74; H, 6.45% Found: C, 67.89; H, 6.51%
$[\alpha]_D^{25}$	**:**	–46.8 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3394, 1724, 1612, 1514, 1249, 1174, 1036, 668 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 3.78 (s, 3H), 3.80 (s, 3H), 3.97 (d, *J* = 3.4 Hz, 1H), 4.11-4.16 (m, 1H), 4.30, 4.56 (2d, *J* = 11.5 Hz, 2H), 4.49, 4.67 (2d, *J* = 11.6 Hz, 2H), 5.29-5.38 (m, 2H), 5.79-5.96 (m, 1H), 6.82, 6.85, 7.17, 7.23 (4d, *J* = 8.7 Hz, 8H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 55.11 (q), 55.14 (q), 70.5 (t), 73.2 (t), 79.7 (d), 80.1 (d), 113.7 (d), 113.8 (d), 119.8 (t), 128.7 (s), 129.4 (s), 129.5 (d), 129.9 (d), 134.0 (d), 159.3 (s), 159.6 (s), 173.4 (s)

Synthesis of 6



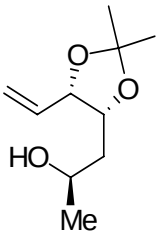
6

To a solution of **7** (200 mg, 1.07 mmol), **8** (500 mg, 1.34 mmol) and TPP (563 mg, 2.15 mmol) in THF (8 mL) at 0 °C was added DEAD (0.34 mL, 2.16 mmol). Stirring was continued at 0 ^oC for 1 h and then at rt for next 2 h at which time it was concentrated and the crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **6**.

Yield	**:**	423 mg, 73%
Mol. Formula	**:**	$C_{31}H_{40}O_8$

Mol. Weight	**:**	540
ESI-MS *m/z*	**:**	563 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 68.89; H, 7.41% Found: C, 69.14; H, 7.67%
$\mathbf{[\alpha]_D^{25}}$	**:**	+47.7 (*c* 1.4, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2936, 1736, 1613, 1586, 1248, 1037 cm^{-1}
^{1}**H NMR** (200 MHz, $CDCl_3$)	**:**	δ 1.25 (d, *J* = 6.3 Hz, 3H), 1.31 (s, 3H), 1.47 (s, 3H), 1.53 (ddd, *J* = 5.3, 7.6, 14.0 Hz, 1H), 1.86 (ddd, *J* = 6.6, 8.7, 14.0 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.93 (d, *J* = 4.8 Hz, 1H), 4.11 (dd, *J* = 4.8, 7.7 Hz, 1H), 4.13-4.23 (m, 1H), 4.33, 4.42, 4.54, 4.70 (4d, *J* = 11.6 Hz, 4H), 4.44 (dd, *J* = 5.3, 13.7 Hz, 1H), 5.01-5.17 (m, 1H), 5.20-5.35 (m, 4H), 5.65-5.96 (m, 2H), 6.82, 6.83, 7.19, 7.24 (4d, *J* = 8.8 Hz, 8H)
^{13}**C NMR** (50 MHz, $CDCl_3$)	**:**	δ 19.6 (q), 25.6 (q), 28.1 (q), 36.3 (t), 55.0 (q), 69.4 (d), 70.3 (t), 72.4 (t), 74.5 (d), 79.4 (d), 80.5 (d), 80.6 (d), 108.3 (s), 113.4 (d), 113.5 (d), 118.5 (t), 119.3 (t), 129.1 (d), 129.2 (s), 129.6 (d), 129.9 (s), 133.9 (d), 134.3 (d), 158.9 (s), 159.9 (s), 169.6 (s)

(2*R*,4*R*,5*S*)-4,5-*O*-isopropylidene-hept-6-ene-2-ol (7-*epi*)



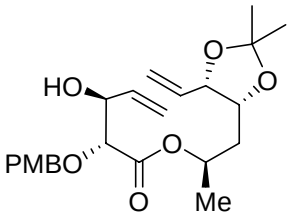
7-epi

To a solution of **6** (50 mg, 0.092 mmol) in moist EtOH (2 mL) was added $LiOH.H_2O$ (7 mg, 0.17 mmol) and the reaction mixture stirred at rt for 0.5 h and

concentrated. The residue was purified on silica gel by eluting with ethyl acetate- light petroleum (1:6) to furnish **7-*epi*** as colorless oil.

Yield	**:**	18 mg, 81%
Mol. Formula	**:**	$C_{10}H_{18}O_3$
Mol. Weight	**:**	186
ESI-MS *m/z*	**:**	209 $[M+Na]^+$
$[\alpha]_D^{25}$	**:**	+8.0 (*c* 0.6, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.20 (d, *J* = 6.2 Hz, 3H), 1.38 (s, 3H), 1.42-1.51 (m, 1H), 1.52 (s, 3H), 1.56-1.64 (m, 1H), 3.93-4.09 (m, 1H), 4.36 (ddd, *J* = 3.6, 6.3, 10.0 Hz, 1H), 4.56 (dd, *J* = 6.5, 7.5 Hz, 1H), 5.24-5.37 (m, 2H), 5.80 (ddd, *J* = 7.5, 10.0, 17.4 Hz, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 23.4 (q), 25.6 (q), 28.0 (q), 39.0 (t), 67.6 (d), 78.4 (d), 79.8 (d), 109.0 (s), 118.7 (t), 133.9 (d)

Synthesis of 32

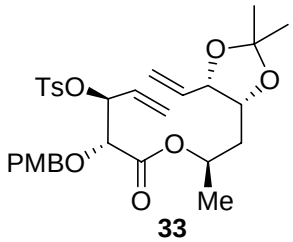


32

To a solution of **6** (350 mg, 0.65 mmol) in DCM (30 mL) at 0 °C was added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7) buffer (12 mL) and DDQ (700 mg, 3.08 mmol). The reaction was allowed to warm to rt. After 4 h at rt, the reaction mixture was filtered through a *Celite* pad and layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:6) to afford **32**, some starting material being recovered (110 mg).

Yield	**:**	104 mg, 56% (based on recovered starting material)
Mol. Formula	**:**	$C_{23}H_{32}O_7$
Mol. Weight	**:**	420
ESI-MS *m/z*	**:**	443 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 65.71; H, 7.62% Found: C, 65.48; H, 7.50%
$[\alpha]_D^{25}$	**:**	+37.7 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3565, 3464, 2988, 1741, 1613, 1586, 1250, 1100, 1038 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$)	**:**	δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.57-1.62 (m, 1H), 1.86 (ddd, *J* = 8.0, 9.0, 14.6 Hz, 1H), 2.85 (br. d, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.88 (d, *J* = 4.5 Hz, 1H), 4.22 (ddd, *J* = 4.0, 6.0, 9.3 Hz, 1H), 4.36-4.40 (br. m, 1H), 4.43, 4.72 (2d, *J* = 11.4 Hz, 2H), 4.51 (dd, *J* = 6.2, 7.8 Hz, 1H), 5.10-5.18 (m, 1H), 5.20-5.37 (m, 4H), 5.76 (ddd, *J* = 7.8, 10.3, 17.1 Hz, 1H), 5.87 (ddd, *J* = 5.8, 10.6, 17.1 Hz, 1H), 6.86, 7.25 (2d, *J* = 8.6 Hz, 4H)
^{13}C NMR (100 MHz, $CDCl_3$)	**:**	δ 20.2 (q), 25.5 (q), 28.0 (q), 36.6 (t), 55.1 (q), 70.1 (d), 72.3 (t), 73.2 (d), 75.3 (d), 79.6 (d), 80.4 (d), 108.6 (s), 113.7 (d), 116.9 (t), 118.7 (t), 129.0 (s), 129.8 (d), 134.0 (d), 136.2 (d), 159.5 (s), 169.8 (s)

Synthesis of 33

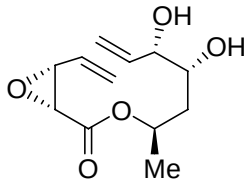


33

A solution of **32** (100 mg, 0.24 mmol), di-isopropylethylamine (120 μL, 0.71 mmol), *p*-toluene sulfonyl chloride (136 mg, 0.71 mmol) and DMAP (27 mg, 0.22 mmol) in dry DCM (5 mL) was stirred at rt for 36 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:6) to furnish the tosyl diene **33**.

Yield	**:**	72 mg, 53%
Mol. Formula	**:**	$C_{30}H_{38}O_9S$
Mol. Weight	**:**	574
Elemental Analysis	**:**	Calcd: C, 62.72; H, 6.62% Found: C, 62.94; H, 6.55%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.25 (d, *J* = 6.4 Hz, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.56 (ddd, *J* = 4.9, 6.7, 14.2 Hz, 1H), 1.89 (ddd, *J* = 6.4, 9.1, 14.2 Hz, 1H), 2.41 (s, 3H), 3.80 (s, 3H), 3.95 (d, *J* = 5.3 Hz, 1H), 4.17-4.28 (m, 1H), 4.34, 4.61 (2d, *J* = 11.5 Hz, 2H), 4.51 (dd, *J* = 6.3, 7.3 Hz, 1H), 5.08 (q, *J* = 6.4Hz, 1H), 5.17-5.36 (m, 5H), 5.67-5.87 (m, 2H), 6.82, 7.15 (2d, *J* = 8.6 Hz, 4H), 7.24, 7.73 (2d, *J* = 8.3 Hz, 4H)

Synthesis of 35

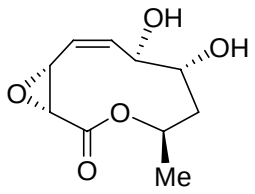


35

A solution of **33** (65 mg, 113 μmol) and trifluroacetic acid (0.05 mL) in DCM (5 mL) was stirred at rt for 35 h. Di-isopropylethylamine (0.5 mL) was introduced to basify the reaction mixture and stirred for 0.5 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1.5) to afford the epoxide diene **35**.

Yield	**:**	14 mg, 51%
Mol. Formula	**:**	$C_{12}H_{18}O_5$
Mol. Weight	**:**	242
ESI-MS *m/z*	**:**	265 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 59.50; H, 7.44% Found: C, 59.52; H, 7.31%
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.33 (d, *J* = 6.4 Hz, 3H), 1.71 (ddd, *J* = 3.7, 6.4, 14.7 Hz, 1H), 1.80 (ddd, *J* = 6.9, 9.2, 14.7 Hz, 1H), 3.62 (dd, *J* = 4.6, 7.8 Hz, 1H), 3.65 (d, *J* = 4.6 Hz, 1H), 3.76 (ddd, *J* = 3.7, 4.1, 9.2 Hz, 1H), 3.81 (br. s, 1H), 4.09-4.11 (m, 1H), 5.18-5.25 (m, 1H), 5.28 (dt, *J* = 1.3, 10.5 Hz, 1H), 5.34 (dt, *J* = 1.4, 17.4 Hz, 1H), 5.46 (br. d, 10.1 Hz, 1H), 5.64 (dd, *J* = 0.9, 17.4 Hz, 1H), 5.79 (ddd, *J* = 7.8, 10.1, 17.4 Hz, 1H), 5.88 (ddd, *J* = 6.4, 10.5, 17.4 Hz, 1H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 20.2 (q), 37.8 (t), 54.3 (d), 57.7 (d), 71.4 (d), 71.6 (d), 75.9 (d), 118.0 (t), 123.3 (t), 130.6 (d), 135.9 (d), 167.3 (s)

Synthesis of 36

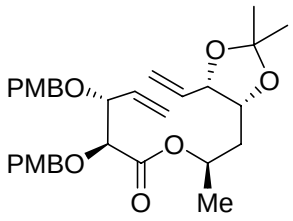


36

To a thoroughly degassed solution of **35 (**12 mg, 49.59 μmol) in anhydrous DCM (15 mL) was added Grubbs' 2nd Generation catalyst (3 mg, 3.42 μmol) under argon atmosphere and the resulting solution was heated to reflux for 1 h. Volatiles were removed under reduced pressure and the residue was purified on silica gel by eluting with ethyl acetate-light petroleum (2:1) to furnish **36**.

Yield	**:**	4 mg, 38%
Mol. Formula	**:**	$C_{10}H_{14}O_5$
Mol. Weight	**:**	214
ESI-MS *m/z*	**:**	237 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 56.07; H, 6.54% Found: C, 55.85; H, 6.71%
$[\alpha]_D^{25}$	**:**	-13.5 (*c* 0.15, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3426, 1755, 1057, 1029 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.39 (d, *J* = 6.9 Hz, 3H), 1.62 (dt, *J* = 2.3, 15.2 Hz, 1H), 2.15 (ddd, *J* = 4.6, 11.9, 15.2 Hz, 1H), 3.79 (d, *J* = 4.6 Hz, 1H), 3.82 (d, *J* = 4.6 Hz, 1H), 4.22 (ddd, *J* = 2.8, 3.2, 11.9 Hz, 1H), 4.62-4.68 (m, 1H), 5.15-5.21 (m, 1H), 5.84-5.87 (m, 2H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 17.7 (q), 35.8 (t), 51.6 (d), 54.9 (d), 68.8 (d), 69.2 (d), 70.6 (d), 126.2 (d), 131.3 (d), 166.5 (s)

Synthesis of 11



11

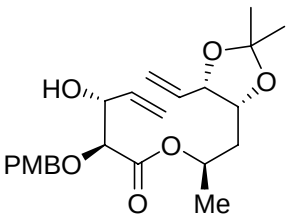
To a solution of **7** (200 mg, 1.07 mmol), **9** (500 mg, 1.34 mmol) and TPP (563 mg, 2.15 mmol) in THF (8 mL) at 0 °C was added DEAD (0.34 mL, 2.16 mmol). Stirring was continued at 0 °C for 1 h and then at rt for next 2 h at which time it was concentrated and the crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **11**.

Yield	**:**	467 mg, 80%
Mol. Formula	**:**	$C_{31}H_{40}O_8$
Mol. Weight	**:**	540
ESI-MS *m/z*	**:**	563 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 68.89; H, 7.41% Found: C, 69.02; H, 7.54%
$[\alpha]_D^{25}$	**:**	–38.9 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2934, 1736, 1612, 1513, 1464, 1381, 1249, 1173, 1037, 667 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.20 (d, *J* = 6.3 Hz, 3H), 1.32 (s, 3H), 1.47 (s, 3H), 1.54 (ddd, *J* = 4.9, 6.6, 14.0 Hz, 1H), 1.86 (ddd, *J* = 6.6, 9.1, 14.0 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.92 (d, *J* = 4.7 Hz, 1H), 4.09 (br. dd, *J* = 4.7, 7.9 Hz, 1H), 4.17 (ddd, *J* = 5.0, 6.0, 9.1 Hz, 1H), 4.31, 4.40, 4.54, 4.69 (4d, *J* = 11.7 Hz, 4H), 4.48 (br. dd, *J* = 6.3, 7.7 Hz, 1H), 5.10 (q, *J* = 6.3 Hz, 1H), 5.20-5.36 (m, 4H), 5.66-5.96

(m, 2H), 6.81, 6.83, 7.19, 7.24 (4d, *J* = 8.7 Hz, 8H)

^{13}C NMR (100 MHz, $CDCl_3$) **:** δ 19.7 (q), 25.7 (q), 28.3 (q), 36.5 (t), 55.2 (q), 69.5 (d), 70.4 (t), 72.6 (t), 74.9 (d), 79.6 (d), 80.5 (d), 80.8 (d), 108.5 (s), 113.6 (d), 113.7 (d), 118.7 (t), 119.4 (t), 129.4 (d), 129.5 (s), 129.7 (d), 130.1 (s), 134.0 (d), 134.6 (d), 159.1 (s), 159.4 (s), 169.6 (s)

Synthesis of 37



37

To a solution of **11** (400 mg, 0.74 mmol) in DCM (35 mL) at 0 °C was added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7) buffer (15 mL) and DDQ (800 mg, 3.52 mmol). The reaction was allowed to warm to room temperature. After 4 h at rt, it was filtered through *Celite* and layers separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over sodium sulphate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:6) to afford unreacted **11** (94 mg) and **37**.

Yield **:** 162 mg, 68% (based on recovered starting material)

Mol. Formula **:** $C_{23}H_{32}O_7$

Mol. Weight **:** 420

ESI-MS *m/z* **:** 443 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 65.71; H, 7.62%

Found: C, 65.95; H, 7.80%

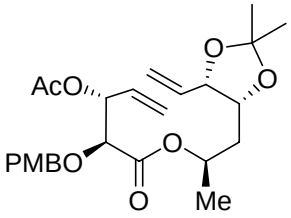
$[\alpha]_D^{25}$ **:** +4.3 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$ **:** 3436, 2925, 2854, 1744, 1615, 1518, 1459, 1379, 1250, 1171, 1097, 1037 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.27 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H), 1.48 (s, 3H), 1.58 (ddd, *J* = 4.6, 5.8, 14.2 Hz, 1H), 1.88 (ddd, *J* = 7.2, 9.0, 14.2 Hz, 1H), 2.68 (br. s, 1H), 3.79 (s, 3H), 3.87 (d, *J* = 4.8 Hz, 1H), 4.22 (ddd, *J* = 4.6, 6.0, 9.0 Hz, 1H), 4.32-4.36 (m, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.50 (br. dd, *J* = 6.2, 7.6 Hz, 1H), 4.69 (d, *J* = 11.2 Hz, 1H), 5.12-5.39 (m, 5H), 5.69-5.94 (m, 2H), 6.86, 7.25 (2d, *J* = 8.7 Hz, 4H)

^{13}C NMR (125 MHz, $CDCl_3$) **:** δ 20.0 (q), 25.6 (q), 28.2 (q), 36.6 (t), 55.2 (q), 70.0 (d), 72.5 (t), 73.4 (d), 75.1 (d), 79.7 (d), 80.7 (d), 108.6 (s), 113.9 (d), 117.2 (t), 118.7 (t), 128.9 (s), 129.9 (d), 134.0 (d), 136.0 (d), 159.6 (s), 169.9 (s)

Synthesis of 40



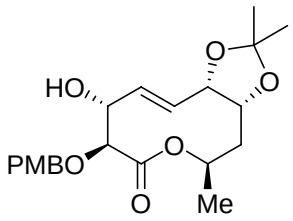
40

To a solution of **37** (20 mg, 47.6 μmol) and pyridine (15.4 μL, 0.19 mmol) in dry DCM (2 mL) was added acetic anhydride (6.7 μL, 71.4 μmol) at 0 ^{0}C and then the reaction mixture was stirred at rt for 3 h. Water was added to the reaction mixture and aqueous layer was extracted with DCM. Combined organic layer was thoroughly washed with water, dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to furnish the acetate derivative **40**.

Yield **:** 19 mg, 86%

Mol. Formula	**:**	$C_{25}H_{34}O_8$
Mol. Weight	**:**	462
Elemental Analysis	**:**	Calcd: C, 64.92; H, 7.36% Found: C, 64.69; H, 7.14%
$[\alpha]_D^{25}$	**:**	-14.47 (*c* 1.3, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.25 (d, *J* = 6.1 Hz, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.58 (ddd, *J* = 4.8, 6.6, 14.0 Hz, 1H), 1.81 (ddd, *J* = 6.7, 9.1, 14.0 Hz, 1H), 2.07 (s, 3H), 3.81 (s, 3H), 4.01 (d, *J* = 4.2 Hz, 1H), 4.19 (ddd, *J* = 4.6, 6.1, 9.1 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.53 (dd, *J* = 6.2, 7.6 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 5.06- 5.19 (m, 1H), 5.24-5.30 (m, 3H), 5.37-5.39 (m, 1H), 5.58-5.63 (m, 1H), 5.79 (ddd, *J* = 7.7, 10.2, 17.1 Hz, 1H) 5.87 (ddd, *J* = 6.6, 10.4, 17.2 Hz, 1H), 6.87, 7.26 (2d, *J* = 8.7 Hz, 4H)
^{13}C NMR (100 MHz, $CDCl_3$)	**:**	δ 19.6 (q), 20.9 (q), 25.7 (q), 28.2 (q), 36.5 (t), 55.2 (q), 70.0 (d), 72.5 (t), 74.3 (d), 74.9 (d), 78.4 (d), 79.6 (d), 108.6 (s), 113.8 (d), 118.8 (t), 119.1 (t), 128.9 (s), 129.8 (d), 132.1 (d), 133.9 (d), 159.5 (s), 168.8 (s), 169.7 (s)

Synthesis of 38



38

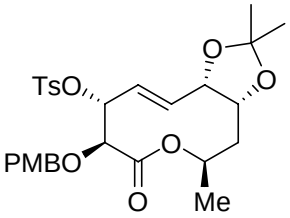
A degassed solution of **37** (124 mg, 0.3 mmol) and Grubbs' 2nd Generation catalyst (7 mg, 8 μmol) in dry benzene (150 mL) was heated to reflux under argon atmosphere for 6 h and then concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:4) to furnish compound **38**.

Yield	**:**	74 mg, 64%
Mol. Formula	**:**	$C_{21}H_{28}O_7$
Mol. Weight	**:**	392
ESI-MS *m/z*	**:**	415 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 64.29; H, 7.14% Found: C, 64.44; H, 7.07%
$[\alpha]_D^{25}$	**:**	+36.4 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3448, 2983, 2934, 1719, 1607, 1514, 1458, 1381, 1253, 1170, 1103 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.35 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.43 (s, 3H), 1.49-1.51 (m, 1H), 2.31 (br. s, 1H), 2.52 (ddd, *J* = 4.3, 9.8, 15.8 Hz, 1H), 3.80 (s, 3H), 4.09 (d, *J* = 3.9 Hz, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.43 (dd, *J* = 6.4, 9.8 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.50-4.55 (m, overlapped, 1H), 4.78 (dd, *J* = 6.6, 8.1 Hz, 1H), 5.05-5.19 (m, 1H), 5.72 (ddd, *J* = 1.2, 8.0, 16.5 Hz, 1H), 5.98 (dd, *J* = 3.0, 16.5 Hz, 1H), 6.86, 7.22 (2d, *J* = 8.7 Hz,

4H)

^{13}C NMR (100 MHz, $CDCl_3$)	**:**	δ 18.2 (q), 25.2 (q), 28.0 (q), 35.2 (t), 55.2 (q), 69.3 (d), 70.0 (d), 72.4 (t), 75.3 (d), 78.5 (d), 83.2 (d), 108.5 (s), 114.0 (d), 126.1 (d), 128.8 (s), 129.8 (d), 133.3 (d), 159.7 (s), 170.7 (s)

Synthesis of 39



39

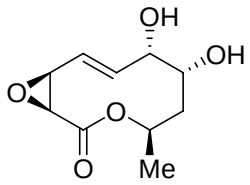
A solution of **38** (71 mg, 0.18 mmol), di-isopropylethylamine (100 μL, 0.58 mmol), *p*-toluene sulfonyl chloride (69 mg, 0.36 mmol) and DMAP (27 mg, 0.22 mmol) in dry DCM (5 mL) was stirred at rt for 20 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:4) to afford **39**.

Yield	**:**	79 mg, 80%
Mol. Formula	**:**	$C_{28}H_{34}O_9S$
Mol. Weight	**:**	546
ESI-MS *m/z*	**:**	569 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 61.54; H, 6.23% Found: C, 61.77; H, 6.41%
$[\alpha]_D^{25}$	**:**	+16.2 (*c* 0.6, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2923, 1733, 1613, 1459, 1374, 1174, 1112, 1070 cm^{-1}
^{1}H NMR (400 MHz,	**:**	δ 1.32 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.40 (s, 3H),

$CDCl_3$) 1.45-1.53 (m, 1H), 2.36-2.41 (m, 1H), 2.44 (s, 3H), 3.81 (s, 3H), 4.20 (d, *J* = 3.5 Hz, 1H), 4.31 (d, *J* = 11.0 Hz, 1H), 4.42 (br. dd, *J* = 6.7, 9.5 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.66 (dd, *J* = 6.7, 7.7 Hz, 1H), 5.10 (dd, *J* = 3.0, 3.5 Hz, 1H), 5.13-5.18 (m, 1H), 5.71 (dd, *J* = 7.8, 16.3 Hz, 1H), 5.80 (dd, *J* = 3.0, 16.3 Hz, 1H), 6.85, 7.16 (2d, *J* = 8.5 Hz, 4H), 7.29, 7.77 (2d, *J* = 8.2 Hz, 4H)

^{13}C NMR (125 MHz, $CDCl_3$) **:** δ 18.2 (q), 21.7 (q), 25.2 (q), 27.9 (q), 35.2 (t), 55.2 (q), 68.6 (d), 72.5 (t), 75.3 (d), 75.4 (d), 78.3 (d), 81.5 (d), 108.6 (s), 113.8 (d), 114.0 (d), 127.1 (d), 128.0 (d), 128.1 (d), 129.4 (s), 129.6 (d), 129.8 (d), 129.9 (d), 133.4 (s), 144.9 (s), 159.7 (s), 167.6 (s)

Multiplolide-A (4)



4

A solution of **39** (47 mg, 86.1 μmol) and trifluroacetic acid (50 μL) in DCM (10 mL) was stirred at rt for 48 h. Di-isopropylethylamine (0.5 mL) was introduced and concentrated. The crude triol (23 mg, 59.6 μmol) was dissolved in THF (4 mL), cooled to 0 ^{o}C and then sodium hydride (60% dispersion in mineral oil, 25 mg, 0.62 mmol) was added. After 1 h, the reaction mixture was diluted with ice-water and extracted with ethyl acetate. The combined organic extract was dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1) to afford **4**.

Yield **:** 11 mg, 60% (over two steps)

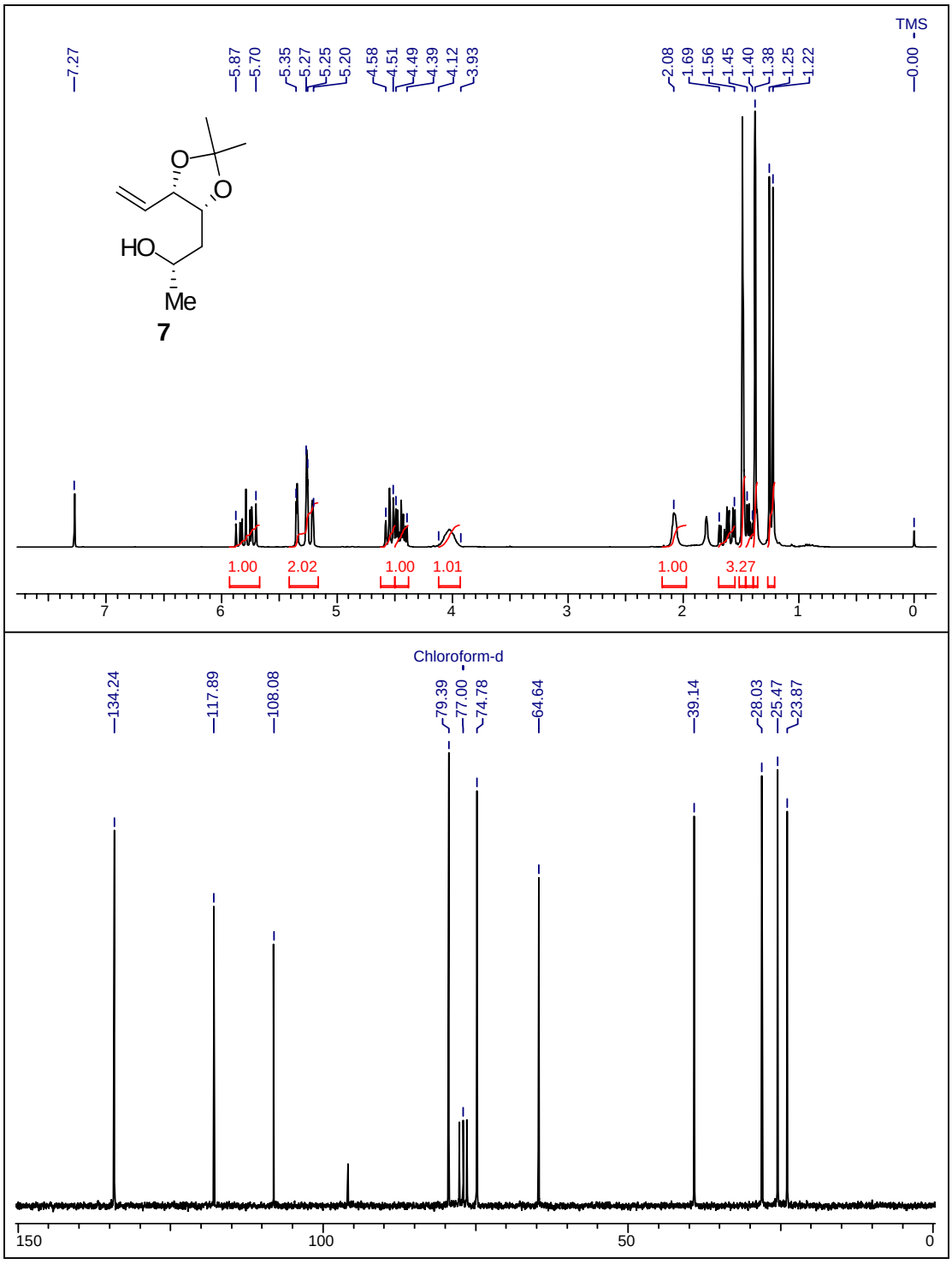
Mol. Formula **:** $C_{10}H_{14}O_5$

Mol. Weight **:** 214

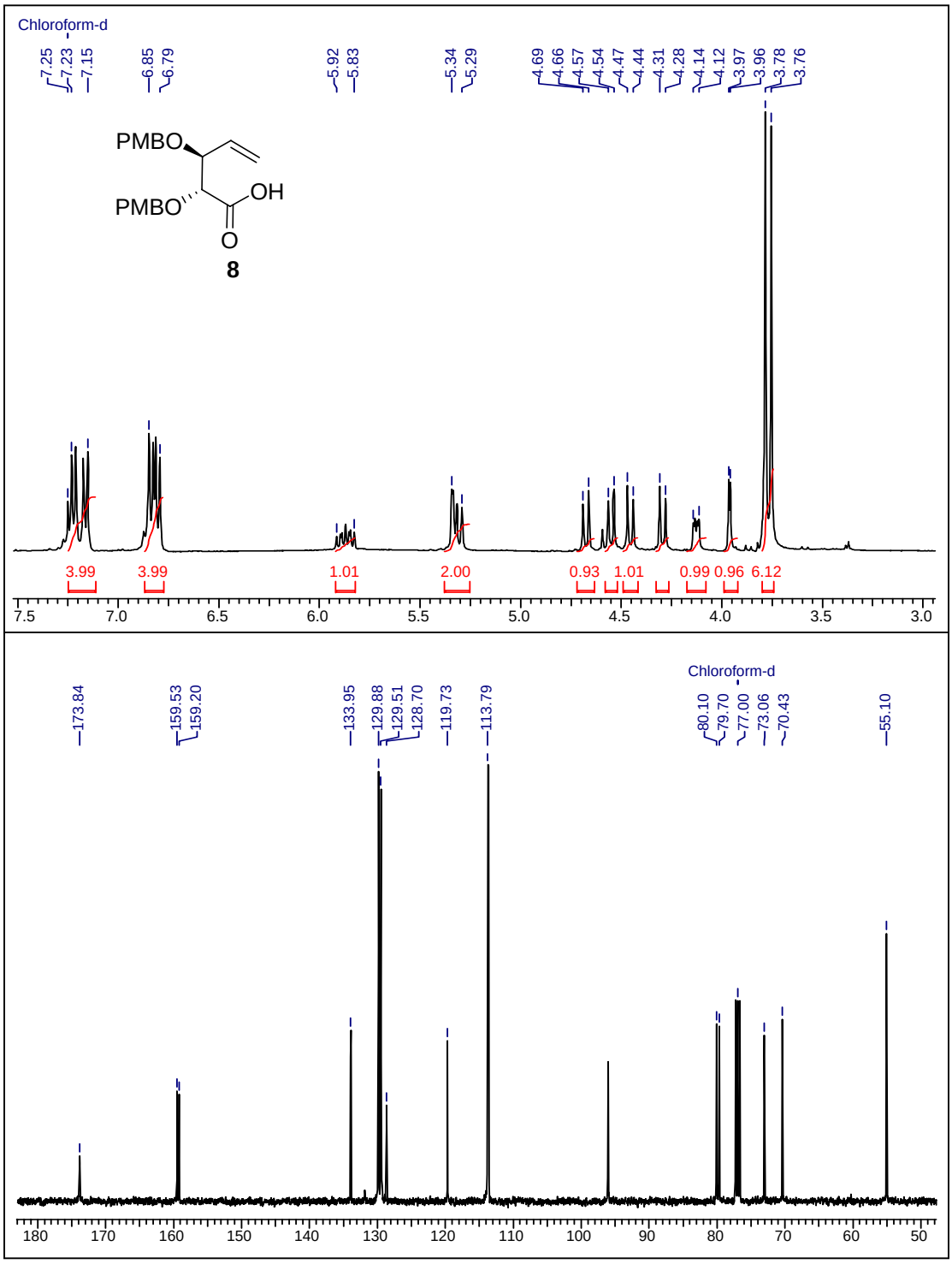
ESI-MS *m/z*	**:**	254 $[M+H+K]^+$
Elemental Analysis	**:**	Calcd: C, 56.07; H, 6.54% Found: C, 55.83; H, 6.68%
$\mathbf{[\alpha]_D^{25}}$	**:**	+22.6 (*c* 0.3, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3430, 1716, 1280, 1217, 1060 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$)	**:**	δ 1.28 (dd, *J* = 4.0, 16.0 Hz, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 2.24 (ddd, *J* = 3.4, 8.5, 16.0 Hz, 1H), 2.24 (br. s, overlapped, 1H), 3.65 (d, *J* = 4.6 Hz, 1H), 3.79-3.81 (m, 1H), 4.05 (dd, *J* = 3.0, 8.4 Hz, 1H), 4.53-4.57 (m, 1H), 5.27-5.34 (m, 1H), 5.76 (ddd, *J* = 1.4, 2.1, 15.6 Hz, 1H), 5.93 (ddd, *J* = 1.1, 2.5, 15.6 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$)	**:**	δ 17.8 (q), 35.4 (t), 54.5 (d), 55.1 (d), 67.9 (d), 68.3 (d), 72.4 (d), 117.7 (d), 133.3 (d), 167.2 (s)

Spectroscopic Data

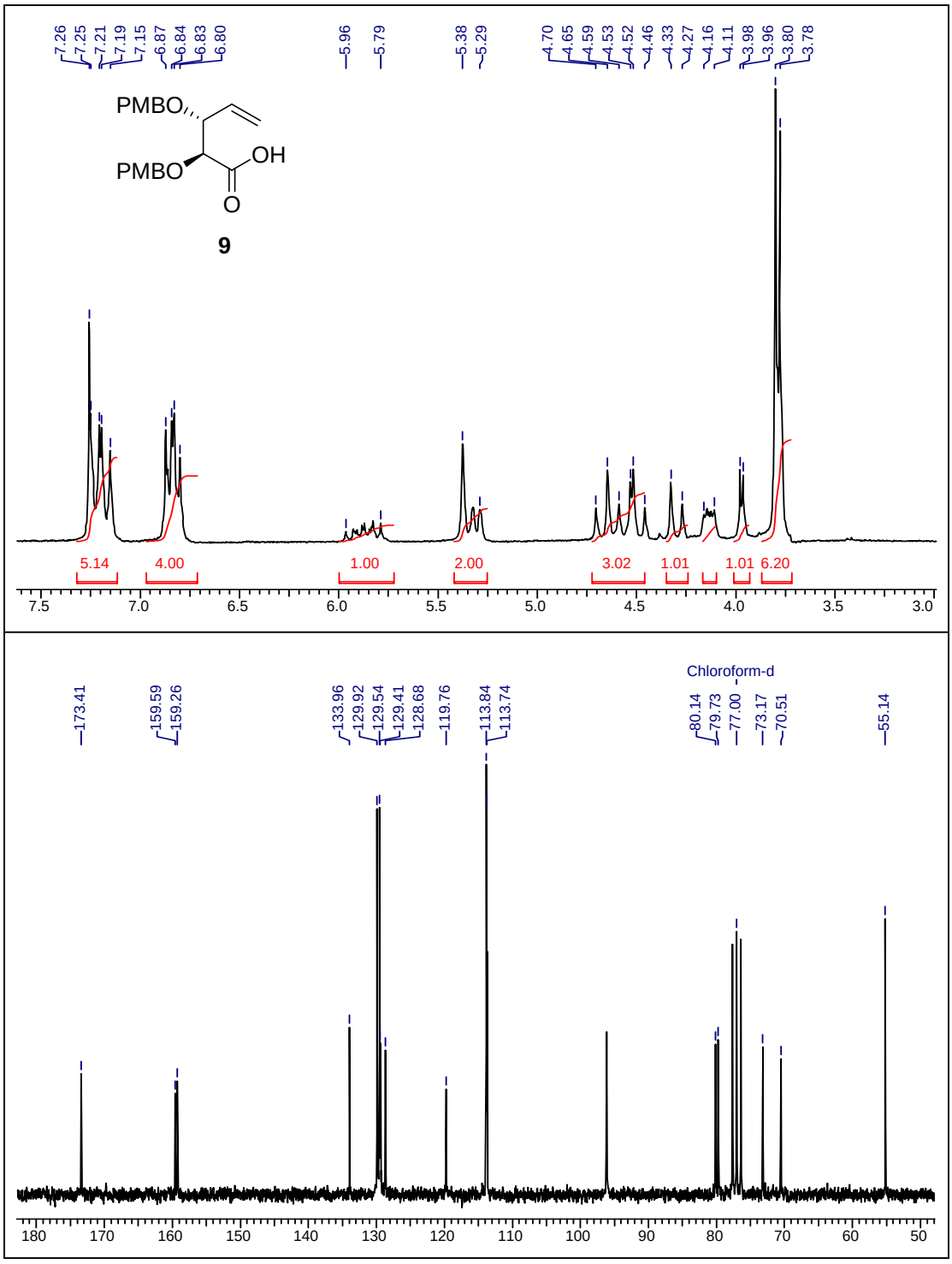
^{1}H and ^{13}C NMR spectra of compound 7 in $CDCl_3$



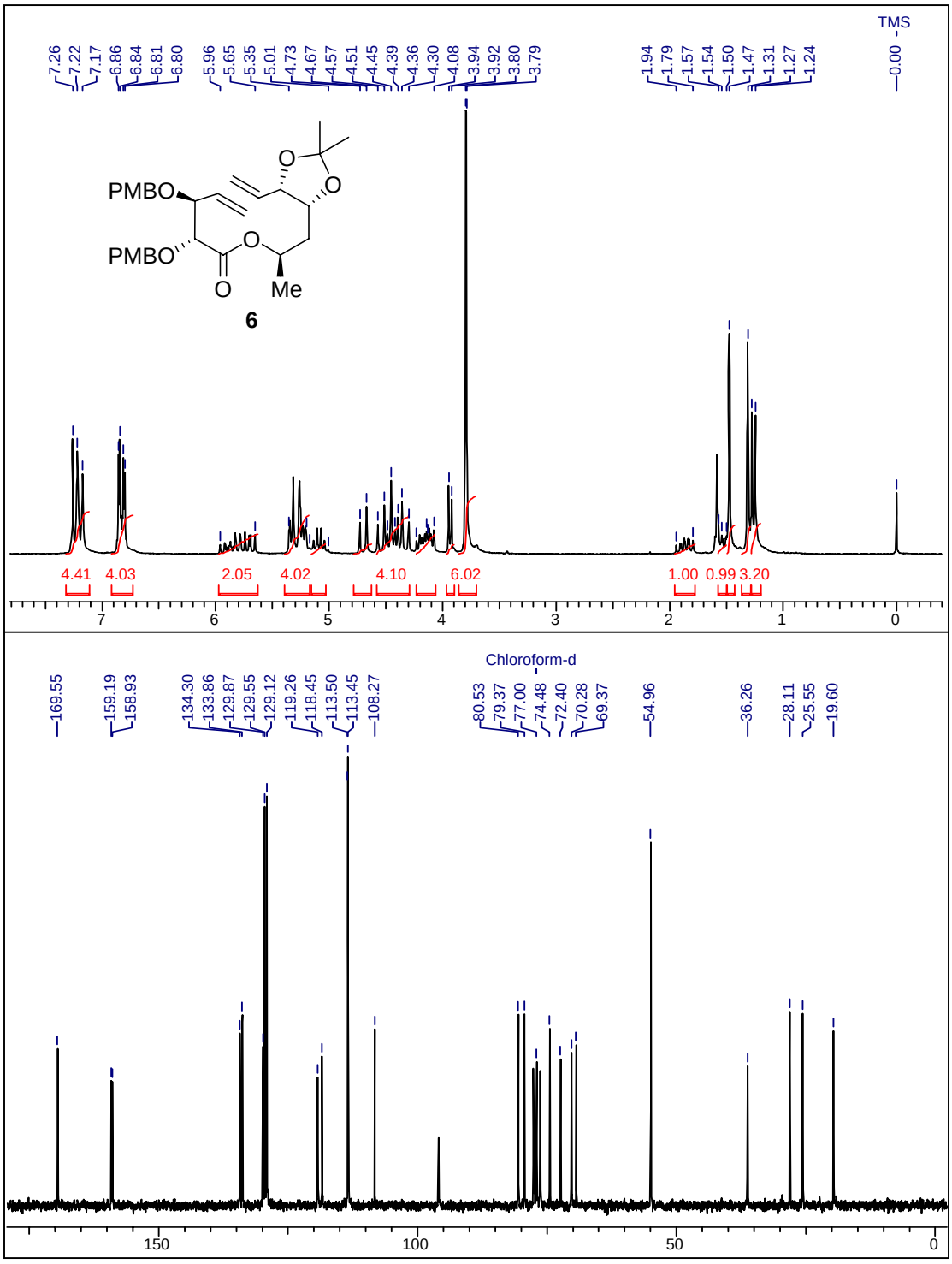
^{1}H and ^{13}C NMR spectra of compound 8 in $CDCl_3$



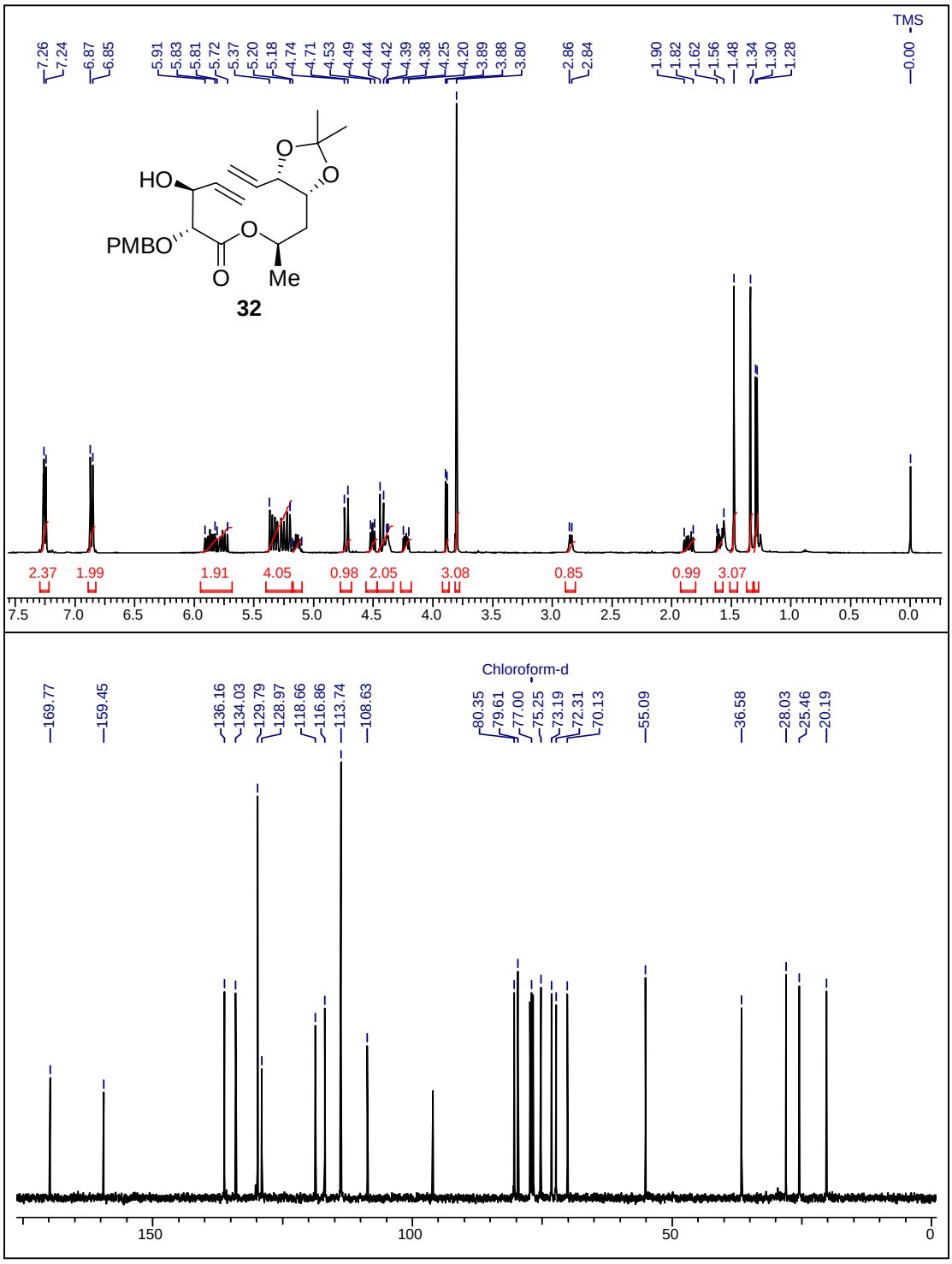
^{1}H and ^{13}C NMR spectra of compound 9 in $CDCl_3$



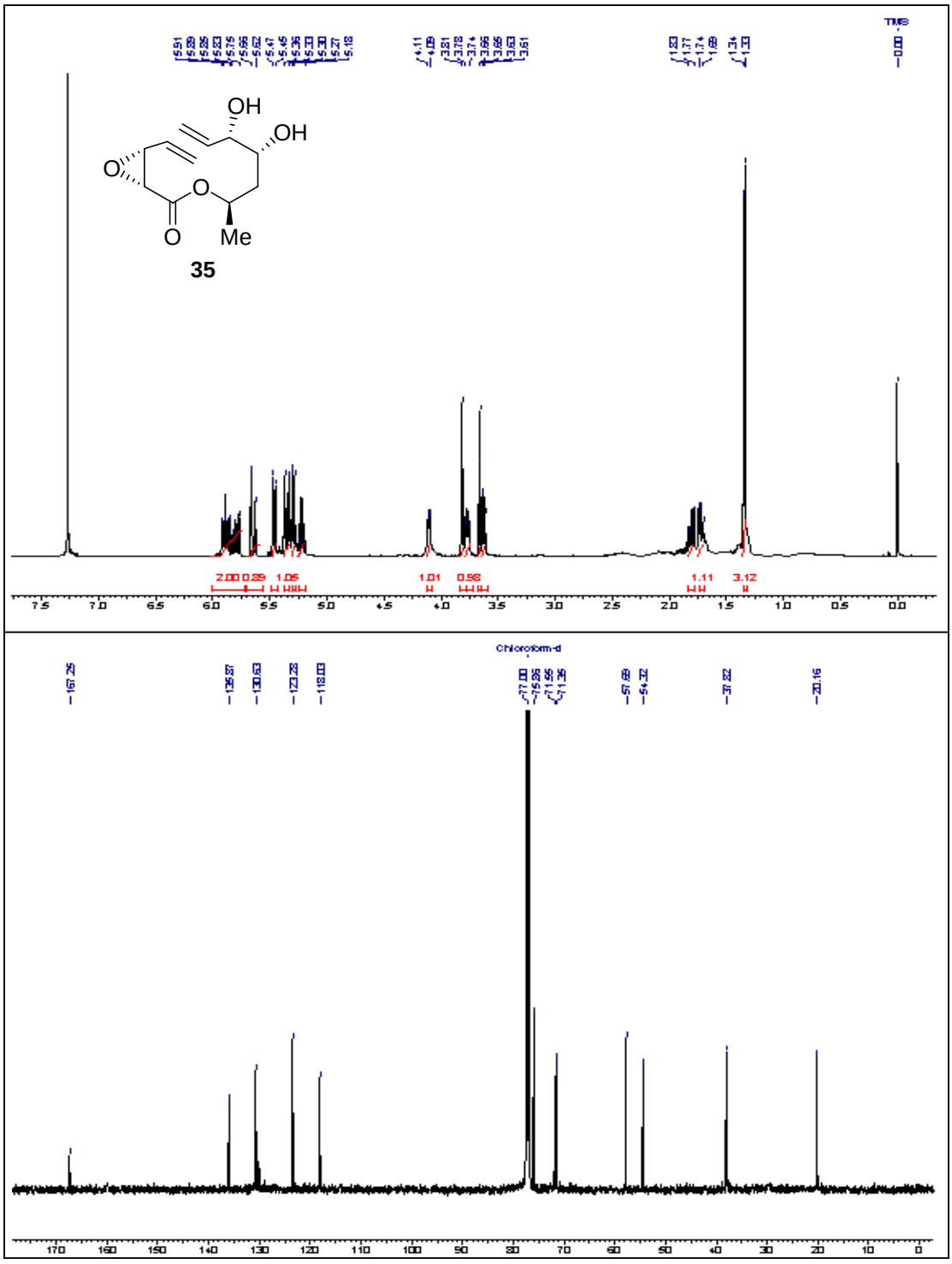
^{1}H and ^{13}C NMR spectra of compound 6 in $CDCl_3$



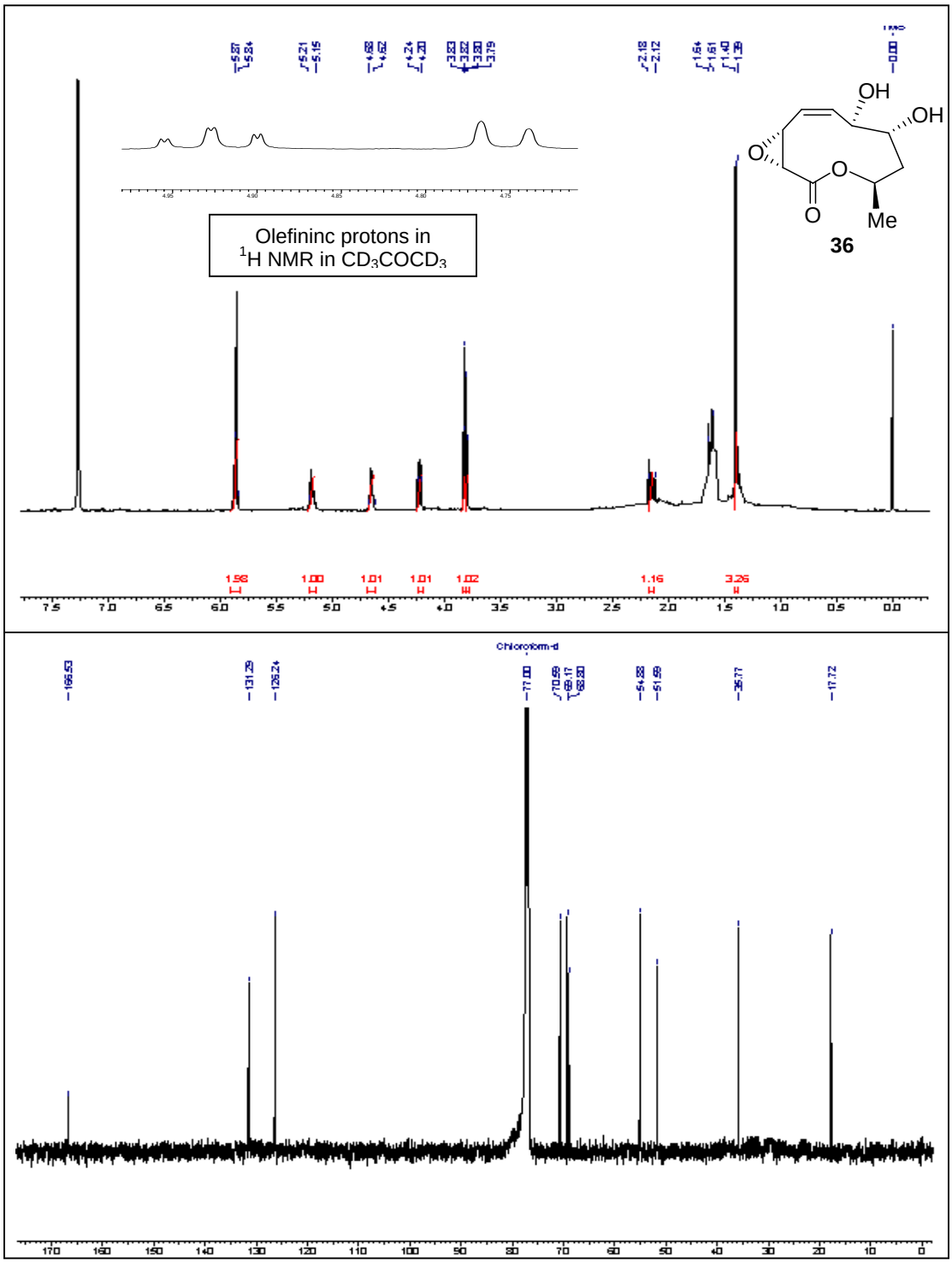
^{1}H and ^{13}C NMR spectra of compound 32 in $CDCl_3$



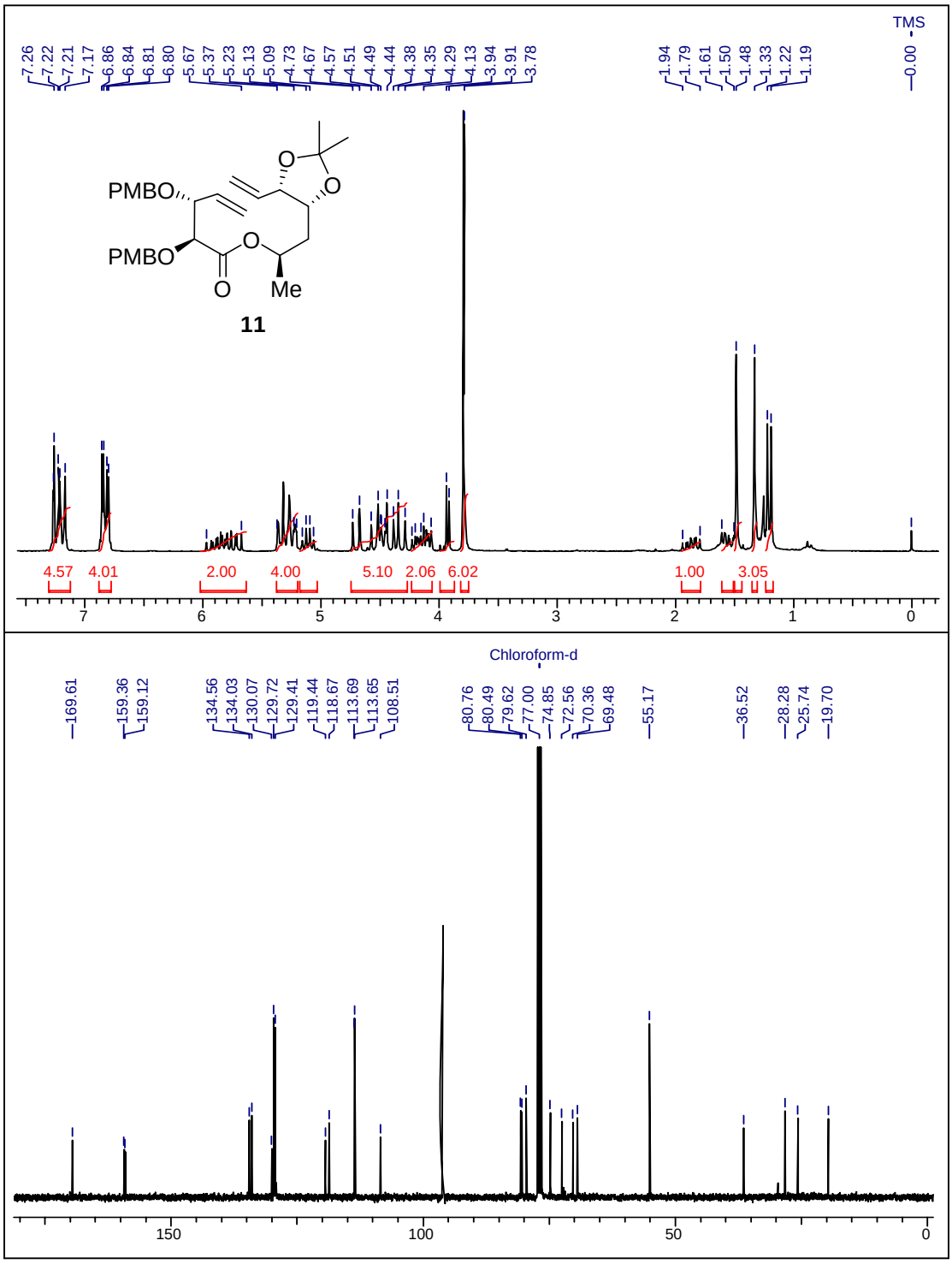
^{1}H and ^{13}C NMR spectra of compound 35 in $CDCl_3$



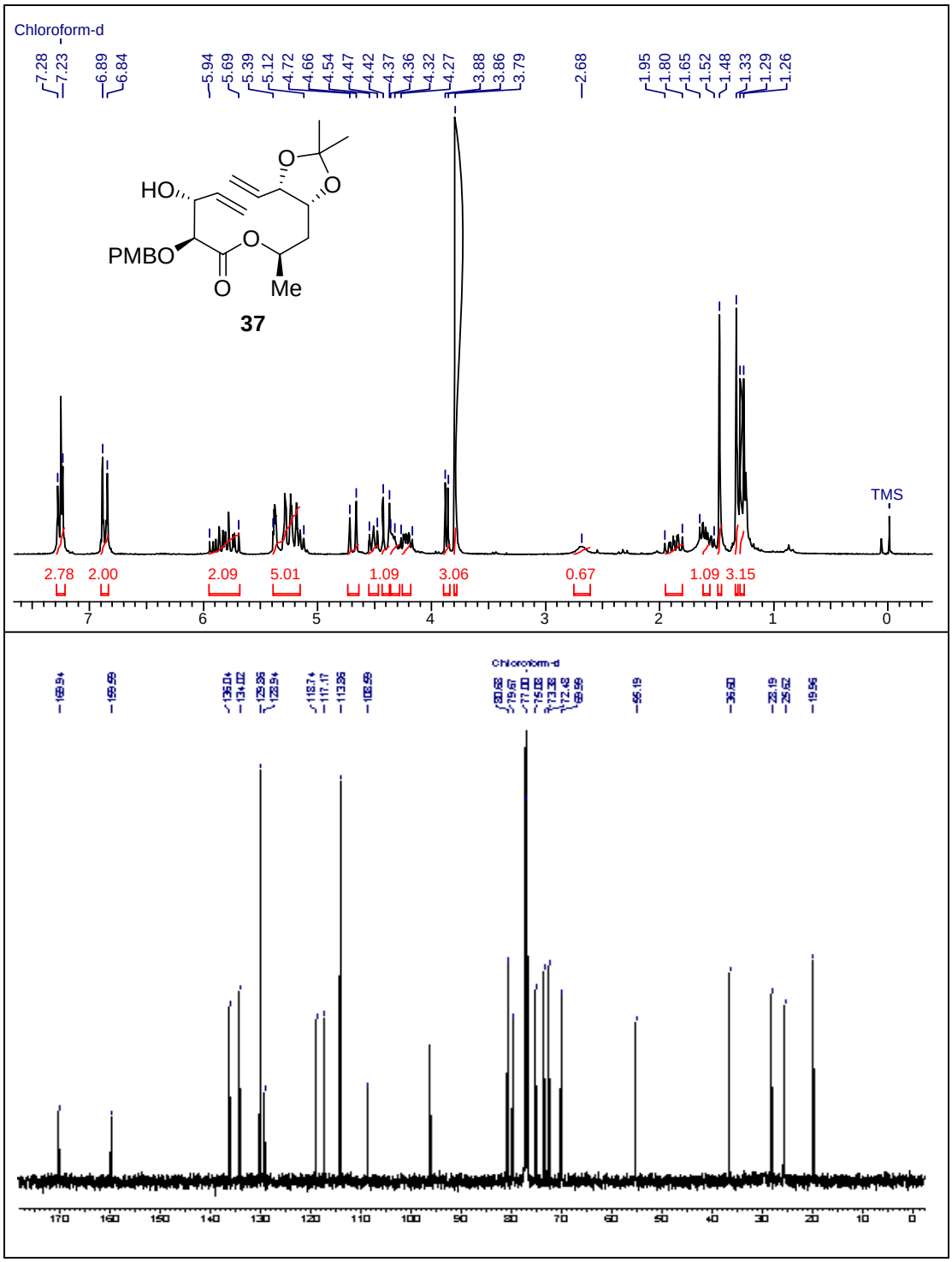
^{1}H and ^{13}C NMR spectra of compound 36 in $CDCl_3$



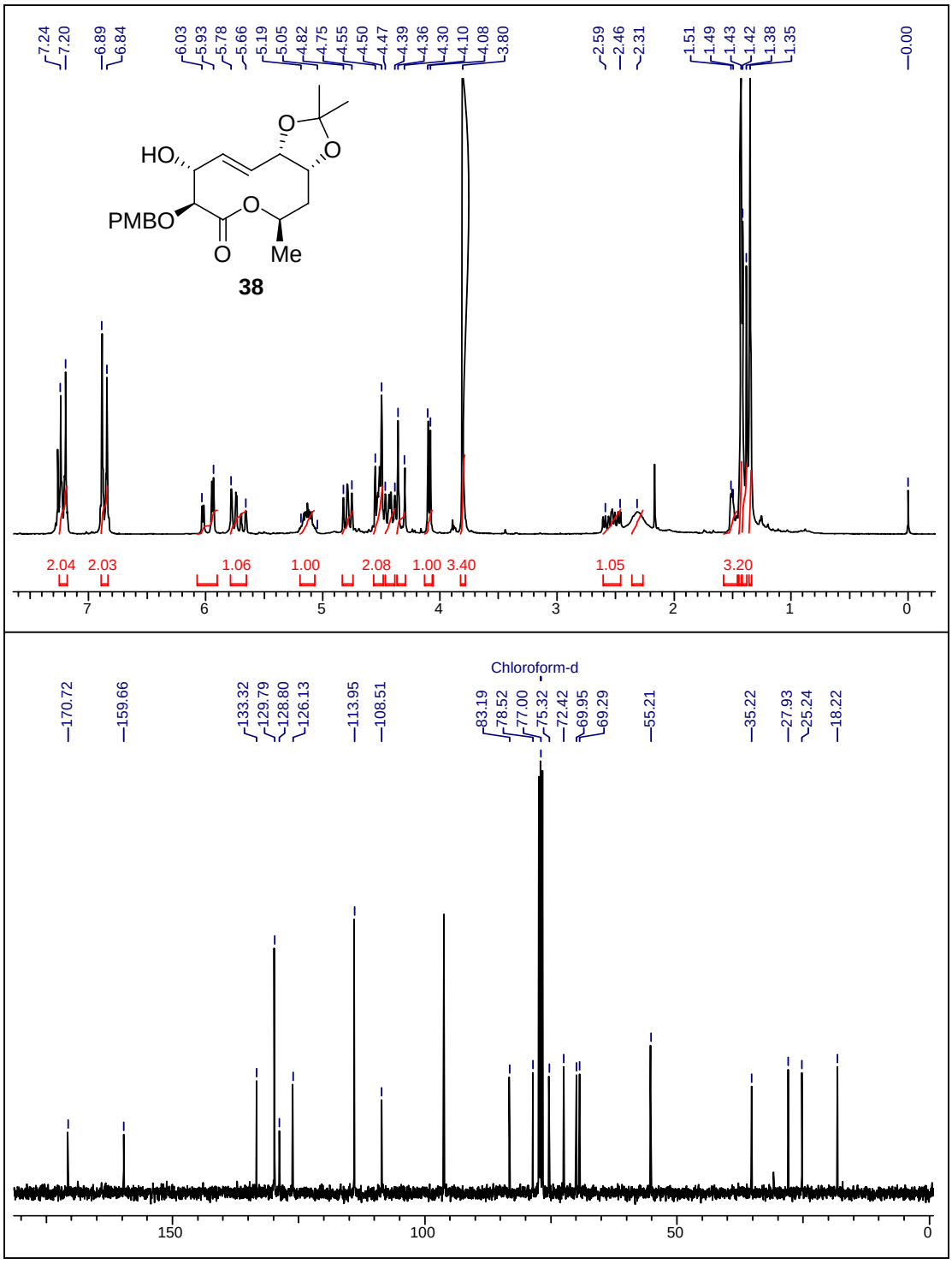
^{1}H and ^{13}C NMR spectra of compound 11 in $CDCl_3$



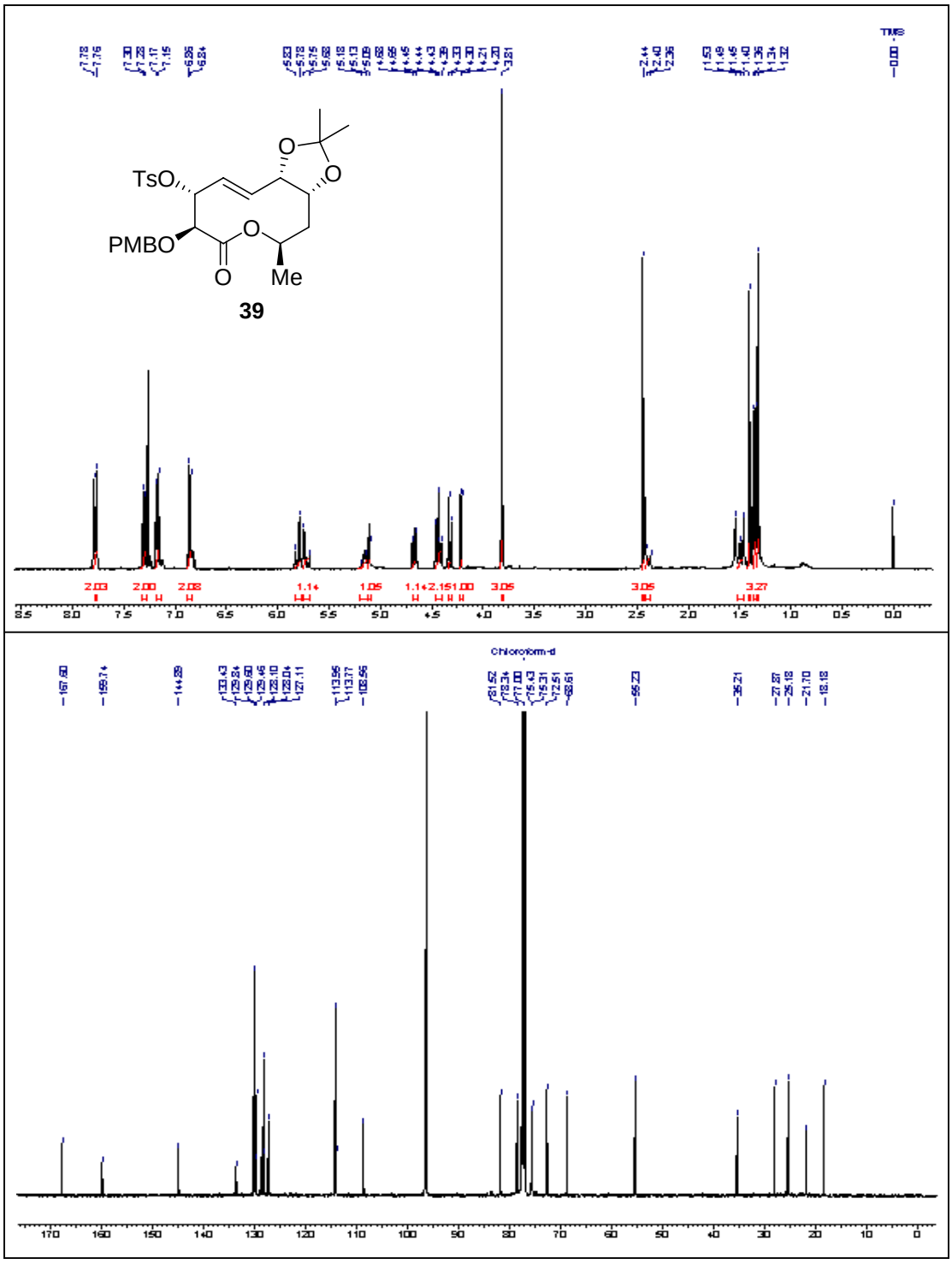
^{1}H and ^{13}C NMR spectra of compound 37 in $CDCl_3$



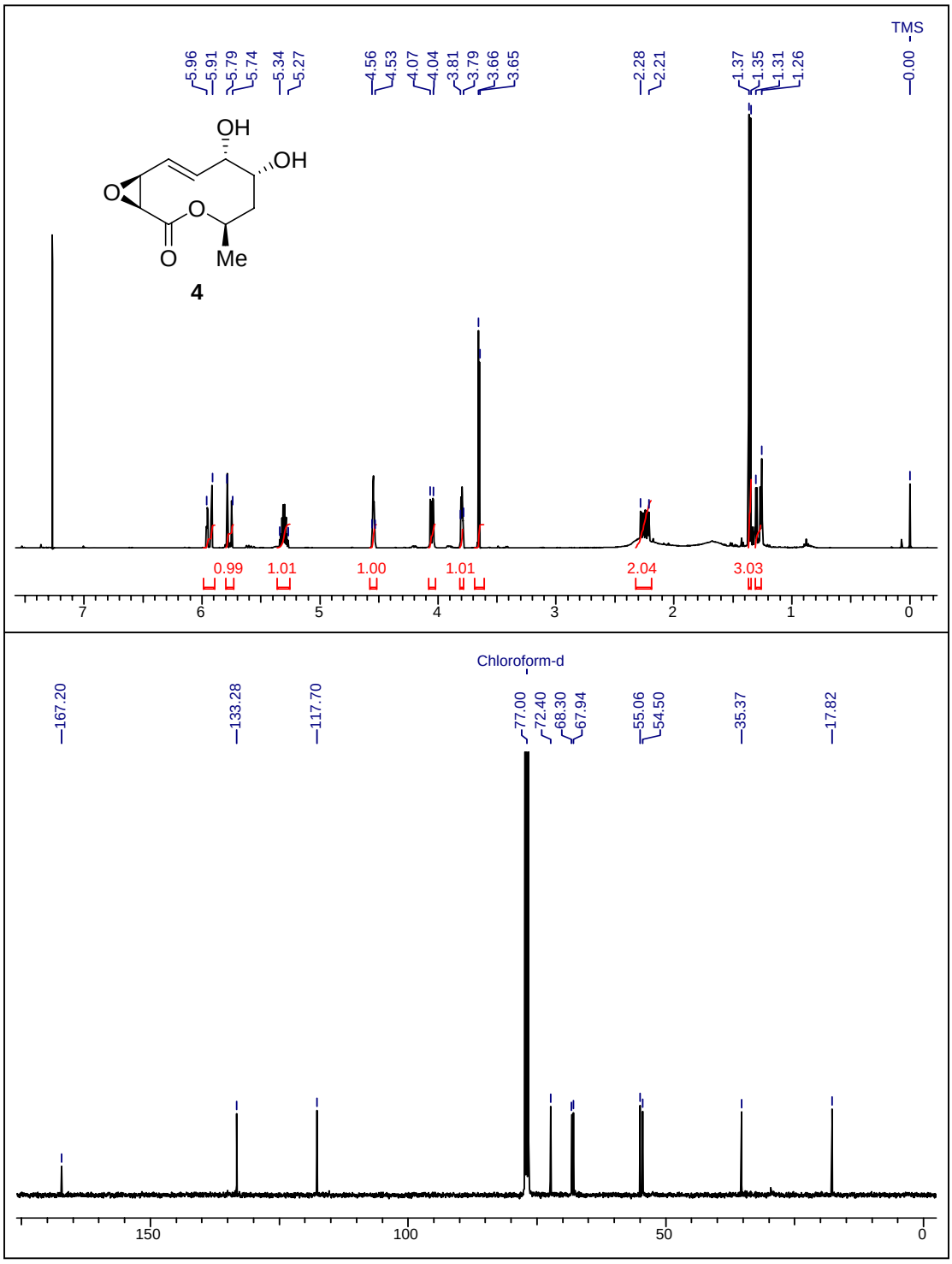
^{1}H and ^{13}C NMR spectra of compound 38 in $CDCl_3$



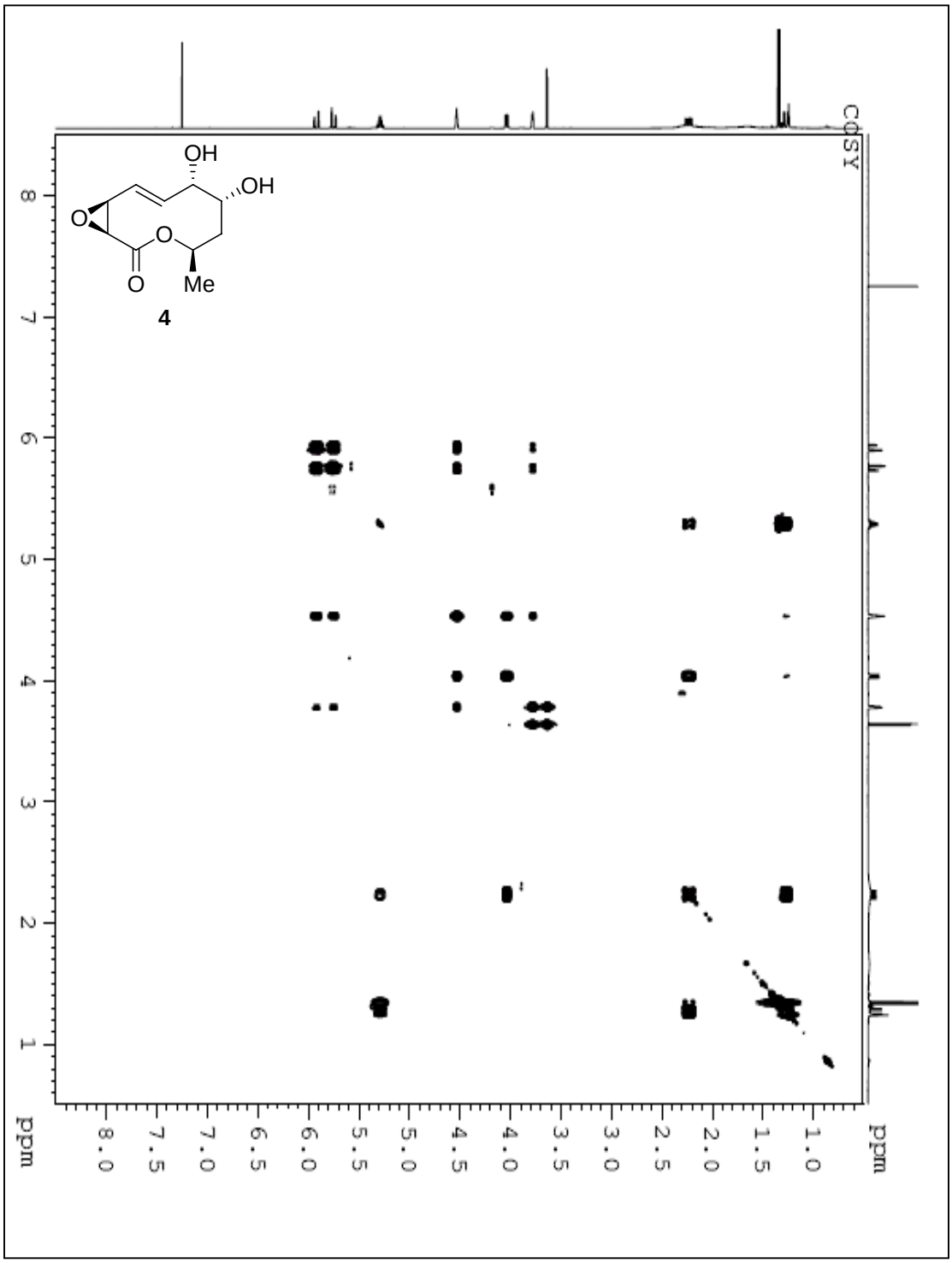
^{1}H and ^{13}C NMR spectra of compound 39 in $CDCl_3$



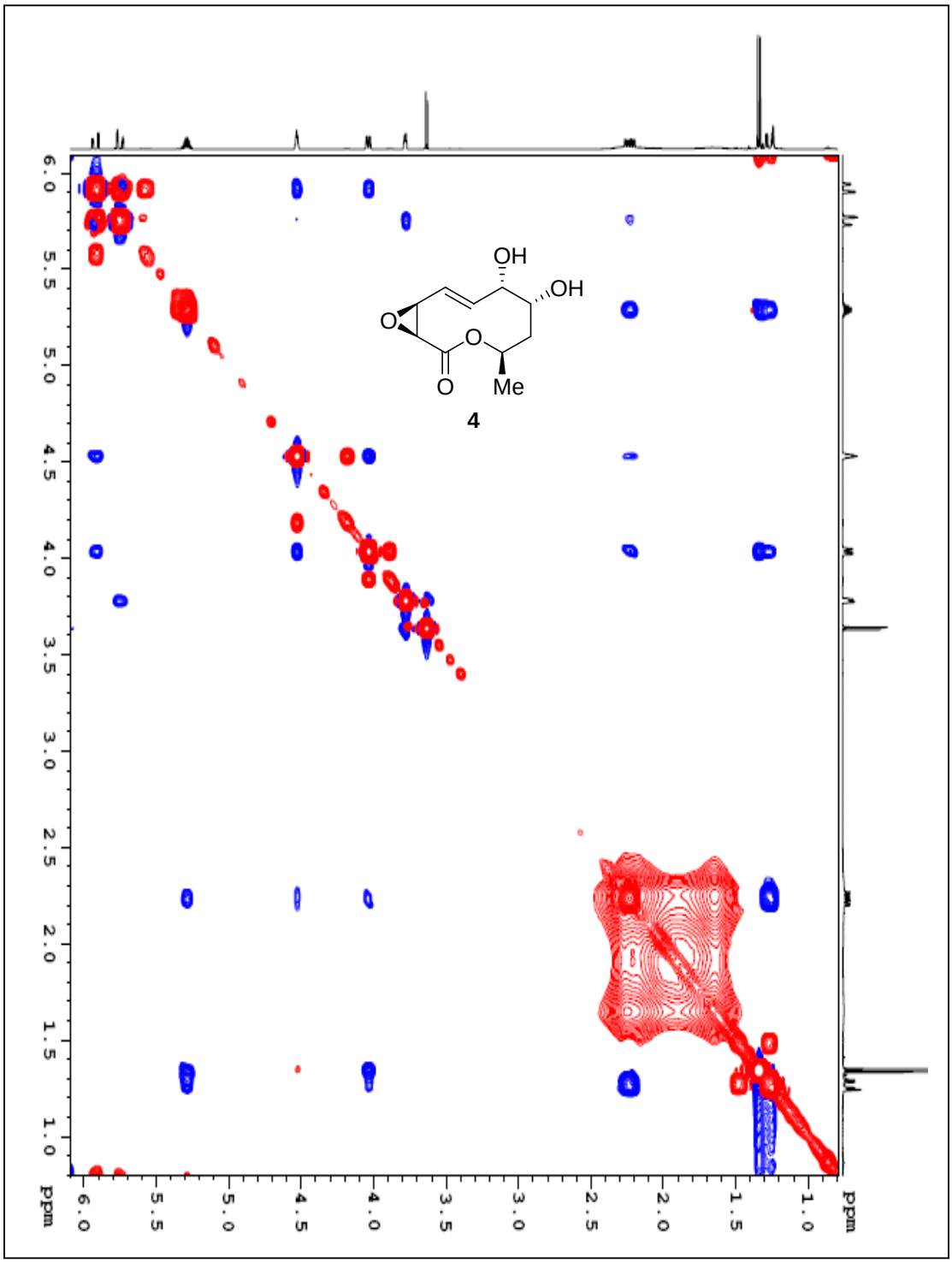
^{1}H and ^{13}C NMR spectra of compound 4 in $CDCl_3$



COSY spectrum of compound 4 in $CDCl_3$



NOESY spectrum of compound 4 in $CDCl_3$



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Chapter II

Synthetic Studies Toward Crocacins A-D

Introduction

Introduction

During the last 20 years myxobacteria have made their way from highly exotic organisms to one of the major sources of microbial secondary metabolites besides actinomycetes and fungi. The pharmaceutical interest in these peculiar prokaryotes lies in their ability to produce a variety of structurally unique compounds and/or metabolites with rare biological activities. Myxobacteria have become known as prolific producers of interesting and biologically active secondary metabolites. More than 7,500 different myxobacteria have been isolated and numerous strains have been analyzed chemically.[1] From these, more than 100 new core structures plus approximately 500 derivatives have been described which has been discussed recently in several reviews.[1,2]

Furthermore, secondary metabolites from myxobacteria often show structural elements, which are rarely produced by other sources. Most of the isolated compounds represent hybrids of polyketides (PKs) and nonribosomally made peptides (NRPs), whereas pure PKs are only rarely reported.[3] Examples for pure PKs are the aurafurons,[4] tuscolid, tuscuron[5] and dawenol.[6]

In contrast to several secondary metabolites from actinomycetes,[7] myxobacterial natural products often lack glycosylations and other biosynthetic steps that take place after the assembly of the core structures. An exception to this general finding is the cytotoxic compound chivosazol bearing a 6-deoxyglucose moiety attached to the aglycon.[8] An example for the chemical diversity generated by myxobacterial secondary metabolism without using typical post-PKS/NRPS steps are the leupyrrins which are derived from a mixed PKs/peptide/isoprenoid biosynthesis. In this case several precursors are assembled, furthermore functionalized and rearranged providing an impressive example for natural combinatorial biosynthesis.[9]

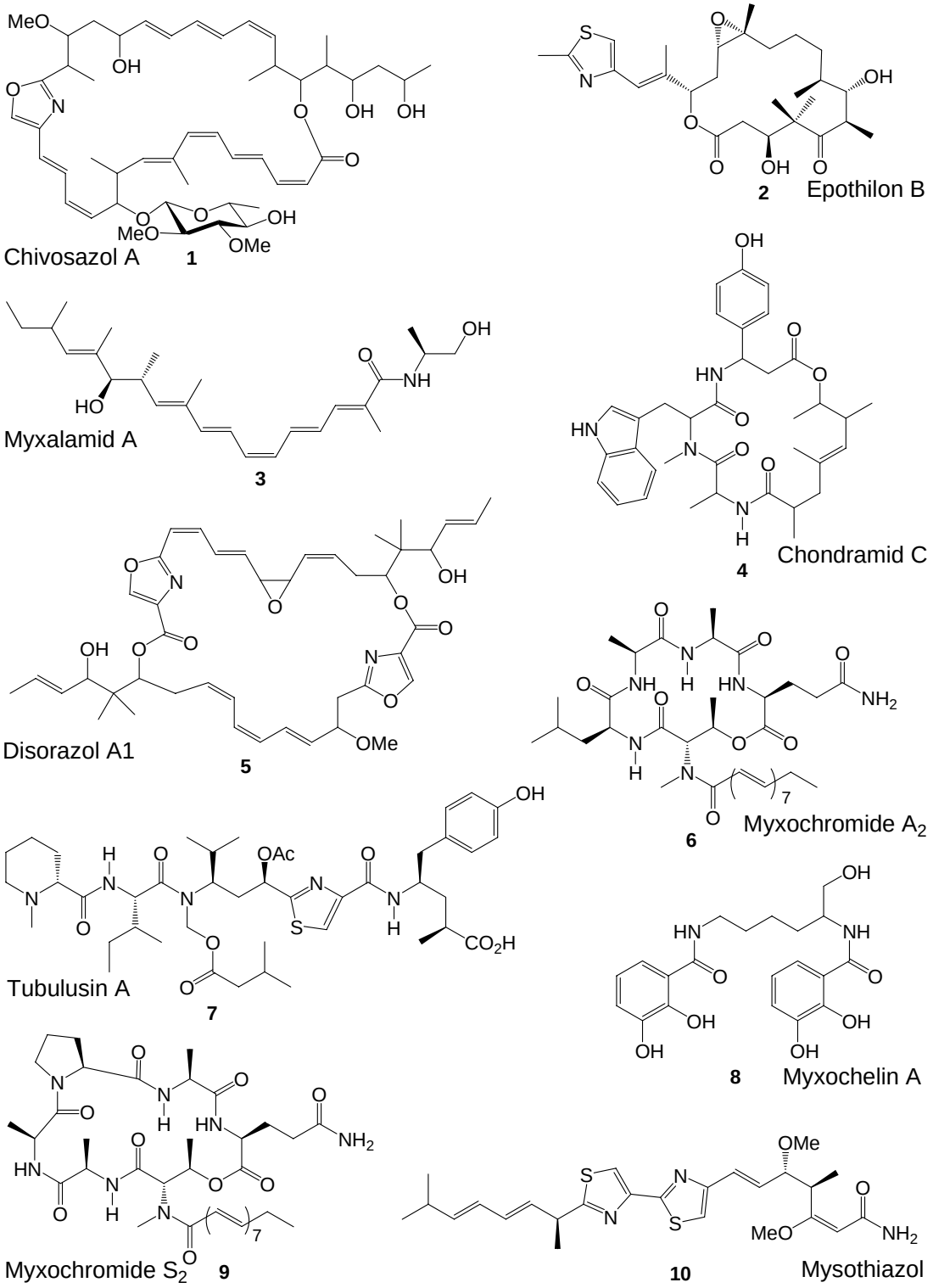
The advanced exploitation of this resource of chemical diversity is of especial interest because the mode of action of natural products from myxobacteria is often unusual as they target cellular structures, which are rarely or not at all hit by other secondary metabolites. Prominent examples are several compounds that interact with the eukaryotic cytoskeleton. Epothilone from Sorangium cellulosum is about to be approved for breast cancer treatment because it is a paclitaxel mimetic.[10] Furthermore,

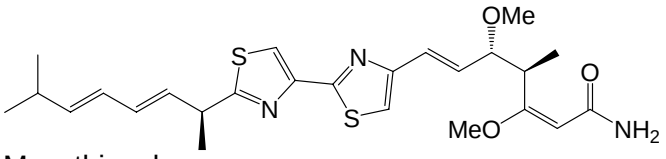
this compound can be used to treat paclitaxel-resistant tumors, shows good water solubility and can be produced by fermentation. Epothilone stabilizes microtubuli in the cell disabling the assembly of functional mitotic spindles required for cell proliferation and thus resulting in the induction of apoptosis. [2a,10] Since the isolation of epothilone additional myxobacterial compounds have been found that exhibit the opposite mode of action by destabilizing microtubuli i.e. disorazol,[11] tubulysin[12] or interfere with the active skeleton i.e. rhizopodin,[13] chondramid.[14] Table 1 summarizes the biosynthetic gene clusters identified from myxobacteria and figure 1 summarizes some myxobacterial secondary metabolites whose biosynthetic gene clusters have been published.

Table 1 *Complete biosynthetic gene clusters identified from myxobacteria*

Compound	Type	Producer	Year	Ref.
Saframycin	NRPS	*Myxococcus xanthus* DSM504/15	1995/ 1996	15
Soraphen	PKS	*Sorangium cellulosum* So ce26	1995/ 2002	16
Myxothiazol	PKS/NRPS	*Stigmatella aurantiaca* DW4/3-1	1999	17
Myxochelin	NRPS	*Stigmatella aurantiaca* Sg a15	2000	18
Epothilone	PKS/NRPS	*Sorangium cellulosum* So ce90	2000	19
Myxalamid	PKS/NRPS	*Stigmatella aurantiaca* Sg a15	2001	20
Stigmatellin	PKS	*Stigmatella aurantiaca* Sg a15	2002	21
Melithiazol	PKS/NRPS	*Melittangium lichenicola* Me l46	2003	22
Tubulysin	PKS/NRPS	*Angiococcus disciformis* An d48	2004	23
Disorazol	PKS/NRPS	*Sorangium cellulosum* So ce12	2005	24
Chivosazol	PKS/NRPS	*Sorangium cellulosum* So ce56	2005	25
Cystothiazol	PKS/NRPS	*Cystobacter fuscus* AJ-13278	2005	26
Myxochromide S	PKS/NRPS	*Stigmatella aurantiaca* DW4/3-1	2005	27
Myxochromide A	PKS/NRPS	*Myxococcus xanthus* DK1622	2006	28
Chondramide	PKS/NRPS	Chondromyces crocatus Cm c5	2006	29

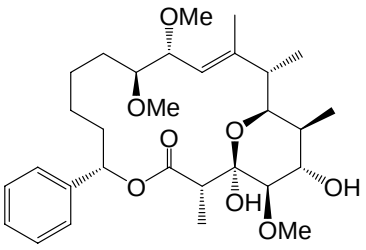
Figure 1 *Myxobacterial secondary metabolites whose biosynthetic gene clusters have been published*



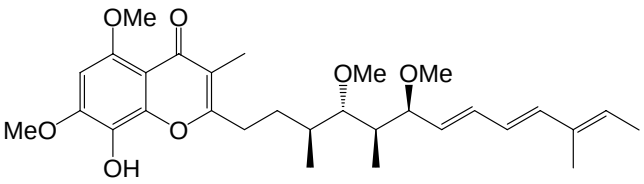


Mysothiazol

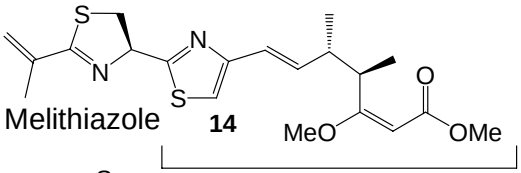
11



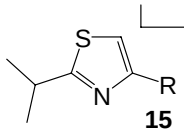
12 Soraphen A



Stigmatellin **13**

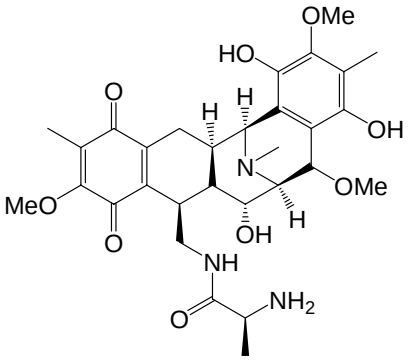


Melithiazole **14**



15

Cystothiazol



Saframycin Mx1

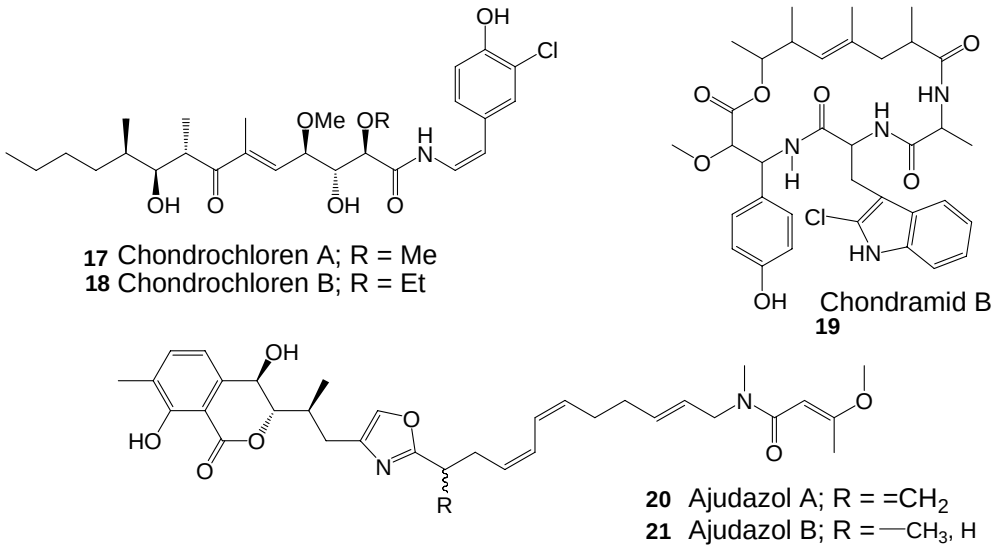
16

Screening fermentations of the myxobacteria Chondromyces crocatus Cm c5 for biologically active metabolites resulted in the isolation of a number of exciting secondary metabolites. Strain Cm c5 was found to produce six entirely novel groups of metabolites, including chondramides, crocacins, ajudazole, crocapeptins, thuggacins, and chondrochlorens.[30-33, 14]

In the course of screening of myxobacteria for new biologically active compounds, crude extracts of the species *Chondromyces crocatus* were noticed for their high antifungal and cytotoxic activity. Subsequently these activities were ascribed to several structural diverse groups of secondary metabolites, which are simultaneously produced by *C. crocatus*. The chondramides A-D[30, 31] are cyclo-depsipeptides structurally related to the sponge metabolite jaspamide/jasplakinolide.[34] They show only weak activity against yeasts, but are highly cytostatic for different cultured mammalian cell lines by interfering with the active cytoskeleton.[14] Advanced analysis of crude extracts of *C. crocatus* led to the discovery of the new β-amino styrenes, the chondrochlorens,[33] and the ajudazols A (**20**) and B (**21**) (Figure 2).[35] Chondrochlorens A (**17**) and B (**18**) are unique chloro-hydroxy-styryl amides of a highly modified C14 carboxylic acid, which comprises an unsaturated ketone, two

hydroxy, two methoxy and three methyl groups. As pure compounds, the chondrochlorens show weak antibiotic activity against *Micrococcus luteus*, *Schizosaccharomyces pombe*, *B. subtilis*, and *Staphylococcus aureus*. Ajudazols are the unique isochromanone derivatives with an extended side chain containing an oxazole, a *Z,Z*-diene, and a 3-methoxybutenoic acid amide as characteristic structural features.[35] The ajudazols are regularly detected in crude extracts of *C. crocatus* strains, *viz.*, of strain Cm c1 to Cm c13. The antimicrobial activitiy of the ajudazols was determined by the agar diffusion assay using paper discs of 6 mm diameter. With 40 μg ajudazols/disc in 20 μL methanol ajudazol B incompletely inhibited growth of the following fungi (data in parentheses indicate diameter of inhibition zone in mm): *Botrytis cinerea* (10), *Trichoderma koningii* (21), *Giberella fujikuroi* (17) and *Ustilago maydis* (13). It was also weakly active against few Gram-positive bacteria. The MIC determined by a serial dilution assay for *Micrococcus luteus* was 12.5 μg /mL. Ajudazol A showed only minor activity against a few fungi and Gram-positive bacteria.

Figure 2 *Some secondary metabolites from chondromyces crocactus*



17 Chondrochloren A; R = Me
18 Chondrochloren B; R = Et

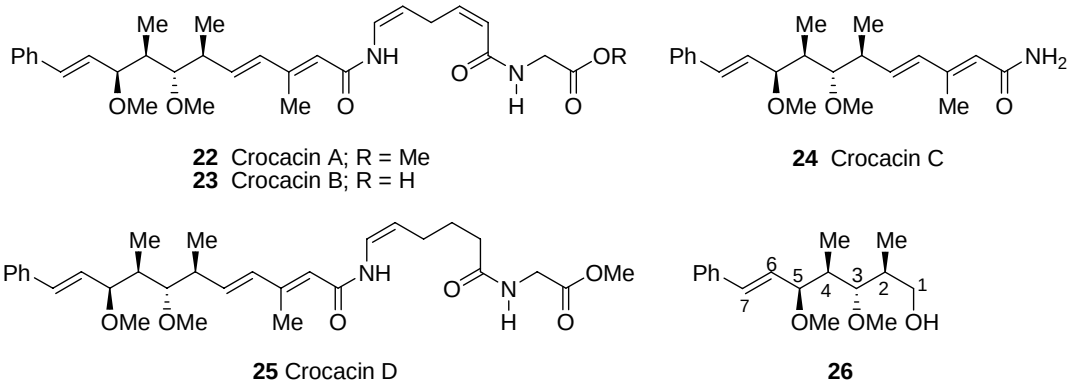
Chondramid B
19

20 Ajudazol A; R = $=CH_2$
21 Ajudazol B; R = $—CH_3$, H

Four novel antifungal and highly cytotoxic metabolites, crocacins A–D (**22**–**25**), were isolated in the screening of the myxobacterial genus Chondromyces from strains of *C. crocatus* and *C. pediculatus*[36] (Figure 3). Crocacin A, B, and D (**22**, **23**, and **25**) are unusual dipeptides of glycine and a 6-amino-hexenoic or hexadienoic acid, which is *N*-protected by a complex polyketide-derived acyl residue. The latter is

a multiply substituted phenylundecatrienoic acid, which is found as its primary amide crocacin C (**24**).

Figure 3 *Chemical structures of crocacins and the common intermediate for their synthesis*



22 Crocacin A; R = Me
23 Crocacin B; R = H

24 Crocacin C

25 Crocacin D

26

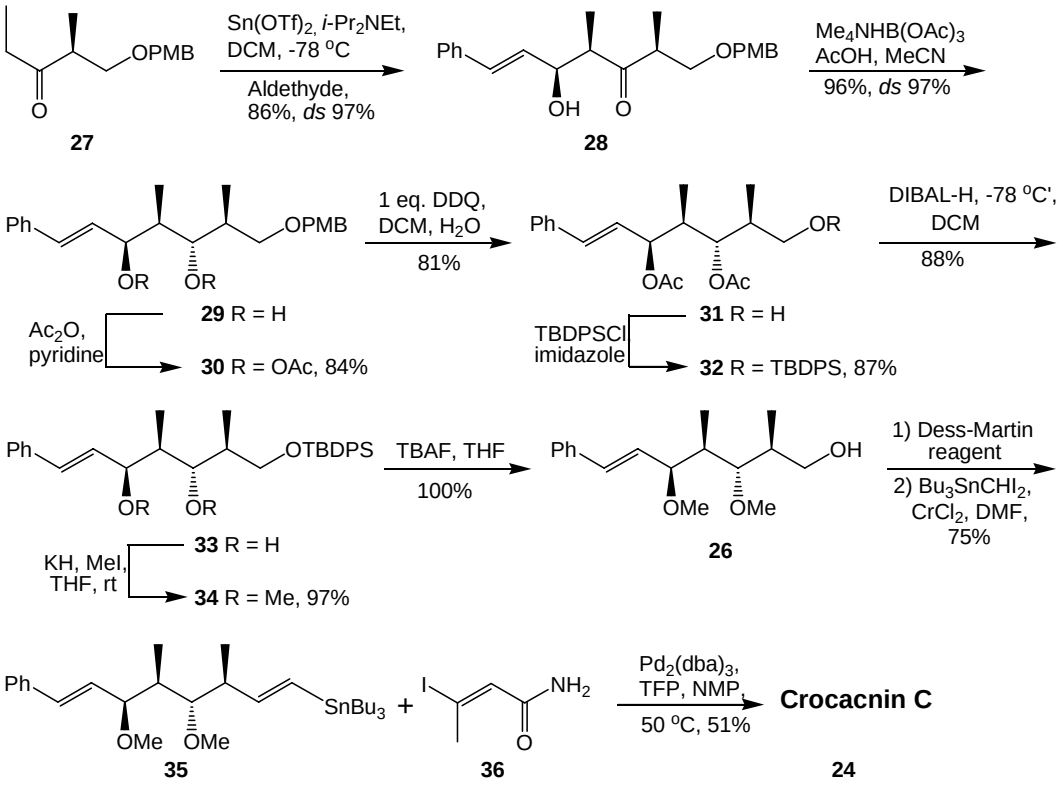
The crocacins moderately inhibit the growth of a few Gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. Crocacin D (**25**) is the most active of the group against the fungus *Saccharmyces cerevisiae* with an MIC of 1.4 ng mL^{-1} compared to 10 μg mL^{-1} for crocacin A (**22**), 12.5 μg mL^{-1} for crocacin B (**23**), and 100 μg mL^{-1} for crocacin C (**24**).[36] A detailed study revealed that crocacin A (**22**) blocks NADH oxidation in beef heart submitochondrial particles, and the site of inhibition within the electron transport chain was identified as the cytochrome *bc*1 segment (complex III). Toxicity was also observed in L929 mouse fibroblast cell culture.[36]

The biological activity coupled with the interesting structural features of the crocacins prompted to undertake their synthesis. As the total syntheses for some of the members of crocacin family were already reported by the time we initiated our work and as all of them have proceeded through the synthesis of the important intermediate **26**, we focused our attention on the synthesis of **26**. At this point it would be germane to summarize some of the synthetic endeavors reported in literature before and after our work.[37]

First total synthesis of one of the crocacin family members, crocacin C, appeared in the year 2000 by Rizzacasa and co-workers (Scheme 1).[38] Tin mediated aldol reaction between the enolate derived from ketone **27** with cinnamaldehyde was the first step, which procured the *syn-syn* adduct **28** in 86% yield and 97%

diastereoselectivity. Stereoselective directed reduction of ketone **28** was achieved using tetramethylammonium triacetoxyborohydride to provide the *anti* diol **29**, which was acetylated to afford the di-acetate derivative **30**. After some protecting group manipulations the key intermediate **26** was synthesized. The primary alcohol **26** on Dess-Martin oxidation provided the aldehyde, which was subjected to chromium-mediated vinylstannylation using the protocol developed by Hodgson to procure the stannane **35**. Treatment of a solution of the stannane 3**5** and iodide 3**6** in NMP with a catalytic amount of $Pd_2(dba)_3$ and TFP at 50 °C afforded (+)-crocacin C (**24**).

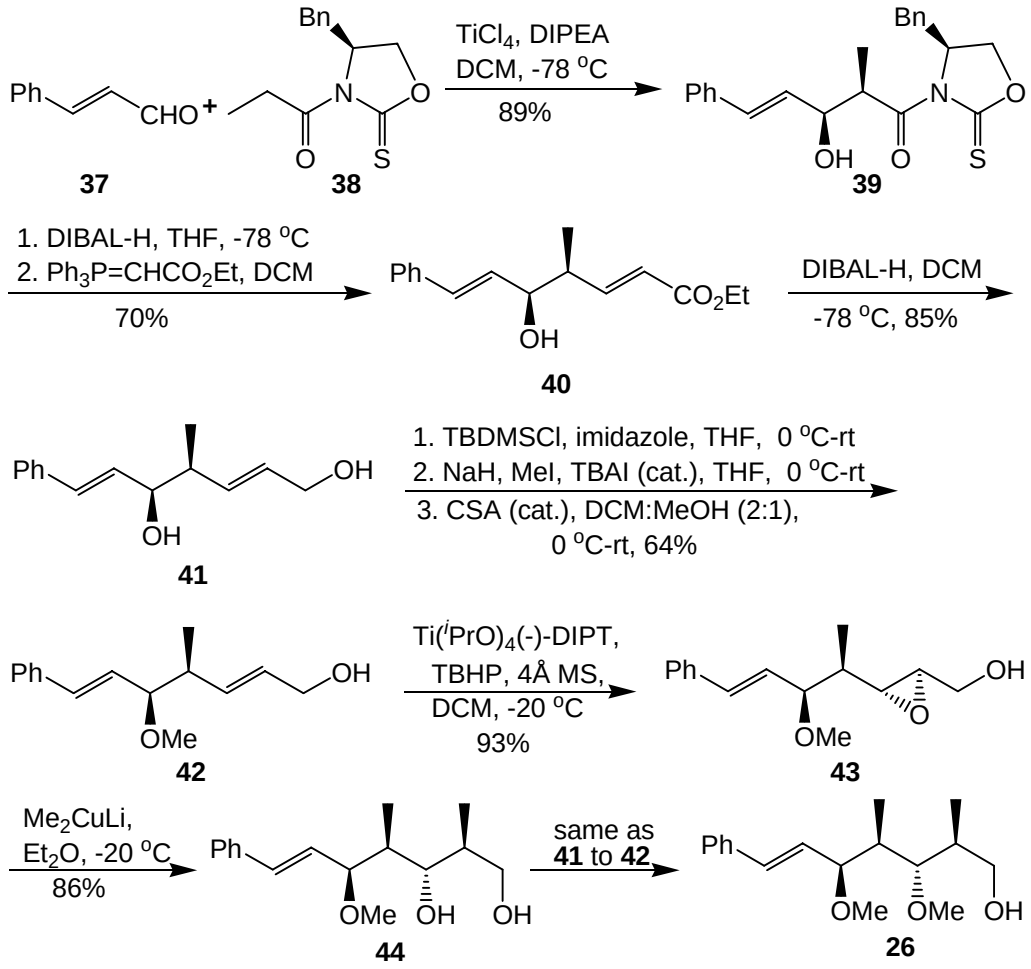
Scheme 1



The second report for the total synthesis of crocacin C came from Chakraborty et al. (Scheme 2).[39] The synthesis proceeded through the preparation of the common intermediate **26**. Henceforth while summarizing the synthetic approaches toward crocacins, the discussion will be restricted to the synthesis of **26**, if it is one of the intermediates. Asymmetric aldol addition of the titanium enolate derived from the acyloxazolidinethione **38** to cinnamaldehyde **37** gave the 'non-Evans' *syn* aldol product **39**. Controlled reduction of **39** with one equivalent of DIBAL-H gave an intermediate aldehyde, which was reacted with the stabilized ylide to obtain α,β-

unsaturated ester **40** in 70% yield from **39**. The ester function of **40** was subsequently reduced to furnish the diol **41** using DIBAL-H. Silyl protection of primary alcohol in **41** was followed by the methyl protection of secondary hydroxyl, finally the removal of silyl ether afforded compound **42**. The resulting allylic alcohol **42** was subjected to the Sharpless asymmetric epoxidation using (-)-DIPT to furnish expected epoxy alcohol **43** as the only diastereomer in 93% isolated yield. Regioselective opening of the epoxy alcohol **43** using Me_2CuLi gave the required 1,3-diol **44** as the major product. Diol **44** was converted to the intermediate **26** over three steps.

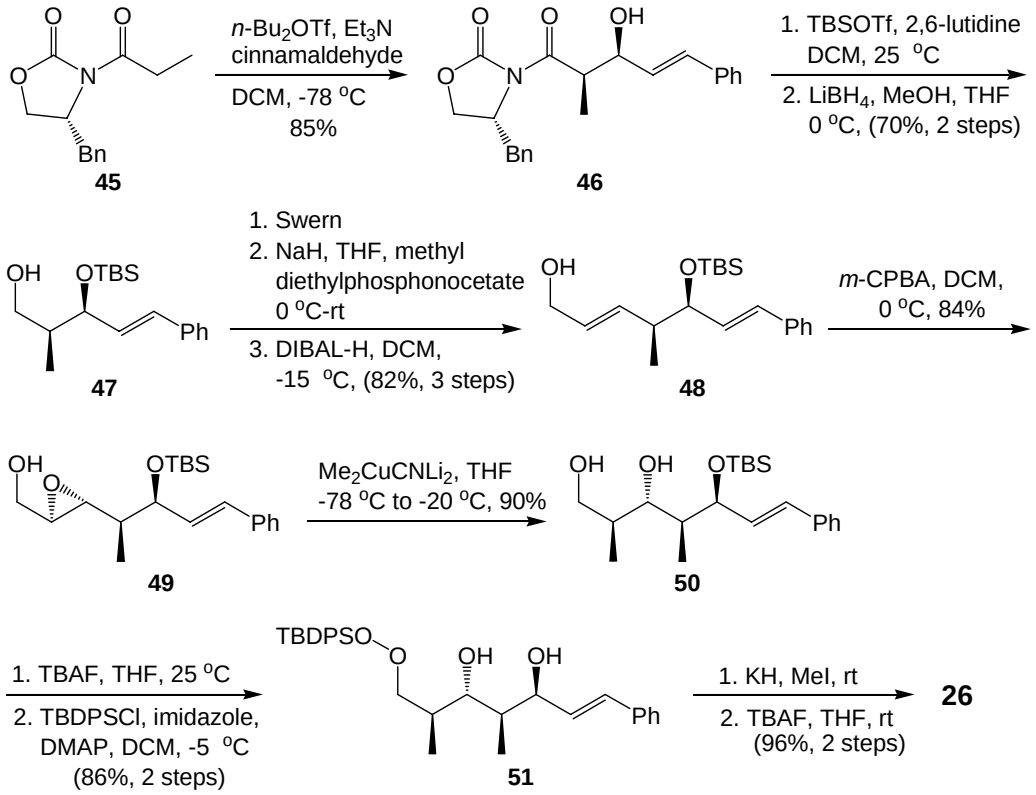
Scheme 2



Shortly after the report from Chakraborty's group, appeared the report from Dias et al. (Scheme 3).[40] The synthetic endeavor began with asymmetric aldol addition of the boron enolate derived from the oxazolidinone **45** with cinnamaldehyde (**37**), which gave the aldol adduct **46**. The aldol adduct **46** was converted to primary alcohol **47** after protection of the secondary hydroxyl group as its TBS ether followed

by the removal of the oxazolidinone auxiliary with $LiBH_4$ in MeOH. The primary alcohol **47** was oxidized under the standard Swern conditions and the unpurified aldehyde was directly subjected to a Horner-Emmons homologation with the requisite stabilized reagent to give an intermediate α,β-unsaturated ester that was treated with 2 equiv of diisobutylaluminum hydride at -15 ^oC, producing allylic alcohol **48** in 82% isolated yield for the three-step sequence.

Scheme 3

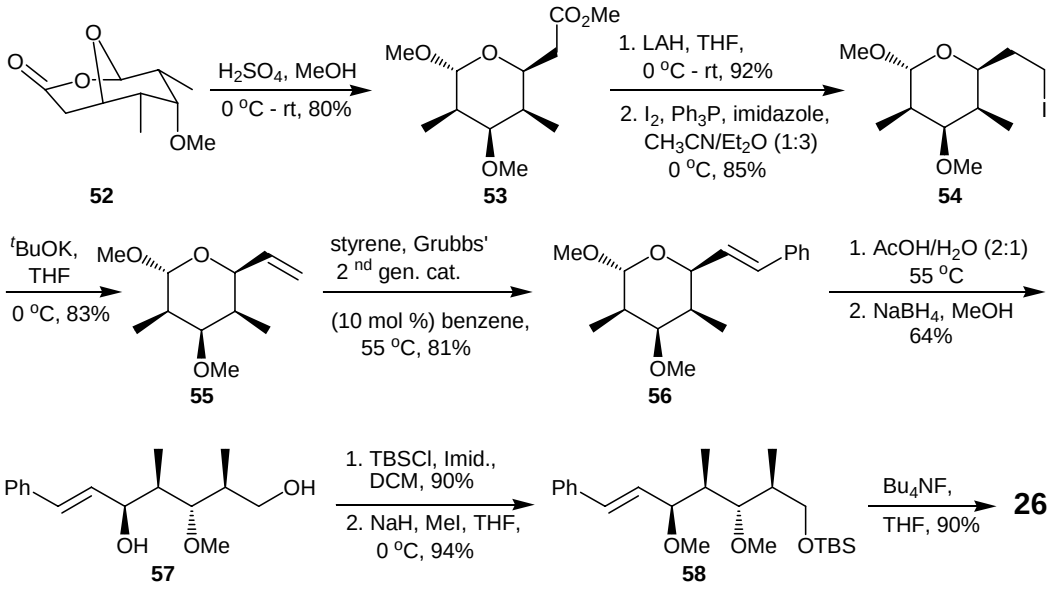


The epoxidation of allylic alcohol **48** with *m*-CPBA proceeded with high regio- and diastereoselectivity from the opposite side of the C-9 *tert*-butyldimethylsilyl group to give the *anti*-epoxy alcohol **49**. Epoxide opening was carried out with high regioselectivity by treatment of epoxy alcohol **49** with $Me_2CuCNLi_2$ to give diol **50**, having the *anti-anti-syn* stereochemistry. Removal of TBS group from diol **50** was followed by the selective primary protection to afford the diol **51**, which was converted to key intermediate **26** in two steps.

The report has appeared from Raghavan and co-workers in 2004 describing the synthesis of the enantiomer of the key intermediate **26**.[41] Yadav et al.[42] reported

the synthesis of **26** starting with the acid catalyzed methanolysis of the bicyclic lactone **52** followed by LAH reduction of the methyl ester **53** (Scheme 4). Resulting primary alcohol was converted into iodo derivative **54**. Upon treatment with base, the iodo derivative was converted to olefin **55**. Cross metathesis of **55** with styrene using Grubbs' second generation catalyst was effected in benzene at elevated temperature to procure the *E*-styrene derivative **56**. Acidic hydrolysis of **56** followed by borohydride reduction of resulting lactol afforded the open chain diol **57**, which was converted to **26** using routine protecting group manipulations.

Scheme 4

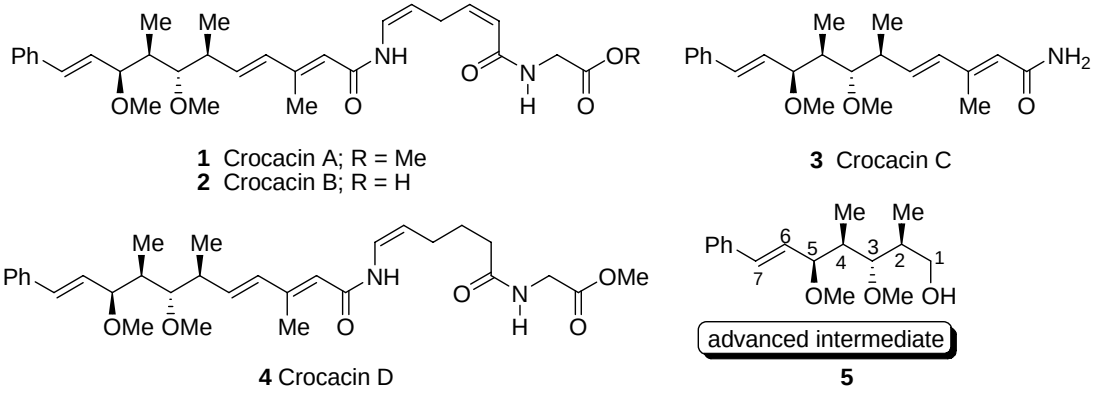


In the reports those appeared in the literature before our work, use of aldol reaction followed either by the chiral reduction of resulting ketone (Rizzacasa) or by stereoselective epoxidation and subsequent epoxide opening using methyl nuceophile (Chakraborty and Dias) happened to be the key transformations for the synthesis of **26**. We contemplated to synthesize **26** using Chiron approach, beginning from cheaply available D-glucose.

Present Work

The crocacins A (**1**) and B (**2**) were isolated from a strain of *Chondromyces crocatus* (Cm c2).[36] These compounds were identified as unusual linear dipeptides of glycine and a 6-aminohexadienoic acid and possess a complex *N*-acylpolyketide residue. The polyketide fragment is a substituted phenylundecatrienoic acid with an *anti-anti-syn* stereotetrad, which is also found in *C. crocatus* as its primary amide crocacin C (**3**). However, compound **3** may form in additional amounts during the isolation process due to cleavage of the acid-sensitive enamide bond in **1** and **2**. Crocacin D (**4**) was isolated from *C. pediculatus* and is a dipeptide of glycine and 6-aminohexenoic acid with the same *N*-acylpolyketide residue. The relative configurations depicted for **1**-**4** (Figure 1) were proposed by Jansen and co-workers using a combination of MM^+ calculations and NOE experiments.[36]

Figure 1 *Chemical structures of crocacins A-D*



The crocacins moderately inhibit the growth of a few Gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. Crocacin D (**4**) is the most active of the group against the fungus *Saccharmyces cerevisiae* with an MIC of 1.4 ng mL^{-1} compared to 10 μg mL^{-1} for crocacin A (**1**), 12.5 μg mL^{-1} for crocacin B (**2**) and 100 μg mL^{-1} for crocacin C (**3**).[36] A detailed study revealed that crocacin A (**1**) blocks NADH oxidation in beef heart submitochondrial particles, and the site of inhibition within the electron transport chain was identified as the cytochrome *bc*1 segment (complex III). Toxicity was also observed in L929 mouse fibroblast cell culture.[36]

The structures of crocacins (Figure 1) offer ample opportunities for synthetic chemists to develop unique approaches. Synthetic efforts toward crocacins A–D[38-42] have been significantly influenced by the synthesis of the advanced intermediate **5** (Figure 1), which is then elaborated to install variable side chains. The aldol reaction based synthetic protocols appears to be the most commonly used strategy for crocacin synthesis. Carbohydrate based protocols seem to be missing from the artillery eventhough chiral centers in D-glucose can be ostensibly transformed to produce the crocacin skeleton. Since there were already reports of synthesis of crocacins A-D from the intermediate **5**, we focused our efforts on the synthesis of **5**, beginning from cheaply available D-glucose.

Figure 2 *Retrosynthetic analysis for crocacins A-D*

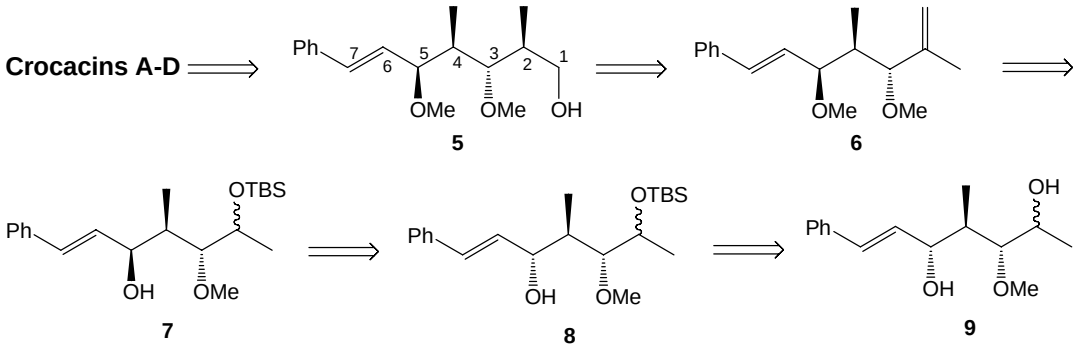
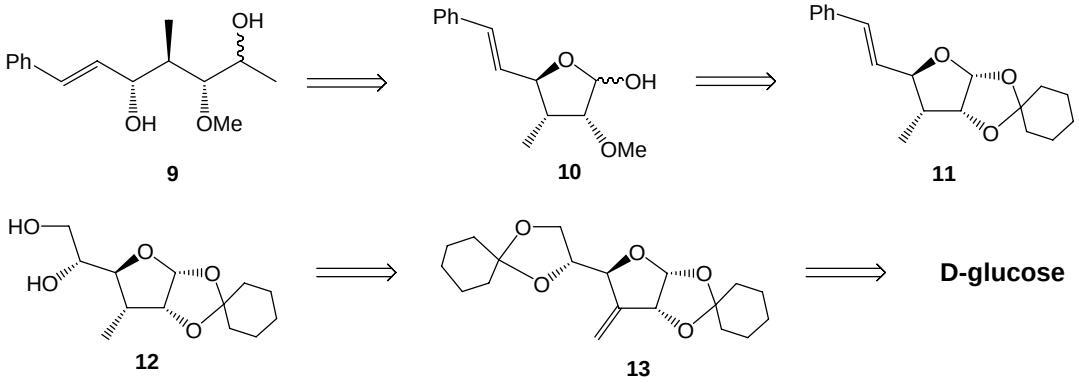


Figure 3 *Retrosynthetic analysis for crocacins A-D*



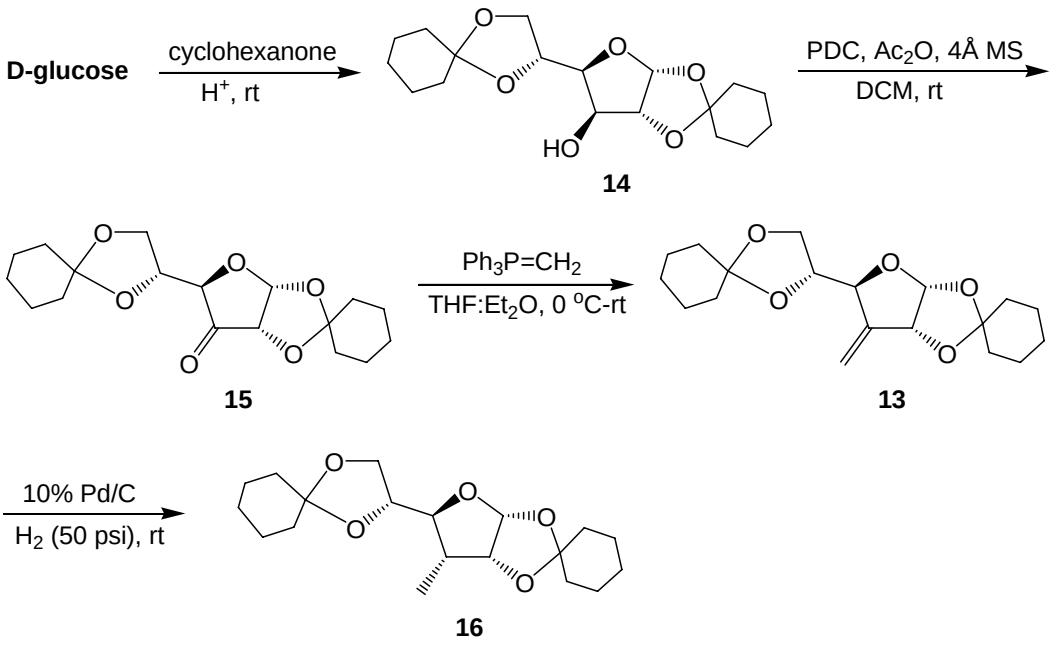
Retrosynthetic analysis for the common intermediate **5** is depicted in figure 2 and figure 3. The C-2 to C-7 skeleton of the target **5** was correlated with C-1 to C-6 skeleton of D-glucose. C-1 of **5** was to be obtained by addition of carbon atom to the sugar skeleton. Stereochemistry of the methyl group at C-2 of **5** could be fixed by the using the stereoselective hydroboration-oxidation of the olefin **6** (Figure 2). Presence

of a chiral center with oxygen function on neighboring carbon directs the stereochemistry of methyl group. It is possible to get the methyl stereochemistry either *syn* or *anti* with respect to adjacent alkoxy group depending upon the reaction conditions employed.[43] Synthesis of olefin **6** was visualized from the alcohol **7**. Careful stereochemical investigations revealed that the inversion of stereochemistry was required at the C-4 of glucose, so as to match the stereochemistry at C-5 of **5**. Mitsunobu reaction[44] of the suitably protected alcohol **8** was the key for this manipulation. Alcohol **8** would be a result of selective protection of non-cinnamyl secondary hydroxyl of diol **9**.

The diol **9** could be obtained by a methyl grignard on the lactol **10** (Figure 3), to be obtained from the compound **11**. Although installation of *E*-styrene moiety on the aptly substituted carbohydrate residue using the Wittig reaction was a legitimate proposition, was a matter of concern as the stereochemical outcome of the Wittig reaction is often a subject of so many parameters. A precursor for the Wittig reaction was the diol **12** which was to be prepared from known olefin **13** and in turn from D-glucose.

Synthetic endeavor began with the conversion of D-glucose into 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**14**) using cyclohexanone as a solvent in presence of H_2SO_4 (Scheme 1).[45] The free hydroxyl at C-3 was converted into corresponding ulose derivative **15** using PDC as an oxidizing agent in presence of molecular sieves and acetic anhydride.[46] The crude ulose derivative was subjected to one carbon Wittig olefination by treatment with methyltriphenylphosphorane to procure the olefin **13**.[47] In the ^{1}H NMR spectrum of **13** olefinic protons appeared at δ 5.43 and δ 5.53, anomeric proton (H-1) resonated as a doublet at δ 5.77 (J = 4.0 Hz), and H-2 appeared as a doublet of doublet at 4.85 ppm (J = 1.2, 4.0 Hz). In the ^{13}C NMR spectrum the olefinic carbons resonated at 113.3 (t) and 147.6 (s) ppm confirming the presence of exo-methylene group. A peak at *m/z* 359 $[M+Na]^+$ in the mass spectrum and all other analytical data were found in accordance with the structure.

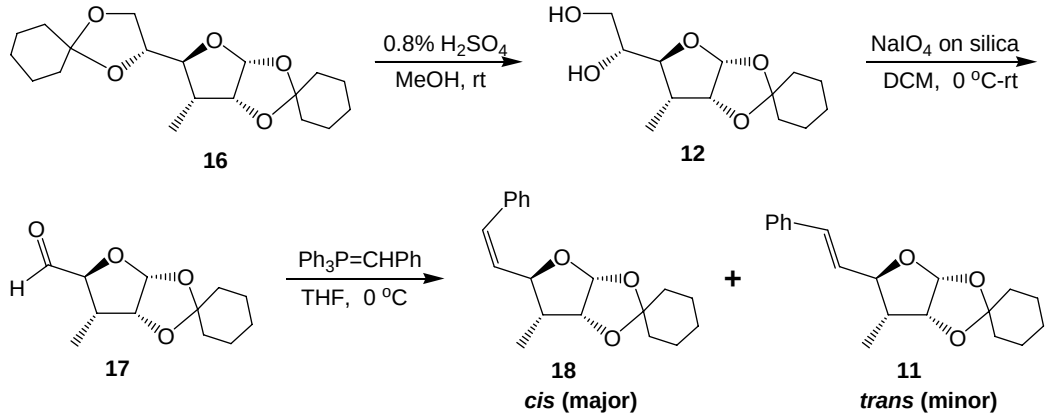
Scheme 1



As expected the hydrogenation of *exo*-methylene derivative **13** over Pd/C at 50 psi and at room temperature was found to be diastereospecific[47] resulting with a single product **16** in almost quantitative yield. In the ^{1}H NMR spectrum of **16**, H-2 appeared as a doublet of doublet at 4.51 ppm (J = 3.6, 4.6 Hz), proximity in the magnitude of the coupling constants clearly indicated a *cis*-relation between H-1 – H-2 and between H-2 – H-3, thus confirming the assigned relative stereochemistry. The newly formed methyl group resonated as a doublet at δ 1.19 (J = 6.8 Hz) and H-3 resonated as a multiplet between δ 1.88-1.95. Further, in the ^{13}C NMR spectrum, methyl at C-3 was located at 10.2 ppm. Peak in mass spectrum of **16** at *m/z* 361 $[M+Na]^{+}$ alongwith other analytical data supported the structure.

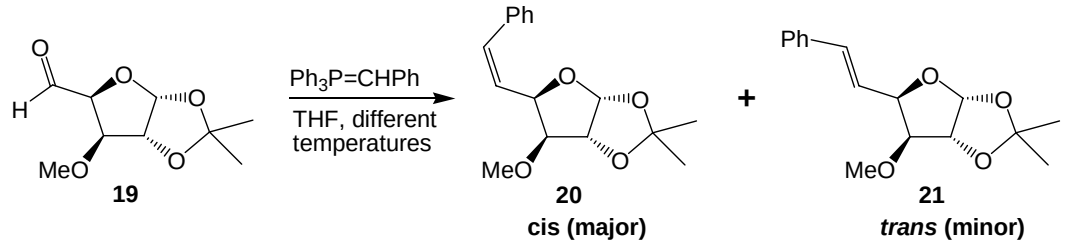
The selective deprotection of the 5,6-*O*-cyclohexylidene group of **16** to afford the diol **12** was accomplished with 0.8% H_2SO_4[48,55] in MeOH at ambient temperature for 24 h (Scheme 2). In the ^{1}H NMR spectrum, deprotection of one of the cyclohexylidene groups was evident from the presence of a multiplet (δ 1.39-1.70) integrating for 10 protons, suggesting the presence of only one cylclohexylidene group. The ^{13}C NMR spectrum, IR absorption at 3436 cm^{-1} indicating the presence of free hydroxyl and a peak in mass spectrum at *m/z* 281 $[M+Na]^{+}$ further supported the structure.

Scheme 2



Having the diol **12** in hand, the next task was the installation of the *E*-styrene moiety on the carbohydrate residue. For this purpose the diol was cleaved using sodium-metaperiodate adsorbed on silica.[49] The resulting aldehyde **17** was then subjected to the Wittig reaction with benzyltriphenylphosphorane (prepared by the action of *n*-BuLi on benzyltriphenylphosphonium bromide in THF) at 0 ºC. The ^{1}H NMR spectrum revealed the product to be predominantly the *Z* isomer (>90%) contaminated by *E* isomer (<10%). The same reaction when conducted at rt and under reflux conditions showed the gradual improvement in the ratio in favor of *E* isomer. However the percentage of *E* isomer could not be increased beyond 30%. All our attempts to prepare the *trans*-isomer with acceptable selectivity and yield *via* the Wittig reaction were unsuccessful. The fact that these geometrical isomers could not be separated either on TLC or by column chromatography had made the matter worse.

Scheme 3

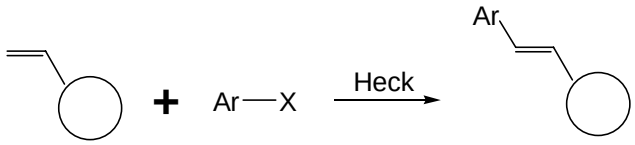


At this stage with a view to understand whether the observed stereochemical outcome of Wittig reaction was a special case pertaining to our current substrate, a model study was carried out on a commonly used sugar derived aldehyde **19**.[50] The Wittig reaction was carried out between aldehyde **19** and benzyltriphenylphosphorane at different temperatures (Scheme 3). The outcome was in accordance with the

preceding case. Though the percentage of *E* isomer increased with increase in temperature, here too, as observed with substrate **17**, it could not cross the barrier of 30% at reflux temperature of THF. This is evident from figure 6, which shows selected region of the ^{1}H NMR spectra of the product obtained by carrying out the Wittig reaction at rt and at 80 ºC in comparison with the spectrum of pure *trans* isomer. The aforementioned ratios were calculated from the ratio of the integrations of the signals in the ^{1}H NMR spectra and hence are approximate. It is pertinent to mention that **20** and **21** were also inseparable on TLC or by column chromatography.

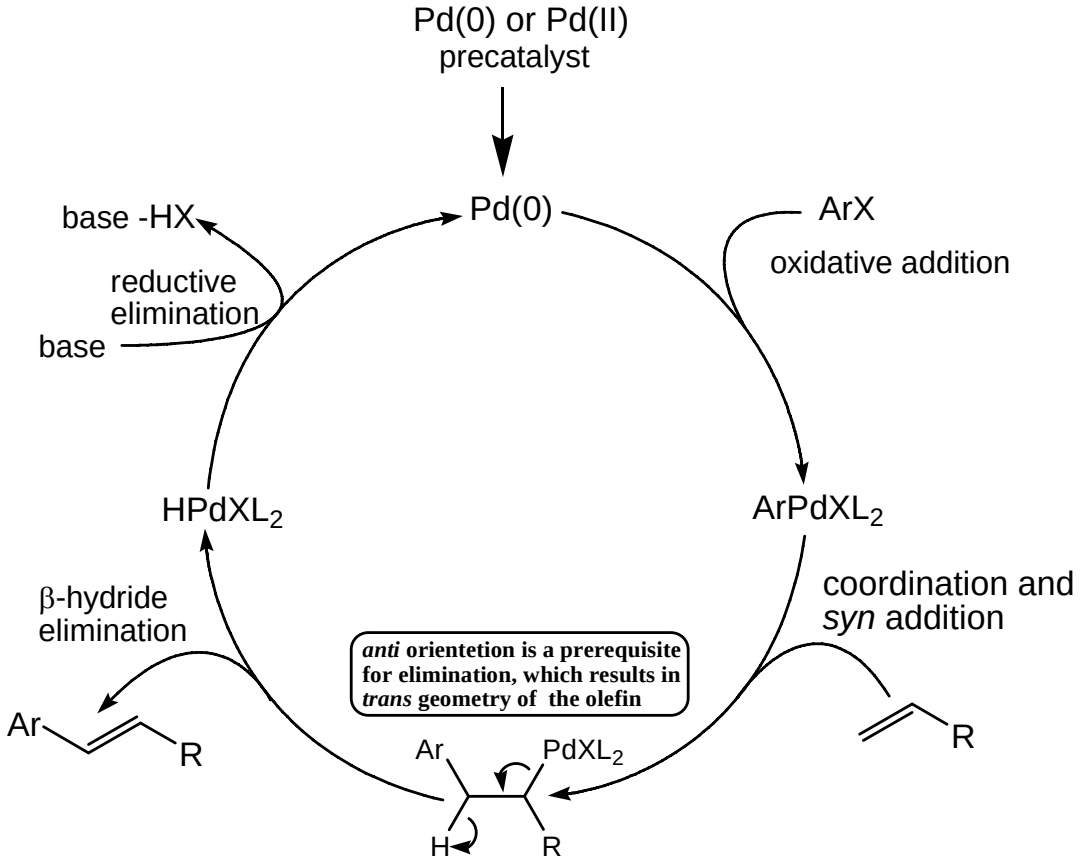
While looking for alternatives to install the *E*-styrene moiety on sugar residue, Julia olefination[51] and Heck[52] reaction emerged as solutions. Out of these Julia olefination, even with modified sulfones, is known to produce the mixtures of the corresponding *E* and *Z* isomers. The ratio of these geometrical isomers depends upon the substrate aldehyde, sulfone and other reaction conditions. Though there was a possibility of achieving acceptable yield and selectivity, the fact that the geometrical isomers were not separable by column chromatography in our case, impeded us from trying this option first.

Figure 4 *Heck reaction for trans di-substituted olefins*



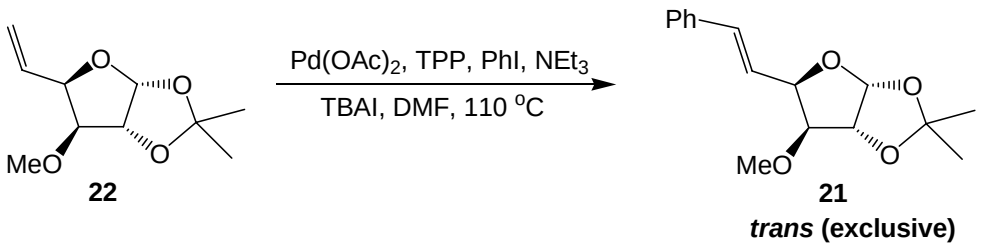
On the other hand Heck reaction between olefin and aromatic halide is known to furnish *E*-olefins exclusively owing to its mechanism (Figure 5). However, the application of this reaction to 5,6-ene derivatives of sugar substrates was not being reported. We thought of utilizing this unexploited tool for our purpose. If successful, it would not only solve our problem, but the generalization of this method would be of great aid in the cases of installation of *E*-styrene moiety on carbohydrate residues in future.

Figure 5 *Mechanism of the Heck reaction*



Keeping this in mind we decided to investigate the Heck reaction on a model substrate **22**[53], prior to its employment in main synthetic sequence (Scheme 4). Much to our pleasure, the Heck reaction of olefin **22** with iodobenzene worked well and produced the *E*-styrene derivative **21** as a sole product (scheme 4). In the ^{1}H NMR spectrum H-5 appeared as a doublet of doublet at δ 6.29 with J = 8.0, 16.0 Hz, whereas H-6 as a doublet at 6.73 with J = 16.0 Hz. Magnitude of the coupling constant between the olefinic protons established the *trans* geometry of the styrene derivative **21** beyond any ambiguity. The ^{13}C NMR spectrum and elemental analysis of **21** were found to support the structure proposed for it.

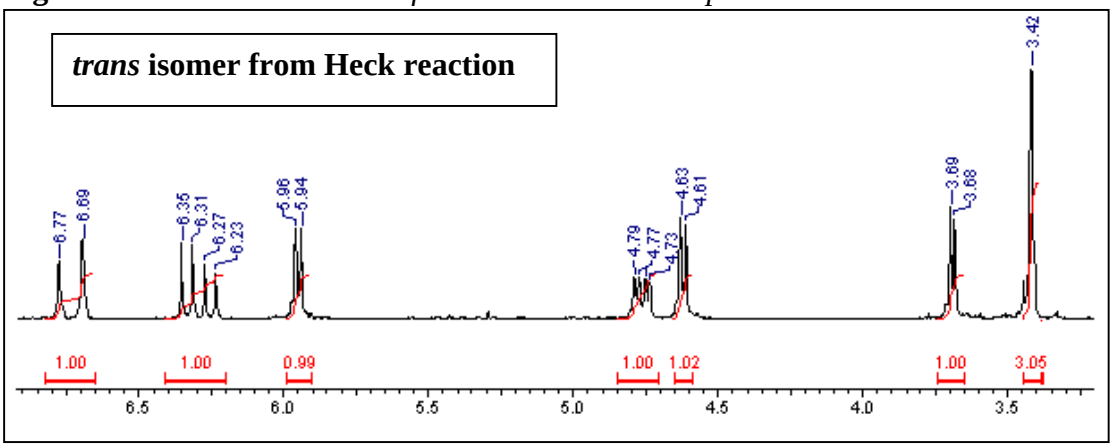
Scheme 4

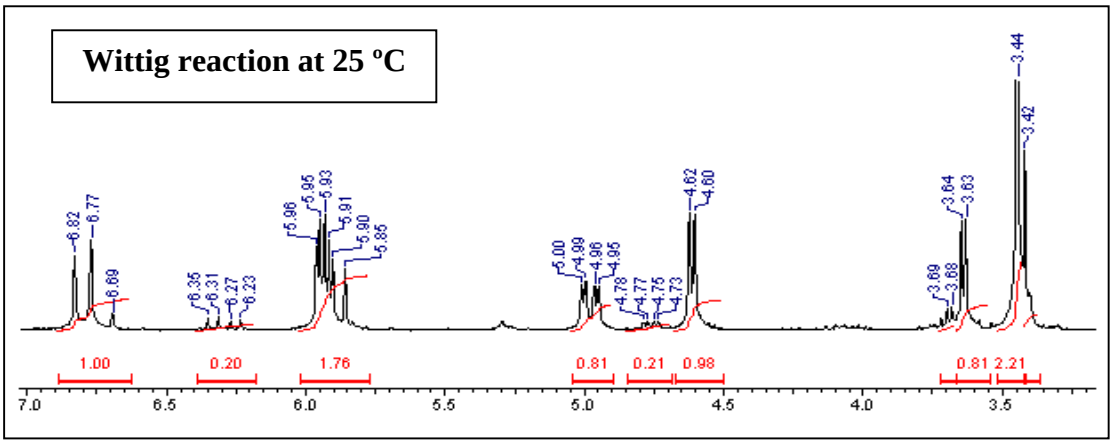


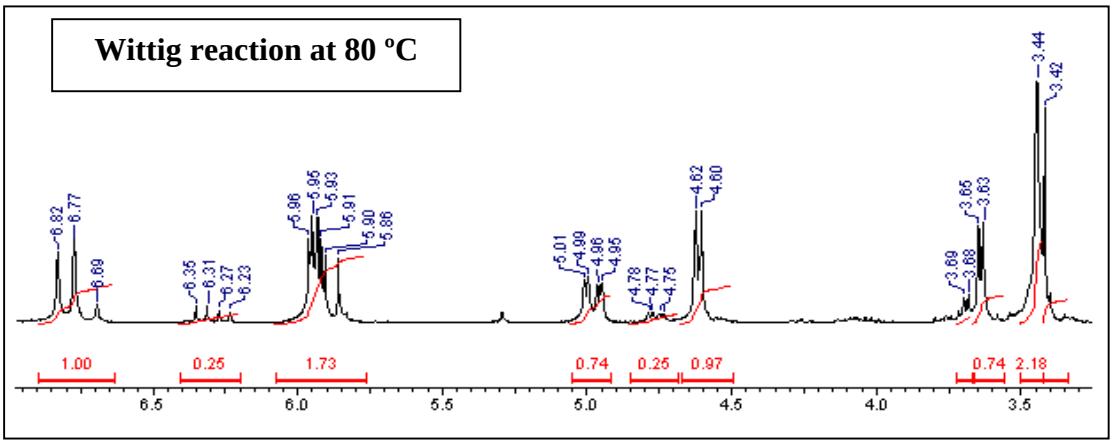
22 **21**

***trans* (exclusive)**

Figure 6 *Increase in the ratio of trans isomer with temperature*

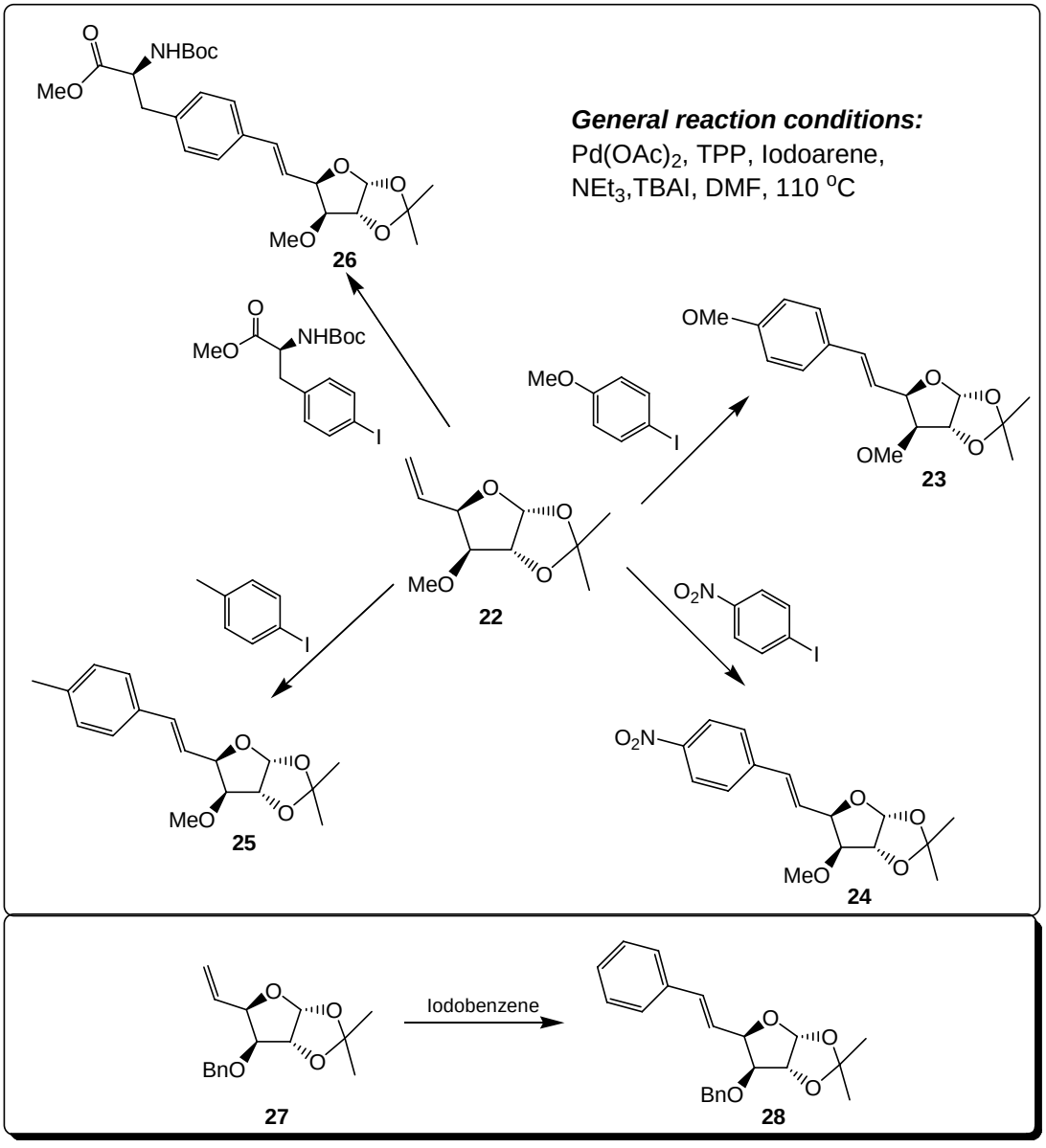






Encouraged by this result, we focused our efforts to explore the versatility of this reaction by changing either of coupling partners, sugar derived olefin and iodoarenes. Though yields and time taken for completion of reaction varied with substrate, all the reactions were successful and produced the corresponding *E*-styrene derivative as a sole product. It was observed that the reaction was fast and yields were better with electron-

Figure 7 *Heck reactions between sugar 5,6-enes and iodoarenes*

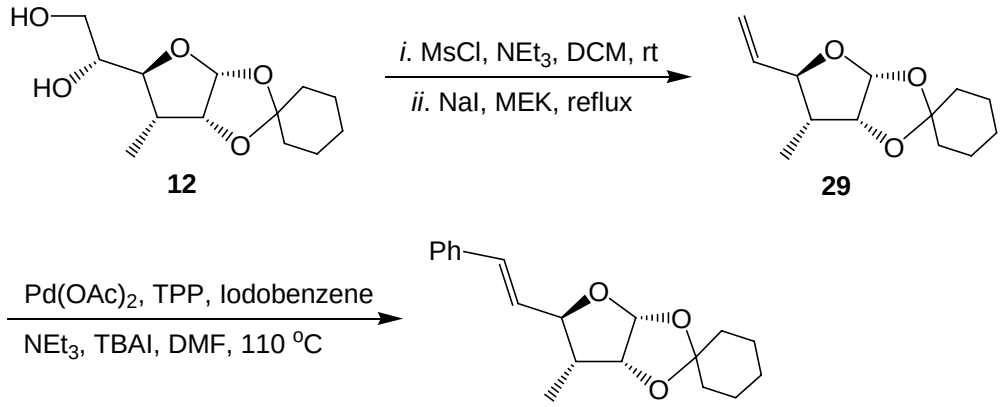


donating substituents such as *p*-methoxy (**23**) or *p*-methyl (**25**)on iodoarene than with electron withdrawer such as *p*-nitro (**24**). The reaction involving the coupling of protected 4-iodophenylalanine[54] with sugar derivative **22** to produce **26** was

interesting. This reaction also worked well, forging a carbon-carbon bond between the representatives of two biologically important classes of compounds, carbohydrates and amino acids. In the ^{1}H NMR spectrum of **26**, two singlets corresponding to isopropylidene group on sugar residue were observed at δ 1.33 and δ 1.52, integrating for three protons each. A singlet at δ 1.40, integrating for nine protons, represented the Boc protecting group on amino acid residue. Olefinic protons appeared at δ 6.24 and δ 6.68 with the coupling constant of 16.1 Hz, establishing the *trans* geometry. The ^{13}C NMR spectrum and elemental analysis were found to support the proposed structure.

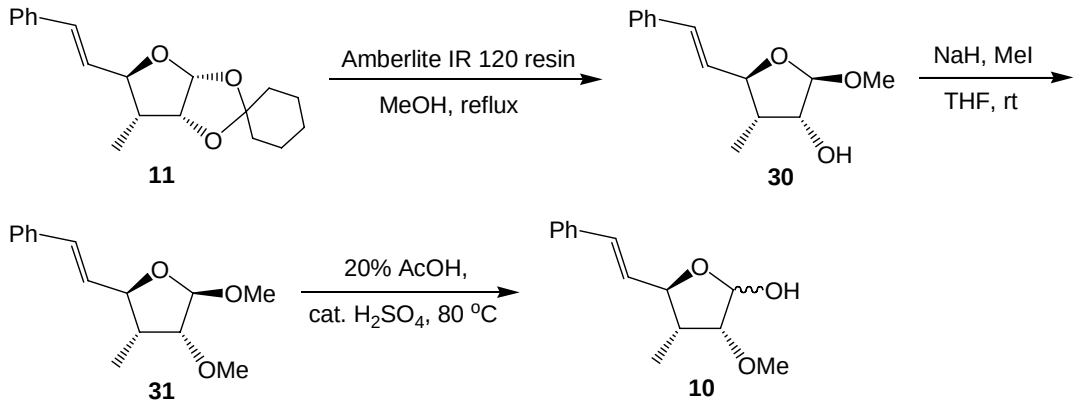
After successfully generalizing the Heck reaction of carbohydrate derivatives, we focused our attention on the original synthetic endeavor. The olefin **29** was prepared from the diol **12**.[55] As established in all other cases, the Heck reaction between the olefin **29** and iodobenzene resulted into the formation of required *E*-styrene derivative **11** as the only product (Scheme 5).

Scheme 5



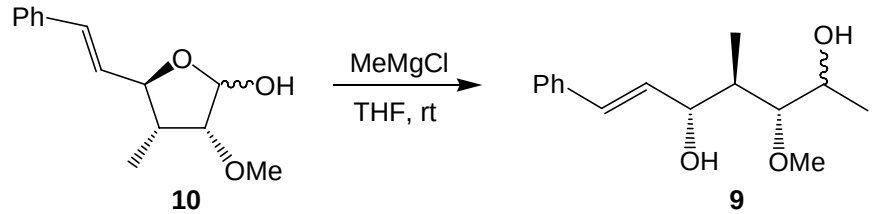
The highest mass peak was seen at *m/z* 323 $[M+Na]^{+}$ in the mass spectrum of compound **11**. In the ^{1}H NMR spectrum, olefinic protons were observed at δ 6.07 and δ 6.63, with the coupling constant of 16.2 Hz, clearly manifesting the geometry of the olefin to be *trans*. The ^{13}C NMR specturm and elemental analysis were found to be in accordance with the structure.

Scheme 6



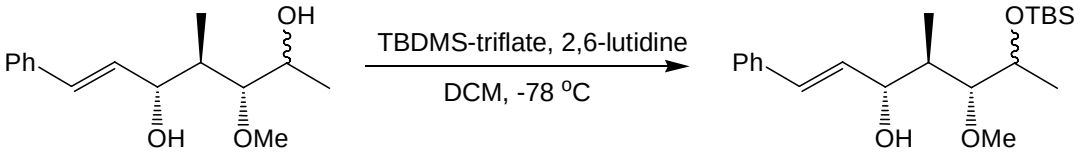
Compound **11** was refluxed with Amberlite IR 120 resin in methanol to effect the deprotection of the cyclohexylidene group (Scheme 6).[56] The methyl glycoside **30** was obtained in good yield. In the ^{1}H NMR spectrum, H-1 appeared at δ 4.85 as a singlet, indicating the presence of β anomer. The anomeric methyl group was seen at δ 3.42, as a singlet, integrating for three protons. The highest mass peak in mass spectrum at *m/z* 257 $[M+Na]^{+}$, supported the structure and the elemental analysis was found to match the calculated values within permissible limits of deviation. The free hydroxyl at C-2 was converted into its methyl ether using NaH and MeI in THF to afford compound **31**.[57] The presence of two singlets at δ 3.41 and δ 3.43 in the ^{1}H NMR spectrum, integrating for three protons each, confirmed the presence of two methyl groups. This was further supported by two signals in the ^{13}C NMR spectrum at δ 54.7 and δ 58.1. The mass spectrum and elemental analysis were in conformity with the structure. The hemiacetal **31** was converted into the lactol **10** on treatment with aqueous acetic acid in presence of catalytic sulfuric acid at elevated temperature. The spectral and analytical data for the lactol **10** was in agreement with the proposed structure.

Scheme 7



Treatment of the lactol **10** with methylmagnesiumchloride in THF afforded the diol **9** (Scheme 7). The presence of the free hydroxyl groups was evident from the IR absorption at 3424 cm^{-1}. In the mass spectrum the mass peak was observed at *m/z* 273 $[M+Na]^+$. The ^1H NMR spectrum of **9** exhibited two doublets in aliphatic region at δ 0.96 and δ 1.26, integrating for three protons each, confirming the addition of the mehyl group at C-1 of lactol. In the ^{13}C NMR spectrum, these two methyl groups were represented by the signals at 13.9 and 20.5 ppm.

Scheme 8

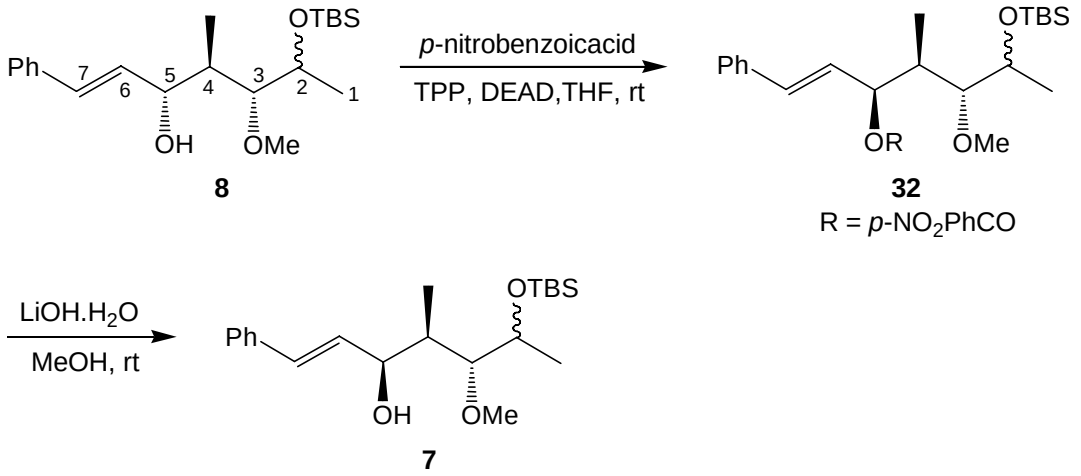


9 **8**

The next critical transformation to be carried out was the inversion of stereochemistry at the C-4. Mitsunobu esterification followed by hydrolysis of the resulting ester was the protocol. For this purpose, it was necessary to protect the other secondary alcohol and this was achieved by treating the diol **9** with TBDMS-triflate,[58] in presence of 2,6-lutidine, at –78 ºC, in anhydrous DCM (Scheme 8). The structure of **8** was supported by the ^1H NMR spectrum, where the signals corresponding to the TBS group integrating for six and nine protons appeared in the upfield region. The prediction of regiochemistry of the TBS protection was difficult at this stage as there was no significant change in the chemical shifts of protons. However, at later stage this was confirmed. Elemental analysis and the peak in mass spectrum at *m/z* 387 $[M+Na]^+$ were found in accordance with the structure of **8**.

Treatment of the mono-TBS derivative **8** with 4-nitrobenzoicacid in presence of TPP and DEAD afforded the benzoate ester **32** (Scheme 9).[44] Presence of benzoate ester was visible in the ^1H NMR spectrum by the appearance of additional signals in aromatic region. The hydrolysis of the benzoate ester **32** was achieved by treatment with lithium hydroxide monohydrate in methanol to afford **7**.

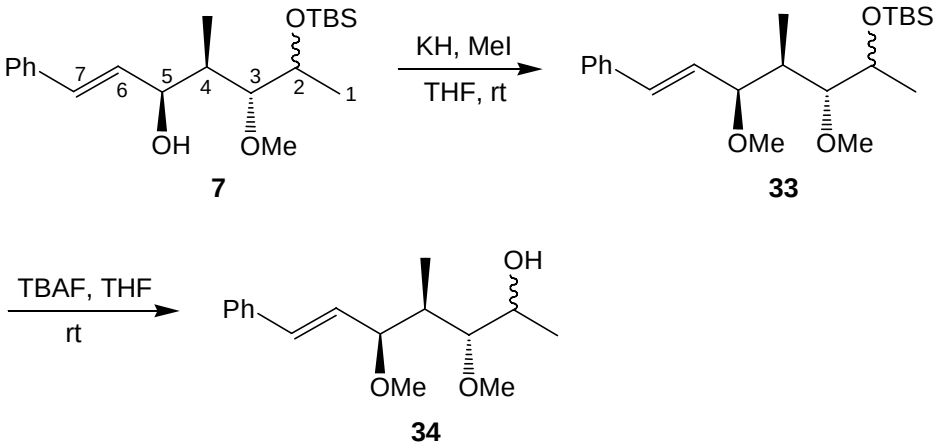
Scheme 9



8 **32** R = *p*-NO_2PhCO **7**

The free hydroxyl function in compound **7** was protected as its methyl ether by treatment with KH and MeI,[57] in THF, to afford compound **33** (Scheme 10). The silyl ether in **33** was subsequently removed by the action of TBAF[59] to give compound **34**. In the ^{1}H and ^{13}C NMR spectra of **34**, the peaks due to TBS group were absent. Elemental analysis for compound **34** was found to support the structure.

Scheme 10

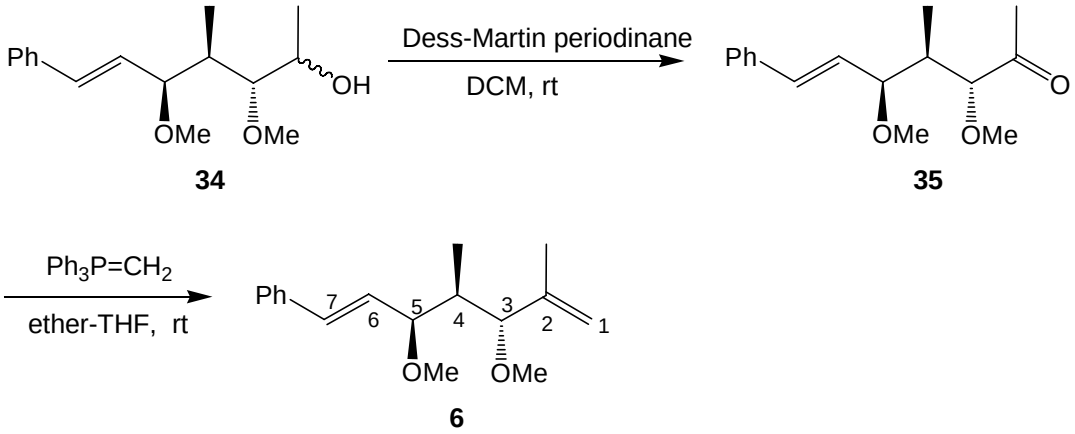


7 **33** **34**

The secondary hydroxyl group liberated after removal of TBS-ether was oxidized using Dess-Martin periodinane[60] in DCM (Scheme 11). The ^{1}H NMR spectrum of the product was gratifying since it unequivocally established the correctness of our annotations. A singlet at δ 2.13 in the ^{1}H NMR spectrum, integrating for three protons, clearly suggested the presence of a methyl ketone and established the structure of the product to be **35**. Two methoxy groups were seen at 3.30 and 3.36 ppm as singlets, integrating for three protons each. The H-3 appeared as

a doublet at δ 3.47 with a coupling constant of 8.8 Hz whereas the H-5 was seen at δ 4.01 as a double doublet with J = 3.4, 7.3 Hz. The resonances due to olefinic protons were seen at δ 6.12 and δ 6.57. Since the reaction carried out on a mixture of alcohols had resulted into formation of a single ketone, our conjecture of compounds **7**, **8**, **33** and **34** being the epimeric mixtures was upgraded to actuality. In the ^{13}C NMR spectrum, the carbonyl carbon resonated at δ 210.5.

Scheme 11



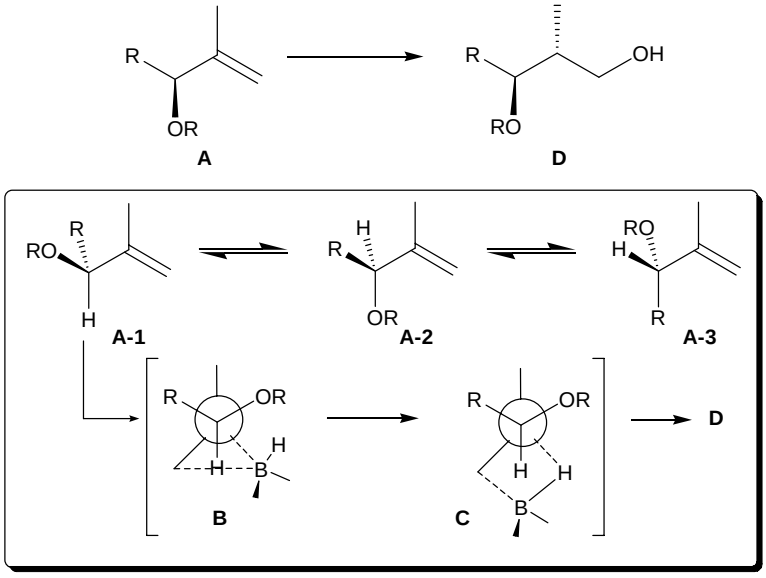
34 **35** **6**

One carbon homologation of the ketone **35** was brought about by treating it with mehyltriphenylphosphorane to furnish olefin **6**. In the ^{1}H NMR spectrum of **6** the olefinic protons on C-1 appeared at δ 4.92 and δ 4.99, as a singlet and multiplet respectively. The allylic methyl group resonated at δ 1.60, as a singlet integrating for three protons. The H-3 appeared as a doublet at 3.49 ppm with J = 10.1 Hz and the H-5 as a double doublet at 4.20 ppm with J = 3.3, 6.8 Hz. Two singlets corresponding to two methoxy groups were seen at 3.22 and 3.34 ppm. In the ^{13}C NMR spectrum the C-1 resonated at 115.8 ppm. Presence of olefinic methylene group was evident from the DEPT spectrum. Two quaternary carbons in olefinic/aromatic region of ^{13}C NMR could be easily co-related to one olefinic and one aromatic quaternary carbon present in compound **6**.

Having the olefin **6** in hand, the stage was set for the last transformation, the stereo selective hydroboration, to achieve our synthetic target. It is well documented in the literature that the hydroborations of the olefins can be directed by the preexisting chiral centers in the molecule. It is possible to get either *syn* or *anti* product in good selectivity by changing reaction conditions. The $Rh(PPh_3)_3Cl$

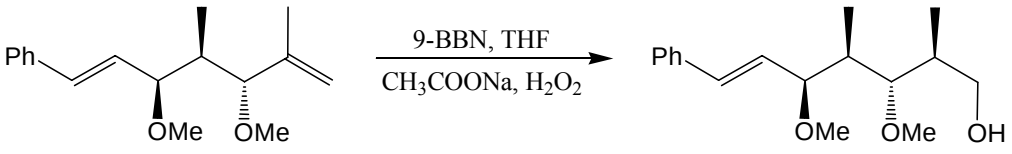
catalyzed hydroboration of 1,1-disubstiturted acyclic alcohol or ether is known to proceed with high levels of *syn* stereoselectivity. Hydroboration of the same substrate when carried out in absence of catalyst, using hindered dialkyl boranes such as 9-BBN, is known to produce the complementary stereochemical outcome, *anti* diastereomer being the major product in this case. The *anti* selectivity with 9-BBN is explained by a simple model shown in the figure below.[43]

Figure 8 *Diastereoselectivity in hydroboration*



Considering the three minimum energy conformations of the allylic ether (**A-1**, **A-2** and **A-3**), one of the lowest energy conformers (say **A-1**) would be expected to be the most reactive since it leads to the probable transition state **B** or **C** in which the smallest substituent (H) is oriented over the face of transition state ring. The approach of borane to the less hindered side of olefinic π system would then lead to the least sterically encumbered transition state and thus to the *threo* product. The minor *erythreo* isomer could arise from olefin addition to more hindered face of **A-1** or, perhaps more likely, to less hindered face of **A-2**.

Scheme 12

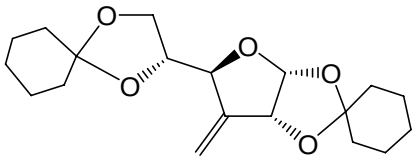


Keeping this in mind the hydroboration-oxidation of the olefin **6** was planned. The initial complex formation took 2 h, after which, saturated sodium acetate and hydrogen peroxide were added and the stirring continued for further 6 h. Mass spectrum of the product exhibited peak at *m/z* 301 $[M+Na]^+$, suggesting the successful conversion into desired product. The ^1H NMR and ^{13}C NMR spectra of the product suggested it to be a single diastereomer. The spectral data of our synthetic **5** was found to be in excellent agreement with the literature reports, indicating that the hydroboration had furnished exclusively the *anti* diastereomer. In the ^1H NMR spectrum protons of the hdroxymethyl group appeared at δ 3.51 and δ 3.82, as double doublets having the geminal coupling constant of 11.2 Hz. The H-3 resonated at δ 3.27 and H-5 at δ 4.05. Two singlets for two methoxy groups were observed at 3.31 and 3.54 ppm, whereas, the two methyl groups resonated at 0.9 and 1.2 ppm, as doublets with J = 7.0 Hz. Signals due to olefinic protons were seen at 6.16 and 6.56 ppm. In the ^{13}C NMR spectrum the hydroxymethyl group was seen at 64.6 ppm. Elemental analysis, IR, and optical rotation for **5** were found in accordance with proposed structure.

Conclusion: Synthesis of the advanced intermediate **5**, for the synthesis of crocacin group of compounds, was successfully completed from D-glucose. Wittig reactions between C-5 sugar aldehydes and benzyltriphenylphosphorane produced the mixtures of *E* and *Z* isomers, in which, the unwanted *Z* isomer always predominated. Heck reaction of carbohydrate 5,6-ene with iodobenzene, was successfully employed to produce the required *E* styrene derivative exclusively, this being the first example of Heck reaction on carbohydrate 5,6-ene. Versatility of this transformation was proved by successful execution using various iodo-arenes and sugar derived olefins. Mitsunobu reaction was used for the desired inversion of stereochemistry at C-5 of the target molecule. Finally the diastereospecific hydroboration using 9-BBN furnished the target molecule **5**.

Experimental

3-Deoxy-3-*C*-methylene-1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranose (13)

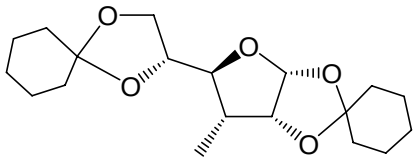


13

Compound **13** was prepared using literature procedre.[47]

Yield	**:**	12.48 g, 84% (over two steps)
Mol. Formula	**:**	$C_{19}H_{28}O_5$
Mol. Weight	**:**	336
ESI-MS *m/z*	**:**	359 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 67.86; H, 8.33% Found: C, 67.51; H, 8.05%
$[\alpha]_D^{25}$	**:**	+105.7 (*c* 1.2, $CHCl_3$), literature[47] $[\alpha]_D^{30}$ 106.0 (*c* 2.0, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3018, 2939, 2862, 1667, 1449, 1215, 1163, 1040, 1018, 827, 757, 668 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.39-1.73 (m, 20H), 3.90 (dd, *J* = 5.9, 8.0 Hz, 1H), 3.99 (dt, *J* = 5.9, 7.9 Hz, 1H), 4.04 (dd, *J* = 5.9, 8.0 Hz, 1H), 4.57 (dd, *J* = 1.8, 7.9 Hz, 1H), 4.85 (dd, *J* = 1.2, 4.0 Hz, 1H), 5.43 (br. d, *J* = 1.8 Hz, 1H), 5.53 (br. d, *J* = 1.2 Hz, 1H), 5.77 (d, *J* = 4.0 Hz, 1H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 23.8 (t), 24.0 (t), 24.1 (t), 25.1 (t), 25.3 (t), 35.2 (t), 36.5 (t), 36.8 (t), 37.1 (t), 66.9 (t), 77.2 (d), 79.6 (d), 81.8 (d), 104.3 (d), 110.4 (s), 113.2 (s), 113.3 (t), 147.6 (s)

3-Deoxy-3-*C*-methyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-allofuranose (16)



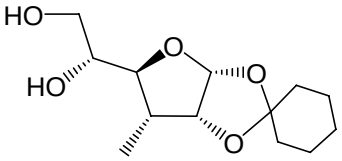
16

A solution of olefin **13** (25 g, 74.4 mmol) in MeOH (250 mL) was hydrogenated in presence of potassium carbonate (10 g, 72.46 mmol) and 10% Pd/C (1 g) at 50 psi pressure at rt. After 3 h, the reaction mixture was filtered through pad of *Celite* and concentrated. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated to afford the crude product **16**, which was used as such for the next reaction. A portion of the product was purified for spectral and analytical purposes.

Yield	**:**	24.39 g, 97%
Mol. Formula	**:**	$C_{19}H_{30}O_5$
Mol. Weight	**:**	338
ESI-MS *m/z*	**:**	361 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 67.46; H, 8.88% Found: C, 67.63; H, 9.24%
$[\alpha]_D^{25}$	**:**	+36.5 (*c* 2.0, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3017, 2939, 2863, 1462, 1367, 1280, 1215, 1163, 1107, 1017, 926, 849, 758, 667 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.19 (d, *J* = 6.8 Hz, 3H), 1.40-1.72 (m, 20H), 1.88-1.95 (m, 1H), 3.64 (dd, *J* = 7.1, 9.7 Hz, 1H), 3.88 (dd, *J* = 5.6, 8.3 Hz, 1H), 3.93-3.97 (m, 1H), 4.05 (dd, *J* = 6.4, 8.4 Hz, 1H), 4.51 (dd, *J* = 3.6, 4.6 Hz, 1H), 5.72 (d, *J* = 3.6 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 10.2, 23.7, 23.9, 24.0, 25.1, 25.2, 35.0, 36.1, 36.3, 36.5, 43.1, 67.4, 77.7, 83.0, 104.6, 111.0, 112.1

3-Deoxy-3-*C*-methyl-1,2-*O*-cyclohexylidene-α-D-allofuranose (12)



12

To a solution of **16** (15.0 g, 44.38 mmol) in MeOH (150 mL), was added 0.8% sulfuric acid solution in water (100 mL). The reaction mixture was stirred for 24 h at rt and then neutralized by addition of solid sodium bicarbonate. Solvents were removed and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1) to procure **12** as sticky white solid.

Yield **:** 9.50 g, 83%

Mol. Formula **:** $C_{13}H_{22}O_5$

Mol. Weight **:** 258

ESI-MS *m/z* **:** 281 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 60.47; H, 8.53%

Found: C, 60.71; H, 8.88%

$[\alpha]_D^{25}$ **:** +34.5 (*c* 2, $CHCl_3$)

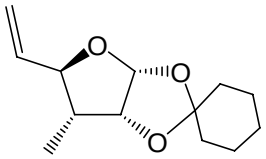
IR ($CHCl_3$) $\tilde{\nu}$ **:** 3436, 3018, 2939, 2864, 1449, 1369, 1280, 1215, 1115, 1037, 1016, 927, 849, 757, 668 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) **:** δ 1.15 (d, *J* = 6.8 Hz, 3H), 1.39-1.70 (m, 10H), 1.96-2.04 (m, 1H), 2.37 (br. s, 1H), 2.66 (br. s, 1H), 3.70-

3.76 (m, 3H), 3.82 (dd, *J* = 4.4, 10.3 Hz, 1H), 4.52 (t, *J* = 4.0 Hz, 1H), 5.75 (d, *J* = 4.0 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) **:** δ 10.3 (q), 23.6 (t), 23.9 (t), 25.0 (t), 36.0 (t), 36.4 (t), 40.4 (d), 63.5 (t), 73.2 (d), 82.9 (d), 83.3 (d), 104.3 (d), 112.1 (s)

3,5,6-Trideoxy-3-*C*-methyl-1,2-*O*-cyclohexylidene -α-D-*ribo*-hex-5-eno-furanose (29)



29

To a solution of diol **12** (5 g, 19.38 mmol) and Et_3N (16.2 mL, 116.45 mmol) in DCM (50 mL) at 0 ºC, was introduced mesyl chloride (4.5 mL, 58.42 mmol) in drop-wise manner. The reaction mixture was allowed to attain room temperature and stirred for 2 h. The reaction mixture was quenched by addition of ice and the aqueous layer was extracted with DCM. The combined organic layer was dried over sodium sulfate and concentrated. The crude residue was used as such for the next reaction. The crude dimesyl derivative (7.62 g, 18.41 mmol), was dissolved in MEK (80 mL) and sodium iodide (16.57 g, 110.47 mmol) was added. The reaction mixture was heated to reflux for 6 h. The solvent was removed and the residue was partitioned between water and ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with saturated sodium thiosulphate, brine, dried over sodium sulfate and concentrated. The crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford the olefin **29** as colorless oil.

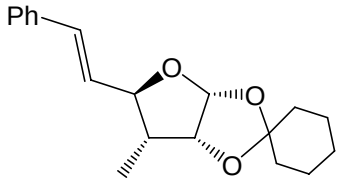
Yield **:** 3.05 g, 70% (over two steps)

Mol. Formula **:** $C_{13}H_{20}O_3$

Mol. Weight **:** 224

Elemental Analysis	**:**	Calcd: C, 69.64; H, 8.93% Found: C, 69.39; H, 9.12%
$[\alpha]_D^{25}$	**:**	+20.1 (*c* 0.9, $CHCl_3$)
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ 1.04 (d, *J* = 6.6 Hz, 3H), 1.38-1.77 (m, 11H), 4.10 (dd, *J* = 7.3, 10.3 Hz, 1H), 4.56 (dd, *J* = 3.7, 4.4 Hz, 1H), 5.21 (d, *J* = 10.3 Hz, 1H), 5.31 (d, *J* = 16.9 Hz, 1H), 5.75 (ddd, *J* = 7.3, 10.3, 16.9 Hz, 1H), 5.83 (d, *J* = 3.7 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$)	**:**	δ 8.3 (q), 23.3 (t), 23.5 (t), 24.7 (t), 35.6 (t), 36.0 (t), 43.9 (d), 81.6 (d), 83.4 (d), 104.2 (d), 111.3 (s), 117.0 (t), 135.7 (d)

(*E*)-3,5,6-Trideoxy-3-*C*-methyl-6-*C*--phenyl-1,2-*O*-cyclohexylidene-α-D-*ribo*-hex-5-enofuranose (11)

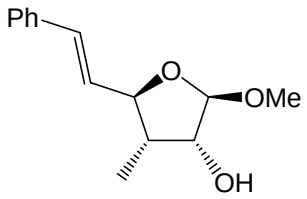


11

To a thoroughly degassed solution of olefin **29** (900 mg, 4.02 mmol), TPP (105 mg, 0.40 mmol), triethyl amine (2.24 mL, 16.10 mmol), tetrabutyl ammonium iodide (1.80 g, 4.88 mmol) and iodobebnzene (0.9 mL, 8.04 mmol) in DMF (20 mL) was added palladium acetate (22 mg, 98.21 μmol) and the reaction mixture was heated at 110 ºC for 6 h. The reaction mixture was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous layer was repeatedly extracted with ethyl acetate and the combined organic extract was washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **11** as a sticky solid.

Yield	**:**	756 mg, 63%
Mol. Formula	**:**	$C_{19}H_{24}O_3$
Mol. Weight	**:**	300
ESI-MS *m/z*	**:**	323 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 76.00; H, 8.00% Found: C, 76.44; H, 8.30%
$[\alpha]_D^{25}$	**:**	+20.1 (*c* 0.9, $CHCl_3$)
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.07 (d, *J* = 6.5 Hz, 3H), 1.37-1.84 (m, 11H), 4.26 (t, *J* = 8.1 Hz, 1H), 4.57 (t, *J* = 3.2, 1H), 5.85 (d, *J* = 3.2 Hz, 1H), 6.07 (dd, *J* = 8.1, 16.2 Hz, 1H), 6.63 (d, *J* = 16.2 Hz, 1H), 7.21-7.37 (m, 5H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 9.0 (q), 23.7 (t), 24.0 (t), 25.1 (t), 36.1 (t), 36.4 (t), 44.7 (d), 82.1 (d), 83.6 (d), 104.6 (d), 111.9 (s), 126.6 (d), 127.0 (d), 127.8 (d), 128.5 (d), 133.1 (d), 136.6 (s)

(*E*)-Methyl 3,5,6-trideoxy-3-*C*-methyl-6-*C*-phenyl-β-D-*ribo*-hex-5-enofuranoside (30)



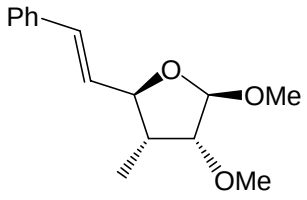
30

Activated amberlite IR-120 resin (7.0 g) was added to a solution of **11** (2 g, 6.67 mmol) in MeOH (25 mL) and the reaction mixture was refluxed for 8 h. The reaction mixture was filtered and the resin was washed with methanol. The filtrate was neutralized by addition of triethyl amine and concentrated. The crude residue was

purified on silica gel using ethyl acetate-light petroleum (1:4) to furnish the methyl glycoside **30**.

Yield	**:**	1.28 g, 82%
Mol. Formula	**:**	$C_{14}H_{18}O_3$
Mol. Weight	**:**	234
ESI-MS *m/z*	**:**	257 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 71.79; H, 7.69% Found: C, 71.54; H, 7.99%
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.07 (d, *J* = 7.1 Hz, 3H), 2.19-2.26 (m, 1H), 3.42 (s, 3H), 4.06 (d, *J* = 4.2 Hz, 1H), 4.33 (t, *J* = 8.1 Hz, 1H), 4.85 (s, 1H), 6.10 (dd, *J* = 8.1, 16.1 Hz, 1H), 6.55 (d, *J* = 16.1 Hz, 1H), 7.23-7.41 (m, 5H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 8.9 (q), 41.8 (d), 54.7 (q), 78.0 (d), 86.1 (d), 109.1 (d), 126.6 (d), 127.7 (d), 128.5 (d), 129.9 (d), 132.2 (d), 136.5 (s)

(*E*)-Methyl-3,5,6-trideoxy-3-*C*-methyl-2-*O*-methyl-6-*C*-phenyl-β-D-*ribo*-hex-5-enofuranoside (31)



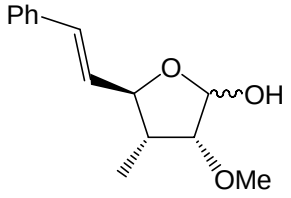
31

To a solution of glycoside **30** (900 mg, 3.85 mmol) in THF (10 mL) was added sodium hydride (60% dispersion in mineral oil, 231 mg, 5.78 mmol) at 0 ºC and then stirred for 0.5 h for the same temperature. Methyl iodide (0.5 mL, 8.03 mmol) was introduced at the same temperature and then the reaction mixture was allowed to attain ambient temperature. After stirring for 3 h the reaction mixture was

quenched by addition of ice, and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, concentrated and purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford compound **31**.

Yield	**:**	906 mg, 95%
Mol. Formula	**:**	$C_{15}H_{20}O_3$
Mol. Weight	**:**	248
ESI-MS *m/z*	**:**	271 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 72.58; H, 8.06% Found: C, 72.29; H, 8.17%
$[\alpha]_D^{25}$	**:**	+18.2 (*c* 1.8, $CHCl_3$)
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 1.04 (d, *J* = 7.2 Hz, 3H), 2.15-2.22 (m, 1H), 3.41 (s, 3H), 3.43 (s, 3H), 3.53 (d, *J* = 4.8 Hz, 1H), 4.26 (dd, *J* = 8.0, 9.3 Hz, 1H), 4.89 (s, 1H), 6.08 (dd, *J* = 8.0, 15.5 Hz, 1H), 6.53 (d, *J* = 15.5 Hz, 1H), 7.21 (tt, *J* = 1.2, 7.2 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.37 (dd, *J* = 1.2, 7.2 Hz, 2H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 9.2 (q), 41.7 (d), 54.7 (q), 58.1 (q), 86.5 (d), 87.2 (d), 105.8 (d), 126.7 (d), 127.7 (d), 128.5 (d), 130.4 (d), 132.1(d), 136.8 (s)

(*E*)-3,5,6-Trideoxy-3-*C*-methyl-2-*O*-methyl-6-*C*-phenyl-α/β-D-*ribo*-hex-5-enofuranose (10)

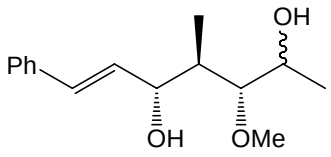


10

The mixture of **31** (600 mg, 2.42 mmol), acetic acid (20% in water, 20 mL) and concentrated H_2SO_4 (catalytic) was heated at 80 ºC for 8 h. After cooling to room temperature the acid was neutralized by addition of solid sodium bicarbonate and the reaction mixture was filtered. The filtrate was concentrated and the residue was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. Combined organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:4) to give the lactol **10**.

Yield	**:**	447 mg, 79%
Mol. Formula	**:**	$C_{14}H_{18}O_3$
Mol. Weight	**:**	234
ESI-MS *m/z*	**:**	257 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 71.79; H, 7.69% Found: C, 72.11; H, 7.45%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.00 (d, *J* = 8.0 Hz, 1.1 H), 1.08 (d, *J* = 8.0 Hz, 1.9H), 1.92-2.04 (m, 0.36H), 2.20-2.35 (m, 0.64H), 3.42 (s, 1.9H), 3.54 (s, 1.1H), 3.53-3.67 (m, 1H), 4.27 (t, 8.1 Hz, 1H), 5.40-5.50 (m, 1H), 6.01-6.20 (m, 1H), 6.42-6.61 (m, 1H), 7.15-7.50 (m, 5H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 9.0, 9.8, 41.4, 44.0, 58.0, 60.7, 83.5, 86.6, 87.7, 88.1, 97.4, 99.4, 126.7, 127.7, 128.1, 128.5, 130.1, 132.3, 132.6, 136.6

(*E*,3*R*,4*R*,5*R*)-3-Methoxy-4-methyl-7-phenylhept-6-ene-2,5-diol (9)



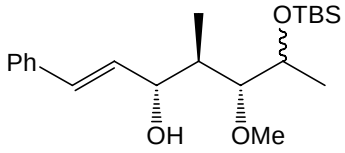
9

The ice-cooled solution of the lactol **10** (400 mg, 1.71 mmol) in THF (10 mL) was treated with methyl magnesium chloride (2.4 mL, 3M solution in THF, 7.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. Saturated ammonium chloride was added to quench the reaction mixture, followed by extraction with ethyl acetate. The combined organic extracts were dried over sodium sulfate, concentrated and the residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:2) to give the diol **9**.

Yield	**:**	320 mg, 75%
Mol. Formula	**:**	$C_{15}H_{22}O_3$
Mol. Weight	**:**	250
ESI-MS *m/z*	**:**	273 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 72.00; H, 8.80% Found: C, 72.23; H, 9.07%
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3424, 3063, 3015, 2977, 2932, 1451, 1376, 1217, 1114, 1090, 1030, 756, 669 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 0.96 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.97-2.07 (m, 1H), 3.06 (dd, *J* = 3.4, 5.4 Hz, 1H), 3.06 (br. s, overlapped, 1H), 3.57 (s, 3H), 3.91 (dq, *J* = 3.4, 6.4 Hz, 1H), 4.30 (t, *J* = 7.8 Hz, 1H), 6.19 (dd, *J* = 7.8, 16.1 Hz, 1H), 6.58 (d, *J* = 16.1 Hz, 1H), 7.22-7.40 (m, 5H)
^{13}C NMR (50 MHz,	**:**	δ 13.9, 20.5, 41.2, 60.6, 67.9, 73.9, 88.1, 126.2, 127.2,

$CDCl_3$) 128.3, 130.8, 131.0, 136.7

(*E*,3*R*,4*R*,5*R*)-6-(*tert*-Butyl-dimethylsilyloxy)-5-methoxy-4-methyl-1-phenylhept-1-en-3-ol (8)



8

A solution of the diol **9** (250 mg, 1 mmol) and 2,6-lutidine (0.25 mL, 2.15 mmol) in DCM (5 mL) was cooled to –78 ºC. TBS-triflate (0.23 mL, 1 mmol) was introduced and the reaction mixture was stirred at the same temperature for 1.5 h, diluted with DCM and then quenched by addition of water. After attaining ambient temperature the aqueous layer was extracted with DCM, the combined organic extract was dried over sodium sulfate and concentrated. The crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:24) to furnish the mono-TBS derivative **8** along with some starting material (90 mg) being recovered.

Yield **:** 201 mg, 86% (based on recovered starting material)

Mol. Formula **:** $C_{21}H_{36}O_3Si$

Mol. Weight **:** 364

ESI-MS *m/z* **:** 387 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 69.23; H, 9.89%

Found: C, 68.97; H, 10.15%

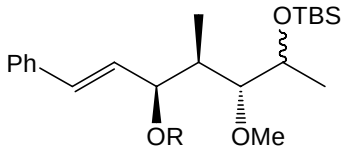
IR ($CHCl_3$) $\tilde{\nu}$ **:** 3018, 2915, 2857, 1661, 1494, 1255, 1083, 836, 757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.04 (s, 1.4H), 0.06 (s, 2H), 0.07 (s, 2.6H), 0.89 (s, 6H), 0.91 (s, 3H), 0.92 (d, overlapped, *J* = 5.5 Hz, 1H), 0.98 (d, *J* = 7.3 Hz, 2H), 1.19 (d, *J* = 6.4 Hz, 2H), 1.25

(d, *J* = 6.4 Hz, 1H), 1.96-2.10 (m, 1H), 3.03-3.08 (m, 1H), 3.49 (s, 1.2H), 3.52 (s, 1.8H), 3.84 (dd, *J* = 3.3, 6.4 Hz, 0.33H), 3.90 (br. d, *J* = 2.5 Hz, 1H), 3.98-4.14 (m, 0.66H), 4.26-4.41 (m, 1H), [6.18 (dd, *J* = 7.8, 15.6 Hz), 6.22 (dd, *J* = 7.8, 15.6 Hz), 1H], 6.50 (d, *J* = 15.6 Hz, 0.33H), 6.61 (d, *J* = 15.6 Hz, 0.66H) 7.23-7.42 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ -4.8, -4.5, -3.9, 11.9, 14.7, 18.0, 18.1, 19.3, 21.1, 25.8, 25.9, 39.9, 42.0, 59.7, 59.8, 67.2, 69.4, 74.9, 75.5, 85.9, 89.9, 126.3, 126.4, 127.2, 127.3, 128.4, 128.5, 130.7, 130.8, 131.1, 131.3, 137.0, 137.1

(*E*,4*R*,5*R*)-6-(*tert*-Butyl-dimethylsilyloxy)-5-methoxy-4-methyl-1-phenylhept-1-en-3-yl 4-nitrobenzoate (32)



32

R = *p*-$NO_2C_6H_4CO$

To a solution of the alcohol **8** (180 mg, 0.495 mmol), TPP (207 mg, 0.79 mmol), 4-nitrobenzoic acid (132 mg, 0.79 mmol) in THF (2 mL) at 0 ºC was added DEAD (0.12 mL, 0.76 mmol). The reaction was allowed to attain ambient temperature and stirred for 5 h. The volatiles were removed and the crude residue was purified on silica gel by eluting with 3% ethyl acetate in light petroleum to afford ester **32** along with some starting material (65 mg).

Yield **:** 107 mg, 66% (based on recovered starting material)

Mol. Formula **:** $C_{28}H_{39}NO_6Si$

Mol. Weight **:** 513

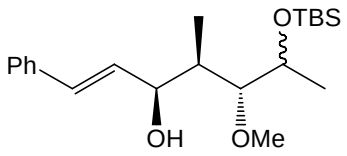
ESI-MS *m/z* **:** 536 $[M+Na]^+$

Elemental Analysis : Calcd: C, 65.50; H, 7.60%

Found: C, 65.75; H, 7.79%

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.05 (s, 3H), 0.07 (s, 0.6H), 0.08 (s, 2.4H), 0.88 (s, 1.8H), 0.91 (s, 7.2H), 0.99 (d, *J* = 7.2 Hz, 2.4H), 1.12 (d, *J* = 7.2 Hz, 0.6H), 1.15 (d, *J* = 6.4 Hz, 0.6H), 1.38 (d, *J* = 6.4 Hz, 2.4H), 1.87-1.94 (m, 1H), 3.01 (dd, *J* = 2.8, 8.7 Hz, 0.2H), 3.31 (dd, *J* = 1.7, 9.3 Hz, 0.8H), 3.43 (s, 0.6H), 3.55 (s, 2.4H), 4.02 (dq, *J* = 2.8, 6.4 Hz, 0.2H), 4.59-4.61 (m, 0.8H), 5.37-5.41 (m, 0.8H), 6.10-6.12 (br. m, 0.2H), 6.16 (dd, *J* = 6.9, 15.9 Hz, 0.8H), 6.23 (dd, *J* = 6.4, 15.9 Hz, 0.2H), 6.49 (d, *J* = 15.9 Hz, 0.8H), 6.61 (d, *J* = 15.9 Hz, 0.2H) 7.19-7.35 (m, 5H), 8.17, 8.27 (2d, *J* = 8.7 Hz, 3.2H), 8.25, 8.32 (2d, *J* = 8.7 Hz, 0.8H)

(*E*,3*R*,4*R*,5*R*)-6-(*tert*-Butyl-dimethylsilyloxy)-5-methoxy-4-methyl-1-phenylhept-1-en-3-ol (7)



7

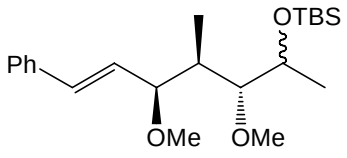
A solution of ester **32** (90mg, 0.175 mmol), in MeOH (6 mL) was treated with lithium hydroxide monohydrate (15 mg, 0.37 mmol) at rt for 2 h. Methanol was evaporated and the residue was partitioned between water and ethyl acetate. The combined organic extracts were dried over sodium sulfate and the crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:19) to give inverted alcohol **7**.

Yield : 58 mg, 91%

Mol. Formula : $C_{21}H_{36}O_3Si$

Mol. Weight	**:**	364
ESI-MS *m/z*	**:**	387 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 69.23; H, 9.89% Found: C, 69.11; H, 10.14%
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ 0.07 (s, 2.2H), 0.08 (s, 1.6H), 0.09 (s, 2.2H), 0.89 (s, 4.5H), 0.90 (s, 4.5H), 0.98 (d, *J* = 7.3 Hz, 1.5H), 1.04 (d, *J* = 7.3 Hz, 1.5H), 1.17 (d, *J* = 6.6 Hz, 1.5H), 1.20 (d, *J* = 6.6 Hz, 1.5H), 1.94-2.04 (m, 1H), 3.07 (t, *J* = 5.7 Hz, 0.5H), 3.13 (dd, *J* = 4.4, 6.6 Hz, 0.5H), 3.51 (s, 1.5H), 3.55 (s, 1.5H), 3.65-3.67 (m, 1H), 3.95-4.09 (m, 1H), 4.53 (br. s, 1H), 6.18 (dd, *J* = 5.1, 16.1 Hz, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 7.18-7.39 (m, 5H)
^{13}C NMR (75 MHz, $CDCl_3$)	**:**	δ -4.6, -4.4, 15.2, 18.2, 19.4, 26.0, 40.1, 60.0, 69.6, 76.1, 90.5, 126.5, 127.5, 128.6, 131.0, 131.4

((*E*,3*R*,4*R*,5*S*)-3,5-Dimethoxy-4-methyl-7-phenylhept-6-en-2-yloxy)(*tert*-butyl)dimethylsilane (33)



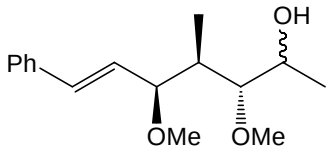
33

Potassium hydride (30% dispersion in mineral oil, 14 mg, 0.105 mmol) was taken in a round bottom flask under Argon atmosphere and washed with dry hexane to make it free from mineral oil. Traces of hexane were removed by applying vacuum and THF (1 mL) was introduced. This suspension was cooled to 0 ºC and a solution of the alcohol **7** (36 mg, 98.9 μmol) in THF (1 mL) was added in a drop wise manner. The reaction mixture was stirred for 0.5 h and then methyl iodide (25 μL, 0.401 mmol) was added. After stirring for 3.5 h at rt the reaction mixture was poured into ethyl acetate containing some pieces of ice. The layers were separated and the

aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified on silica gel by eluting with 2.5% ethyl acetate in light petroleum to afford **33** as colorless oil.

Yield	**:**	36 mg, 96%
Mol. Formula	**:**	$C_{22}H_{38}O_3Si$
Mol. Weight	**:**	378
ESI-MS *m/z*	**:**	417 $[M+K]^+$
Elemental Analysis	**:**	Calcd: C, 69.84; H, 10.05% Found: C, 69.61; H, 9.77%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ -0.01, 0.00 (2s, 6H), 0.81 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.71-1.87 (m, 1H), 2.98 (dd, *J* = 2.5, 9.3 Hz, 1H), 3.26 (s, 3H), 3.41 (s, 3H), 3.96 (dq, *J* = 2.5, 6.4 Hz, 1H), 4.03 (dd, *J* = 2.0, 6.8 Hz, 1H), 6.11 (dd, *J* = 6.8, 16.1 Hz, 1H), 6.49 (d, *J* = 16.1 Hz, 1H), 7.12-7.35 (m, 5H)

(*E*,3*R*,4*R*,5*S*)-3,5-Dimethoxy-4-methyl-7-phenylhept-6-en-2-ol (34)

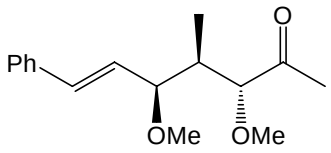


34

To a solution of **33** (29 mg, 76.72 μmol) in THF (1 mL) was added TBAF (1 M solution in THF, 0.4 mL, 0.4 mmol) and the reaction mixture was stirred at rt for 36 h. Volatiles were removed and the crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:4) to procure alcohol **34**.

Yield	**:**	19 mg, 94%
Mol. Formula	**:**	$C_{16}H_{24}O_3$
Mol. Weight	**:**	264
ESI-MS *m/z*	**:**	303 $[M+K]^+$
Elemental Analysis	**:**	Calcd: C, 72.73; H, 9.09% Found: C, 72.33; H, 8.82%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 0.93 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.78-2.04 (br. m, 2H), 3.02 (d, *J* = 8.3 Hz, 1H), 3.31 (s, 3H), 3.55 (s, 3H), 3.78-3.87 (m, 1H), 4.00 (br. d, *J* = 6.8 Hz, 1H), 6.15 (dd, *J* = 6.8, 16.1 Hz, 1H), 6.54 (d, *J* = 16.1 Hz, 1H), 7.21-7.39 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 10.5, 21.6, 40.9, 56.3, 61.3, 67.3, 81.6, 86.1, 126.5, 127.6, 128.6, 129.3, 132.3, 136.8

(*E*,3*R*,4*R*,5*S*)-3,5-Dimethoxy-4-methyl-7-phenylhept-6-en-2-one (35)

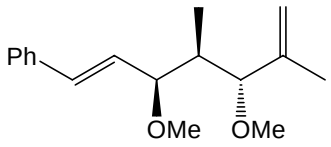


35

To a solution of **34** (17 mg, 64.39 μmol) in DCM (2 mL) was added Dess-Martin periodinane (54 mg, 128.78 μmol) and the reaction mixture was stirred for 2 h and then diluted with DCM and quenched with ice. The aqueous layer was extracted with DCM. Combined organic extract was dried over sodium sulfate and concentrated to a crude residue, which was purified on silica gel by eluting with ethyl acetate-light petroleum (1:19) to furnish the ketone **35**.

Yield	**:**	15.3 mg, 91%
Mol. Formula	**:**	$C_{16}H_{22}O_3$
Mol. Weight	**:**	262
ESI-MS *m/z*	**:**	285 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 73.28; H, 8.40% Found: C, 73.07; H, 8.17%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 0.86 (d, *J* = 7.3 Hz, 3H), 1.88-1.98 (m, 1H), 2.13 (s, 3H), 3.30 (s, 3H), 3.36 (s, 3H), 3.47 (d, *J* = 8.8 Hz, 1H), 4.01 (dd, *J* = 3.4, 7.3 Hz, 1H), 6.12 (dd, *J* = 7.3, 16.1 Hz, 1H), 6.57 (d, *J* = 16.1 Hz, 1H), 7. 23-7.41 (m, 5H)
^{13}C NMR (75 MHz, $CDCl_3$)	**:**	δ 10.0, 25.2, 41.2, 57.0, 58.4, 81.2, 89.2, 126.5, 127.7, 128.6, 128.8, 132.5, 136.8, 210.5

1-((*E*,3*S*,4*R*,5*R*)-3,5-Dimethoxy-4,6-dimethylhepta-1,6-dienyl)benzene (6)

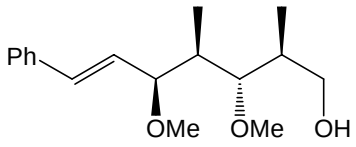


6

A solution of the ketone **35** (12 mg, 45.8 μmol) in THF (1 mL) at –10 ºC was treated with methyltriphenylphosphorane ylide [generated by action of sodamide (29 mg, 0.743 mmol) on $Ph_3P^+CH_3I^-$ (370 mg, 0.916 mmol) in ether:THF (2:1) mixture]. The reaction mixture was stirred at rt for 8 h and then quenched by addition of saturated ammonium chloride solution. The solids were filtered off and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over sodium sulfate, concentrated, and the residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:19) to give the olefin **6**.

Yield	**:**	10.1 mg, 85%
Mol. Formula	**:**	$C_{17}H_{24}O_2$
Mol. Weight	**:**	260
ESI-MS *m/z*	**:**	299 $[M+K]^+$
Elemental Analysis	**:**	Calcd: C, 78.46; H, 9.23% Found: C, 78.03; H, 9.52%
$[\alpha]_D^{25}$	**:**	+18.2 (*c* 1.8, $CHCl_3$)
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 0.75 (d, *J* = 7.1 Hz, 3H), 1.60 (s, 3H), 1.66-1.73 (m, 1H), 3.22 (s, 3H), 3.34 (s, 3H), 3.49 (d, *J* = 10.1 Hz, 1H), 4.20 (dd, *J* = 3.3, 6.8 Hz, 1H), 4.92 (s, 1H), 4.99 (m, 1H), 6.17 (dd, *J* = 6.7, 16.1Hz, 1H), 6.57 (d, *J* = 16.1Hz, 1H), 7.20-7.38, m, 5H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 9.7 (q), 15.9 (q), 41.0 (d), 55.9 (q), 57.3 (q), 80.7 (d), 87.0 (d), 115.8 (t), 126.5 (d), 127.4 (d), 128.6 (d), 130.0 (d), 131.3 (d), 137.2 (s), 143.1 (s)

(*E*,2*S*,3*S*,4*R*,5*S*)-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol (5)



5

To a solution of the olefin **6** (8 mg, 30.77 μmol) in THF (1 mL) was added 9-BBN dimmer (4.1 mg, 16.8 μmol) at 0 ºC and the reaction mixture was brought to rt and stirred for 2 h. It was again cooled to 0 ºC and saturated sodium acetate was added, followed by the addition of hydrogen peroxide (30% solution in water). The reaction mixture was brought to rt and stirred for 6 h. The reaction mixture was diluted with ethyl acetate and water and the aqueous layer was extracted with ethyl

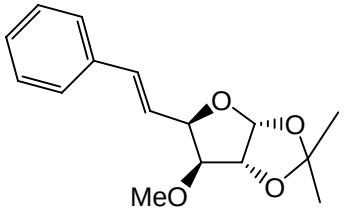
acetate. The combined organic extract was dried over sodium sulfate, concentrated, and the residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:4) to afford **5**.

Yield	**:**	5.5 mg, 64%
Mol. Formula	**:**	$C_{17}H_{26}O_3$
Mol. Weight	**:**	278
ESI-MS *m/z*	**:**	301 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 73.38; H, 9.35% Found: C, 73.92; H, 8.97%
$[\alpha]_D^{25}$	**:**	-3.2 (*c* 0.3, DCM), literature[38-40] $[\alpha]_D$ = -4.16 (*c* 1.87, DCM)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3453, 2936, 1520, 1384, 1140, 1079, 1051, 929, 669 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 0.9 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.82-1.90 (m, 2H), 2.77 (br. s, 1H), 3.27 (dd, *J* = 2.7, 9.5 Hz, 1H), 3.31 (s, 3H), 3.51 (dd, *J* = 4.3, 11.2 Hz, 1H), 3.54 (s, 3H), 3.82 (dd, *J* = 3.4, 11.2 Hz, 1H), 4.05 (dd, *J* = 2.0, 7.2 Hz, 1H), 6.16 (dd, *J* = 7.2, 16.3 Hz, 1H), 6.56 (d, *J* = 16.3 Hz, 1H), 7.20-7.40 (m, 5H)
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 10.5 (q), 16.4 (q), 36.1 (d), 42.5 (d), 56.4 (q), 61.6 (q), 64.6 (t), 81.2 (d), 88.6 (d), 126.5 (d), 127.7 (d), 128.6 (d), 129.4 (d), 132.3 (d), 136.9 (s)

Heck reactions

All the Heck reactions were carried out using the procedure described for the preparation of **11** from **29**. All the reactions were carried out starting from 100 mg of starting material.

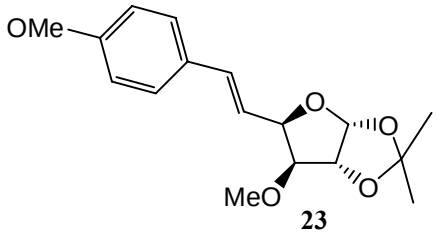
(*E*)-5,6-Dideoxy-3-*O*-methyl-6-*C*-phenyl-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (21)



21

Yield	**:**	75 mg, 54%
Mol. Formula	**:**	$C_{16}H_{20}O_4$
Mol. Weight	**:**	276
Elemental Analysis	**:**	Calcd: C, 69.56; H, 7.24% Found: C, 70.30; H, 7.10%
$[\alpha]_D^{25}$	**:**	-56.7 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.34 (s, 3H), 1.54 (s, 3H), 3.42 (s, 3H), 3.68 (d, *J* = 3.5 Hz, 1H), 4.62 (d, *J* = 3.5 Hz, 1H), 4.71-4.79 (m, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 6.29 (dd, *J* = 8.0, 16.0 Hz, 1H), 6.73 (d, *J* = 16.0 Hz, 1H), 7.23-7.43 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 26.1 (q), 26.7 (q), 58.1 (q), 81.2 (d), 82.2 (d), 86.1 (d), 104.7 (d), 111.4 (s), 123.1 (d), 126.6 (d), 127.8 (d), 128.4 (d), 133.8 (d), 136.5 (s)

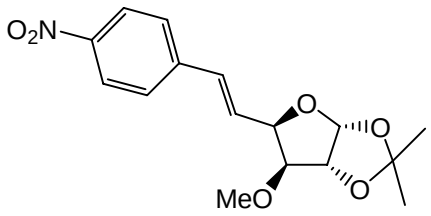
(*E*)-5,6-Dideoxy-3-*O*-methyl-6-*C*-(4-methoxyphenyl)-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (23)



23

Yield	**:**	95 mg, 62%
Mol. Formula	**:**	$C_{17}H_{22}O_5$
Mol. Weight	**:**	306
Elemental Analysis	**:**	Calcd: C, 66.67; H, 7.19% Found: C, 66.39; H, 7.05%
$[\alpha]_D^{25}$	**:**	-45.7 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.26 (s, 3H), 1.46 (s, 3H), 3.33 (s, 3H), 3.58 (d, *J* = 3.4 Hz, 1H), 3.71 (s, 3H), 4.53 (d, *J* = 3.4 Hz, 1H), 4.65 (dd, *J* = 3.4, 7.8 Hz, 1H), 5.85 (d, *J* = 3.4 Hz, 1H), 6.07 (dd, *J* = 7.8, 16.1 Hz, 1H), 6.59 (d, *J* = 16.1 Hz, 1H), 6.75, 7.25 (2d, *J* = 8.3 Hz, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 26.2 (q), 26.8 (q), 55.0 (q), 58.1 (q), 81.4 (d), 82.2 (d), 86.2 (d), 104.4 (d), 111.2 (s), 113.9 (d), 120.7 (d), 127.8 (d), 129.3 (s), 133.6 (d), 159.4 (s)

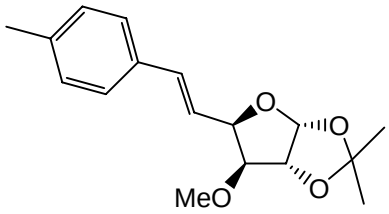
(*E*)-5,6-Dideoxy-3-*O*-methyl-6-*C*-(4-nitrophenyl)-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (24)



24

Yield	**:**	64 mg, 40%
Mol. Formula	**:**	$C_{16}H_{19}NO_6$
Mol. Weight	**:**	321
Elemental Analysis	**:**	Calcd: C, 59.81; H, 5.90% Found: C, 59.59; H, 6.15%
$[\alpha]_D^{25}$	**:**	-38.5 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.35 (s, 3H), 1.54 (s, 3H), 3.42 (s, 3H), 3.75 (d, *J* = 3.4 Hz, 1H), 4.65 (d, *J* = 3.9 Hz, 1H), 4.81 (dd, *J* = 3.4, 6.8 Hz, 1H), 5.96 (d, *J* = 3.9 Hz, 1H), 6.46 (dd, *J* = 6.8, 16.1 Hz, 1H), 6.81 (d, *J* = 16.1 Hz, 1H), 7.54, 8.18 (2d, *J* = 8.8 Hz, 4H)
^{13}C NMR (75 MHz, $CDCl_3$)	**:**	δ 26.2 (q), 26.8 (q), 58.2 (q), 80.6 (d), 82.2 (d), 86.1 (d), 104.9 (d), 111.8 (s), 124.0 (d), 127.2 (d), 128.5 (d), 131.2 (d), 143.0 (s), 147.2 (s)

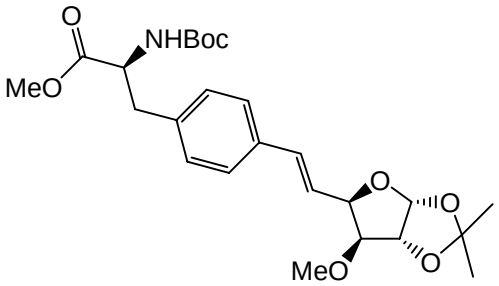
(*E*)-5,6-Dideoxy-3-*O*-methyl-6-*C*-(4-methylphenyl)-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (25)



25

Yield	**:**	81 mg, 56%
Mol. Formula	**:**	$C_{17}H_{22}O_4$
Mol. Weight	**:**	290
Elemental Analysis	**:**	Calcd: C, 70.34; H, 7.58% Found: C, 70.62; H, 7.67%
$[\alpha]_D^{25}$	**:**	-55.9 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.34 (s, 3H), 1.54 (s, 3H), 2.34 (s, 3H), 3.41 (s, 3H), 3.67 (d, *J* = 2.4 Hz, 1H), 4.61 (d, *J* = 3.8 Hz, 1H), 4.74 (dd, *J* = 2.4, 7.4 Hz, 1H), 5.93 (d, *J* = 3.6 Hz, 1H), 6.23 (dd, *J* = 7.7, 16.1 Hz, 1H), 6.69 (d, *J* = 16.1 Hz, 1H), 7.11, 7.30 (2d, *J* = 7.8 Hz, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 21.1 (q), 26.1 (q), 26.7 (q), 58.0 (q), 81.3 (d), 82.2 (d), 86.1 (d), 104.6 (d), 111.2 (s), 122.0 (d), 122.1 (s), 126.5 (d), 129.1 (d), 133.8 (d), 137.4 (s)

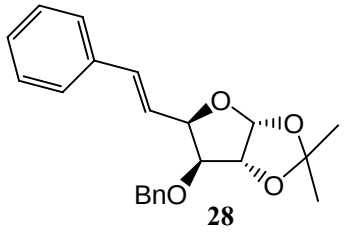
Synthesis of compound 26



26

Yield	**:**	133 mg, 56%
Mol. Formula	**:**	$C_{25}H_{35}NO_8$
Mol. Weight	**:**	477
Elemental Analysis	**:**	Calcd: C, 62.88; H, 7.34% Found: C, 62.65; H, 7.17%
$[\alpha]_D^{25}$	**:**	+3.83 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.33 (s, 3H), 1.40 (s, 9H), 1.52 (s, 3H), 2.94-3.13 (m, 2H), 3.39 (s, 3H), 3.66 (d, *J* = 3.4 Hz, 1H), 3.69 (s, 3H), 4.49-4.56 (br. m, 1H), 4.60 (d, *J* = 3.9 Hz, 1H), 4.73 (dd, *J* = 3.4, 7.6 Hz, 1H), 4.95 (d, *J* = 8.3 Hz, 1H), 5.92 (d, *J* = 3.9 Hz, 1H), 6.24 (dd, *J* = 7.4, 16.1 Hz, 1H), 6.68 (d, *J* = 16.1 Hz, 1H), 7.05, 7.31 (2d, *J* = 7.8 Hz, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 26.3, 26.9, 28.3, 38.2, 52.1, 54.4, 58.2, 79.9, 81.3, 82.3, 86.3, 104.8, 111.4, 123.2, 126.9, 128.2, 129.0, 129.5, 133.5, 135.5, 135.7, 154.9, 172.1

(*E*)-5,6-Dideoxy-3-*O*-benzyl-6-*C*-phenyl-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (28)

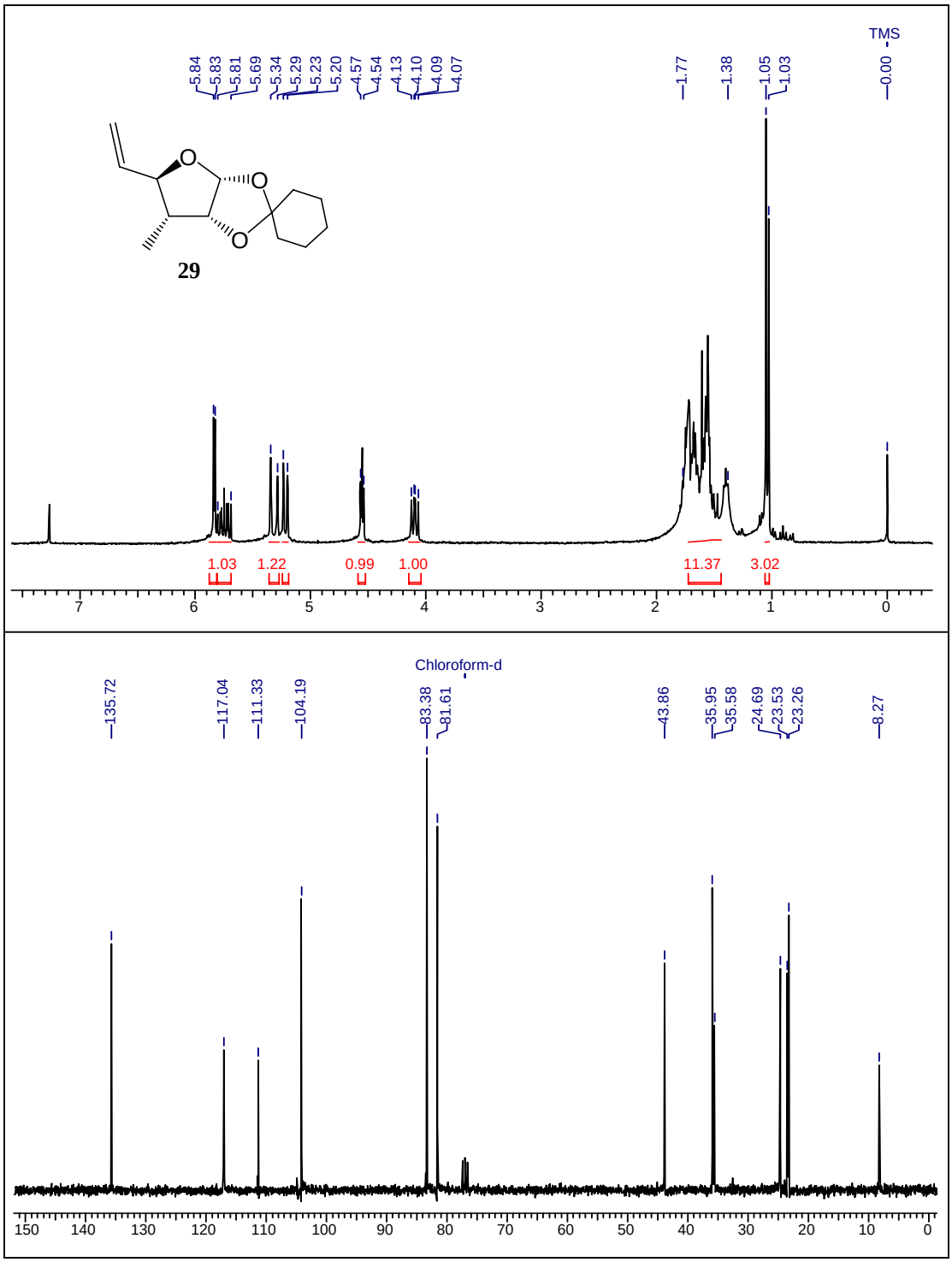


28

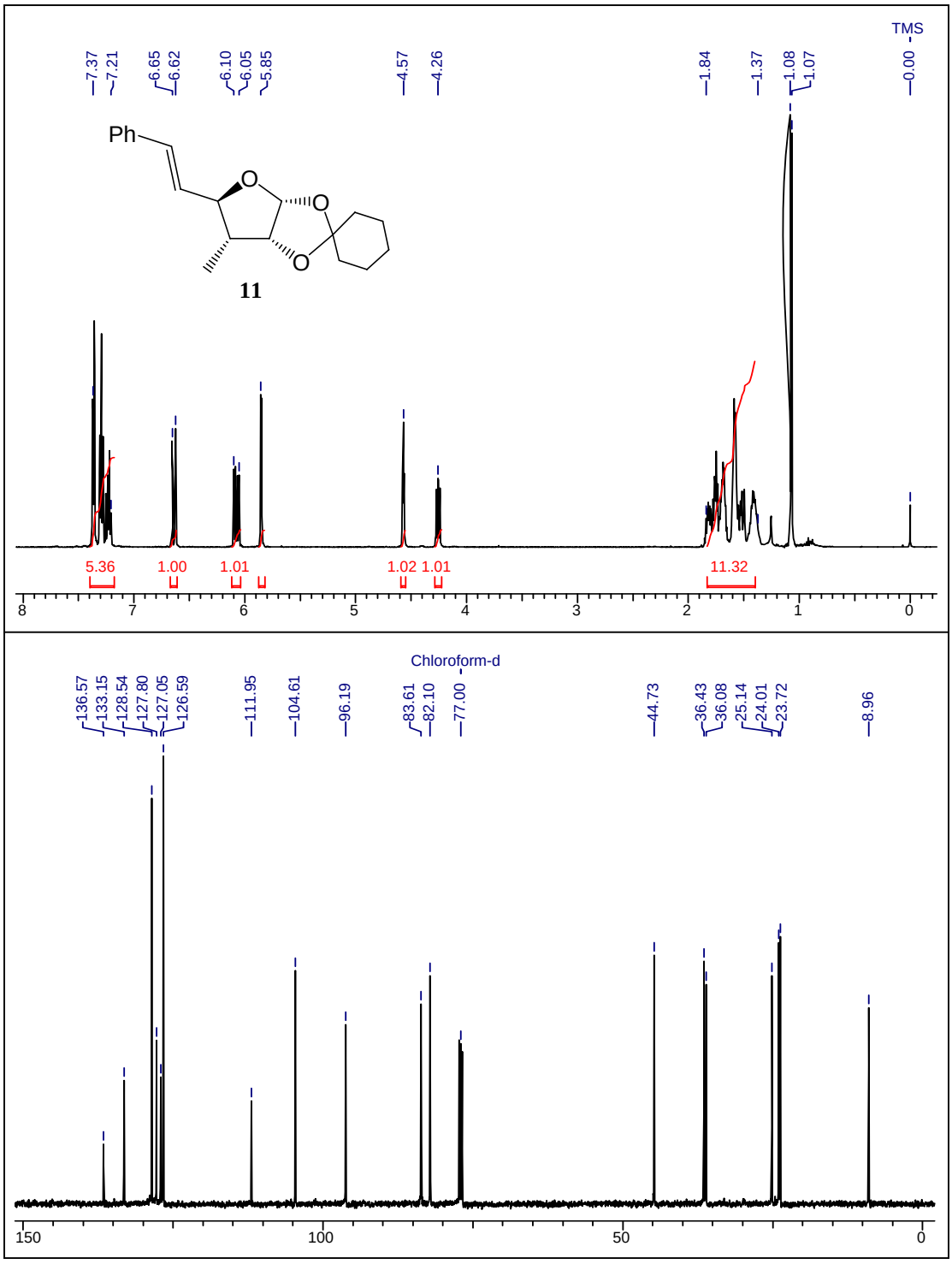
Yield	**:**	70 mg, 55%
Mol. Formula	**:**	$C_{22}H_{24}O_4$
Mol. Weight	**:**	352
Elemental Analysis	**:**	Calcd: C, 75.0; H, 6.82% Found: C, 74.65; H, 7.11%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.34 (s, 3H), 1.53 (s, 3H), 3.92 (d, *J* = 3.5 Hz, 1H), 4.52-4.85 (m, 4H), 6.00 (d, *J* = 3.5 Hz, 1H), 6.38 (dd, *J* = 8.0, 16.0 Hz, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 7.20-7.50 (m, 10H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 26.3 (q), 26.9 (q), 72.2 (t), 81.4 (d), 83.1 (d), 83.8 (d), 104.9 (d), 111.4 (s), 123.6 (d), 126.6 (d), 127.5 (d), 128.4 (d), 128.5 (d), 133.8 (d), 136.6 (s), 137.5 (s)

Spectroscopic Data

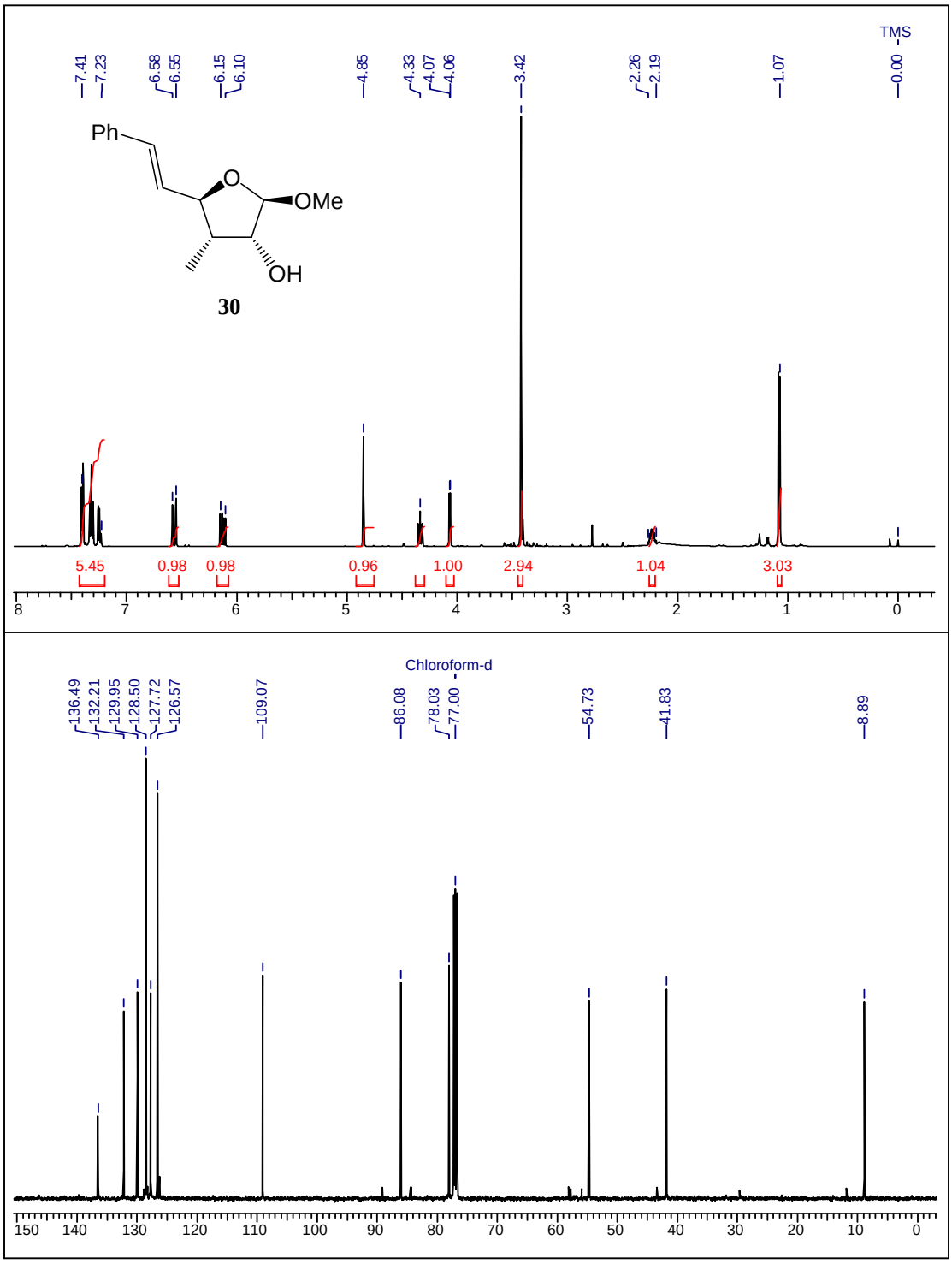
^{1}H and ^{13}C NMR spectra of compound 29 in $CDCl_3$



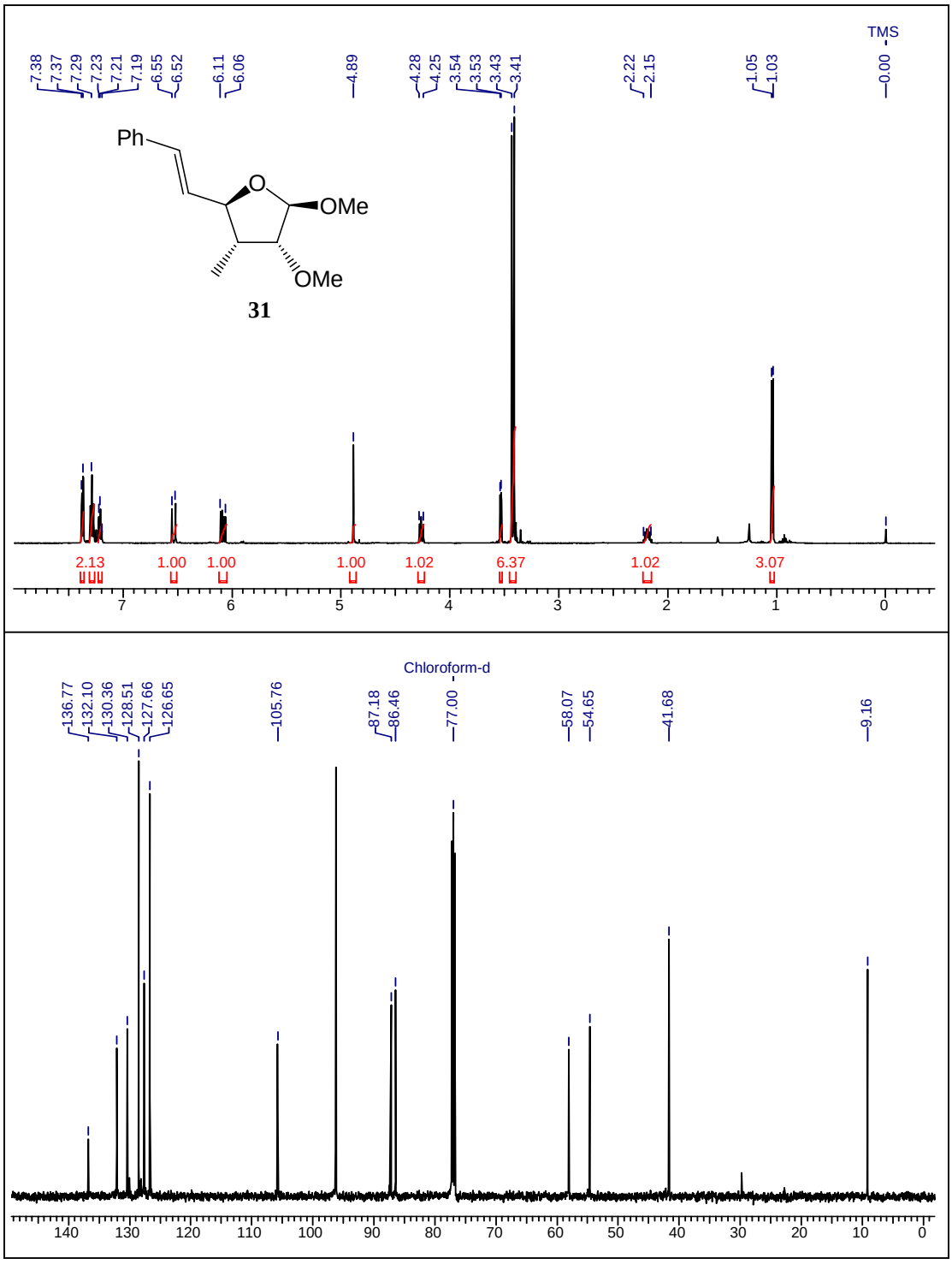
^{1}H and ^{13}C NMR spectra of compound 11 in $CDCl_3$



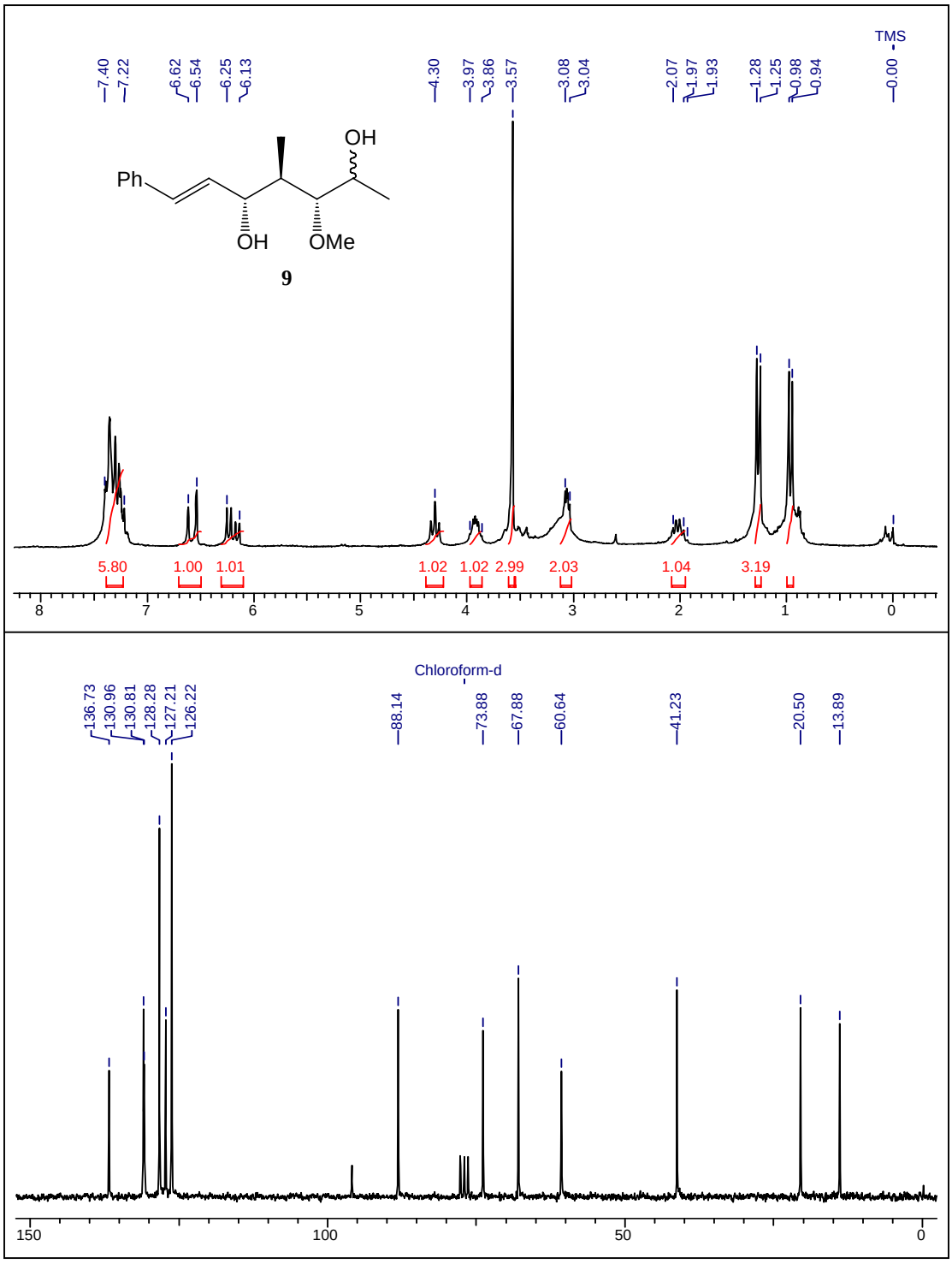
^{1}H and ^{13}C NMR spectra of compound 30 in $CDCl_3$



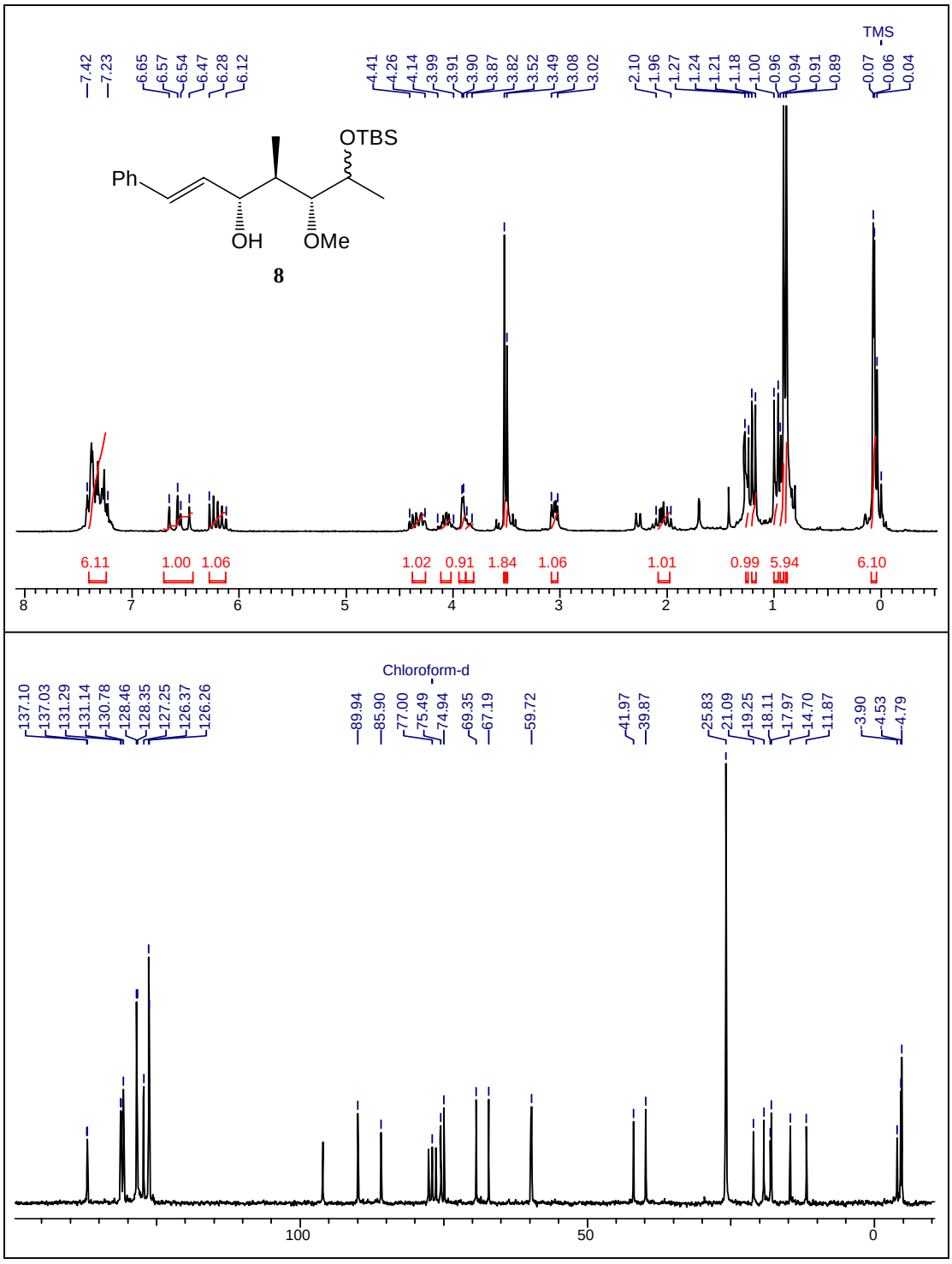
^{1}H and ^{13}C NMR spectra of compound 31 in $CDCl_3$



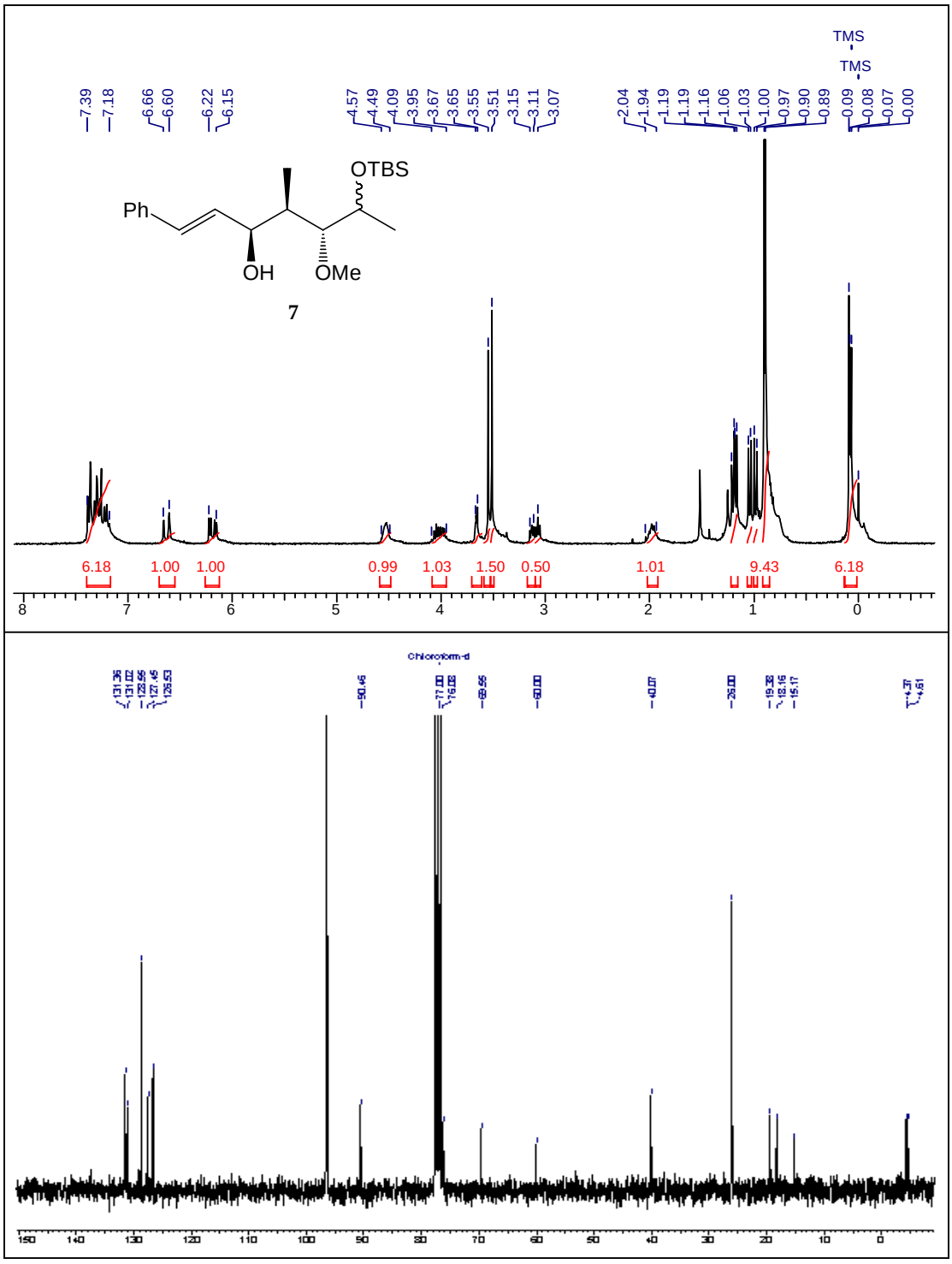
^{1}H and ^{13}C NMR spectra of compound 9 in $CDCl_3$



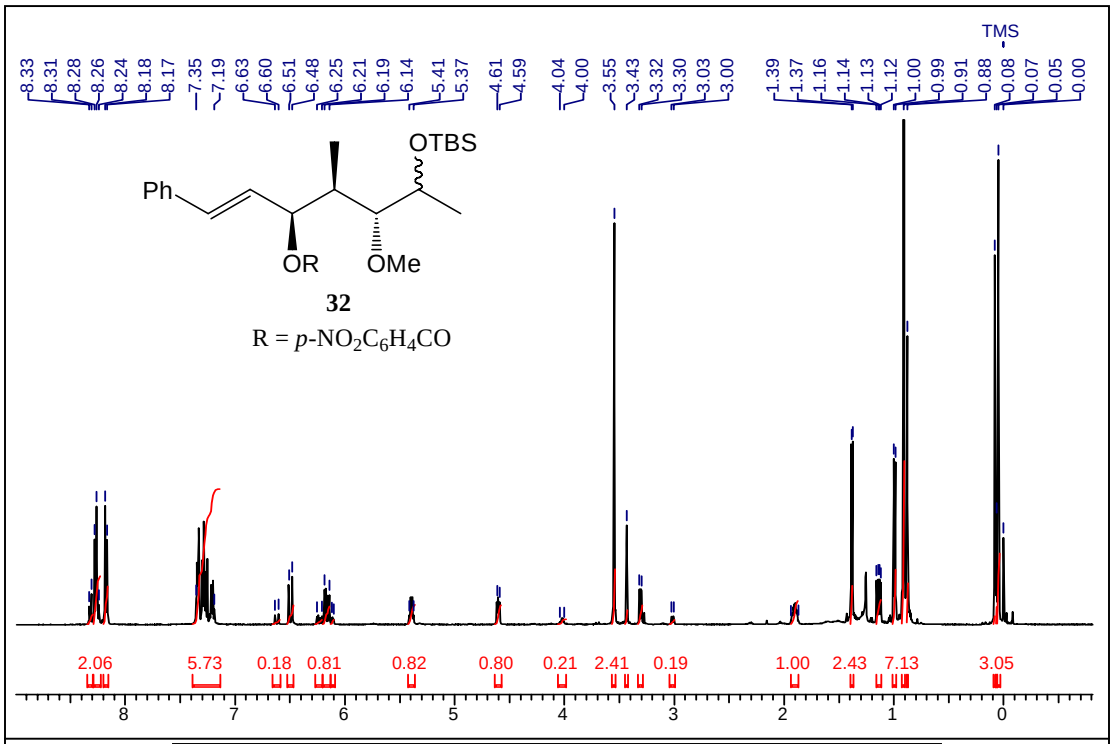
^{1}H and ^{13}C NMR spectra of compound 8 in $CDCl_3$



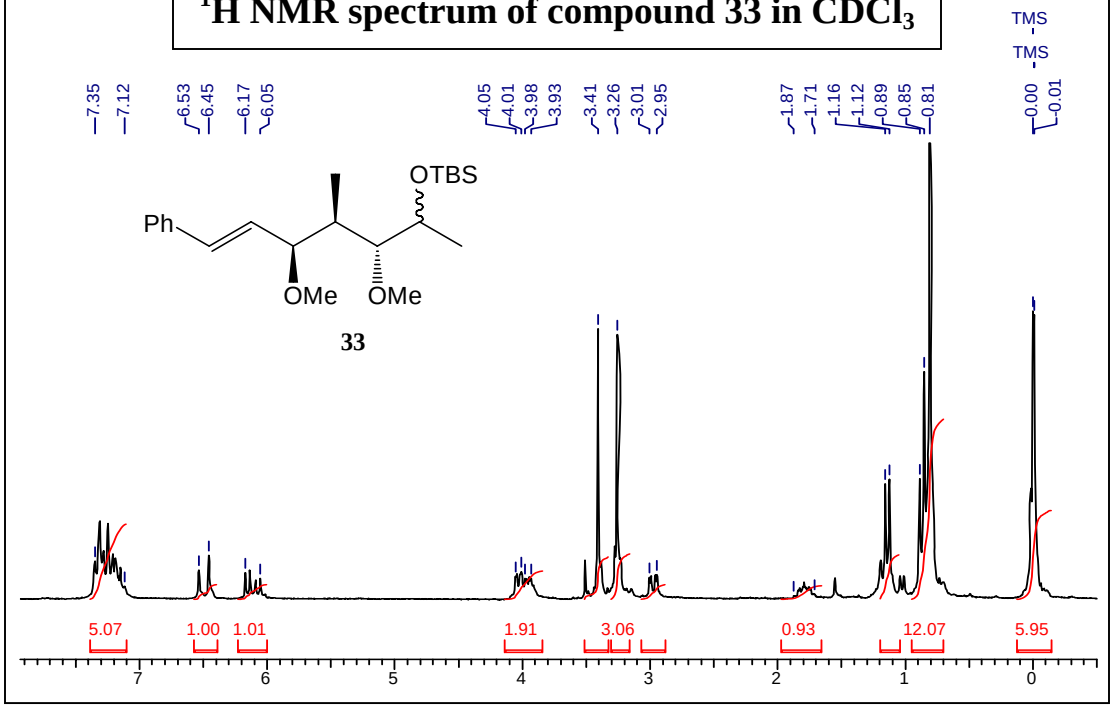
^{1}H and ^{13}C NMR spectra of compound 7 in $CDCl_3$



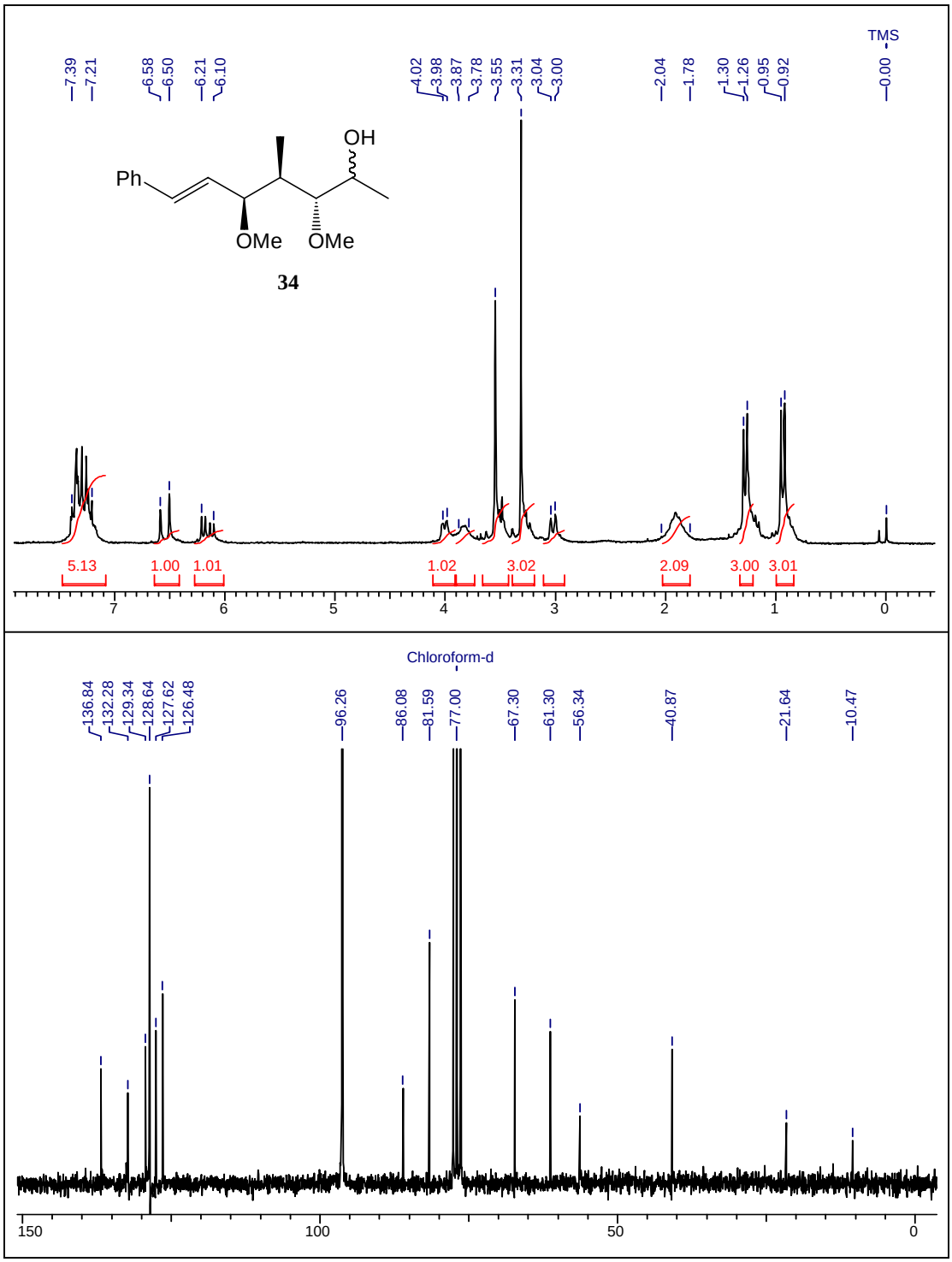
^{1}H NMR spectrum of compound 32 $CDCl_3$



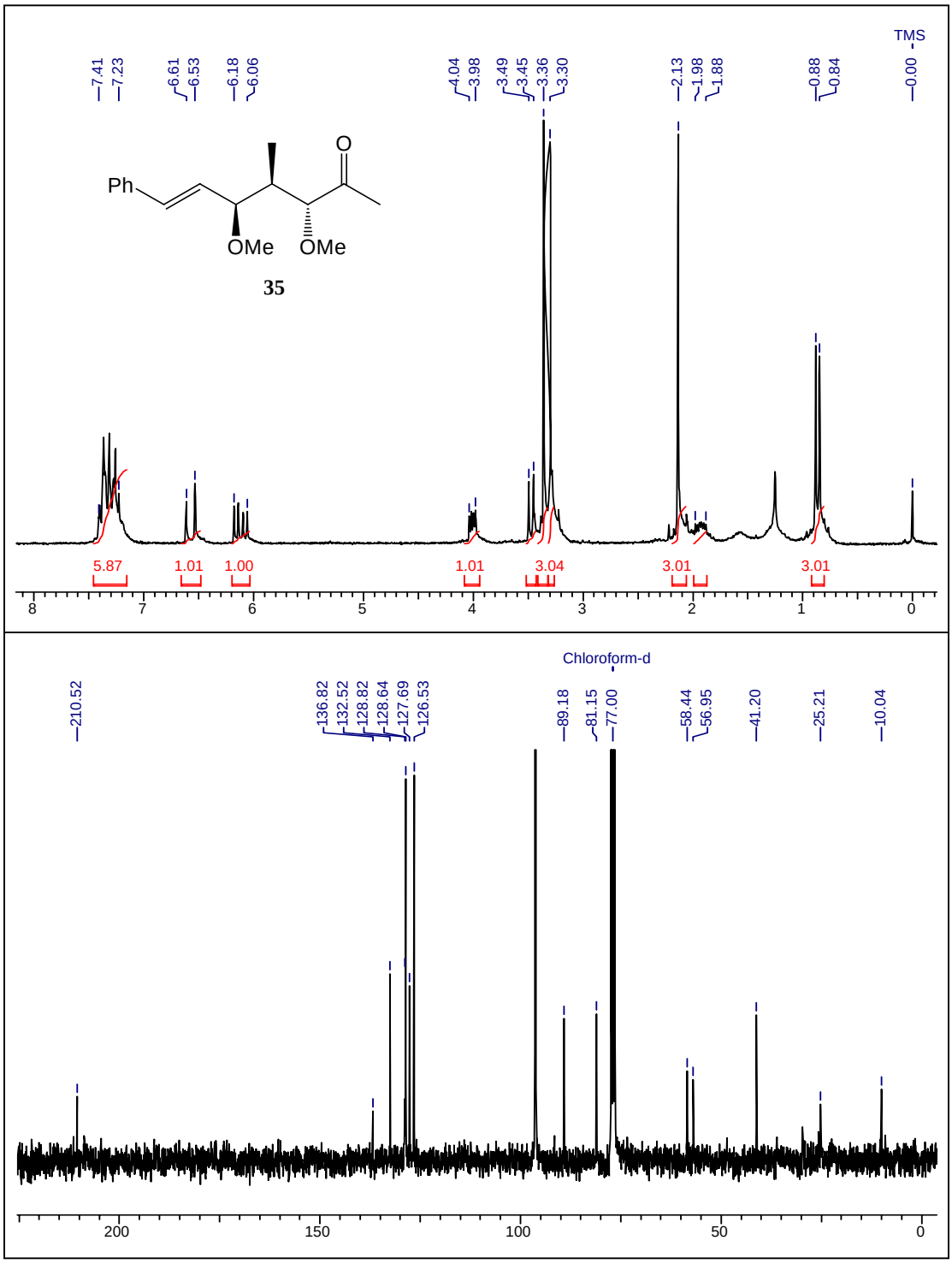
^{1}H NMR spectrum of compound 33 in $CDCl_3$



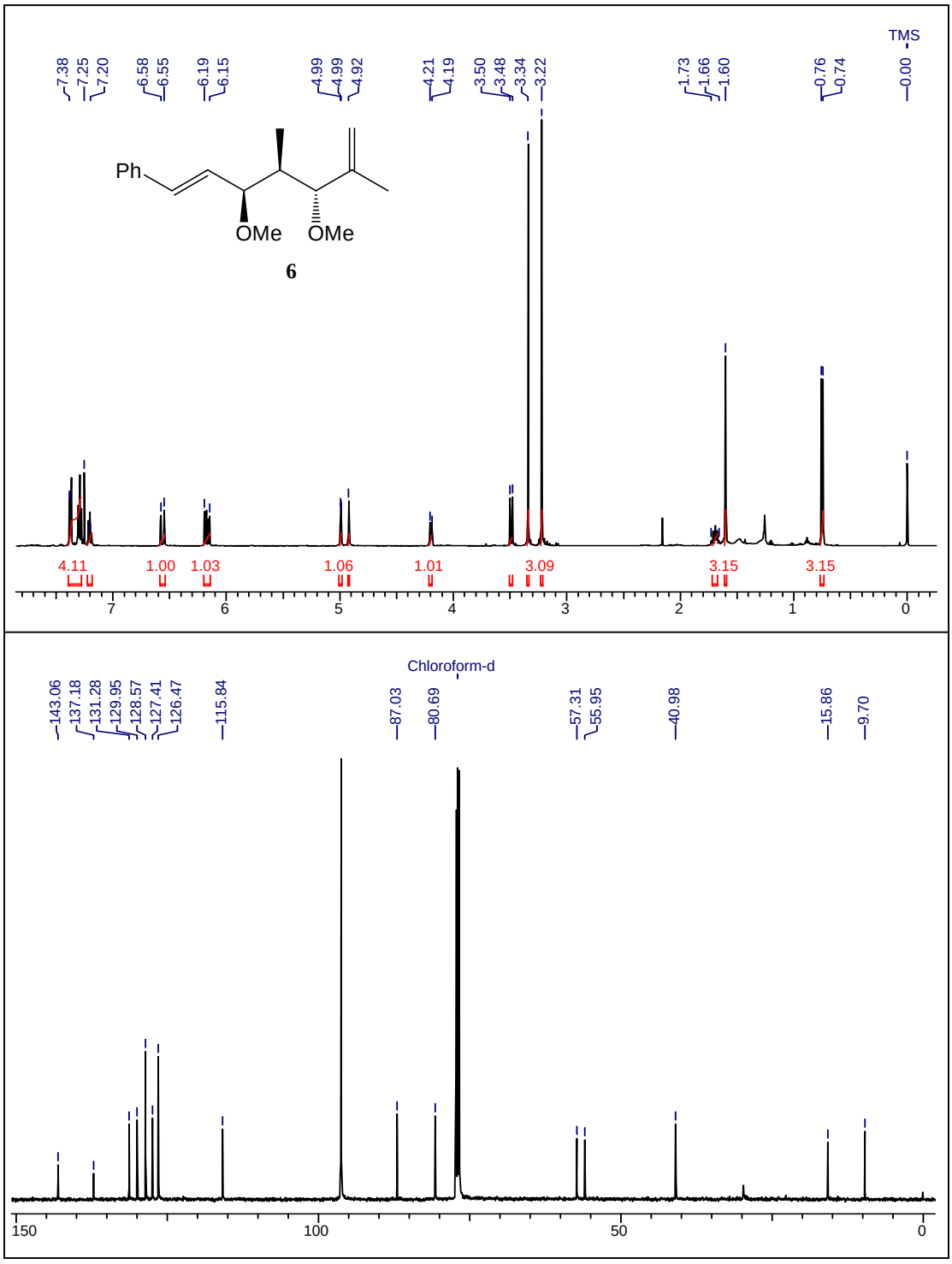
^{1}H and ^{13}C NMR spectra of compound 34 in $CDCl_3$



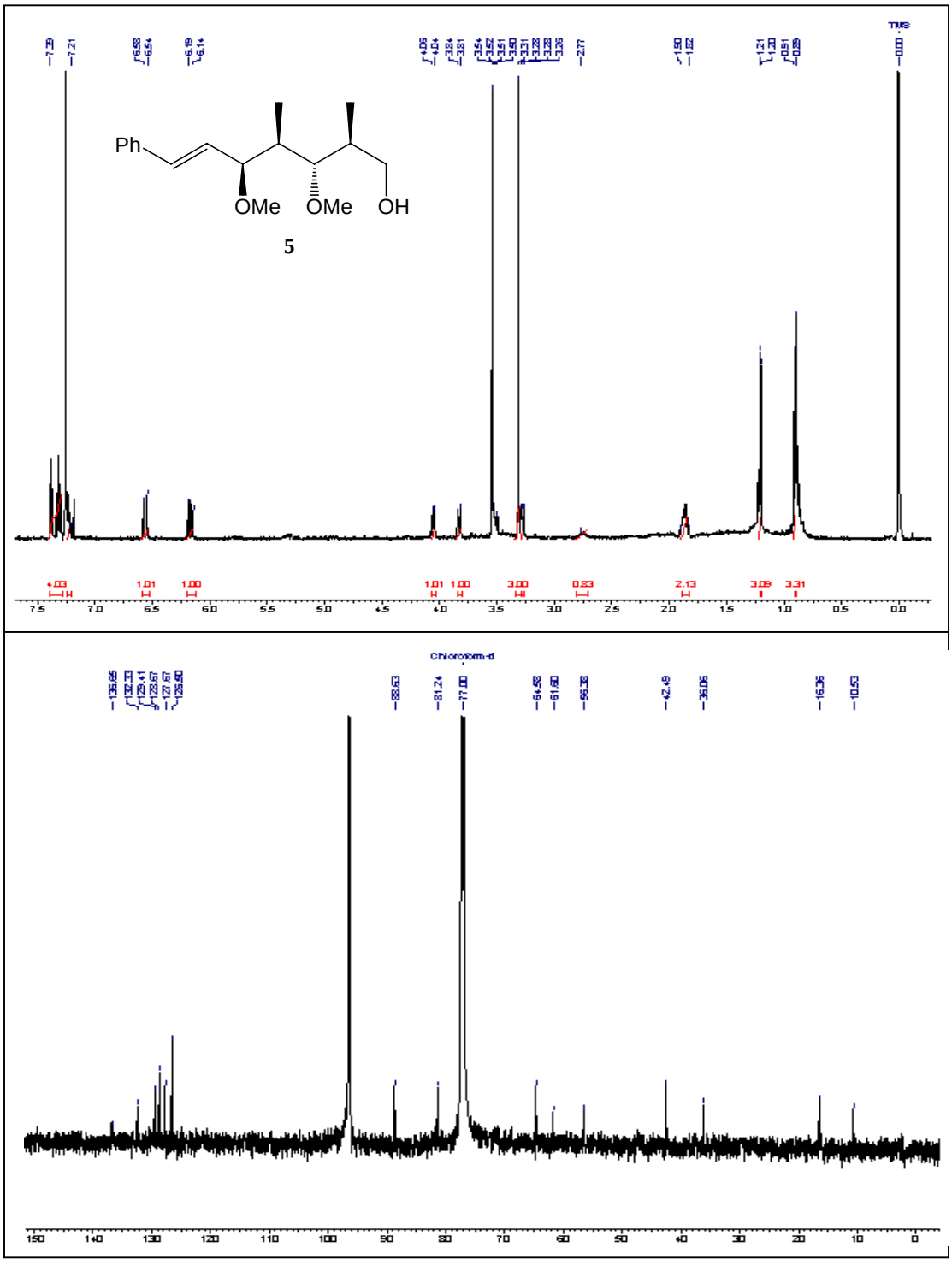
^{1}H and ^{13}C NMR spectra of compound 35 in $CDCl_3$



^{1}H and ^{13}C NMR spectra of compound 6 in $CDCl_3$



^{1}H and ^{13}C NMR spectra of compound 5 in $CDCl_3$



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Publications

1. *"Carbohydrate-based synthesis of crocacin: stereoselective Heck reaction of carbohydrate 5,6-ene- and 5,6-yne-derivatives with aromatic halides"* Mukund K. Gurjar, Tushar P. Khaladkar, Ramdas G. Borhade and A. Murugan, *Tetrahedron Letters*, **2003**, *44*, 5183.

2. *"Total Synthesis and Determination of Relative and Absolute Configuration of Multiplolide A"* C. V. Ramana, Tushar P. Khaladkar, Soumitra Chatterjee and Mukund K. Gurjar, Manuscript communicated for publication.